UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

PEDIATRIC ADVISORY COMMITTEE

MEETING

WEDNESDAY, NOVEMBER 28, 2007

The meeting came to order at 8:00 a.m. in the Grand Ballroom of the Hilton Washington DC North, 620 Perry Parkway, Gaithersburg, Maryland. Marsha D. Rappley, M.D., Chairperson, presiding.

PRESENT:

MARSHA D. RAPPLEY, M.D., CHAIRPERSON
CARLOS PENA, PH.D., M.S. EXECUTIVE SECRETARY
DENNIS BIER, M.D., MEMBER
AVITAL CNAAN, PH.D., M.S., MEMBER
ROBERT S. DAUM, M.D., MEMBER
MICHAEL E. FANT, M.D., PH.D., MEMBER
MELISSA MARIA HUDSON, M.D., MEMBER
KEITH KOCIS, M.D., M.S., MEMBER
THOMAS NEWMAN, M.D., M.P.H., MEMBER
GEOFFREY L. ROSENTHAL, M.D., PH.D. MEMBER
ROBERT WARD, M.D., MEMBER
RICHARD L. GORMAN, M.D., CONSULTANT
JESSE JOAD, M.D., M.S., CONSULTANT
RICHARD MALONE, M.D., CONSULTANT
AMY J. CELENTO, PATIENT REPRESENTATIVE
ELIZABETH GAROFALO, M.D., INDUSTRY REPRESENTATIVE
ELAINE VINING, CONSUMER REPRESENTATIVE
RICHARD L. GORMAN, M.D., PEDIATRIC HEALTH ORGANIZATION REPRESENTATIVE

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

8:01 a.m.

DR. RAPPLEY: Thank you and again, good morning. And I'd like to thank everyone for coming out this morning and participating in another day's session, I think because we do have new people here at the table for today's discussion I'd like for us to start again at the end of the table and have people introduce themselves. If you would say your name, your institution and the discipline that you represent that would be helpful. Would you like to start?

DR. BIER: I'm Dennis Bier. I'm from Baylor College of Medicine and I'm here as a nutrition representative.

MS. CELENTO: Amy Celento, patient representative.

DR. CNAAN: I'm Avital Cnaan, University of Pennsylvania and Children's Hospital of Philadelphia and I'm a biostatistician.

DR. FANT: I'm Michael Fant from the University of Texas, Health Science Center in Houston. I'm a neonatalogist and biochemist.

DR. GAROFALO: I'm Elizabeth Garofalo. I'm from Ann Arbor, Michigan. I am a pharmaceutical consultant and I'm the industry representative, non-voting member.

DR. GORMAN: Richard Gorman, pediatrician from Baltimore representing professional pediatric healthcare organizations, a non-voting member of the committee.

DR. JOAD: I'm Jesse Joad from University of California at Davis and I'm a pediatric allergist and pulmonologist.

DR. HUDSON: Melissa Hudson from St. Jude Children's Research Hospital in Memphis and I'm a pediatric oncologist.

DR. RAPPLEY: Marsha Rappley from Michigan State and I'm in developmental and behavioral pediatrics.

DR. PENA: Carlos Pena, Executive Secretary, FDA.

DR. KOCIS: Good morning, Keith Kocis from the University of North Carolina in Chapel Hill and I'm a pediatric cardiologist and intensivist.

DR. MALONE: Richard Malone from Drexel University College of Medicine and I'm a child psychiatrist.

DR. NEWMAN: Tom Newman from the University of California, San Francisco. I'm a general pediatrician and epidemiologist.

DR. ROSENTHAL: Jeff Rosenthal, Cleveland Clinic. I'm a pediatric cardiologist and an epidemiologist.

DR. WARD: I'm Bob Ward, University of Utah, a neonatalogist and clinical pharmacologist.

MS. VINING: I'm Elaine Vining. I'm a consumer representative.

DR. MURPHY: Diane Murphy, pediatric infectious disease, Director of the

Office of Pediatric Therapeutics at the FDA.

DR. MATHIS: Lisa Mathis, general pediatrician, Associate Director in the Office of New Drugs for the Pediatric and Maternal Health Staff.

DR. McMAHON: Ann McMahon, pediatric infectious disease, Office of Surveillance and Epidemiology, FDA.

DR. CHAMBERS: I'm Wiley Chambers. I'm an opthamologist. I'm the Acting Director for the Division of Anti-Infective and Opthamology Products.

DR. RAPPLEY: Thank you very much. I'm going to turn this over to Diane for a few comments this morning. Oh, I'm sorry, Carlos needs to make an announcement first.

DR. PENA: Thank you and good morning. The following announcement addresses the issue of conflict of interest with regards to today's discussion, a report by the Agency on adverse event reporting as mandated in Section 17 of the Best Pharmaceuticals for

Children Act. The Pediatric Advisory Committee will hear and discuss reports by the agency as mandated in Section 17 of the Act on adverse events reports for Serevent, Provigil, Azopt, Bextaxon, Emgriva and Gleevec. The Pediatric Advisory Committee will also hear about and discussion the pediatric initiatives between the FDA and the European Medicines Agency. This statement is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interest reported by the Committee participants, it has been determined that all interest in firms regulated by the Food and Drug Administration present no potential for an appearance of a conflict of interest at today's meeting.

In the event that the discussions involve any other products or firms not already on the agenda for which a participant has a financial interest, the participants are

aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record. We note and Ms. Amy Celento is participating as the pediatric healthcare representative, Ms. Elaine Vining is participating as the consumer representative and Drs. Jesse Joad and Richard Malone are participating as temporary voting members.

We'd also like to note that Dr. Elizabeth Garofalo is participating as the non-voting industry representative acting on behalf of regulated industry, Dr. Richard Gorman is participating as a temporary non-voting pediatric health organization representative acting on behalf of the American Academy of Pediatrics.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product that they may wish to comment

upon. We have an open public comment scheduled for 11:00 a.m. as well as 3:00 p.m. I would just remind everyone to turn on your microphones when you speak so that the transcriber can pick up everything that you state and turn them off when you are not speaking. I'd also ask participants to make sure that their cell phones are on silent mode. Thank you.

DR. MURPHY: Again, welcome. You've now completed reviewed at least 10 of the 66 documents, so today we're going to go through the remaining 50 some. I wanted to spend a moment just noting and reviewing for the Committee and for those people who are not as familiar with the Committee that the approach today is a little different from yesterday. Yesterday we had a very extensive discussion.

The Committee received a number of questions for that individual product. You will note today that we are going to have two

products that are being presented in an abbreviated format. I would remind the Committee that you said that this was okay as long as you received all of the background information and we gave you all the background information, and that this occurs where we feel that there is very little new information or any additional concerns that we want to focus on.

You then will have a couple of products that will receive a standard presentation again, you get all the background material that you normally get and that situation occurs when the Agency has a product that has -- that background disease itself may have a number of deaths or serious adverse events and the Committee has said you want to focus on deaths and serious adverse events. So we think it's a better part of wisdom to at least go through the standard process because it's always hard to differentiate when you have a high background rate with deaths and

serious adverse events.

Then we have a couple of products that we'll be providing, not the extensive all-day reviews, but what we call somewhat of a our expanded review. And these are products that either have had safety issues that have been discussed and addressed but because this is an opportunity for the Committee to focus on the pediatric component, we are providing you some additional information and in one of these situations in the products, you will note that we have an evolving process, that this review process, we get the data from our Office of Surveillance and Epidemiology.

We look at it. As you note, we sometimes ask them to do additional analysis. You have received some of those additional analyses and then we are sometimes at this point where we want your input but we're not ready to come to any final conclusions as to what we think about a signal that we may have identified during that process.

So you'll see a variety of recommendations. You are always, as you know, welcome to give us any of your thoughts but I wanted to outline for you why you see the -- remind you why you see this difference in the approach to the products.

And the last thing is, is if we have time at the day, it's not on the agenda, but Dr. Nelson wanted to -- Dr. Robert Nelson, our pediatric ethicist, wanted to spend about five minutes talking to you about some upcoming ethical issues. So I wanted to remind those of you who are looking about when you might be able to end the day, that we are going to try to add at least five more minutes at the end of the day, if we have time permitting. Thank you very much, and we very much look forward to your discussion today.

DR. RAPPLEY: Okay, I think we'd like to proceed then. Dr. Collins will make a presentation.

DR. COLLINS: Good morning. Today

I will be presenting two abbreviated presentations for the one-year, post-exclusivity adverse event review for brinzolamide ophthalmic suspension and levobetaxolol hydrochloride ophthalmic solution which are two products which are both sponsored by the same pharmaceutical company and I will begin my presentation with brinzolamide.

Brinzolamide opthmalic suspension or Azopt is a carbonic anhydrase inhibitor sponsored by Alcon that is indicated for the treatment of elevated intra ocular pressure in patients with ocular hypertension or open angle glaucoma. It was originally approved for marketing on April 1st, 1998 and pediatric exclusivity was granted on June 28th, 2006.

Pediatric drug use during the one year post-exclusivity period was low at 2.6 percent of all patients receiving an outpatient prescription from a U.S. retail pharmacy from July 2006 to June 2007. There

have been no pediatric adverse event cases reported to the adverse event reporting system during the one-year post-exclusivity period. Of note, there was one case labeled a pediatric case but on further review it was determined to be an adult case.

There has been one pediatric adverse event case since marketing approval and that involved a 14-year old female who developed dizziness, headache, abdominal discomfort, circulatory collapse and unconsciousness after several month's use of brinzolamide ophthalmic suspension. She was treated with volume replacement and regained consciousness without need for any other treatment. EEG and blood tests were normal and she resumed use of the drug later without any difficulties. Of note, the report does not comment on any renal or other organ system abnormality in this patient.

This case led us to ask the clinical pharmacology reviewer to consider the

likelihood ocular brinzolamide would result in systemic effects. It is known that carbonic anhydrase II inhibition results in decreased aqueous humour secretion and intra ocular pressure in the eye and decreased bicarbonate resorption in the proximal renal tube.

Brinzolamide distributes almost entirely in red blood cells due to it high affinity for carbonic anhydrase II and brinzolamide saturation of red blood cell carbonic anhydrase II results in a level of carbonic anhydrase inhibition below that expected for renal effects.

Therefore, the clinical pharmacologists concluded that; one, its unlikely that ocular brinzolamide given TID would result in systemic carbon anhydrase II inhibition in pediatric patients with normal renal function; and two, other factors, such as impaired renal function, may increase systemic brinzolamide concentrations and carbonic anhydrase II inhibition causing a

diuretic effect.

During the adverse event review, the drug safety reviewer identified the following foreign pediatric case report involving dorzolamide, which is a drug in the same class as brinzolamide. This is the case of a neonate with bilateral Peter's anomaly who developed metabolic acidosis while on ocular dorzolamide for seven days. The infant was treated with antibiotics and bicarbonate for three days but remained acidotic and unwell.

Dorzolamide was discontinued five days later with next-day resolution of the infant's metabolic acidosis. There were negative blood, urine, stool, throat and nasal cultures and the anion gap electrolytes, liver function test and urinalysis were normal. Renal ultrasound and DMSA scan revealed a normal functioning single left kidney. The authors concluded that factors such as prematurity, low birth weight, renal tubular

immaturity and one functioning kidney may have led to poor dorzolamide elimination and higher systemic concentration.

Thus, this completes the one-year post-exclusivity adverse event report for brinzolamide ophthalmic suspension. FDA recommends routine monitoring of this drug for adverse events in all populations. If the FDA identifies any additional pediatric cases suggesting systemic absorption of brinzolamide ophthalmic suspension, these cases will be presented to the Advisory Committee.

Does the Advisory Committee concur? And if there are no objections, I will actually just move onto the second presentation so the Advisory Committee can consider both of those during its discussion.

So I'm also pleased to be able to present to you today the one-year post-exclusivity adverse event review for levobetaxolol hydrochloride ophthalmic solution. Betaxon or levobetaxolol

hydrochloride ophthalmic solution is a beta blocker sponsored by Alcon and it is indicated for lowering intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension.

It was originally approved for marketing on February 23rd, 2000 and pediatric exclusivity was granted on June 28th, 2006. Betaxon has never been marketed in the US and currently, it is not being studied under an IND. In addition, there are no cases for any age group in the adverse event reporting system as of August 30th, 2007. Thus, this completes the one-year post-exclusivity adverse event report for levobetaxolol hydrochloride ophthalmic solution. And in closing, I would just like to acknowledge the assistance I received in preparing for these presentations from the FDA staff that are listed here. Thank you.

DR. RAPPLEY: Thank you very much. I'd like to ask the committee to pose any

questions or if there's a motion to accept the recommendation. The recommendation would be for routine monitoring of brinzolamide.

DR. MALONE: So moved.

DR. RAPPLEY: And now we will be voting all at the same time from this point forward, so those in favor of that motion, please raise your hand and indicate so.

That looks to be unanimous. Any opposed. Okay, thank you. So the Committee recommends routine monitoring for brinzolamide and will you clarify, is there a question then about the second medication that we should respond to?

DR. COLLINS: No. It's not marked that it's so.

DR. RAPPLEY: Yes, okay, so thank you very much. Next Dr. Sachs?

DR. SACHS: Good morning. I'm one of the medical officers in the Pediatric and Maternal Health Staff. And I also have been in practice in the local area for over 20

years. And first we'll be talking about the adverse events for emtricitabine, one of the anti-retro viral agents that's marketed for HIV.

You all may be familiar with the format of our standard presentation. Emtricitabine is a synthetic nucleoside anolog marketed by Gilead as Emtriva. A capsule form was approved in July of 2003 and an oral solution in September of 2005. The combination product Truvada, which has tenofovir and Atripla, which adds efavirenz were approved August 2004 and July 2006 respectively.

Pediatric exclusivity was granted in May 2006. Emtricitabine is indicated for the treatment of HIV infection in combination with other anti-retro viral agents. Dosage depends on the formulation since the relative bio-availability of the oral solution is 80 percent that of the capsule and dosing is available for patients of all ages including

neonates.

As far as the use goes, the total number of retail prescriptions for all nucleoside reverse transcriptase inhibitors actually increased during the post-exclusivity period and the single product represented only a portion of the NRTIs but the combination form that contained emtricitabine represent a quarter of the agents.

And overall, total use of the emtricitabine products have increased due, in part, to the large increasing use of combination therapies containing emtricitabine. A similar trend is observed for patients in and out of the hospital. Now, the greatest use of these agents is in adults with pediatric patients accounting for only a small proportion of use, less than one and a half percent and the majority of prescribers, not surprising, are infectious disease specialists and internists.

Now, let's look at the exclusivity

studies and note that if you go to the web page, there's actually two summaries available since the data was submitted in stages.

Several studies were preformed in response to the written request, a pharmacokinetic, safety and efficacy study which also examined anti-viral activity in pediatric patients greater than three months and a PK and safety study in HIV exposed infants. The data was submitted in two stages in March 2005 and March 2006.

In the older children a single dose escalation study was performed in 77 HIV infected children ages three months to 17 years and these kids were divided -- I'm sorry, these pediatric patients were divided into four age groups, three to 24 months, age two to six, seven to 12, and 13 to 17. The study revealed that exposures from either formulation at doses of six milligrams per kilo with a maximum of 240 milligrams for the oral solution and 200 milligrams for the

capsule were similar to the exposure noted in adults.

The efficacy in children over three months of age is supported by data from three open label, non-randomized studies in 169 HIV infected children and young adults, ages three months to 21 years. And patients could either be treatment naive or experienced and received emtricitabine with at least two other anti-viral agents.

A majority of patients in these trials showed evidence of decreased viral load and mean CD4 counts also increased. The frequency of adverse events in children were similar to those in adults with the exception of hyperpigmentation which was noted in 32 percent of the children compared to the adult rate of 13 percent. Other common treatment emergent adverse events included infections, otitis, increased cough, rhinitis, vomiting, diarrhea, rash and fever.

Now, in the HIV exposed neonates,

an open label, non-randomized study in term infants that were born to HIV infected mothers was performed. All of these infants were treated with six weeks postnatal ZDV plus two four-day courses of emtricitabine that were administered at various weeks after birth.

Okay. And note that all of the mothers received at a minimum intrapartum IV zidovudine or at the discretion of the investigator, nevarapine or a short course of oral zidovudine. Antepartum treatment was also offered and postpartum treatment with an effective commercially available antiviral regiment was offered for six months.

The study revealed that the single dose of three milligrams per kilo per day in infants that were term and greater than two and a half kilos found that the pharmokinetics were similar to those in older children. As far as safety, there were no deaths, but there were three serious adverse events reported and these included one case each of necrotizing

entercolitis with gastroenteritis, I'm sorry, and anemia, a case of gastroenteritis and bronchopneumonia, and a case of bronchiolitis. Fever was the most common reason for discontinuation and there was one patient who discontinued because of necrotizing entercolitis and a anemia before receiving any study drug.

Now, since the data was submitted in stages, the labeling was updated twice, first in September and then in December of 2006. And I have included the dates and then if anyone is all that interested. The PK findings are described under the clinical pharmacology sections and under the precautions, pediatric use, the labeling states that safety and efficacy has been established for patients older than three months but not for those younger. The clinical trials are described along with the greater frequency of hyper-pigmentation and neonatal adverse events are also described.

The adverse reaction section describes the adverse reaction profile which was observed as well as the laboratory abnormalities that were noted during the trial. Now, dosing is provided for children three months to 17 years of age added -- I mean, for ages three years to 17 and the dosing for neonates and infants is given based on the PK finding of the HIV exposed neonates, although safety and efficacy has not been determined in these patients. And this is really due to the part -- due to the fact that luckily, there are really low number of HIV infected infants now and there's extreme difficulty in performing studies in this particularly unique population.

Before we move to the adverse events, I just would like to draw your attention to certain parts of the labeling that may help with interpreting the adverse events that we saw. There's additional safety labeling that includes a box warning

describing lactic acidosis and severe hepatomegaly, which is a class label for all the agents, as well as a lack of indication for chronic HBV and that occurs in all the forms that contain emtricitabine. And these warnings are reiterated in the warning section. Precautions discusses the need to reduce the dosage in patients with impaired renal function, the fact that you can have redistribution of fat and the occurrence of the immune reconstitution syndrome.

Emtricitabine is currently classified as Pregnancy Category B and that's because the animal data show no risk but there have been no formal studies in humans. Contact information is provided for the anti-retroviral pregnancy registry and healthcare providers are encouraged to report any patient who inadvertently becomes pregnant while receiving these therapies.

When you look at the raw counts for these drugs, you'll see that there's a lot of

duplicates and we just wanted to briefly explain why. Most patients that receive these therapies are multiple combination therapies and they're initiated and terminated simultaneously. By law, each company must report an adverse event, must submit an adverse event report when they receive one, and direct reports may also be received from consumers or lawyers or healthcare professionals and so you could see for one drug you could theoretically get six reports, if not more. So since market approval, there are almost 1,000 reports in all patients with 899 serious adverse events and 108 fatalities, and as I said, these include -- duplicates the raw accounts.

Pediatric patients accounted for 35 of these reports which is less than one percent. All of these were serious and there were six fatalities but there are duplicates as you'll hear. During the one-year post-exclusivity period, there were 497 reports

received in all ages, 478 of these were serious and 45 included fatalities. Pediatric patients accounted for 20 which is less than four percent of these with five deaths, but accounting for duplicates, there was actually only 15 cases and three fatalities.

General exposures accounted for 11 of the 15 unduplicated pediatric adverse events and -- I'm sorry, four of these were fatal. Three of there were premature infants who had multiple anomalies or intra-cranial hemorrhage. One was a male twin who died in his infancy from febrile gastroenteritis and malnutrition. There was no clear pattern detected in these events and they occurred after exposure to multiple agents and at varying gestational ages.

Annual reports from the anti-viral pregnancy registry are not remarkable and that was just updated last month. Note that emtricitabine alone or in combination with tenoforvir is considered to be a Category B

drug while the triple combination with efavirenz may be -- may cause fetal harm and is characterized as a Category C.

Three of the remaining four adverse events involved hepatic dysfunction. One adolescent developed hepatitis and jaundice a few weeks after changing anti-viral therapy to include emtricitabine and other agents in particular tipranavir while another developed asymptomatic elevations of bilirubin when two drugs including atazanavir were added to the existing regimen. Note that the labeling for emtricitabine includes elevated liver enzymes and tipranavir carries a box warning for hepato-toxicity. The precaution section for atazanavir also includes asymptomatic elevations of bilirubin.

The last case with hepatic elevation was a 14-month old with HIV and congenital toxoplasmosis who was on combination therapy and he developed elevated liver enzymes after receiving inadvertently

three times the dose of emtricitabine. The elevated levels declined once all his drugs were discontinued and this case was compounded by multiple factors including the underlying disease, hyperalimentation, surgery, sepsis, and the other therapies he received. But note that the labeling for all three drugs does include information regarding hepato-toxicity although there is no specific information regarding increased LFTs in the overdose section.

The last case is a six-year old female who had diarrhea and suspected meningitis but gastroenteritis is listed under the adverse reactions in pediatric patients and meningitis was actually ruled out. So in summary, labeling has been updated from the exclusivity studies with safety and efficacy established in patients three months and older but not in infants although dosing is provided for patients of all ages. The adverse events that we saw during the exclusivity -- I mean,

during the pediatric exclusivity studies were very similar to adults except for hyper-pigmentation. There were no unique pediatric adverse events noted during the one-year exclusivity trial period and thus, the FDA recommends routine monitoring of emtricitabine for all ages if this advisory committee concurs.

I'd also like to acknowledge the help from many, many folks, including Dr. Lewis, who is sitting at the table.

DR. RAPPLEY: Thank you very much. So the question to the Committee is do we concur with the recommendation of routine monitoring for emtricitabine in all populations? Do I have discussion, questions or a motion for that?

DR. WARD: Marsha, could I ask a question of Dr. Sachs?

DR. RAPPLEY: Yes.

DR. WARD: In Table 1 about the pharmacokinetics, it looks like the clearance

is really significantly less in the one to -- the newborn, immediate newborn to three-week old infants. And is that reflected -- I was trying to work my way through the label and didn't find any sort of refinement of dosing for that younger age group and this is a group that probably will be treated.

DR. SACHS: The dosing for the infants is three milligrams per kilogram --

DR. WARD: And --

DR. SACHS: -- whereas the dosing for older patients is six.

DR. WARD: And are we defining infants up to --

DR. SACHS: Three months.

DR. WARD: -- three months? Okay. It just looks like there's a break point in clearance at three weeks on up, probably related to renal function.

DR. SACHS: I think that's why the dosage is lower.

DR. WARD: Okay.

DR. SACHS: Linda, do you have anything to add?

DR. LEWIS: No, as you may imagine, it's become very, very difficult to study this age group in the United States and so our requirements for the company have tried to match that difficulty. We, fortunately, have been very successful in preventing HIV infection in the United States in infants. And so many of these studies are done outside of the U.S.

And we get pharmacokinetics in kind of unusual little blocks. As Hari pointed out, the way this was done was in two separate sections or two separate PK analyses in each cohort but they were staggered at different ages up to three months. But within that, it was -- there was some overlap between those groups because of the stagger.

And the clinical pharmacologist felt that there was not enough either information about the therapeutic toxic ratio

to warrant making another division in the dosing. The toxicity profile of this drug is really quite good and particularly in this age group. Children are unlikely to be on some of the other drugs that might contribute to the more severe toxicity such as the ones that Hari mentioned in the one-year post-exclusivity review such as the severe liver toxicity and things like that. So neonates are unlikely to be on those concomitant medications. So we thought that the toxic therapeutic ratio was such that we could use one dosing across that younger age group.

DR. WARD: Thank you. That clarifies it for me.

DR. RAPPLEY: Dr. Fant, any thoughts? Michael any thoughts about that? No, okay. Yes.

DR. CNAAN: A question for Dr. Lewis. Is this also the explanation, the experimental conditions, if you will, for why the coefficients of variations in the six

weeks to three months old are that large?

DR. LEWIS: For almost all of these products the coefficient of variation is somewhere between 30 and 50 percent. We've never really been able to determine why that's true but it seems to be the case for all of the nucleoside analogues. And it may be partly because the compartment that we can measure is circulating blood, clearly, but the active site of these drugs is actually the intra-cellular concentration that's the most important. And so there's probably less variation in the intra-cellular levels than there are in the circulating blood. So we get efficacy even in the face of fairly wide variations.

DR. RAPPLEY: Dr. Kocis.

DR. KOCIS: I don't want to get us off track and I want to make sure I'm doing this in the right time, but before adverse events show up in our next meeting on this, is there some reason that we dose the children up

above the adult dose of 200 milligrams and the liquid form goes to 240 which is essentially in a kid over 35 kilos will get above the adult dose? Is there some reason for that?

DR. LEWIS: That's based on the pharmacokinetics of the liquid as compared to the capsules. It is more bio-available. And so if you're using the liquid, you -- I'm sorry, less, you need to use a little bit more of it and so we just increased the maximum dose. The per kilo dose seems to be that gives the targeted PK level, so which would be equivalent to the adult dose shown to be safe and effective in the larger adult trials.

DR. RAPPLEY: Any other questions?

DR. MURPHY: This isn't a question. I just wanted the Committee to put this away in their memory bank. This is a very unusual situation that we put a dose in the label and say we haven't proven efficacy but you have to put it in the context which Dr. Lewis has explained that we actually have a situation in

which that division and if I misstate this but having worked with that division, I hope I get it correct that what they do is they do PK/PD. They feel like they can -- the disease is the same in kids as it is in adults but they fundamentally verify that with a PK/PD because they can look at viral load activity, get the dose and do the safety and that's sort of, you know, on your extrapolation. I'm bringing it up because the issue of extrapolation is a big issue for this group, for pediatrics.

And therefore, you are in essence testing your extrapolation hypothesis, getting the dose, getting the safety and then when they get down to this very young group, they are unique. They have differences in the disease but the division has made the assessment that they need to state, "We haven't proven it but we also think there's enough reasonableness to provide the dose," which is very unusual. So this goes into your memory bank. It's not our standard operating

procedure, but something to be able to think about when these issues come up in the future.

DR. LEWIS: Just one other clarification is that clearly babies don't stay under three months for very long and so if we have efficacy data starting at three months or so, given the rate of decline of HIV viral load, it's very difficult to test efficacy in a narrow window of time because what we are really looking at is efficacy over six months to a year to two years of chronic dosing. So we feel that if we have a good PK/PD group, and a good match and we have safety and efficacy in slightly older children, then we can say, yes, that's the correct dose but we can't technically say that we have shown safety and efficacy in that age group. DR. RAPPLEY: Do I have a motion to concur with routine monitoring for this medication? Dr. Newman, second?

DR. NEWMAN: Second.

DR. RAPPLEY: A show of hands,

those in support of this motion? Opposed? It's unanimous support of this motion. Thank you.

Dr. Sachs, would you like to continue?

DR. SACHS: Okay. Thank you. Thanks, Dr. Lewis. Is Dr. Cohen here from oncology. So you want to come up to the table? All right, we're going to switch gears to oncology. I will now discuss the adverse events for imatinib mesylate. Again, this is going to follow the standard presentation. Imatinib mesylate is a protein kinase inhibitor marketed by Novartis as Gleevec. The currently marketed formulation, a tablet, was approved April of 2003 and pediatric exclusivity was granted on June 2006. Indications in adults and children include newly diagnosed and some forms of relapse, Philadelphia chromosome positive chronic myeloid leukemia which from now on I will call CML. In adults only, imatinib is approved to

treat other forms of leukemia and myelodysplasias as well metastatic dermatofibrosacromas and gastrointestinal stormal tumors or GIST.

The dosage does depend on the indication in adults with doses ranging from 400 milligrams to a max of 800 milligrams daily or divided twice daily. The dose in children is related to body surface area and as you can see, is higher in newly diagnosed patients.

I wanted to point out to you all that the labeling for this product is now in the new PLR format with highlights and summary which is actually a lot easier to read than this slide, I hope you guys found. Now, looking at the use, as you can see imatinib is purchased primarily in the outpatient setting by either retail or mail order pharmacies and the vast majority of use is in adults, over 98 percent of the use.

Imatinib use is increased slightly

by approximately four percent in adults comparing the year before exclusivity and the year after exclusivity. The trend was similar in children but because the numbers are small and therefore, less reliable, it's not presented on the slide.

Since data was not available before 2005 for mail order prescriptions, you'll note there is only data for the year before exclusivity. Hematologists and oncologists were the primary prescribers and all the surveyed pediatric office visits were associated with lymphoproliferative disorders.

Now, let's talk about the pediatric exclusivity studies. Now, several studies were performed in response to the written request; a Phase 1 dose finding study, which included pharmacokinetics, and determined the maximum tolerated dose for all the appropriate pediatric age groups, and a Phase 2 cytogenic response study which included population PK on a subset of patients. Intensive

pharmacokinetics sampling in 17 patients revealed that pharmacokinetics were similar between adults and pediatric patients and showed that a dose of 340 milligrams per meter squared per day was comparable to the adult dose of 400 milligrams. Sparse pharmacokinetic sampling in a subset of patients in the cytogenetic response study did not reveal a significant relationships between measures of exposure and high grade toxicities and these findings were incorporated in the labeling in the various sections you see.

The cytogenetic response was determined in 51 newly diagnosed patients who received the 340 milligram per meter squared dose and 78 percent of these patients experienced a complete hematological response after eight weeks and 65 percent had a complete cytogenetic response. An additional 16 percent had a partial cytogenetic response.

In a second study, 14 patients with a recurrent CML after transplant or interferon

therapy received 260 to 257 milligrams per meter squared per day of imatinib and half of these patients had a complete response. An additional four experienced a partial cytogenetic response.

Of the three interferon dosed alpha resistant patients, two of them achieved a complete cytogenetic response to doses less than 260 milligrams per meter squared per day. And then for all of you non-hematologists, oncologists, a complete response was no metaphases where a partial response is up to 35 percent, one to 35 percent.

So the new indication for pediatric patients is listed in the labeling under Section 1.3 with a caveat that there is a lack of controlled studies demonstrating clinical benefits such as improved symptoms or survival and labeling under the pediatric use section which is 8.4 reiterates that the safety and efficacy has been established in newly diagnosed and chronic patients with CML and

labeling indicates that there's no data available for children younger than two and follow-up is limited.

The clinical studies themselves are described under the clinical study section 14.2, Pediatric CML. Now as far as safety, there were no deaths in the 54 patient study. High grade toxicities were primarily hematologic and the incidents of myelosuppression was higher in children than in adult patients.

Non-hematologic high grade toxicities included allergic reactions, hypersensitivity, avascular necrosis, and desquamating rashes. Weight gain and edema was low compared to adults and one patient discontinued therapy due to elevated liver enzymes while another experienced a high grade increase, although that patient had auto-immune hepatitis. And unlike adults, only sporadic muscle cramps were reported and there was no GI hemorrhage seen, a finding that

primarily in GIST patients as I understand.

So these toxicities are described under Section 5.3, hematologic toxicities and the adverse event profile is described in Section 6.4 and that is actually based on an overall pediatric experience which includes some additional patients with ALL, and it reflects while the overall safety profile is comparable to adults, musculoskeletal pain is less frequent and peripheral edema is not reported.

Nausea and vomiting is the most common adverse event and the incidents of high grade adverse events is low in children. Now, I just wanted to show you the format for the new labeling and talk about some of the things which are relevant for the adverse events that we saw during the exclusivity period.

The warning and precautions section of the labeling admonishes that women of child-bearing potential should avoid pregnancy due to the risk of teratogenecity, and

patients and prescribers are alerted to the development of fluid and edema which can occur and those can result in things like cardiac tamponade, increased inter-cranial pressure, pulmonary edema, et cetera.

I've mentioned the hematologic toxicities in pediatric patients and for that reason frequent monitoring of blood counts is recommended. In addition, severe congestive heart failure and liver -- and left ventricular dysfunction may occur and so all patients, including those with congestive heart failure should be monitored closely.

Patients should also be monitored for hepatic toxicity with periodic liver function tests and a greater risk of high grade hemorrhages reported in patients with GIST compared with those with CML. GI irritation can be avoided by taking this with food and water, but rarely GI perforation has been reported and hypereosinophilic syndrome or hypereosinophilic cardiac toxicity, which

is treatable with steroids, may occur in patients with hypereosinophilic syndrome or myelodysplasias.

Dermatologic toxicities such as Steven-Johnson and erythema multiforme are described and not unexpectedly, very important for children, long-term toxicities may occur typically involving the liver, kidney, heart and immune system. And as I mentioned imatinib is Category D and in adults the most frequent adverse reactions are edema, gastrointestinal symptoms, musculoskeletal systems and rashes.

Turning to the adverse events, here are the raw counts. Since market approval there have been over 4,000 reports in patients of all ages of which 4,071 have been serious and there have been approximately 800 deaths reflecting the population. Adverse events in children roughly parallel the use with 93, which is less than 0.1 percent, of adverse events reported in children. Eight-two of

these were serious and nine were related to fatalities. And once again, these include the duplicates.

We did look at the pediatric fatality since market approval. Three of these occurred during the one-year post-exclusivity period and you'll see them shortly. The remaining events were highly confounded by multiple medications, progression of disease or complications such as sepsis and pancytopenia and this is true for the serious events as well.

During the one-year post-exclusivity period, there were approximately 900 reports in all ages, the majority of which were serious and just under 200 deaths in adults. Pediatric patients accounted for 25, 19 of those were unduplicated and four deaths, one of which was a duplicate.

So as you see, there's three fatalities during the post-exclusivity period, one of which is related to maternal exposure

and for the non-fatal adverse events, two of them are associated with maternal exposure, two are associated with growth retardation and the remaining events are highly confounded.

I wanted to give you a sense of the type of events that we saw and how they are confounded and you can see that these events occur with exposure to multiple chemotherapeutic agents or represented a single report and I'm highlighting some of them just to give you an idea of the range of events.

There was a 13-year old female with ALL who developed biopsy proven retroperitineal fibrosis with hydroneuphrosis and obstruction after three months of therapy. Although long-term renal toxicity is mentioned in the labeling, fibrosis is not. A 9-year old female with ALL on imatinib and other agents developed hypernatrenia, hypertension and seizures with posterior encephalopathy findings on MRI and her

symptoms improved with sodium replacement, blood pressure control and anti-convulsants. And you can see that these were patients that received the therapy for what is currently an off-label use in children although an approved indication in adults.

There was also multiple congenital anomalies in a 30-week old pre-term infant who was treated during the first trimester with imatinib for CML and notably that patient -- this event is confounded by consanguinity as well as the medications that the mother received.

There were three gestational exposures and I apologize because the prompter is not there, so the one was the fatal case with -- that I previously described. Another was a healthy pre-term infant who was 35 weeks of age and the last was a term female infant, who had a hypoplastic thumb during first trimester exposure. And as I said, that labeling does state that pregnant women should

avoid -- I mean, that women should avoid becoming pregnant while on this therapy and to use contraception.

Two patients developed growth deprivation which is an event of interest given the effects of imatinib on bone metabolism. Growth disturbance in these patients may be -- may reflect the underlying tumors and chronic illness as well as the recognized impact on growth from chemotherapy.

Anyway, I apologize, here are the three fatalities. There were two that were -- occurred in older children that had ALL and one had relapsed after multiple chemotherapeutic regiments and multiple antibiotics and anti-fungals and he had developed pulmonary edema, cardiac failure and he died after multiple cardiac arrests.

There was an eight-year old who had relapsed ALL after core blood transplant who received imatinib as part of chemo. She was switched to another regimen and died after

multi-organ failure and her course was complicated by Aspergillus and pneumonia.

Okay, so in summary, the labeling has been updated with a new pediatric indication. Differences in the adverse event experienced between adults and children such as the higher incidents of myelosuppression and less peripheral edema have been incorporated. There are no new pediatric adverse events that we identified during the one-year post-exclusivity period and the FDA recommends routine monitoring of imatinib if this Committee concurs.

Once again, thanks to all the folks that have helped with this presentation.

DR. RAPPLEY: Thank you, Dr. Sachs. And we're open for clarifying questions. Dr. Fant.

DR. FANT: Just out of curiosity, the healthy 35-week pre-term infant, do you have any more details about the nature of that exposure? Was it late in gestation, brief?

DR. SACHS: I want to say it was first trimester exposure and actually there's very few details. It just says that the baby was delivered at week 35 of pregnancy. The mom had been on Gleevec, I mean, it looks like first semester, but there's really not any details.

DR. FANT: Okay, and one just general interest question, I'm not sure if you have the answer for it; is there any data from the sponsor with respect to the effects of this drug on metabolic parameters, such as insulin resistance or diabetes management and that sort of thing given the way it works?

DR. COHEN: I might answer that. Thus far there doesn't appear to be any problems in those area with Gleevec.

DR. SACHS: And I was going to say the labeling only says that there can be some infrequent hypophosphatemia as far as metabolic and nutritional.

DR. RAPPLEY: Dr. Ward?

DR. WARD: I'd just like to comment; this new labeling format is a dramatic improvement and I think it makes it much easier to digest the information. And the other is to the sponsor. In 1998, just after FDAMA, there was a meeting about oncology drugs and that they were not serving the oncology -- or FDAMA was not serving the oncology population and I'm very appreciative to see pediatric labeling actually being incorporated for some of the oncology drugs. Thanks.

DR. RAPPLEY: Other comments or questions? So the question to the Committee is do we concur with routing monitoring of imatinib in all populations? Do I have such a motion? Dr. Hudson moves. Support, Dr. Rosenthal? Can we have a show of hands supporting this motion? Those opposed? So that's unanimous support of this motion. Thank you. Thank you, Dr. Sachs.

Before we move onto our next

presentation, I would like to just stop for a minute. I think that we see a number of slides repeatedly over the course of our meetings that list the many contributors to this work. And I think that those contributors as well as all of those who present to us deserve an acknowledgment and an expression of thanks for the work that goes into this Committee's responsibility, meeting this Committee's responsibility.

I'd like to say that the Committee members as well as the general public rely on the diligence and the integrity of the staff in preparing this information for us. And in my experience over the last four years, you consistently go above and beyond the call of duty. And so I want to thank you for that and tell you that it makes me proud to be associated with this activity at the Pediatric Advisory Committee and I just wanted to take a minute to express that.

Okay, can we move on then to --

DR. SACHS: Thank you all very much.

DR. RAPPLEY: Our presentation then is from Dr. Mosholder.

DR. SACHS: Actually, I think I go first.

DR. RAPPLEY: I'm sorry, Dr. Sachs.

DR. SACHS: Okay, hopefully you guys won't be tired of seeing me and start hyperventilating. We're going to be switching gears and talking about asthma. Now, this presentation does deviate slightly from our general format so let me just give you a quick overview. In addition to the usual background drug information, I'll be presenting relevant safety information including the existing box warning which is underpinned by the findings of the SMART study and supported by pulmonary, allergy, drug advisory committee, deliberations. I will briefly describe the current asthma treatment guidelines as they related to long-acting beta agonists in

children and the pediatric trials which proceeded exclusivity that resulted in labeling for children ages four years and older.

Finally, I'll discuss the drug use trends and findings that we saw during the pediatric exclusivity study which did not result in a labeling change and you'll see why. At this point, Dr. Andrew Mosholder from the Office of Surveillance and Epidemiology will describe the adverse events which have been seen in children during the one-year exclusivity period and emerging information regarding pediatric hospitalizations from clinical trial and epidemiologic findings.

And at that point, I think, the sponsor will present and we'll take a break and then I'll return to provide a wrap-up. I also want to acknowledge Dr. Seymour and Peter Starke from the Division who are here.

Salmeterol is marketed by GSK and the meter dose inhaler was approved in February of

1994 and the inhalation powder or the diskus was approved in September of 1997. There are two combination products which contain fluticasone and Salmeterol that have been approved at diskus in 2000 and an HFA product last year. Pediatric exclusivity was awarded for the studies performed with Salmeterol meter dose inhaler in March of 2006; however, the meter dose inhaler is no longer marketed as part of the chlorofluorocarbon, CFC, phase-out.

Salmeterol is indicated for the maintenance, treatment and prevention of asthma and exercise induced asthma in adults and children four years of age and older and COPD in adults. Labeling states that since long-acting beta agonists such as Salmeterol may increase the risk of asthma related deaths, Salmeterol should only be used as additional therapy for patients not adequately controlled on other medications such as inhaled corticosteroids or those with severe

enough disease to require two maintenance therapies. These statements emphasize those found in the box warning and the dosage is the same in adults and children.

Now, as I mentioned, labeling carries a box warning and you'll see this sprinkled throughout our presentations, that Salmeterol may increase the risk of death and states that Salmeterol is to be used only as additional therapy. This warnings is based on findings from the Severent Multi-center Asthma Research Trial or SMART and was originally incorporated in August of 2003. The SMART was a randomized placebo controlled trial initiated in 1996 to examine the effects of chronic beta agonist use and it detected an increase risk of severe asthma exacerbations, including death.

Importantly, there's a similar box warning for this whole class, including another long-acting beta agonist formoterol as well as the combination products and in

addition, medication guides for each including the combination products are required and these medication guides include the statement that in patients with asthma, LABA medications may increase the chance of death from asthma problems.

A detailed description of the SMART study is found in the body of the labeling and includes a statement that data from the trial is not adequate to tell whether or not inhaled corticosteroid use or other medication mitigates the risk of death.

Now, I'd like to also highlight some of the labeling which reinforces all these warnings. Hypersensitivity to Salmeterol or one of its components is the only contraindication. In addition to the boxed warning, there are several warnings and these include the need to watch for signs of worsening asthma, an admonition not to treat acute or deteriorating asthma or use Salmeterol as a substitute for

corticosteroids. A reminder that increasing use of short acting agents is a marker of deteriorating asthma, a warning that Salmeterol should not be used with other long-acting beta agonists and the dose should not be exceeded. There's also description of the risk of paradoxical bronchospasm or immediate hypersensitivity or other allergic kind of reactions like vocal spasm.

And finally, there's the advice to use with caution in patients with underlying cardiovascular disorders. Now, as I mentioned, the SMART study was a large simple safety study and it involved approximately 26,000 patients ultimately, although there were 60,000 patients planned to be enrolled.

These patients were 12 years and older with diagnosed asthma and they received either Salmeterol, 42 micrograms twice a day versus placebo for 28 weeks and they were randomized one to one. This study was initiated in 1996 and was halted prematurely

in January 2003 based in large part because the interim analysis showed that Salmeterol may be associated with an increased risk of severe asthma and death. The primary end point of the study was a combined one of respiratory related deaths and life threatening experience which include intubation and mechanical ventilation.

The secondary end points included asthma related deaths, life threatening experiences and all-cause hospitalizations. Now, as you can see in this trial, a little over 3200 or 12 percent of patients involved in SMART were children 12 to 18 years of age with only a handful of patients under 11 enrolled, and since the trial was to exclude patients under 12, that's not surprising.

The 12 percent use, as you'll see -- the 12 percent is roughly equivalent to the use of Salmeterol as you'll see in the use slides. Now, the numbers for the primary end points here are really too small to make a

conclusion about the risk of death but it's certainly not unreasonable to suppose that the risk is the same but we can see that all-cause hospitalization in children is increased.

You will note that this analysis does include 18-year olds who do not fit the regulatory definition of pediatrics, although having an 18-year old myself as some of you with adolescents will know, I might differ about that. And Dr. Mosholder will be elaborating on these findings shortly.

Now, a pulmonary advisory allergy -- a pulmonary allergy advisory committee was convened in June of 2005 to discuss these key issues that were involved in weighing the risk and benefit of using Salmeterol and other long-acting beta agonists, given the signal of severe asthma exacerbation and asthma related deaths. And this signal was recognized during the post-marketing of Salmeterol but not during the clinical development program and the risk was confirmed by the SMART trial and

then incorporated into the labeling as the box warning.

At the same time, during phase -- or roughly the same time, Phase 3 trials of formoterol there was an increased risk of these events noted for a high 24 microgram dose compared with the lower and subsequently approved dose of formoterol. And the post-marketing findings for Salmeterol as well as the SMART trial and the trial data on formoterol raised the issue of class labeling. Note that the clinical guidelines at the time as well as today identified LABAs as important treatment options for patients with severe chronic asthma.

After deliberating, based on the information available, the Committee voted as follows; there was unanimous agreement to keep both Salmeterol and formoterol on the market and almost unanimous agreement to include the findings in the formoterol labeling, that is to have class labeling and as you know, that

has happened. The National Asthma Education and Prevention Program Guidelines were updated this summer and I'd like to highlight some key points regarding long-acting beta use in children and the complete set of guidelines can be downloaded from the link provided.

According to the guidelines, long-acting betas are not to be used as monotherapy for long-term control and should be used with inhaled corticosteroids although the evidence for this combination is not as strong in children five to 11 years of age. An A grading is based on a rich body of data which includes randomized control trials, while a more limited body of data which does include some randomized control trials results in a B rating.

Now, the original approval was for adults and adolescents older than 12 years in age and was based on multiple clinical studies in thousands of patients and while I'm not going to go through the details of every

single study, I would like to give you some flavor of the pivotal efficacy trials so you can have an idea of what was performed.

During two randomized double blind studies with approximately 450 adults and adolescents, the diskus was compared to placebo and albuterol over a 12-week period and there were significant improvements observed in pulmonary function as well as the key secondary end points such as percent night awakenings and a decrease in rest inhalations. There were similar rates of asthma exacerbations in the study noted and tachyphylaxis was not noted in the 12-week treatment period.

Similarly in another set of randomized double blind trials looking at the two different formulations of Salmeterol, that is the MDI and the Diskus compared to placebo. Both of the active treatment arms experienced significant improvements in pulmonary function and there were not significant differences

noted between the two formulations. And as I understand it, this is a trial of over 240.

Now, these results were supported by a six-month trial in 925 adults and adolescents and actually another trial in adults who received concomitant inhaled corticosteroids in the from of fluticasone. Patients who were not adequately controlled on 88 micrograms of fluticasone were randomized to either add on Salmeterol or more than double the fluticasone to 220 micrograms. Patients on the combination therapy experienced significantly greater improvements in pulmonary function and asthma symptoms as well as a reduction in supplemental inhaler use and importantly, in this 24-week trial, fewer patients experienced asthma exacerbations in the Salmeterol group compared with patients who more than doubled their fluticasone. Try as I could, I could not find how many patients were adolescents. The way the study was stratified, it's under 50 and

over 50.

Now, as you can see, approval for exercise induced bronchospasm was based on two randomized single dose cross-over studies in 53 adults and adolescents and in that study a single 50 microgram dose 30 minutes prior to exercise prevented exercise-induced wheezing with a duration up to eight and a half hours.

Now, for younger pediatric patients, ages four to 11, the approval was based on part of the findings in the adults and adolescents but also in clinical studies, one set being a 449 patient randomized controlled study which showed that twice daily dosing of the Diskus over 12 weeks, consistently improved pulmonary expiratory flow and FEV I over placebo. The efficacy was supported by an additional placebo controlled trial in 207 patients using the meter dose inhaler and the efficacy for exercise induced bronchospasm was established in another random -- set of randomized control trials in 50

children and in this case, protection from exercise induced wheezing lasted 11-1/2 hours after a single dose.

The safety database for the younger children included 2500 patients ages four to 11 of which 346 were treated for over a year. And if you started to try to add up all the numbers and get to 2500 you're not going to be able to because in addition to all the patients enrolled in the efficacy trial, there were actually seven trials conducted outside the United States with other Salmeterol formulations and although those trials did not contribute to dose selection or determining efficacy, the data was used in an integrated review of safety and there was no deaths seen and no specific safety signal identified.

The labeling does say that adverse events such as ear signs and symptoms, pharyngitis and headache did occur more frequently in the Salmeterol treatment group compared with placebo and as you can see, a

slightly higher rate of asthma was noted.

Okay, moving to drug use and I apologize that this slide is busy but I will walk you through it. The majority of inhaled albuterol, I mean, inhaled beta agonist use does occur in outpatients with Salmeterol accounting for only a portion of use, less than five percent. The majority of use, as you can see, is in adults for both the individual product and the combination and pediatric patients account for -- and I apologize, I didn't put the percentage in, about five percent of the single product and about 13 percent of the combination.

The primary prescribers are general practitioners, internists and pulmonologists and use -- and pediatricians write less than 10 percent of the prescriptions. Not surprisingly, the most common diagnosis is asthma for children. Now, the trend during the pre- and post-exclusivity period reveals a marked decline in the use of the

single product in both adults and children with an approximate 10 percent increase in the combination product and if we look at the specific pediatric sub-groups, the use declined for both, although greater decline in the single product.

Now, let's talk about the exclusivity studies. And you will note that a clinical pharmacology summary is not provided as Salmeterol acts locally in the lungs and therefore, plasma levels do not predict the therapeutic effect. In response to the written request, there were four safety and efficacy studies performed in children less than four years of age using the valved holding chamber and the children were divided into two age cohorts, six months to 23 months and two to four years. In both cohorts there was a dose ranging, safety study and a four-week double blind placebo controlled efficacy and safety study. There were 21 patients in each of the dose ranging studies and 338

patients in the older cohort and 167 patients in the younger cohort.

All of the studies were double dummy. Drug or placebo was administered by the holding chamber with a face mask and note that the studies were performed with the meter dose inhaler which is no longer marketed and in vitro delivery was required to confirm adequate drug delivery via the spacer. Unfortunately the in vitro data was not adequate to characterize the delivery of medication through the valved holding chamber and it's unclear if patients actually received the study medication. In addition, the data did not establish superiority over placebo since there was no difference for change in asthma symptom scores. Because of the in vitro data, the clinical relevance of these findings is unclear and therefore, labeling change was not made.

Interpretation of the safety data is limited as drug delivery was also -- was

limited as well since drug delivery was not assured but there were no deaths among the 500 children studied and the adverse events were more common in the younger age cohort, although in general they were similar to the adults and adolescents. Fever was the most common adverse event, infection, irritability and some psychomotor disorders was more frequent in the tremor group and tremor in particular was a little more frequent in the treated group during one study but did not occur in the majority of patients and when it did occur it was mild.

There's a slight shift towards abnormal nasal secretions but laboratory measurements and vital signs and EKGs which did include Holter monitoring, were not different.

Just so you can keep all this information on the same page, I'm going to give you a quick summary before I turn the mike over to Dr. Mosholder. So Salmeterol is

approved currently down to age four years and older based on well-controlled efficacy and safety studies including a six-month trial in adolescents and adults.

In contrast, the pediatric exclusivity studies did not establish efficacy of the meter dose inhaler using a spacer in children less than four years of age and that was due to the inadequate in vitro data. Labeling was not changed and the MDI is not marketed any more. An analysis of the SMART data suggests an increased risk in hospitalization and you will hear more about that. Current labeling includes a box warning regarding potential fatalities which does apply to all patients and a description of the SMART trial which, as I mentioned, includes pediatric patients and warnings against use as a single agent or during exacerbation and that is recommended as additional therapy. In addition, there's a med guide required for all Salmeterol containing products including the

combination products.

And with that, I'd like to introduce Dr. Andrew Mosholder, from the Office of Safety and Epidemiology who is going to take over and go over the adverse events.

DR. MOSHOLDER: Thank you, Hari, and good morning everyone. I'm going to share with you over the next few minutes the review of Salmeterol pediatric safety that we conducted in the Division of Drug Risk Evaluation. And I'd like to start by acknowledging the many people who contributed to our review. As you can see, there is quite a -- it was quite a team effort and very appreciative of all the help we received.

Okay, this will orient you to the topics I'll be covering today. First, I'll be talking about pediatric AERS data for Salmeterol as part of the Best Pharmaceuticals for Children Act review. I'll be covering briefly some pharmacoepidemiology studies mainly done with adult data that relate to

Salmeterol safety. I'll be looking at some data from large primarily adult safety trials with Salmeterol which you've already heard about the SMART trial. We'll be examining pediatric clinical trial data for the two long-acting beta agonists, Salmeterol and the other drug which is currently marketed, formoterol and looking at data that is relevant to the issue of whether there's an effective adding concomitant inhaled corticosteroids to Salmeterol and then finally summary and conclusions.

Okay, first let's talk about the pediatric adverse event data from the adverse event reporting system and you heard about the adverse event reporting system yesterday and again earlier this morning. So these will be spontaneous reports that FDA has received. And this is the standard display of the -- what we call raw counts, uncorrected for duplicates received for Salmeterol since approval in 1994. And you can see there are

about 4,000 reports total of which some 500 are with fatal outcome and for the pediatric group, roughly 200 and we'll be focusing on these.

And this is drilling down into the one-year post-exclusivity period and here we have a total of just over 200 reports for all ages and in the pediatric age group we have a total of nine reports with five fatal outcomes and I'll be describing those next. All right, as I said, these are the reports during the one-year post-exclusivity period which was from March through April of this year, ages zero to 16 and this excludes the combination product of fluticasone with Salmeterol which is marketed under the trade name Advair. So this is Salmeterol alone.

We have, as I said, a total of nine cases with five -- five of which had fatal outcomes and the majority were U.S., seven out of the nine. The specific adverse events were described as lack of response, including one

which involved the death from asthma. Three were described as overdose including one death from viral pneumonia. Non-serious report of dizziness and leg cramps. One report involved a device said to be leaking and this was a fatal outcome report.

There was one death from asthma and finally a death from an unspecified cause. Although it was not clear, the patient may have been receiving Advair and not Salmeterol. Well, the fact that five of the nine reports involved a fatal outcome caught our attention, so we decided to expand the review to look at all reported pediatric deaths with Salmeterol from market approval through this past spring. And again, we're excluding the combination products with fluticasone and so the total here is 23 pediatric fatal reports with median age of 13 and ranging from seven to 16. A preponderance of male gender, 15 out of the 23 and the majority were domestic. There were only three from foreign sources. The

reporters were primarily physicians, also some attorneys and consumer reports. And seven of the cases involved or reported concomitant use of an inhaled corticosteroid. And the majority of reports, 14 out of the 23 deaths was attributed to as asthma exacerbation either based on the autopsy report or the physician's assessment.

Looking at some more details about some of these reports, we had 10 of the case reports described specific circumstances surrounding the death. In two of the cases, the children were found clutching an inhaler of some type. In one case it was albuterol, in the other it wasn't specified.

In four of the fatal events, sports participation immediately preceded the death. One appeared to be an asthma attack after exposure to a trigger, specifically a cat. One case involved high altitude hiking so there may have been an element of the high altitude contributing to the event. One child

was found beside the swimming pool, again, perhaps suggesting exercise and in one case there was partially digested food in the bronchial passages on autopsy.

In nine of the cases, there was some type of misuse or improper use of the product and three of which were described as overdose. In two there was off-label use for acute attack and as Dr. Sachs went over, Serevent is not to be used for treatment of an acute exacerbation.

Non-compliance was a factor. Failure to use what was called a breathing attachment in one case and in another case the device itself may have been leaking. So we also decided to look at pediatric fatal reports for the combination product which is marketed as Advair and again, this is from approval of Advair which was in 2000, through this past summer.

So here we have a total of 15 fatal pediatric reports with Advair. Age range five

to 16 with a median of 13. Again, a preponderance of male gender, nine out of the 15, and the -- you know, 14 out of the 15 were domestic with one foreign report. The reporter sources: attorneys and physicians and one report from a nurse practitioner.

And again, the majority of cases were described as death due to asthma exacerbation with a total of nine of the 15. And once again, there was reports of improper use in a number of the cases, either non-compliance or overdose of another type of -- or another asthma product. Because of the reports of improper use or misuse, we asked our colleagues from the Division of Medication Errors and Technical Support to do a medication errors review and this was done by Walter Fava and they found in the pediatric age group a total of 11 reports of medication errors in the AERS data base, some of which I've already described because they involve the fatal reports. And contributing factors

were knowledge deficit, improper prescribing of more than twice a day, use either more or less than twice a day, use to treat acute symptoms and finally, it was pointed out that patients cannot taste or feel the medication which may contribute to excessive use, if the patients don't realize they've actually received a dose.

So what can we conclude from the review of the errors data? First of all, there are no unique adverse events in the pediatric population that we identified from the spontaneous reports. Secondly, we do have reports of deaths due to asthma exacerbation, both with Salmeterol and with the Salmeterol fluticasone combination. Some of the fatal cases involved reports of misuse, although, of course, we can't say that this was necessarily the cause of the deaths, and most importantly it's difficult to assess drug causality when the cause of death is actually the indication for which the drug product was prescribed. So

because reporting varies depending on the level of use and other undetermined factors, that's the nature of spontaneous reporting data, as you know, to determine whether Salmeterol use could have been causally related to some of these deaths we have to look at more systematic sources of data. So the remainder of the talk I'll be giving you an overview of some other data sources that we looked at.

So I want to start first by looking at some observational pharmacoepidemiology studies that relate to safety of Salmeterol. And this is just a high level overview of several published studies. First of all, there was a case control study looking at ICU admissions for asthma and there was a higher frequency with Salmeterol use but this appeared to be accounted for by increased asthma severity among the patients prescribed Salmeterol. There was a general practice research database study which you may remember

we heard some about that yesterday. It's in the UK and did not show an association with asthma deaths. However, the number of events was rather small, so there were wide confidence intervals on those risk estimates.

There's a healthcare claim study looking at serious but non-fatal asthma outcomes with Salmeterol and again, there was somewhat higher rates of these events with Salmeterol but it appeared to be accounted for by greater disease severity among Salmeterol users. There was a case control study in the UK which had large samples, over 500, asthma deaths that were studied and the most salient findings were among former users there was an increase with short acting beta agonists and actually a reduced risk estimate for former users of long acting beta agonists.

For current use there was no association with long-acting beta agonists; however, the control group was patients hospitalized for asthma who did not die but as

we'll talk about in an moment, it seems quite possible that Salmeterol may be associated both with asthma deaths and increased asthma hospitalization. So that may not have been the best comparison group.

There was a second general practice research data base study of asthma deaths found in association with heavy users of short acting beta agonists and an increased risk estimate for Salmeterol of about three but which was not statistically significant. And then finally, GlaxoSmithKline, the sponsor, undertook a Medicaid cohort study of asthma deaths and this was discussed at the 2005 advisory committee meeting, although it was recently reported that this study had to be abandoned because of lack of statistical power.

So what conclusions can we draw from the observational studies? Well, first of all, there are limited data relevant to the pediatric population and as we saw earlier,

most of the uses in adults so that's not surprising. There was no clear evidence of association with catastrophic asthma outcomes; however, there's some challenges including obtaining adequate statistical power and accounting for differences in asthma severity between comparison groups in these non-randomized data sources. So on balance, we would regard observational studies to be of less inferential value than controlled clinical trial data.

So with that introduction, we'll turn next to look at the controlled clinical trial data for serious asthma outcomes with Salmeterol and one of these studies, the SMART study, Dr. Sachs has already introduced. And there's another study, the so-called SNS study and then there's also a recent meta-analysis of publicly available controlled clinical trial data that is also informative.

And by way of preface, one definition to cover which I think will be

familiar to people but just briefly, the Number Needed to Harm is one metric of risk and it's basically asking the question how many patients would be exposed to produce one excess event of interest, and the calculation is simple. One, it's the inverse or the reciprocal of the risk difference. So for example, if the incidence is four percent on drug and two percent on placebo, the risk difference would be two percent, 2.02 and the inverse of that is 50. So in other words, a two percent excess risk, as I think will be obvious, translate to one excess event for every 50 patients treated. And that's what's meant by the Number Needed to Harm. And in the following slides I'll show the outcomes that were statistically significant in terms of Number Needed to Harm.

So this is the SNS study which is the Serevent Nationwide Surveillance Study. It was published -- it was a UK study published in 1993 and it was a randomized,

double-blind, 16-week trial. The comparison was Salmeterol versus albuterol and it was a 2 to 1 randomization ratio which is important when you're looking at the results to remember that it's twice as many patients randomized to Salmeterol. It was primarily adult. There were six percent of the subjects that were adolescent and data on concomitant inhaled corticosteroid use is, unfortunately, lacking.

So this presents the results and we see almost 17,000 patients randomized to Salmeterol, some 8,000 to albuterol. Asthma related withdrawals were actually less frequent with Salmeterol, so that gives a relative risk below one of .8 which was statistically significant. However, asthma related deaths was increased with Salmeterol, giving a -- it was 12 to 2 so with 2 to 1 ratio, that's a relative risk of 3 which was of marginal statistical significance, t value .105. And so we see here this discrepancy which is that Salmeterol appears to be

helping, sort of control asthma symptoms to the extent that there are fewer withdrawals for those types of symptoms. But yet, catastrophic events leading to asthma deaths are actually increased and that's sort of a recurring theme when one looks at the data on long-acting beta agonists and there have been some -- a number of proposed mechanisms to explain that apparent paradox which I won't go into at the moment. And then finally, for all caused deaths, a slight increase, not statistically significant.

So next we have the SMART study, which Dr. Sachs already presented the data so this should look familiar. Again, just briefly, it was a 28-week trial, comparing Salmeterol to placebo with a 1 to 1 randomization ratio and there were, as we heard, some adolescent subjects and I'll be getting to the results for that sub-group in a moment. And again, data on concomitant inhaled corticosteroid use was lacking. So

here we have -- this is the primary outcomes which again, should be familiar to you from Dr. Sachs' presentation. And there was -- for the primary which was a combination end point to the respiratory related death or life-threatening experience, there was a numerical excess not quite statistically significant. For asthma deaths, again, it was 13 versus three, yielding a relative risk of 4.4 and translating that into number needed to harm, it was about one excess death for every 1300 patients randomized to Salmeterol.

For respiratory related death which you see the numbers are larger than for asthma deaths because this is including other types of respiratory deaths as well as asthma deaths, again, it was increased with a relative risk of 2.2 and a Number Needed to Harm of about one in 1,000. And then for all cause hospitalization, in the total sample, it was only a slight excess relative risk of 1.1.

These are two displays that are in

the label for Serevent and Advair and it's a display of cumulative asthma related death incidents and a couple points to note here, first of all the number of deaths is not great so it's a little coarse but I think one can see that it seems to be a linear pattern, in other words, there's not a peak early during exposure and it's not an increase towards the later period of exposure, so we would say this is a constant hazard function perhaps or that the deaths seem to accumulate at the same rate throughout the study.

And the second point to make here, we see the African American sub-group and the risk appears to be greater than it was for the all subjects. So what can we conclude from the large safety studies of Salmeterol? And here I put up some quotes from some journal editorials which I thought put it quite nicely. Hasford and Virchow; "In view of the results of the two studies both of the highest evidence class, the existence of Salmeterol

related excess mortality has to be assumed with near certainty".

And I should add if one combines the results from the two studies, statistically with the Mantel-Haenszel odds ratio, the P value is out to three decimal places. And then Martinez in the New England Journal, "One death was attributable to Salmeterol for every 700 patient years of treatment in SMART, a result strikingly similar to that of the United Kingdom study. Unfortunately, the limitations of the trials preclude definitive conclusions regarding the potential for inhaled corticosteroid to limit or prevent these adverse outcomes". And so here this is a Number Needed to Harm in terms of a rate per patient year adjusting for the length of the study. And he's saying that it actually is similar between the SMART and the SNS, about one in 700 per patient year -- one in 700 patient years.

And one point to make there is that

an excess death rate of that nature would have, of course, public health implications but would not be apparent to prescribers, especially if the drug is effective in relieving what you might call the day-to-day symptoms of asthma in the asthma patients.

So that's our view of the safety findings from the large trial. So let's take a look now at whether there are any specific findings for the pediatric age group. Unfortunately, pediatric data are not available from the SNS at this time. We do have pediatric sub-group data as Dr. Sachs mentioned, for SMART and from other clinical studies.

So these are the SMART pediatric results and again, this should look familiar. For the primary outcome, there were two events in Salmeterol and placebo, each very inconclusive because of the small number. There was one respiratory related death in a Salmeterol teenager and for all cause

hospitalization, there was an excess with Salmeterol about a relative risk of about 2.3 and with the help of GSK we were able to obtain the case report forms for these hospitalizations and categorize them according to whether they were caused by asthma or some other indication for hospitalization. And in fact, there's a numeric excess of asthma hospitalizations with Salmeterol and if one combines it with the primary outcome measure, it's 15 versus nine for a relative risk of 1.6, which is not statistically significant but as I said, numerical excess.

So there's also been, since the 2005 Advisory Committee, there was a meta-analysis published last year in the Annals of Internal Medicine. You should have seen it in your briefing materials. And the purpose of this meta-analysis was to assess the risk for severe asthma exacerbations with long-acting beta agonists looking at both Salmeterol and the related compound, formoterol. And the

authors took 19 randomized placebo controlled trials which they're required to be at least three months in duration. Six of these were pediatric studies and they performed Peto odds ratios with confidence intervals for the outcomes of interest.

And the overall results, this is for all ages combined now, showed that the long-acting beta agonists were associated with increased asthma hospitalizations with an odds ratio of 2.6, the confidence limits shown there and also asthma exacerbations considered life-threatening which is defined as requiring intubation and mechanical ventilation and there the odds ratio was 1.8, again statistically significant.

Now, this is a display of the pediatric trials which reported data on asthma hospitalizations. For the other outcomes, or for life-threatening exacerbations, there weren't enough outcomes to do a meta-analysis, but so looking at asthma hospitalizations, and

this is a forest plot, so-called which I think is probably familiar but just to orient you, each study here is listed individually with a marker showing the point estimate for the odds ratio within that study. The size of the marker shows the relative weight in the combined odds ratio estimate and the whiskers, if you will, show the confidence limits. And Dr. Salpeter was kind enough to update her analysis with the recently available SMART data on pediatric hospitalizations for asthma, so that's included here in the middle row.

Now, the first two studies in this display are with formoterol and these three are with Salmeterol. The bench study, I should add, too, although it had 18 hospitalizations with formoterol, zero with placebo, some of these patients received a dose which is higher than currently approved. And you can see that all of the studies line up above one for an odds ratio and here's the SMART data that we just talked about. And so

the overall odds ratio for asthma hospitalization is 2.7 with confidence limits that you see here and the P value for the overall effect of .0009.

So what can we conclude from the pediatric trial data? Well, first of all, the trial data in pediatrics are limited with respect to serious outcomes. However, there was a numerical increase in asthma hospitalizations with Salmeterol versus placebo in SMART. And the meta-analysis pediatric trials with both long-acting beta agonists showed an increase in asthma hospitalizations with those drugs. And also, we don't see anything in the clinical trial data that would make us believe the increased risk of asthma deaths and life-threatening exacerbations which has been seen in adults would not also apply to children.

So I want to turn next to the issue of whether concomitant inhaled corticosteroid therapy or ICS has any protective effects

against these catastrophic asthma outcomes. And this is by way of introduction, a slide showing the prescribing in the pediatric age group for the Salmeterol/fluticasone combination which is Advair, compared to Salmeterol which is the Serevent product. And as you see, the prescribing of the combination product completely dwarfs the prescribing of the Serevent mono product and so if this is really the safer alternative, then it would look like the field is on the right track, essentially by minimizing use of Salmeterol monotherapy. However, if the concomitant ICS is not protective then we actually have a large number of patients being exposed to that risk. So that's why it's important to examine this. Now, unfortunately, as we heard already in SMART, data on ICS use was not collected during the trial. However, they did collect data on ICS use at baseline and if one takes that as a proxy for ICS use during the trial, there's an

impression that the increase in asthma deaths was more prominent among patients who were not receiving ICS when they started the trial, however, my own calculations were that the risk differences estimates overlap in their confidence intervals.

So anyway, so that's sort of an unanswered question from the SMART data that we have. There are two recent meta-analyses of clinical trial data, one with Salmeterol, one with formoterol, which have reported that ICS mitigates the increase in the asthma hospitalizations. So far they're published only in abstract form, although I understand that this paper is forthcoming in the Annals of Internal Medicine.

And this is a quote from the recent NIH guidelines Dr. Sachs mentioned. "While the data did not necessarily support an increased risk of severe or serious exacerbations in patients who were taking long-acting beta agonists and are receiving

concomitant ICS, data are also insufficient to establish definitively that ICS therapy completely obviates the risk".

So do we have any pediatric data on this question, specifically, and for Salmeterol the data are limited. The meta-analysis that I just mentioned included five GSK sponsored pediatric trials with -- and about 1200; however, in this data set there's only one asthma hospitalization which was in an ICS alone subject, but obviously, not enough data to be conclusive.

In the case of formoterol, however, there are two studies which had the design of comparing formoterol plus concomitant ICS treatment to treatment with ICS minus formoterol, which is the type of design you'd want to answer this question. And in both studies, the serious asthma events were more frequent in the formoterol arm despite the concomitant ICS. So overall we would say that definitive data are lacking on the question of

the effects of ICS combined with the long-acting beta agonists, especially for Salmeterol but as I just mentioned, for formoterol there was serious asthma events being increased despite concomitant ICS.

So just to wrap up and say what we've concluded here, first of all, from the review of the AERS spontaneous reporting data. There were no unique adverse events identified in pediatric patients. However, fatal asthma exacerbations were reported and in some cases there was evidence of misuse although this was not necessarily causal.

And most importantly, it's difficult to assess drug causality from these types of spontaneous reports when it's confounded by the indication for the drug itself. Pediatric clinical trial data which has been -- become available since the 2005 Advisory Committee as not currently in the label, suggests increase in asthma hospitalizations with long-acting beta agonist

and we don't have clear evidence at the moment that ICS mitigates this risk.

It would be desirable, of course, to have additional clinical trial data to assess these safety issues regarding serious and fatal asthma outcomes but I would argue that this is going to be difficult to obtain. First of all, there's difficulty recruiting subjects for large trials and as you may recall, the SMART study had a lot of difficulty enrolling patients and, in fact, never reached its targeted or enrollment. So it seems like it would be hard to reproduce that, especially with pediatric age group. And then secondly, there's ethical issues, perhaps particularly salient in the pediatric age group and the question of whether equipoise would really exist with respect to all the treatments to which the subjects might be randomized. So overall there's no basis to believe that the increased risk of asthma death and life-threatening asthma

exacerbations which has been observed in adults would not also apply to children and so this leaves the situation that the drug which is indicated for the treatment of asthma actually is expected to increase death from asthma and asthma hospitalizations. So this raises a question of what clinical benefits to the patients would justify exposing them to these risks and I'll stop there and I think the next is to take questions. Is that --

DR. RAPPLEY: So we're open for clarifying questions.

DR. WARD: Andy, would you look at Slide 25 and then 27? It's about the SMART trial and you had done some additional analysis that wasn't on there about you said a numerical excess of asthma hospitalizations and would you give us those numbers again? I couldn't make them match up with the numbers.

DR. MOSHOLDER: Yes, well, actually -- well, yes, and I may have confused things by not breaking it out. Here what I've done

is well, with the hands-on review of the asthma hospitalizations, there were 13 with Salmeterol and seven with placebo. And then what I did here is I combined them with these two in the primary outcome to give 15 and nine.

DR. WARD: Okay.

DR. MOSHOLDER: And then actually, it's -- whoops, sorry, I'm going to wrong way here. Then, when Dr. Salpeter took this data, she actually just used the hospitalizations which were 13 and seven. So that's -- I think is that --

DR. WARD: On this slide, could you describe what the weight percent is? I first thought it had to do with the number of subjects in the study but it didn't match up. Like Weinstein has a little over 200 and a weight of 13 and the one right above has 300 and a weight of two.

DR. MOSHOLDER: Yes. Well, there may be other people that can explain the

methodology better than I, but my understanding is that the Peto method of combining these different odds ratios, there's a calculation for weight which is a function of not only the sample size but also the number of events. And so it's a complicated relationship between -- I can't give you the actual formula, but it's -- it depends on both of those factors. And that's why you've got the percentages that vary in that way. That's my understanding of it.

DR. MURPHY: I just want to point out that this log is different than your handout because the SMART study -- not the one was gave you but the one that we may have sent to you because the SMART study was added this week.

DR. MOSHOLDER: Just over the weekend actually from the -- yes.

DR. MURPHY: So, I just wanted to make sure everybody -- when you see different numbers, you get confused, but that's why the

slide and why you have it at the table, too.

DR. RAPPLEY: Other questions? Yes.

DR. MALONE: This is really a general question but if asthma occurs in both children and adults, why is it that this drug is used so much less in children than adults? I thought that asthma had an onset during childhood, so I couldn't understand it.

DR. RAPPLEY: Could the Division give us their opinion?

DR. SEYMOUR: Can you clarify what information Andy gave you that you were basing that statement on that it's used much less in pediatrics than adults?

DR. MALONE: I thought that the prescriptions were more in adults than in children.

DR. SEYMOUR: I'm not quite sure why it's being used less in pediatrics versus adults. I don't know if the additional labeling and warnings have cut down on

pediatric use. I'm not sure I can answer that.

DR. STARKE: This is Dr. Starke. I'm a pediatrician. I don't think I know the answer either but let me just say that in general in pediatrics we see a lot of asthma but not necessarily of the severity that requires a second drug in addition to other controller therapy such as inhaled corticosteroids. That may be the answer, I don't know.

DR. MOSHOLDER: I would venture that it's still probably true that most asthma patients in the population are adults rather than kids. The other issue is that this also is an indication for COPD so that would bring in even more adults.

DR. RAPPLEY: Dr. Joad?

DR. JOAD: The reason it might not be used in young children is that until a year ago, it was just available as a Diskus until there would be -- young children wouldn't be

able to get it. But otherwise, I'm not sure. Most people had been following the guidelines which would put, you know, a certain level of severity would suggest that you should use Salmeterol for that. So I'm not sure why it wouldn't be following or --

DR. RAPPLEY: Dr. Ward?

DR. WARD: Is the dosage form of Salmeterol the meter dose inhalers, too high, for example, for smaller children, so you generally wouldn't use it?

DR. JOAD: Well, they're new but they're coming -- they came out so that they're exactly an -- well, you can speak to this, but analogous to the Diskus as far as if you use two puffs twice a day of them, it's the same as if you use one inhalation twice a day of the three Diskus forms.

DR. SEYMOUR: I can add a little bit to that. The dose is the same in pediatrics as it is in adults. The clinical program developed from the sponsor did look --

did perform pediatric studies that you heard about and those included a dose ranging study that looked at lower as well as higher doses and even one of the pivotal studies I believe, also included a lower dose. And all the doses of Salmeterol were effective on the end points, but it was felt that on trends of the data for the 50 micrograms and some of the secondary end points favored the 50 microgram dose over the 25.

DR. RAPPLEY: Dr. Gorman?

DR. GORMAN: I was wondering if there was any hint in the data since this has been delivered through two different delivery systems, the meter dose inhaler and the Diskus, whether there's any hint in the data that would allow you to state whether the safety and/or efficacy was different between those two dosage forms. The original data or one of the statements that was made was when it was used with a spacer, the delivery of the dose was in question. So with the Diskus form

versus the meter dose inhaler is there any data that says that one is more effective than the other in getting a drug into a person?

DR. MOSHOLDER: I don't know of such data myself. Maybe I'll turn to Dr. Seymour or Dr. Stark to address that.

DR. SEYMOUR: I'm not aware of head-to-head comparisons of the Diskus versus the CFC/MDI formulation that's no longer on the market. The sponsor may be able to add anything to that. Unfortunately, a lot of the big studies were performed with the MDI which is no longer available. And in terms of some of the studies that contributed to the Salpeter meta-analysis, I'd have to go through them and figure out which ones actually is the MDI versus the Diskus to see if there's any difference there. I don't know that that's been really looked at though, since the MDI is no longer available.

DR. MOSHOLDER: My understanding is the switch was driven by the minimizing use of

CFCs rather than any clinical considerations.

DR. SACHS: And there was on the one study where they did look at the MDI versus the Diskus, remember I showed you in the kids four to 11, and they didn't see any differences. There was actually asthma exacerbations in that study and there was -- they were really comparable among the groups.

DR. RAPPLEY: Dr. Joad, then Dr. Garofalo.

DR. JOAD: Do you have any sense of other risks that a child takes everyday and how a risk hazard of 700 fits, like getting in a car to go to school or, you know, skiing, anything else a child might do? Where does this fit in the risk that people take every day in their lives?

DR. MOSHOLDER: Well, I guess you're thinking of leading, you know, leading causes of deaths in the pediatric age group, I think they're -- they're going to be less than

one out of 700 per year, so I don't know if I can -- off the top of my head, I'm not sure I can give you the exact figures but is that sort of what you're -- how does that -- that's an adult figure by the way. We don't -- and it is true that asthma deaths in children are less frequent than in the adult population.

DR. MURPHY: Dr. Nelson might be able to add to this conversation.

DR. NELSON: There was a paper recently published in JAMA where David Wengler was one of the authors. The issue was minimal risk interpretation within -- the bottom line is one out of 700 would be a lot higher than the risk of either death in car injury or through sports. It was something -- I don't recall the exact number but it was more on the order of five digits and not three digits.

DR. JOAD: Exactly what I was looking for, thank you.

DR. RAPPLEY: Dr. Garofalo?

DR. GAROFALO: I just wanted to go

back to the SMART study and the SNS study for a moment, Slide 31. You mentioned that there were some imbalance potentially in terms of ICS use and I know these are large and they're well-controlled trials but do they look at baseline, you know, sort of demographics or other things that might have been different between the randomized groups?

DR. MOSHOLDER: Yes, well, they did of course, and as I recall, there weren't any important characteristics that would think that you failed to sort of equalize them by randomization that I can recall, so the baseline ICS use being among them. There's a table in the publication which I can look at but my -- to the best of my recollection there wasn't any glaring -- sometimes you see that, randomization fails to you know, sort of equal out certain factors but I don't remember anything like that in SMART, no.

DR. RAPPLEY: Any other questions? Oh, yes, Dr. Cnaan.

DR. CNAAN: In Slide Number 20 in the SMS study, you showed that the withdrawals were more in the albuterol than in the Salmeterol. And then the next calculations show the asthma related deaths relative risks. How did they account in the denominator for the withdrawals?

DR. MOSHOLDER: Well, that's a good point and actually my understanding is they did not. And one of the editorials that I quoted, that was one of their critiques that they should have done a timed event type analysis which was done for SMART, that the used a life table method of estimating this relative risks.

But on the other hand, the publication also said that for patients who dropped out, the investigator was to determine if they remained alive at the end of the -- what would have been the treatment period. So -- but perhaps the sponsor would be able to address some of those issues in more detail,

since I really only had the publication.

DR. RAPPLEY: Dr. Rosenthal and then Dr. Newman.

DR. ROSENTHAL: Thank you. I'm just sitting here thinking about the degree to which the agents that we talk about are the effects of the agents are to some extent confounded by the delivery route or vehicle or device and I'm wondering in this case, I just don't know. I understand that the CFCs were taken out of the meter dose inhaler, I guess because of environmental reasons and but I don't have a sense for whether that is a completely physiologically inert class of vehicles or not, so if someone could educate me on that.

And then the other question is that if this Diskus delivery system has been implicated in some ways or in certain cases in bad -- as a contributor to some of the bad outcomes. What are the mechanisms that we have for looking at safety related to that

delivery mechanism?

DR. RAPPLEY: Anybody want to respond to the first question? Dr. Ward?

DR. WARD: I hesitate to do this but my recollection is that CFCs exposure from repeated frequent administrations are associated with arrhythmias but I think in this setting the effects of the beta agonists would far outweigh the toxicity from any arrhythmia from the CFCs.

DR. RAPPLEY: Do you want to add anything, Dr. Kocis?

DR. KOCIS: I could -- there are several things I could think of as far as ICU medicine and the management of asthma, which is way different than what we're talking about here and the extrapolation of that and in my practice has moved from when I trained here in DC which is urban city population to more of a suburban academic setting, so my views are somewhat skewed nowadays. But, you know, we don't see children die from asthma when they

hit our ICU. They just don't die in the ICU.

How much therapy we have to apply to them to get them through that differs and there are extreme cases where we go to extremes to resuscitate them. Generally, the data set we see are failure to come to medical attention in the ER or being a referral center for the State of North Carolina, and being at an institution, an adult emergency room far away and we're trying to get the kid to our institution and we've seen deaths in that setting. I can't remember in the seven years that I've been here, that we've had an asthma death in our institution in the ICU.

So first, sort of broadly thing. Then talking about delivery systems and arrhythmias, I'm not aware of any difference with the MDI doser versus the Diskus. We do use, though, I have to think about how we're doing this but we are using MDI still in the ICU setting on ventilated patients and you know, I've seen and reviewed data looking at

particle size and distribution to the lung segments in ventilated patients and I'd have to say I don't recall of any drug delivery distribution studies that looked at that with the Diskus and we don't use that in the ICU setting. So again, I'm not going to be very helpful there. And I think those are the relevant comments.

DR. SEYMOUR: I was going to address your question about the CFC. When we do clinical studies with inhaled products, the comparator placebo contains everything, including the CFC excipient except the active ingredient. So when you see these placebo controlled studies, typically the placebo group has also been exposed to that CFC.

DR. RAPPLEY: Any other questions? Oh, yes, Dr. Newman, sorry.

DR. NEWMAN: Yes, just one, I'll come to the issue of whether the inhaled corticosteroids protect against this and you mentioned there were two meta-analyses where

abstracts were not -- they weren't full publications that suggested that maybe the steroids do mitigate that and I was wondering whether, as much as you could tell from AFTRAK whether they actually said that it was a statistically significant interaction where, you know, there was clear evidence that the effect was different among those who were or were not getting inhaled corticosteroids or was it simply that when you stratify on steroid use in the group who got steroids, it was no longer statistically significant harm?

DR. MOSHOLDER: Well, as I recall, I can look it up in a minute, but both meta-analyses were taking trials that had that design where they were being directly compared, the long-acting beta agonists plus ICS versus ICS without a long-acting beta agonist and they did a meta-analysis with an outcome of asthma hospitalization. In the case of the Salmeterol, as I recall, the risk ratio came out around one with confidence

limits like from .5 to 1.5. With formoterol actually came out, it looked protective where the risk estimate was below one. So it's --

DR. NEWMAN: And those are studies of adults and children both or --

DR. MOSHOLDER: Yes, yes. Yes, well, at least the Salmeterol was, you know.

DR. NEWMAN: Because, you know the two -- the Tall study and the Bisgaard study that you included in the packet had mentioned both -- I mean, if you combine those two, it's 13 hospitalizations versus one. It's a very striking increase in hospitalizations when you add the long-acting beta agonist to the steroids.

DR. MOSHOLDER: Yes, right. That's right, yes. Although -- so, yes, if you look at those individual trials, it does not look like there's any protection. The meta-analysis that, you know, from the abstract, it seemed to be suggesting there was protection, but whether that's different for adults versus

the pediatric group, it's hard to know.

DR. RAPPLEY: Any other questions? Dr. Joad?

DR. JOAD: Well, just that when we're analyzing this, it's -- the question is whether you get in the same product is the steroid and the Serevent and Salmeterol together. That's been an argument along the last few years that I've heard is that people are more likely to comply with their inhaled steroid because it's got Salmeterol. So the fact that they're together in the same device makes a difference versus just the two drugs separately being given.

And so I take it we're not to that level when we're looking at these -- when we're looking at this, is that right? There are always two separate events, giving the Salmeterol and the steroid or the steroid and the placebo?

DR. MURPHY: Andy, can you address that question?

DR. MOSHOLDER: No, sorry, the --

DR. RAPPLEY: So I hear the question is, has the product Advair or a combination product been part of these trials or not, or some other combination product?

DR. SEYMOUR: The big trials that really have shown the signals the SNS and the SMART have been with the mono therapy, Salmeterol, but I think you have shown some other data where they've been given in combination but I don't know if it was the free-form combination or as a combination product in those studies that he's shown. I don't know if that answers your question but I'm not quite sure there is an answer to -- I mean, I don't think -- we haven't made any distinction in the labeling about administering them free-form together versus a combination.

DR. JOAD: I guess these mysterious meta-analyses that we haven't seen yet. Do you know whether they're being given as a

single device with two things in it or they're given separately?

DR. MOSHOLDER: Actually, okay. Actually, the posters presented Dr. Nelson was the first author was presented at the American Thoracic Society this past spring and they did seem to feel that there might be a difference between whether it was a single device or two separate devices. Is that what you're -- I think that's the question. I'm reading here from the abstract, let's see. "The meta-analysis showed no increased instances of hospitalizations with addition of Salmeterol to an inhaled corticosteroid. Asthma related hospitalizations were lowest in patients receiving fluticasone plus Salmeterol in a single device." But as I said, I don't have the full details but I think that -- is that your -- so there's a suggestion that that might be superior.

DR. RAPPLEY: Thank you. I think we can move onto our presentation from

GlaxoSmithKline. Thank you, Dr. Mosholder.

DR. JONES: Good morning. My name is Elaine Jones, and I'm Vice President of Regulatory Affairs at GlaxoSmithKline. On behalf of GlaxoSmithKline, I would like to thank the Agency and the Advisory Committee for this opportunity to participate in the review of the safety data of Salmeterol in children. GlaxoSmithKline recognizes that review of the safety data over the one-year period following the granting of pediatric exclusivity for Salmeterol and Salmeterol containing products is required by the Best Pharmaceuticals for Children Act. This morning we will summarize this information which is described in more detail in your briefing document.

Recognizing that the focus of today's review is safety, and due to the limited amount of time for the presentation, we will not review the efficacy of these products. However, we would be remiss to

ignore the proven efficacy on lung function, symptom control, and reduction in rescue albuterol use that these products provide in a very serious disease.

Asthma is a chronic disease associated with significant morbidity and mortality. In the United States, asthma effects approximately 21 million Americans including 6 million children under the age of 18. Asthma exerts a tremendous societal burden and is the most common reason for both hospitalizations and school absences resulting in 200,000 hospitalizations and 13 million missed school days annually.

Long acting beta agonists, bronchodialators, such as Salmeterol act on the Beta 2 adrenergic receptors in the lung which relax smooth muscle and therefore, aid in breathing. Salmeterol, like albuterol is a partial agonist. By comparison the other approved lung acting beta agonists, formoterol is a full agonist. The different pharmacology

of Salmeterol and formoterol may effect the clinical profile of these medications.

In addition, I would just like to point out that in the FDA briefing document, formoterol is characterized as a partial and Salmeterol as a full, where actually it's the other way around. Salmeterol was first approved in the United Kingdom in 1990 and to date it has been approved in over 100 countries. In the United States, there have been four Salmeterol containing products approved. The first product developed was Serevent inhalation aerosol which contained CFCs and was discontinued by GlaxoSmithKline in 2002 as part of the phase-out of CFC containing products consistent with the Montreal Protocol.

Advair combines Salmeterol with the inhaled corticosteroid, fluticasone proportionate and is available as a dry powder inhaler or Diskus or as a HFA metered dose inhaler. As you can see Serevent Diskus and

Advair Diskus are approved for the treatment of asthma in children four years of age and older while Advair HFA is approved for the treatment of children 12 years of age and older.

Serevent is approved for use in children if they are symptomatic on another asthma controller medication such as inhaled corticosteroids. Similarly, in children four to 11 years of age, Advair Diskus is approved for the use in children symptomatically inhaled corticosteroids.

The approved dose of Salmeterol in the US is 50 micrograms twice daily and is the same for all products. In May 1999 the agency issued a written request of GlaxoSmithKline to conduct additional studies of Serevent CFC inhalation aerosol in children as part of the pediatric exclusivity section of the FDA Modernization Act. In December 2005, after completing the requested studies, GlaxoSmithKline submitted an SNDA containing

the full report of the studies that had been done in response to the written request. The application consisted of four pediatric trials, as shown on this slide.

Pediatric exclusivity for Salmeterol containing products was granted by the agency on March the 9th, 2006. The agency also requested additional in vitro studies; however, as mentioned previously, Serevent CFC inhalation aerosol had been discontinued and withdrawn from the market and we were unable to comply with this request. Therefore, results from these studies have not been incorporated into the label for either Advair or Serevent.

Salmeterol has become a well-established therapy for the treatment of asthma and is afforded many patients improved asthma control. And clinicians have gained considerable experience, especially its use in children. In addition, national and international treatment guidelines which have

recently been updated, continue to recommend the use of inhaled long-acting beta agonists like Salmeterol in conjunction with an inhaled corticosteroid for children and adults with moderate to severe persistent asthma.

GlaxoSmithKline regularly reviews data from clinical trials and post-marketing surveillance to insure that our product labels are updated with the relevant information. Today's meeting provides an important opportunity to share the pediatric safety data of Salmeterol and we look forward to reviewing this data with the committee.

GlaxoSmithKline believes that Salmeterol exhibits a favorable safety profile in children which is comparable to adults. The labeling contains appropriate information to allow healthcare professionals to make informed prescribing decisions for Advair and Serevent. Our extensive review of the Salmeterol data substantiates this. Dr. Kathy Rickard, Vice President of the Respiratory

Medicines Development Center at GlaxoSmithKline will now present the safety data.

DR. RICKARD: Thank you, Dr. Jones. Good morning. For my presentation today, I will focus on two key sources that help inform on pediatric safety of Salmeterol. I will summarize data from spontaneous adverse event reports and review data from randomized clinical trials. Given time limitations, I will not be able to cover the information from all the data sources reviewed in your briefing materials. However, any questions that you may have can be addressed during the question and answer period.

One of the sources to evaluate pediatric safety data includes review of spontaneous reported adverse events. It's important to remember that spontaneous reports are voluntary, are often incomplete and frequently lack medical verification. Adverse events may be reported by healthcare

providers, patients and other interested parties. Your briefing document provides a detailed review and analysis of spontaneous reported adverse events. I will provide a brief summary of the results as the agency has already provided details during their presentation.

As expected, worldwide spontaneous reported adverse events for both Serevent and Advair have increased with increased exposure over the time they have been marketed both in adult and pediatric patients. GlaxoSmithKline assessed the reports received during the year following the grant of pediatric exclusivity relative to prior experience. Since granting pediatric exclusivity did not result in labeling revisions for Serevent or Advair, there was no expectation that the use of the products or spontaneous reporting of adverse events would change in children. This expectation was confirmed as the pattern of serious and non-serious spontaneous reported

adverse events for Serevent and Advair was similar during the one-year post-grant period compared with the reporting period prior to granting exclusivity.

Serious fatal events reported during this post-grant period yield no unexpected signals. Reported cases in children generally occurred in patients with a history of severe or unstable asthma including prior hospitalizations for asthma and a history of non-compliance with filling asthma prescriptions or physician visits.

In summary, we conclude that following the grant of exclusivity, reporting patterns of non-serious, serious and fatal adverse events for Serevent and Advair remain consistent with prior experience.

I will now review the results from a large surveillance trial that enrolled nearly 27,000 patients including over 3,000 children. The Salmeterol Multi-Center Asthma Trial, also known as SMART was initiated in

1996 after consultation with FDA to provide safety information on the use of Serevent. During this review, I will describe the study design, the results for the total population and a post hoc analysis which provides results for children. I will also share with you how the results of the study impacted the product labeling for Salmeterol containing products.

SMART was a randomized double-blind surveillance study of 28 weeks duration. Patients with asthma who were at least 12 years of age with no previous use of inhaled long-acting beta agonists were included. Approximately half of the study population reported using inhaled corticosteroids at baseline.

SMART consisted of a single clinic visit at which patients were assessed for eligibility and then randomized to receive either Salmeterol or a placebo which was added to their usual asthma therapy. Subjects were given a 28 week supply of study medication and

were not required to return for clinic visits. Instead of scheduled clinic visits, subjects were contacted by phone every four weeks to collect information about serious adverse events.

Compliance with study medications or concurrent asthma medications was not reinforced during study conduct. I wanted to just address quickly some of the questions that we had from the Committee about the baseline characteristics. The characteristics of the patients entering SMART were -- and some of the ones I'll list for you was about 60 percent of them experienced one or more nights awakening from asthma prior to coming into the study. Six to nine percent had experienced a hospitalization and 26 percent had an emergency room visit. Now, interesting, we also talked about the differences in the populations. The African American ones seemed to be even -- had more types of these visits. They had also more ER

visits, more hospitalizations. They used inhalant corticosteroids less frequently as they reported about a 39 percent use at baseline versus 48 percent for Caucasians.

This also borders some of the questions that maybe just could lead to considering the behavioral aspects of the treatment of asthma, whether they have behavioral issues, whether they take their medications, whether they have access to care similar to other people in the study.

The trial was terminated in 2003 following the results of a planned interim analysis. The complete study results were published in January 2006. First, I would like to review for you the total population of 12 years of age and older, followed by a discussion of the results for children. For the primary end point defined as combined respiratory related deaths or life-threatening experience, there is an increase in the number of events for patients receiving Salmeterol

compared with placebo. This difference was not statistically significant as the lower bound of the confidence interval is 0.91 and does not exceed one. The respirator and asthma-related secondary end points shown now, are a subset of the primary end point.

There were statistically significantly more respiratory and asthma-related secondary events in patients receiving Salmeterol compared with placebo. There are also more all cost hospitalizations in patients receiving Salmeterol although this difference was not statistically significant. The results from SMART led to label revisions for Serevent and Advair in 2003 informing on the risk of severe respiratory related events including a boxed warning. Further, warning was added stating that the data from SMART was not adequate to determine whether or not concurrent use of inhaled corticosteroids modifies the risk of serious events. As part of an ongoing evaluation of the safety of

long-acting beta agonists, the FDA subsequently convened a pulmonary and allergy advisory committee in July 2005 and they were asked to consider what additional communications were necessary to manage a risk of respiratory related events seen with long-acting beta agonists.

After reviewing the safety data from SMART, as well as safety data from other control clinical trials and from spontaneous reports, the Pulmonary and Allergy Advisory Committee concluded that the benefits of long-acting beta agonists, Salmeterol and formoterol, outweighed the risks in the treatment of asthma. The committee recommended the addition of a medication guide and further changes to the product labels for Salmeterol containing products. These recommendations were incorporated into product labeling for both Serevent and Advair in March 2006.

I will now highlight important

revisions incorporated into the product labels as a result of the recommendations from the advisory committee. The full indication for Serevent was provided in your briefing information. Now I'd like to highlight three sections from the indication which inform on respiratory events seen in SMART.

First, information about an association between the use of Salmeterol and asthma-related death is prominent. Details about this are also present in the box warning and additional information about the results of SMART are in the clinical trial section. Wording was also added that Serevent Diskus should not be used as -- should only be used as additional therapy for patients who are not adequately controlled on other asthma-controller medications. For example, Salmeterol should only be added to asthma-controller medications such as low to medium dose inhaled corticosteroids or in patients whose disease severity clearly warrants

indication of treatment with two maintenance therapies.

Furthermore, to manage the risk of respiratory events seen in SMART, wording was added to inform that Serevent is not indicated for patients whose asthma can be successfully managed by inhaled corticosteroids or other controller medications along with occasional use of inhaled short-acting beta agonists. These same revisions have been made to the labeling of Advair and are communicated in the medication guide and applied to patients four years of age and older.

Since 1995, the labeling contained language highlighting the risk of serious respiratory events including fatalities. This This slide says one particular warning contained in the labeling for Serevent and Advair regarding serious respiratory events. Within the warnings, physicians and patients are advised to watch for signs of deteriorating asthma such as an increased use

of short-acting beta agonists, increase in symptoms or unresponsiveness to usual medications. The medication guide specifically advises patients to alert their physician if they experience any sign of deteriorating asthma. All of these are precursors to events that may lead to hospitalizations. These warnings apply to both children and adults.

The result of SMART in the labeling revisions that I've just discussed apply to all populations including children. To further understand SMART results in children relative to adults we conducted a post hoc analysis reported in your briefing document. The results in children are shown on the right with the total population as discussed previously shown in gray for reference. In this analysis, children were defined as patients between 12 and 18 years of age and comprised 12 percent of the population. As shown here, the number of events in children

was low for the primary end point with two events occurring in each group.

There are no additional patients that contributed to any other respiratory or asthma related secondary end point as shown now as these are a subset of the primary end point. The difference noted in asthma-related deaths in the total population was not apparent in children as one event occurred in Salmeterol and zero in placebo. It's important to note that the warnings regarding SMART are worded broadly and apply to all patients with asthma including children and adults. More children receiving Salmeterol were hospitalized compared with placebo consistent with the pattern seen in the total population. I will describe the results in children in more detail on the following slide. There was a statistically significant difference in all cause hospitalization in children. To better understand the reason for hospitalization, each adverse event report was

reviewed and categorized as respiratory or non-respiratory related. As shown now, a breakdown of hospitalization into these categories did not show statistically significant differences between Salmeterol and placebo. In over 3200 children, there were 18 and nine respiratory related events identified for Salmeterol and placebo respectively.

Of these 13 and nine events were specifically identified as an asthma related for Salmeterol and placebo. Five events were specifically identified as other respiratory related illnesses in children receiving Salmeterol compared with zero in placebo patients. These events included pneumonia, pharyngitis and viral infection. There was a greater number of non-respiratory related hospitalizations identified for Salmeterol patients. A complete listing of all events for Salmeterol are described on the next slide. Causes of non-respiratory hospitalizations listed on the med watch forms

included conditions such as depression, vomiting, cellulitis, as well as other typical reasons for childhood hospitalizations shown here. As you can see, they occurred as isolated cases and no pattern was apparent.

In summary, in the total population, there were more respiratory and asthma related events in patients receiving Salmeterol and a greater incidence of all cause hospitalizations. In the post hoc analysis of children, respiratory and asthma related events were similar between Salmeterol and placebo. There is a statistically significant increase in all cause hospitalizations. However, there was no statistically significant difference in respiratory related and asthma related hospitalizations or non-respiratory related hospitalizations in children receiving Salmeterol. In addition, a review of the non-respiratory related reports found no pattern in events leading to hospitalization.

The labeling for Serevent and Advair contains warnings for serious respiratory events including the box warning about the most serious outcome, asthma related death. These warnings apply to both children and adults. Further, physicians and patients are advised to watch for signs of deteriorating asthma such as an increased use of short-acting beta agonists, increasing symptoms or unresponsiveness to usual medications.

The medication guide specifically advises patients to alert physicians if they experience any signs of deteriorating asthma as all of these are precursors to events that may lead to hospitalizations. In addition to SMART, GlaxoSmithKline collected over 70 randomized control trials with Salmeterol containing products in the United States. I will now summarize key safety data in children from these full trials.

Excluding SMART, we identified 72

randomized control trials of Salmeterol in the United States that included children 18 years of age and under. Studies with the following treatment groups were included, Salmeterol, placebo, Salmeterol plus inhaled corticosteroids or inhaled corticosteroids alone. And to answer a previous question, in this analysis, approximately half the studies that were included in the analysis used Advair in a single device. So Salmeterol and fluticasone were given in a single device.

On the left we will compare Salmeterol with placebo. In the right we will compare Salmeterol used in combination with an inhaled corticosteroids versus inhaled corticosteroids alone, which will allow us to observe any differences in outcomes. The review of all 72 studies found no deaths in children. A total of five deaths occurred in the adult population. Of these, two were asthma related deaths and both subjects had received Salmeterol.

In addition to review of fatalities, we analyzed data for serious adverse events in the cardiovascular and respiratory body systems. Results for children are shown in the top panel and adults are shown in the bottom panel. There were no cardiovascular related serious adverse events reported in children. The incidence of respiratory related serious adverse events was low, less than or equal to two percent across treatment groups for children and adults. Asthma and status asthmatic comprised the majority of these events. To gain additional insight into respiratory related events we examined studies that collected information about asthma exacerbations.

Fifty-four of the 72 studies collected specific information about asthma exacerbation and contributed to this analysis. These studies included nearly 3500 children. This slide provides information on asthma related exacerbations and hospitalizations

from the 54 studies. In children the incidence of asthma exacerbations was 21 percent for Salmeterol compared with 23 percent for placebo.

In adults the incidence was 15 percent and 25 percent for Salmeterol and placebo respectively. Shown on the right, the percent of children experiencing exacerbation was five percent for Salmeterol plus an inhaled corticosteroid and 10 percent for inhaled corticosteroids alone, compared with six and 12 percent in adults respectively.

When looking specifically at asthma exacerbations, the incidence was lowest and never elevated compared with inhaled corticosteroids alone when Salmeterol was used with an inhaled corticosteroid. Now, shown on the left, the percent that asthma related hospitalizations in children was higher for Salmeterol, three percent compared with placebo, one percent, although there were only eight and five events respectively. The same

pattern was seen in adults. In the upper right panel, the percent of asthma related hospitalizations in children was the same, two percent, for both Salmeterol plus inhaled corticosteroids and inhaled corticosteroids alone. Likewise the percent of asthma related hospitalization was also two percent for each treatment group in adults.

In fact, no studies with randomized treatment arms of Salmeterol used in combination with an inhaled corticosteroid have shown a clinically relevant increase in asthma related hospitalizations compared with inhaled corticosteroids alone. In summary this pooled analysis of over 22,000 patients, including over 4600 children, show that the safety profile Salmeterol is similar between children and adults. There are no fatalities and no cardiovascular serious adverse events in children. The incidents of respiratory related serious adverse events was low for Salmeterol used with or without inhaled

corticosteroids. Finally, asthma related exacerbations or hospitalizations were lowest when Salmeterol was used in combination with inhaled corticosteroids. To help put this into context, current exposure to Salmeterol in children is predominantly in combination with inhaled corticosteroid. Data from 2006 in US managed care organizations shows that approximately 99 percent of all Salmeterol exposure in children occurs in combination with inhaled corticosteroids.

Other evidence evaluating asthma related hospitalizations include observational studies and a metea-analysis conducted by GlaxoSmithKline which is referenced in your briefing materials. The observational studies included over 300,000 children and the meta-analysis included over 20,000 patients of which 1254 were children. None of these sources showed an increased risk of asthma related hospitalization in clinical practice or clinical trials.

In conclusion, Salmeterol is one of the most extensively studied and widely used asthma medication. More than 15 years of clinical trial and post-marketing experience have established a favorable safety and efficacy profile for Salmeterol. GlaxoSmithKline regularly reviews data from clinical trials and post-marketing pharmaco-vigilance to insure that the product labels are updated with relevant information. This review of pediatric safety information included in your briefing package and today's overview were conducted to meet regulatory requirements for pediatric exclusivity. The totality of the evidence confirms a favorable safety profile of Serevent and Advair and indicates that the profile is similar between children and adults. Serevent and Advair are only indicated in patients who cannot be managed with other controller medications alone such as inhaled corticosteroids. In addition, the labels inform on the safe and

effective use of these products in children. Further, medication guides are provided to inform patients of the risk associated with these medications.

Thank you for your attention this morning and I am happy to address any questions that you have.

DR. RAPPLEY: Thank you very much. I would like at this time because it's 11:00 a.m. to ask if anybody is requesting an opportunity to speak at the public hearing. I would like us then to take our break, our 15-minute break and resume back at 11:15 for questions for this presentation from the sponsor. Thank you, so let's resume here at 11:15 sharp, thank you.

(Whereupon, the above-entitled matter went off the record at 10:56 a.m., and resumed at 11:16 a.m.)

DR. RAPPLEY: We are going to resume with questions for the sponsor presentation. I'd like to keep these

questions focused and answers concise, just so that we can remain on schedule. We are open for questions. Dr. Newman and then Dr. Ward.

DR. NEWMAN: There was a question I have that actually came up with Dr. Mosholder's presentation which was about the -- in the SMART trial the patients who withdrew and I think what Dr. Mosholder said is that deaths and those who withdrew were supposed to be counted but it wasn't totally clear to me that there was an intention to treat analysis and that all deaths in both groups were tracked including those who withdrew from the trial.

DR. RICKARD: That's correct. We did our utmost ability to find every patient and I don't remember how many patients we weren't able to track. Steve, do you remember that?

DR. YANCY: Hi. Steve Yancy, GlaxoSmithKline from the Respiratory Medicines Development Center. I think what Kathy is

referring to, Dr. Rickard is referring to is the fact that we did conduct a survey using the National Death Index to try to find all deaths so we didn't miss any during the trial period. If you recall, it's been mentioned by both presenters that SMART was terminated prematurely. So there was at that time, about a six percent loss to follow. We wanted to make sure that even those patients were going to contribute to the primary and secondary end points that we captured them. So it did take some time to go ahead, go through that process, query the National Death Index database and therefore, we did try to find all patients independent of their completion within or outside of the study.

DR. NEWMAN: Those are the data that we saw, those are the numbers that include those.

DR. YANCY: Yes, it is.

DR. NEWMAN: Thank you.

DR. YANCY: And it's a life table

now so it takes into account the loss of denominator over time.

DR. RAPPLEY: Dr. Ward?

DR. WARD: Would the sponsor comment on asthma related exacerbations and why they seem to be equal in the zero to 18 group between placebo and Salmterol? In other words, I see no evidence of efficacy in there.

DR. RICKARD: This is in the SMART presentation.

DR. WARD: This is the presentation that Dr. Rickard made this morning, I believe. Slide Number A25.

DR. RICKARD: Right, thank you. Can we have the slide, please? So the question is the number of exacerbations between --

DR. WARD: Between placebo and Salmterol that they appear to be equal so I don't see evidence of efficacy.

DR. RICKARD: This is actually from the pooled analysis, not from the SMART study.

And this includes those 54 studies out of the 72 we had and as you can see here, and if you're looking at Salmterol versus placebo, the number is lower for Salmterol compared to placebo.

DR. WARD: The percentage appears to be 21 and 23.

DR. RICKARD: The percentage.

DR. WARD: I think those are statistically different.

DR. RICKARD: Well, I think the numbers are statistically -- they're not -- no? I think the point is that we're seeing a lower number in these patients of exacerbation so you're not seeing an increased risk.

DR. WARD: Well, the number is irrelevant because you have different sample sizes, but the percentage appears to be 21 percent and 23 percent.

DR. JONES: Yes, I'll give it to Steve Yancy in a second but actually just to clarify, these are not efficacy studies. The

end points here, these are safety assessments.

DR. WARD: I understand what they are, but I think that they do speak to efficacy.

DR. YANCY: I would agree. I think it does speak to efficacy and what -- if you go further into the brief that we provided, it does talk a bit about changes in lung function, et cetera. So the benefit that is seen in efficacy has much to do with symptom control, reduction in nocturnal symptoms, daytime symptoms, reductions in LABA use, et cetera. As an end point of reducing exacerbations, it's not showing in this instance of Salmterol versus placebo. You don't really see that benefit, probably primarily because all patients -- some of these patients are receiving background ICS. If you go into the other side, you'll see that Salmterol plus ICS compared with ICS in that more controlled environment, you do begin to see greater differentiation and it's doubling.

These numbers are incredibly low because all of these patients are fairly well controlled once they're on the controller medication such as an ICS.

DR. RAPPLEY: Dr. Ward.

DR. WARD: Are you saying then on that slide, 264 placebo patients were not just on placebo but they were getting steroids? Is that what you meant?

DR. YANCY: Some of those patients do have a background steroid and it's probably about 50 percent so what you look at -- these are trials in the left panel in which the randomized drug arm was Salmterol and it was added to background therapy. About half of that therapy would be without a controller. Some of it has controller. Now, the thing to recognize is that within control trials, or if you look through the compliance literature, use of medication and medication adherence is very poor.

It tends to go up with randomized

treatments, it tends to go down with background treatments, so we don't have good information about their background use of steroids, but it is -- probably about half of that population is without steroids, whereas if you look at the right, it's tightly controlled. You get a very clean look at the use of the steroid compared with the use of the steroid and the addition of the LABA and that's where you see the additional benefit of symptom control, et cetera, but you also see the reduction here in exacerbations without any increase in asthma-related hospitalization.

DR. RAPPLEY: So we really cannot compare the use of Salmterol alone because half of that population was likely to have taken an enhanced steroid. So we're not comparing the left and the right here; is that correct? I mean we have use of inhaled steroids across all arms. Is that the point? Yes. It's not controlled for that, yes,

correct. Okay.

DR. RICKARD: I think the important point is you're not seeing an increase in exacerbations in a situation where the background is -- could be on steroids or could not be on steroids.

DR. RAPPLEY: Okay, thank you. Other questions? Yes, Dr. Malone?

DR. MALONE: I think part of the recommendation would be that if you had failed steroids then you would add the slow acting agent but the data doesn't seem to suggest it would help decrease exacerbations if you just look at the left-hand side.

DR. RAPPLEY: I think that was Dr. Ward's point as well. Dr. Newman?

DR. NEWMAN: Yes, I'm just -- I'm wondering -- I think your concluding slide was that Serevent and Advair exhibit a favorable safety profile and I'm just wondering how you can justify that statement for Serevent for the Salmterol alone when it really doesn't

seem to have a very favorable safety profile since it seems to increase mortality.

DR. JONES: I'll just take this as a labeling perspective. This is a safety profile that's favorable when it's used in accordance with the prescribing information and the prescribing information specifies that Salmterol should only be used when patients fail on an inhaled corticosteroid. And I'll let Dr. Rickard do the clinical portion.

DR. RICKARD: I think you have to look at many aspects of Salmterol. I mean, Salmterol is a drug who is very effective to treat patients who are suffering from symptoms, symptoms that keep them up at night, symptoms that prevent them from exercising, symptoms that may keep them locked in the house, and that's the purpose of what Salmterol is for. If I can put it into an abstract, it's patients who have heart disease and have angina, they use nitroglycerin to relieve symptoms. Now, if you just use

nitroglycerin and you don't treat the underlying disease, that's still a problem.

So for asthma, you need to treat both components. You treat the inflammation with an inhaled corticosteroid and you treat symptoms with a beta agonist. We know the patients who are on inhaled corticosteroids often continue to have significant symptoms that bother their daily life. So by using the two components together, you get optimal care for patients for it from a symptom perspective.

DR. NEWMAN: Right, but you're speaking to efficacy and the statement refers to safety.

DR. JONES: I still mention that the label advises that Salmterol should be used within, you know, the background of an inhaled corticosteroid, either separately or in conjunction as it is with Advair and therefore, the profile that we have -- we look at looks at as you would use it in practice

and therefore, it does exhibit a favorable safety profile when used according to the prescribing information.

DR. RAPPLEY: Excuse me, Dr. Cnaan and then Dr. Joad.

DR. CNAAN: I understand that the SMART study was not stratified on ICS in its design. However, you have the information of ICS as baseline. I have two questions. A, how was -- was ICS used comparable of baseline between the two randomized groups as randomized and B, can you do a post hoc analysis since quite a few post hoc analyses were already done to look at the subset of patients with ICS use and look at all the outcomes within that subset?

DR. RICKARD: Well, first of all, we need to be clear about the study design for SMART. Patients were not required or not encouraged at any time or told that they need to stay on their inhaled corticosteroids. We purely assessed at the beginning of the trial

whether they said they have an inhaled corticosteroid or not. We didn't know if they told us they did, they actually took it. We didn't know any aspect of whether they were compliant to any therapy for all.

All we know is that when the time they came into the study is 47 percent of the entire population said they were -- they have an inhaled corticosteroid. Now, as we go further into the study, we can't tell you how many people discontinued. We know asthma rates or drug rates, patients are very poorly compliant to medications. So we can't tell you that if they all used it in the same way from that standpoint. We can tell you from some different numbers if you look at the events, that it did appear that more events occurred in patients who did not use inhaled corticosteroids or who did not -- I don't want to use that word "use" because that presumes that we know that they used it, who did not state that they had a background of inhaled

corticosteroids. So there were more events in those patients who stated that they did not have an inhaled corticosteroid at baseline.

DR. CNAAN: I understand all these shortcomings and we hear every time on every drug that we look at here on the shortcomings of the AERS systems and so forth. We know the world is not perfect and it wasn't designed this way. With these caveats, I think that it would be important in quoting it correctly as reported uses baseline, not as observed, not as monitored, not as anything, reported. I still think it would provide some additional valuable insights.

DR. RICKARD: Right, and that information is actually in the manuscript.

DR. RAPPLEY: Dr. Joad?

DR. JOAD: We haven't discussed Salmterol for exercise in these bronchospasms. Is that still on the table also, right, for that indication? I just wondered why -- whether your company still supported Salmterol

alone for EIB given that some people might have that everyday.

DR. JONES: I'll start from a labeling perspective, yes, we still have the indication for exercise induced bronchospasm and Salmterol is supposed to be taken 30 minutes before exercise, that's how it's labeled. I believe if you were taking it every day, I'd turn it over to Kathy because that, to me, sounds like much more of a persistent asthma than exercise induced.

DR. RICKARD: Right, exactly. So if patients are having symptoms every day, they fall into a different category of persistent asthma and then according to the guidelines, they would need other treatment. So they should be on inhaled corticosteroid and if they need it, a long acting beta agonist and certainly a short acting beta agonist. If they have pure exercise induced bronchospasm, so this would be occasional use to treat exercise symptoms, then yes, this

could be appropriate to use at that time and it may be appropriate in the childhood populations when they are attending school and the parents cannot be there, you know, throughout the whole day to give them a dose so it's the 12-hour duration of action for that so they can dose them in the morning and the kids can go to school and they don't have to worry about whether they get their medication or not throughout the day.

DR. RAPPLEY: Dr. Rosenthal?

DR. ROSENTHAL: I just have a pharmacology question. It's been mentioned that Salmterol is a partial agonist and I'm just wondering at what point relative to the doses that it -- the recommended doses is it a beta blocker. I'm just trying to figure out if patients are receiving lower than intended doses because of a delivery device or an unclear label or anything like that, whether that could be contributing some to the safety signal that we're trying to sort through.

DR. JONES: Actually, I'm going to ask Dr. Wayne Anderson from GSK who is our pharmacologist. Thank you.

DR. ANDERSON: I'm Wayne Anderson, Head of our Pharmacogenetics Division for Marketed Products, also a pharmacologist. I don't know of any data that we certainly have that shows that increasing the dose makes it an antagonist versus a low affinity -- sorry, an agonist. So I'm just not aware that that actually does happen. We have not seen that in any of our data.

DR. RAPPLEY: Dr. Gorman?

DR. GORMAN: This is a variant on the question about exercise induced asthma. When this drug was first introduced to the pediatric population, one of the other indications or proposed uses was for nocturnal cough. Is that still a labeled indication and a condition for which the company markets this agent?

DR. JONES: No, it's not.

DR. RAPPLEY: When I review our data, our information and listen to the presentation, it's my impression that the strongest evidence for efficacy for Salmterol is in symptom reduction and the signals in safety concern increased number of deaths and increased number of hospitalizations. Would you agree with that or do you have a different take on that?

DR. YANCY: Well, perhaps I can add a little insight to that. The med analysis which was in your briefing document provided by the FDA actually mentions an abstract which was presented at ATS this year. That paper is moving through. What we provided for you in this pooled analysis were data from US studies, since this is a US population and we're treating patients in the US. When you look internationally, that population of studies that are on the right-hand panel move to about 60 studies and in that circumstance you then see a statistically significant

reduction in asthma exacerbations, so it's not just the benefit of symptoms. This is where you begin to see additional benefit.

There is no statistically significant difference in asthma related hospitalization. It's not elevated at a risk ratio of around one.

DR. RAPPLEY: So we should be watching for more information, for publication of information that would inform us about this.

DR. YANCY: And if I could just do one follow-up about the question of the use of the product, we queried some managed care health databases from 2006. Salmterol exposure in children, 99 percent of it is with a concurrent inhaled corticosteroid. So I don't think there's a lot of even EIB use in the current use of the product.

DR. RAPPLEY: Dr. Joad?

DR. JOAD: I wondered if you'd like to respond to the Salpeter comments in their

discussion that when you're looking at -- when you've been looking at exacerbations or reduction of exacerbations as a measure of efficacy of Salmterol that really it is able to mask mild exacerbations. It just can't mask severe ones that bring you to the hospital but that the same process could explain both sets of data, the improvement in mild exacerbations and yet, more hospitalizations and more deaths.

DR. RICKARD: Yes, I'll just start with that. We have done several studies looking at patients that are on Salmterol and not and track their symptoms and peak flows and for several weeks before an exacerbation and then afterwards. And we see no difference in the patients who are using Salmterol or not as far as whether they, in the declines and peak flow, any other kind of signals, the use of short acting -- or these signals they may have that predict that they're having an asthma exacerbation. So they were very

similar. It wasn't that patients weren't experienced in use of short athane or these signals that would indicate, "Hey, I need to do something else".

The only difference we saw in these patients -- in these groups was that once they did have an exacerbation, the patients who had Salmterol recovered faster, so it took less number of days for them to get back up to their baseline of pulmonary function.

DR. RAPPLEY: One more question, then we'll move on for our summary. Dr. Malone?

DR. MALONE: You may have covered this but I would think that a long-acting agent would be better than a short-acting agent. Do these side effects come up with albuterol? Does the issue of hospitalizations, death, has the been looked at as well or --

DR. RICKARD: Well, it hasn't been studied, but I mean, if you go back to the

early 1960s there's been controversy about the use of short-acting beta agonists and the increase in asthma death. There are many things that have looked at other types of short-acting beta agonists and older ones in the past that have been implicated is because they're more a full agonist that probably had more cardiovascular events.

But also a lot of studies point out that the use of a short-acting is more of a signal to worsening asthma or severe disease so that they're using a lot of albuterol, it just means you have worse disease and you need another institution of therapy to do that. So there's a broad data in the literature. There's a lot of controversy going back.

Albuterol really has not been studied that I'm aware of in that way.

DR. YANCY: I'm going to add to that. There are studies, as Dr. Rickard has already mentioned. There are studies that have looked at short acting broncho-dialators.

And most of these studies, if you look at them carefully, it's a series of publications that follow through and perhaps the most recent ones around, short-acting beta agonists is the best example from Saskatchewan databases in Canada.

Now, there were a series of publications that were released which suggested that the use of short-acting bronchodialator, even albuterol, was associated with untoward serious outcomes. It wasn't until you really managed the confounding by severity that these signals basically completely disappear. So you will see signals. You have to be very careful in these types of databases because it's very hard to study these in a clinical setting, a controlled clinical setting. Most of this is done in observational studies and it began with studies in New Zealand and moved through the UK into Canada. So I don't know if that helps you or gives you any additional

perspective. If I can follow-up, I'd be happy to.

DR. MALONE: All of your studies are confounded by having albuterol as a rescue medicine or the patients -- I mean, I guess that would be true, isn't it?

DR. YANCY: I would say that any asthma study would be confounded by that because the use of rescue short-acting bronchodialators is ubiquitous in the asthma population.

DR. RAPPLEY: Well, I see that this continues to need to be addressed, so Dr. Kocis and then Dr. Newman, concise, if you can, please.

DR. KOCIS: I'll be brief. So we certainly in the ICU care for all the exacerbations and the deaths, as I mentioned, we don't have then any more. They don't happen because everyone receives; one, IV steroids, and two, continuous short-acting beta agonists inhaled on top of, you know, and

everyone comes into us with a whole potpourri of what they've seen or not seen, but everyone is treated with those and that treats most of the severe asthma and the severe asthma exacerbations and certainly you can escalate into more unproven therapies that we also add as their symptoms worsen to get them through those episodes.

DR. RAPPLEY: Dr. Newman?

DR. NEWMAN: Yes, I just want to urge precision in use of language because to say that all these studies are confounded by use of beta agonists just isn't right. These are meta-analyses of randomized double blind trials in which the beta agonists should be equally distributed and there are analyses that show, you know, mortality and increased hospitalizations you know, with P values significant at three decimal places. So confounding is not the issue. It's true for the observations studies. That is certainly an issue but we don't really need to be

looking at observational studies and adverse event reports when we have meta-analyses of randomized trials.

DR. RAPPLEY: Thank you to the team from GlaxoSmithKline.

DR. JONES: I just have one additional -- sorry. I just have one additional point actually that I'd like Dr. Yancy to talk to. It's the number that was raised this morning of this one in 700. It was raised at the previous Advisory Committee and we have some data that clarifies that one in 700 and I'd like Steve to just go through those numbers if you can. Thank you.

DR. YANCY: Well, the number is one excess event in 700 patient years of exposure. So it's not one in 700 patients. It's one in 700 patient years. If you use that level of exposure, or use that ratio, one in 700 patient years, and you extrapolate that to the exposure of Salmterol in the US population, we've done this and presented this as an

abstract at a chest meeting in 2006, what it illustrates is that from the SMART data, it would have predicted about 7500 asthma deaths in 2004 based on the exposure of Salmterol.

And then if you include the same rate that was seen from the placebo arm or usual care, that adds nearly an additional 3,000 patients. So in total if SMART truly translates completely into the clinic, we would have predicted over 10,000 deaths reported to the CDC that year where in effect it's about 3800.

And I think it's also important to note that asthma death has been decreasing in the US since about 1996. And that is on the background of large increasing exposures to both inhaled corticosteroids as well as Salmterol.

DR. RAPPLEY: Thank you.

DR. JONES: Thank you very much.

DR. RAPPLEY: Dr. Sachs.

DR. SACHS: Okay, as usual, we

don't leave you with the easy questions. So I'd like to provide a little bit of a recap so everyone is on the same page. Salmterol is currently approved down to four years of age based on a number of well-controlled efficacy and safety studies for both the maintenance treatment of asthma and exercised induced bronchospasm. Clinical trial experience ranges from 12 to 24 weeks, six months, and the pediatric exclusivity studies that were performed with the metered dose inhaler which is no longer marketed, did not result in an indication or a change in labeling for that age group.

The SMART trial showed an increased incidence of asthma related deaths and life-threatening experiences in all patients and there's no -- in adult patients and there's no reason to believe that this increased risk does not apply to pediatric patients even though the numbers in the subgroup analysis were really too small to make a determination.

In addition, an increase in all cause and primarily asthma-related hospitalizations were noted. Although fatalities were observed in the pediatric patients during a review of AERS, during the one-year post-exclusivity period there was not a trend that was unique to the pediatric population.

A review of the literature is consistent with the findings of the SMART trial and the findings of increased respiratory related hospitalizations in pediatric patients likely reflects the known risk of asthma-related deaths and life-threatening asthma exacerbations in adults.

According to treatment guidelines, Salmterol like other long-acting beta agonists, is considered an asthma controller medication recommended as additional therapy for patients with moderate to severe persistent asthma who are already on inhaled corticosteroids or other medications. Current

labeling includes a box warning regarding asthma-related deaths which applies to all patients including children and this box warning appears in drugs of the class as well as in combination products. There are additional warnings which include the need to use Salmterol only as additional therapy and only to use the product in patients who are not well-controlled on other medications.

In addition, the SMART trial is described, particularly the data regarding the increased risk of asthma-related deaths. The labeling does not include a description of the increase in hospitalizations in children and the labeling section on -- that describes the SMART trial contains a statement that the data are not adequate to determine whether or not the concurrent use of inhaled corticosteroids or other controllers may mitigate that risk. There are additional warnings, as you heard not to use for acute treatment and not to double to dose, et cetera. The pediatric use

section summarizes the studies in children for ages four to 11 for both asthma and exercise-induced bronchospasm.

And finally, there's a MedGuide that's required for all the products containing the LABAs including the combination products. And just for review, here's the warning in its entirety and with the current labeling in mind, let's turn to the questions for discussion.

This Committee has been provided background information on safety issues related to Salmterol including previous deliberations by the Pulmonary Allergy Advisory Committee of June 2005 in relationship to the class labeling box warning for asthma related deaths and that Salmterol should only be used as additional therapy for patients not adequately controlled on other asthma controller medicines. Since this meeting, there has been additional safety information concerning the pediatric

population and the Office of Surveillance and Epidemiology has provided an analysis of the available observational pharmaco-epidemiological studies in a subgroup analysis of pediatric populations in clinical trials.

In view of the evolving issue of risk for hospitalizations in the pediatric population, the Agency thinks further assessment of the role of this product in the treatment of pediatric asthma is warranted and plans to bring this issue forward to any further Advisory Committee. But in the interim please address the following questions.

Pending the completion of further analysis regarding the risk and benefit of Salmterol in pediatric patients, please discuss whether the current labeling and MedGuide adequately communicates the potential risks in children and please include in your discussions whether the present warning and asthma deaths is adequate for the pediatric

population. As you do that, please address the observation that increased pediatric hospitalizations and whether or not the current labeling adequately addresses this issue.

Secondly, please discuss whether the current labeling and MedGuide are clear in the recommendation that Salmterol should only be used as additional therapy for patients not adequately controlled on other asthma controller medicines such as low to medium dose inhaled corticosteroids or whose disease clearly warrants treatment of two maintenance therapies.

In particular, please comment on whether or not the current labeling and MedGuide clearly communicate that there's no clear evidence that using an inhaled corticosteroid mitigates the risk of asthma-related deaths in patients receiving Salmterol.

DR. RAPPLEY: Thank you. So I see

two questions before us immediately and they both refer to adequacy of the current labeling. So the first set of questions is asking us is the current labeling adequate on three issues. One is describing potential risk for children, warning on asthma deaths and adequately addressing the signal of increased hospitalization? So those are three areas in which the Agency asks us specifically, is the current label adequate? Does the current labeling adequately cover that? Open for discussion. Yes, Amy.

DR. CELENTO: First, can we see the box warning up on the screen to make sure we have the same thing here?

DR. RAPPLEY: Yes, good point.

DR. CELENTO: Thank you. So in answer to these questions, I do not believe that this adequately indicates the risk in children. It speaks of asthma patients. There's nothing that refers to children or pediatric patients and that's consistent

throughout the MedGuide as well. So I do not feel that that is adequately addressed and it really should be broken out to indicate adults and children or pediatric patients.

DR. RAPPLEY: Dr. Ward?

DR. WARD: The other aspect that Dr. Mosholder's presentation communicated was the increased risk in African Americans and I think if I was a prescribing physician, it would be helpful to have that specified as well.

DR. RAPPLEY: Dr. Cnaan and then Dr. Joad.

DR. CNAAN: Pediatrics loose page has a specific statement about being well-tolerated and no safety issues. And so I think if I were a parent reading everything, the front part doesn't separate out and the back part tells me that there are no issues in pediatrics, no safety issues, I would read that all the death story relates to adults. So I think it needs to be added.

DR. RAPPLEY: Dr. Joad.

DR. JOAD: Well, having dealt with this black box warning as a clinician, I just have to say it's very hard for a clinician to know what to do with it, to use it, to explain it to a patient and I guess if it's -- if our question is not so much what should happen with Salmterol which I wish we could address, but I guess we're not going to get to --

DR. RAPPLEY: I think that may be dealt with later, but because we still are awaiting further information that seems to be coming fairly soon but yet isn't available here today. So that's why we're addressing labeling. Is the labeling adequate at this point in time understanding that we will need to revisit this?

DR. JOAD: So I think one in 700 patient years is clearer than this and that the average risk of your daily life is 100 fold more than that or something that makes you be able to say to yourself and to your

patient, "What does this number mean?", because I found this number very hard to live with as a clinician. I didn't know how to use it or put it into perspective.

DR. RAPPLEY: Other comments or questions? Dr. Garofalo?

DR. GAROFALO: I mean, this is just a question for the statisticians about the whole -- I mean the one in 700 patient years aside, even the number needed to harm which I'm familiar with, you know, seeing in other reviews of adverse events and doing the subtraction and inversion but when you get to very small percentages, you know, and it changes just a little bit. Won't that really be magnified in this number needed to harm? I'm concerned about how -- you know, how scientific, how realistic that is and how it relates to other risks.

DR. RAPPLEY: Dr. Ward and Dr. Newman?

DR. WARD: I found an estimate of

accidental deaths in children on the net of 20 to 50 per 100,000, so if we can put it in that perspective. I think you're question thought is quite relevant and I would turn to the statisticians as well because we're talking about things that were out to two decimal points, you know, .02, .04 and then we're going to extrapolate to something with three or four decimal points, or three or four significant figures.

DR. RAPPLEY: Dr. Newman?

DR. NEWMAN: I'm just -- to address that point, you know, if the risk difference is based on small numbers, then the number needed to treat will be high and the risk difference has a confidence interval and the number needed to treat can have a confidence interval as well. So, and I mean, and it will be wide if, you know, if the differences are small compared to the sample size. I mean, I can't tell you more than that.

DR. RAPPLEY: Dr. Cnaan.

DR. CNAAN: The only thing I would strengthen is that you have to use and the number needed to harm the confidence interval bounds of the percentages to begin with, so that the at least you get some sense of the uncertainty and that the little bit would make a big, big change.

DR. RAPPLEY: Dr. -- Ms. Vining.

MS. VINING: Under the indications and usage section I think much of the discussion has indicated that this therapy is an additional therapy and only to be used as an additional therapy but under that usage and indication section, it's not until the second paragraph, the second line of the second paragraph that that information is made available.

I don't know if there's a way to move that important information to the first paragraph or even the first sentence to talk about it as -- only as an additional therapy versus a standalone therapy.

DR. RAPPLEY: So at this point in time, I hear the following suggestions, and if we sort of stay with the idea of giving the agency the major concepts we'd like to have included as opposed to particular wording, that the potential risks in children, specifically, are not well-addressed and we would like to see that change.

That the risk for African Americans in particular needs to be included, that there are issues with the pediatric use section; one, that it seems contradictory to the evidence at hand when it states, "No safety issues in pediatrics", and so that should be revised.

And second that the very important information about the use of Salmterol as an additional medication only should be moved to a more prominent place in the insert and then lastly, that there should be a way to portray the risks that's reasonable to allow physicians and families to make informed

decisions but acknowledges the limitations of what we currently know. Other comments? Dr. Kocis and then Dr. Gorman?

DR. KOCIS: Sort of I want to just continue on the them of what a pediatric patient is and how we lump this label which applies for everybody zero to 100 and you're trying to make sense of what to do with that and even where you began to focus on the quote, unquote "pediatric safety data", we're really focused on the 12 to 18 range. There is breakdowns by the different ages.

We know non-efficacy in the kids less than four and they're not asking for label changing, which is good and yet realize that, you know, parents see a child, they may say, "Well, my child is three and a half, three", and we know off-label use and we even saw that, that had some results in the younger age group that people can begin to say, you know, it's safe for kids, "And so my kid is just a little younger than this and maybe" --

so it's somewhat of a slippery slope.

I think we have an obligation to look at all children and I'll define children not at 16. I'll do my definition of 18 which I understand is not regulatory and we can address at a later time, but you know, it seems to me that we have a lot of data in the 12 to 18 relative to most pediatric trials and we should probably draw most of our conclusions from that for that age group. We have some data and we can probably delve into that further and stuff in the four to 11 plus age group. You know, it's broken down in their handout, but we really didn't go through that in depth and I think while that -- I think we may come to different safety and efficacy conclusions for that age group and then we should say something also about what data we do have in that zero to four group.

Again, it sounds negative data, I mean, the sense of lack of efficacy and then you know, I didn't get a chance to go through

all the safety concerns in that age group but I'd be concerned about that. So those would be my comments and whether that's into the main front black box or now that we have our new form and our new pediatric dosing and concerns whether we need to focus more on that area of the label.

DR. RAPPLEY: So to summarize, you're suggesting that the discussion of the risk be broken down into different age categories according to the information we have at hand. Dr. Gorman.

DR. GORMAN: If the Committee decides to redo this particular warning on the label, I would caution against using any particular language about when to insert this particular agent and although I hate to use one document to refer to another document, the treatment recommendations for asthma are a moving target and the ones that are in the label even today might be widely misinterpreted. So I might suggest that if

the wording is changed that some recommendation be made to another body's recommendation on how to treat asthma.

DR. RAPPLEY: Yes.

DR. MATHIS: I just wanted to get one clarifying question regarding the labeling and the negative studies. I was hearing you say that you would like to see the efficacy information in the younger patients from the negative studies included in labeling as well so that way people didn't say, "Well, my kid's only a little bit younger than this so I'll go ahead and use this product". So you would like to see the negative studies included in labeling not only with regards to safety but also with efficacy.

DR. KOCIS: Yes, and you know, I actually didn't bring it up with the first drug we reviewed, with the eye drop but when you show a drug and you say, "Well, we've shown there's no benefit to it," and then you say, "Well, in the label, we're not precluding

pediatric use", to me, and I'm bringing it up on that point, but focusing back on here, when we have negative data, we should say that, and that's different than no data.

And in pediatrics that's important because negative data, we won't use it; no data, we'll begin to extrapolate based on what we have to offer and other things until we may use it.

DR. MATHIS: And just in response to that, I mean, Congress and many of the people who advocated for the re-authorization of both BBCA and PREA, saw that as an issue and actually have now included that into the law for both PREA and BBCA. So from now on, you will always see that. But I think that it's a very good point in this situation where you do have safety concerns, that perhaps we need to revisit that for this drug.

DR. RAPPLEY: Dr. Newman?

DR. NEWMAN: Yes, I think this is -- these data we've heard are very troubling

because I mean, both increase in hospitalizations and increase in mortality is so different from what we think of when we tell our patients what they really need to do is take their medicine and that will make them better and keep them safe. And it seems like that's not the case here. So I'm not sure when the drugs would be indicated at all but when I read the label, one thing I was looking for was, "Okay, so there is" -- I was at least able to quantify the hazard but the benefits are all expressed in terms of there's a benefit in FEV 1 or there's a benefit in pulmonary function. And I was trying to find something that I could translate into the expectation that a patient would be able to understand how much benefit there would be.

And so actually, I went to the literature. There's a Cochrane review. There are some other studies and it seems like the actual benefit is something like a 12 percent decrease in or 12 percent increase in

asymptomatic days or an asymptomatic nights meaning every eighth day or every eighth night, you would have -- or both actually, you would have -- be symptom free when otherwise you would have had symptoms or it's an average of one puff on the meter dose inhaler per day is the difference between getting this medicine or not.

And I think quantifying the benefit in some way that the patient would be able to relate that to this risk would be helpful as opposed to statistically it's never going to benefit in PFTs which a patient can't translate into their -- how it effects their life.

DR. RAPPLEY: So you are suggesting that further the discussion on evidence for efficacy be in terms of people can readily understand and apply to their own life. Dr. Malone.

DR. MALONE: And also because of the concern about exacerbation or worsening,

it might pay to define that a little bit within either the patient handout or the label that exacerbation could be indicated by increased rescue medicine or however you might want to define it so the patients would know when they should call somebody that they might be in trouble.

DR. RAPPLEY: Okay, so are there other suggestions for concepts that should be included in a label change? Dr. Joad.

DR. JOAD: Actually, I just want to make sure that we do get a chance to comment on the drug availability in general. Do we get to? I mean, I think these data have been very concerning and I think -- I just think as a pediatric group, we certainly could or I would want it to be very carefully looked at again. I think one in 700 is very worrisome and if I were to look at it just that, I would -- I personally would say it should not be on the market. I understand that it may be totally different with inhaled

corticosteroids. I hope it is, but I don't -- with the information we have right now -- and I think putting it on the individual patient and individual physician is just kind of an unfair thing to do because for them and us, it's very hard to make an individual decision about that, and that's what this whole labeling thing is, is if you could really use that to be informed and somehow you're going to prevent these deaths and hospitalizations and I just don't -- I think it's much bigger than that.

Each physician, as I mentioned, doesn't see enough patients for them to see it and certainly an individual patient can't really fathom it, I don't think.

DR. RAPPLEY: The agency has stated that they will bring this back to Committee. What do people think about requesting this be brought back to this Committee? Is anyone opposed to that? So I think that is a recommendation then. And then in the interim

we're strengthening the labeling as much as the evidence allows us to. Did you want to further comment?

DR. SEYMOUR: Yes, I just wanted to ask a clarifying question and then address one recommendation that was made. One was a recommendation for additional information about African Americans and I just wanted some clarification on that because there is a fairly detailed description of SMART with a table that breaks out African Americans and Caucasians and even the Kaplan-meier curves for Caucasians and African Americans. So I wasn't quite sure what additional information. Dr. Ward?

DR. WARD: Well, we may be looking at two different labels then. I was looking for the Kaplan-meier Curve, couldn't find it in the information we had which in our book --

DR. RAPPLEY: Can I clarify? Dr. Ward, did you suggest -- did you request more information regarding use of the African

Americans or only strengthening the label --

DR. WARD: No, right, strengthening the label, yes.

DR. RAPPLEY: -- to state that specifically?

DR. WARD: What I'm looking at has an effective date 3/31/2006. It starts Serevent Diskus and I did not find a Kaplan-meier Curve in it.

DR. NEWMAN: Figure 2 looks like it's just the wrong figure. The caption doesn't match the figure. This one right here. The label says "cumulative incidents of asthma-related deaths" and then the figure is percent change in FEV 1. So I think there's some problem with that.

DR. RAPPLEY: Yes, because Figure -- I mean, Figure 2 and the approved product label has the keynote of incidents curves. I'm not sure why the label you have in your package does not have that. Maybe there was a copying mistake.

DR. MURPHY: I think that is the only thing I can come up with --

DR. RAPPLEY: Okay.

DR. MURPHY: -- because it was transmitted electronically, so somehow --

DR. RAPPLEY: But, I guess, could we just discuss this then as another concept that we'd like to see in language that people can understand, that the risk is higher in African Americans?

DR. SEYMOUR: Okay, that point is taken. And I think there might be come confusion because the copy of the label that you have, so I understand that. The second point that was brought up that I wanted to address, too, was including the information from the studies in patients zero to four years of age which were the exclusivity studies, I think you're talking about, just a couple comments about that. One is that they were performed with MDI which is no longer on the market. So I'm not sure how relevant it

is for the Diskus and you know, we really weren't convinced that you could interpret the data from those studies, the safety or efficacy data. So I'm not sure how much that would add to label for the Diskus and the Diskus is not approved in children less than four.

DR. MURPHY: I think, Sally, they're just saying they want that in there. I mean, we can find words to say what we think it does or doesn't mean, but this Committee has been pretty consistent that they want negative information.

DR. RAPPLEY: Correct, I think that is the message there. Available negative information should be included in the packaging insert, yes.

DR. STARKE: Can I just respond for us? This is Dr. Starke. The problem is with the MDI and the way it was used with the spacer and when you look at in vitro data, you can't be sure that the patients actually got

the drug. And if you say that, then what information are you actually putting in that's of value?

DR. RAPPLEY: I think we understand that.

DR. STARKE: And that's where we have difficulty.

DR. RAPPLEY: I think we understand that and it's not that we would want information included that would be misleading. It's clear that the product is not labeled for use under four. If we could include some language that would prevent or discourage people from drifting down into youths under four, because in pediatrics we often, all of us, use medications that are not approved by the FDA for children because we don't have other options. In this case, as limited as it may be, for all these limitations, we have actual negative information about the impact of these meds in zero to four.

DR. MURPHY: I think what Peter is

saying is that we don't know that we have negative information if we don't know that we've got the drug and I think that what I'm trying to say is that we can say that. You guys are smart enough, I know you can figure out how to do it.

DR. RAPPLEY: Fair enough. Dr. Joad.

DR. JOAD: I think that I could speak for more than myself. We're pretty confident that MDI with spacer and mask work very well as a drug delivery for young children. And many of us only us that to treat our children. We don't -- young children, we're not using nebulizers any more. In fact, our whole hospital pathway for treating acute exacerbations is with a meter dose inhaler and a mask. So I don't know if they did something bizarre with it, but if they used it the way it's supposed to be done, we're pretty happy with delivery in the infants.

And the other thing is now Advair is available which it didn't used to be, as an MDI. So there will be a strong, you know, urge to use it in young kids. So if there's -- in kids who are not able to use the Diskus which is kids under four. So I think that's why I think this negative information is quite useful at this point. The only information we have so far is it doesn't work and I think it's reasonable information.

DR. SEYMOUR: That's fine. Your point is taken and I'm not opposed to putting negative efficacy studies in the label. That wasn't the purpose of my comment. It was more just the fact that I'm not confident the study showed anything and that can be something we can consider. And I just want to make one statement, too, just in response to what you said, Dr. Joad. When MDIs are approved, the clinical studies for the most part, don't use spacers with masks. So the drug is approved for use as they're used in the clinical

studies. So that's one of the reasons why we do ask for additional data for the exclusivity studies actually to show that patients are getting the drug and the data can be relied upon.

DR. RAPPLEY: Dr. Malone?

DR. MALONE: Didn't that data show side effects though, even though it didn't show efficacy for drug versus placebo? I thought it had showed side effects for drug versus placebo but not efficacy.

DR. SEYMOUR: There were some adverse events noted and it was pretty much consistent with what we've seen in other studies. So I mean, there wasn't anything startlingly new. We just didn't have the confidence that the drug was actually received.

DR. CNAAN: I think the point of this comment was which was what I was going to make, is that the fact that there were the consistent side effects with the older age

group is supportive evidence the drug was delivered and that's why we think that the negative results are for real.

DR. RAPPLEY: Okay, I think -- any further comments on this issue? I'd like to move to question 2. All right, the second question then, again, is regarding the label. And in this case, they asked, is the label clear on two issues? One, is the label clear that Salmterol should only be used as additional therapy? And two, is the label clear that inhaled corticosteroids mitigates asthma related deaths in patients receiving Salmterol? Discussion? Shall we take the first, "Is the label clear on Salmterol only as an additional therapy", I think we've heard one comment already, that that could be strengthened by putting it into a more prominent place in the package insert. Are there other thoughts about that?

MS. CELENTO: I'm not quite certain that this is a standard template for the

MedGuide but there's quite a bit of the important information bolded, so it sort of all beads together. So moving that information will help and there really should be some way to call that out, whether it's a call-out box or something. It just seems like it's a lot of stuff that runs together when you take a quick read through this.

DR. RAPPLEY: Other thoughts about this question. So then the suggestion -- okay, we have two more, Dr. Joad and then Dr. Fant.

DR. JOAD: I'm happy with it saying this. I just want to point out that it's not logically -- doesn't logically fit an indication for EIB to say it's only to be given as a second drug and then to say it can be used for exercise induced bronchospasms as it can be used as a single drug, so it's not logical.

DR. RAPPLEY: Dr. Fant.

DR. FANT: Yes, a general question

for the pulmonologist, people who treat asthma routinely; just as someone who's sort of watched -- you know, looks at it from a distance, you know, there are a number of medications that apparently are being used to treat bronchospasm in addition to beta agonists and corticosteroids and most notably in recent times, you know, Singular for instance.

And you know, and it just sort of increases a complexity of the pharmacologic regiment that's being used to treat this, so, you know, it will kind of up the ante a little bit in -- you know, in sort of sorting out the, you know, a danger signal with any one particular medication and make it even more challenging.

Is there anything known about the potential interaction of this drug with other classes of bronchodialators other than corticosteroids which is really the only other drug that's mentioned, you know, that's been

mentioned here. But it's also mentioned in the context, it should only be used when more than one drug. So you've got more than corticosteroids as options.

So how does this fit into when -- you know, when that second drug is not a corticosteroid but is Singular, which is advertised as a drug with that helps you get off corticosteroids?

DR. RAPPLEY: Any response from Committee members? Dr. Joad?

DR. JOAD: I would guess a very few -- there are very few patients who are using Singular as their controller and then having in addition Salmterol added on top of it. It's almost always inhaled corticosteroids with Salmterol all on top of it. I think it's not very common. There's people who add the leukotriene modifiers to inhaled corticosteroids rather than adding the inhaled long-acting beta agonists or who try to do all three but by far it's inhaled

corticosteroids first and then adding Salmeterol.

DR. RAPPLEY: So, Dr. Fant, I would sort of play your thought out. Are you suggesting that the insert should specifically say in addition to inhaled corticosteroids rather than in addition to other medications?

DR. FANT: Yes, I think we need to keep it to what we know something about, what there is some data about. I mean, this -- you know, this seems like -- you know, emergence of potentially a new confounder which may have to be dealt with at a later time and I'd hate to sort of embark on this journey by you know, sort of treating them as if they were equivalent when they may not be.

DR. RAPPLEY: Does the Agency feel that they can work with that concept in a way that doesn't prescribe medical practice?

DR. MATHIS: I'm sorry, just for clarification, Dr. Joad is the reason why most of the patients who have Salmeterol added onto

-- on corticosteroids is because they have more severe asthma and the montelukast, the other drugs, leukotriene drugs don't -- aren't good at controlling severe asthma? Is that what you're saying?

DR. JOAD: Right, plus it comes as Advair. So I think, as they pointed out, the vast majority of use of Salmeterol is with inhaled corticosteroids as a single product. So it's for moderate to severe persistent asthma and it's usually used as a combined product.

DR. RAPPLEY: And following up on a comment Dr. Joad made earlier, is the Agency comfortable with working with the manufacturer about language that becomes more logical so that we're not suggesting it be a single agent in one part of the insert and suggesting that it not be used as a single agent in another part?

DR. SEYMOUR: Yes, I mean, we'll take all that into consideration and try and

address your comments.

DR. RAPPLEY: Nothing like field testing our labels.

DR. SEYMOUR: Field testing your labels, there you go.

DR. RAPPLEY: So I think we've talked about the question posed to us about is the label clear on Salmeterol as only being used as additional therapy. The second part of this question is the -- does the label adequately convey that we don't have good evidence that the inhaled steroids mitigate the asthma-related deaths in patients receiving Salmeterol? Yes.

MS. CELENTO: I actually don't see that information in here anywhere, so I don't think it's clear at all. It just seems like it's not addressed unless I've missed it.

DR. MURPHY: Sally, is there some part you want to read to them that you think covers that since we seem to have had a copying error so we make sure that we have for

them what the original part that should relay the -- I just want to -- since we've discovered this, I want to at least have that read to everybody. Okay?

DR. SEYMOUR: The copy of the approved label has quite a lengthy description of SMART and after it presents the data, before the table of the results, it says, "The data from SMART are not adequate to determine whether risks -- whether the current use of inhaled corticosteroids or other asthma controller therapy modifies the risk of asthma-related death". So that's --

MS. CELENTO: So, in the MedGuide, can you point that out? Is there something similar?

DR. SEYMOUR: I'll have to look.

MS. CELENTO: Okay, because that's part of the question.

DR. RAPPLEY: Dr. Newman?

DR. NEWMAN: Can I make sure that we're all looking at the same -- is the label

that we're looking at the one that says "effective date 3/31/2006", and it comes right after the Salpeter meta-analysis?

DR. MURPHY: Yes, that's the one that's in the handout but apparently, as you all have pointed out -- let me put it this way, Dr. Seymour has handed me a label which is very different than what you have, and it does have the life tables for the African American, Kaplan-meier tables and so therefore, we're trying to make sure that you all have the same language everywhere.

DR. NEWMAN: Online, the Salmeterol label didn't have the Kaplan-Meier tables in it. The Advair label did, so apparently there must be a label that has those combined.

DR. SEYMOUR: Yes, is that the online --

DR. NEWMAN: Yes, but it's from your website.

DR. SEYMOUR: From our website? We'll have to check in the back because it

sounds like it's not the right label.

DR. NEWMAN: Okay.

DR. SEYMOUR: So that's why I was asking that. The box warning that you saw is the same. So that's not the issue. It's, is there any other place in the label? So the wording of -- the box wording, that's not the issue. It's is there wording before the SMART trial which is apparently not in part of this label, okay, does that say anything else in the label about this issue? So that's why I was asking her to read it to you.

DR. RAPPLEY: Can I make a suggestion but I'm open to ideas about this? Perhaps we can convey that we want this included in the labeling, that there is not evidence that the steroids mitigate the increased number of asthma-related deaths in use of patients who are taking Salmeterol. And then if it's possible, some time later today, for you to give us a copy of the actual package insert that patients and pharmacists

and physicians receive. We'll just double-check it and return to you if we have additional concerns.

DR. MURPHY: Actually, what we will do is we will get a copy of the label that Sally has in her hand and we will get that to you during lunch, so that you'll have time and I think at the end of the day, we will come back and ask you this question after you've read the label, that part of the label, too.

DR. RAPPLEY: Is the Committee okay with that? Dr. Cnaan, did you want to --

DR. CNAAN: I just wanted to make the comment that the text that you just read before Table 3 from the SMART study yes, indeed, exactly covers the second part of question 2, but I really feel that it gets lost inside the description of the clinical trial which I think is probably the part least read by parents. So it should just probably be repeated elsewhere.

DR. RAPPLEY: Okay, I believe --

does the Agency feel we have answered their two questions?

DR. MURPHY: Yes, thank you.

DR. RAPPLEY: Okay. Then I suggest we break for lunch and return at 1:00 o'clock. Thank you.

(Whereupon, at 12:24 p.m. a luncheon recess was taken.)

DR. RAPPLEY: Okay, actually we can get started because we do have a quorum. So I apologize to those who are waiting a decision on Salmeterol. I was not considering your needs to leave for the day. So let's revisit that. We now have the appropriate product insert before us and some of us had a chance to review it over lunch. Are there any additional things that the committee wishes to recommend to the Agency after reviewing the current product insert? Yes, Dr. Newman.

DR. NEWMAN: Yes, just so it's clear to me that we're talking about Serevent and not Advair, that the Serevent is the

topic, so I sort of want to come back to what Dr. Joad said at the beginning, is I actually don't see why this should be on the market. I don't see any benefit for it and all the evidence we have is this chemical, compared to placebo, increases hospitalizations and increases deaths from asthma. So, although the FDA didn't actually ask us to do that, I wonder if we might want to vote or express an opinion about that. That -- I think there is more data from when the allergy committee looked at this in 2005, and it's hard for me, in good conscious, to just deal with the labeling without dealing with this bigger question of whether it should even be sold.

DR. RAPPLEY: I think the agency has told us that they are committed to bringing this back to us. If you'll excuse me a minute. Can I ask people in the audience to please take their calls outside of the room? It's distracting to hear the conversation. Thank you.

So the Agency has made a commitment to bring this back to us and I think Dr. Joad has expressed a similar sentiment. Is that not strong enough for you?

DR. NEWMAN: Yes, that's not strong enough for me.

DR. RAPPLEY: So, Dr. Murphy?

DR. MURPHY: Dr. Newman, I missed your comment. It was whispered to me that you also had the same concern Dr. Joad did? Okay. I think one of the things that we will be putting on the table is that issue because what we're going to be looking at is -- and we didn't put all this in there because we had a lot of discussions about this before, is the risk/benefit. But because this committee really wasn't set up, as you know, as I told you, that involves to do a complete risk/benefit analysis at this point, we thought that that's why we needed an additional meeting. So that part of the component -- question is being discussed.

The only other thing I do want to say is that that question, I want to remind the committee, though, too, that that question was asked in 2005. And of course, that was for adults, I mean, not adults, it was for everybody, but they didn't focus in on the pediatric part of it and that's the whole point of why we're saying we think we need another meeting, is we now have new data and we think we need to look at the whole risk/benefit analysis at this point.

DR. NEWMAN: I guess I'd just say in response to the question, is the label adequate, the label that says "Advise patients that these medications increase mortality in people with asthma or may increase mortality", I just think that's not a very realistic approach to tell the physician to tell their patients that these medications increase the risk of mortality. And then if we add "and hospitalization," since we have data that both of these are true, this single medication, the

Salmeterol by itself seems to do that, that's what we know. So I guess I would say that just saying to advise the patients that the medicines increase mortality on the label, I think sort of doesn't do it for the label.

DR. RAPPLEY: So what I hear from the Agency is that they don't feel we have enough evidence before us or enough time on this agenda to give a fair discussion to the risk benefit for Salmeterol to reach a categorical or a yes/no answer about whether it should continue to be marketed to children and that they would like an opportunity to bring that back to us with that full set of information.

But I also, then, hear from Dr. Newman and from Dr. Joad that is an interim then in which we understand that we do have new information and I have not really made a conclusive recommendation. Can you give us a sense about when this could return to Committee?

DR. MURPHY: Could I say something? I mean, the reason we asked you the second -- the two questions we have is because we do have an interim and so we do need -- because we don't think it's appropriate to say, "Well, we don't know what to do so let's take it off the market". We don't think that's appropriate. We think we need more data, more analysis. So what we're saying is -- but in the interim, having seen what you've seen, with the tools that we have, how can we relay information best to people? Now, to the question of how long that could be, since negotiating a new label sometimes takes a while itself, I can tell you that it's going to be more than a couple of months.

I don't think, and this is my personal opinion that I've stated it internally thus far, I don't think we can be ready for the March meeting if we have a March meeting. I should say we don't know that yet. We're polling. We always have, you know, at

least two meetings and you've already had three this year. So -- but for the next meeting, whenever it is, I don't think we'll be ready for that. So I would say it would be beyond that.

Does the Pulmonary Division have any other insights, or the OSE? Andy?

DR. SEYMOUR: I think that this review of the pediatric data has sort of been evolving in the Agency and so this recommendation for another advisory committee is a recent recommendation within the Agency and so we haven't, at this point, planned any dates for that, or even discussed what committees should be involved. So I think it's something we internally still have to discuss the process for.

DR. MURPHY: Do you have any suggestions, Andy? I mean, do you have any idea about the databases, how long an analysis would take?

DR. MOSHOLDER: So the question is

how long would an extended analysis take? That's obviously, hard to predict. I -- we tried to beat the bushes pretty thoroughly for Salmeterol for this meeting. So I don't know that there's a whole lot more to flesh out as far as additional safety data. And -- but, of course, you know, with the public health importance of this would, you know, be on the side of doing it very urgently because, you know, this -- if you include Advair, there's about 6 million patients taking the compound.

So we would have to try to do it as quickly as possible. I don't have any time frames for my management for the plan --

DR. MURPHY: And we would be looking at the LABAs, right, not just one product.

DR. MOSHOLDER: Well, we said in our review that you would have to consider not just Salmeterol for pediatric use but also formoterol and also the adult data for the total picture. That's what we said in our

DDRU regime.

DR. RAPPLEY: Dr. Gorman?

DR. GORMAN: In your preparations for this future meeting which will have a more robust discussion, would you make sure the committee is aware of what we can do for the moiety, the chemical moiety, versus the products if there is a difference in what we can do, because sometimes we talk about the chemical and sometimes we talk about the products and I would want to be sure that that was clear before we started a discussion going forward.

DR. MURPHY: Yes, we will. So what I'm trying to outline is that the Agency will do this as quickly as possible but I think what you've heard is that we already -- as we progress this time we started looking at more -- you could tell, you were getting analysis over the weekend.

So we're going to be out looking for even more data and other products in that

class. And so that's going to take us a little while. I don't think it will be March. If that will help you in your deliberations, it will be after the next meeting.

DR. NEWMAN: I think the March meeting is my last on the committee.

DR. MURPHY: We can extend you.

DR. RAPPLEY: So, given this concern, and then the process which needs to unfold to gather adequate amounts of information to make decisions, is there more that needs to be done to the labeling that would make Dr. Newman, Dr. Joad feel more confident in where we move between today and our next meeting about this subject?

DR. JOAD: Well, I kind of said what I thought. One in 700 patient-years risk of death and what that means in comparison to other risks that everybody takes every day, I think would really help.

DR. NEWMAN: Well, we are the Pediatric Committee so I guess we could

recommend on the label do not use in children.

DR. RAPPLEY: Well, I think that is what the Agency is saying, they don't feel we're prepared to make that decision until we have more data. That would be the question, the very question on the table at the next meeting. I guess I feel the need to convey, then, to the Agency that the members of this committee feel this is an urgent and, I agree, a public health issue and that we do need to meet on this very soon and that it's difficult to bring forward this level of concern and then move forward with interim measures that we know will take a considerable amount of time to be instituted. Is there more to be added? Okay.

DR. MURPHY: So while I was late, you didn't finish up the second question; did you?

DR. RAPPLEY: I did pose a question to the group, is there more to be added to the label, given that we've had a chance to look

at this copy of the real deal, and so Dr. Kocis and then Ms. Celento.

DR. KOCIS: Yes, I'm just thinking through, as we continue to deliberate about this, in looking at the warning box, I guess there's a lot of words between "therefore, when treating patients with asthma, Serevent should only be used" and then da, da, da, da. I guess I might suggest you cut to the chase and get more direct and I think we've all said this, that it should not be used as monotherapy without inhaled steroids. Do we have the data now, today, and I think I do. I feel convinced that that statement could be made, instead of leaving a lot of words, more obtuse, and then bringing in the chance that all of a sudden Singular with all their TV commercials are just going to start showing up and that, you know, the combination, not that it seems likely, but --

DR. RAPPLEY: Ms. Celento?

MS. CELENTO: And just following on

with that, I agree that it should be more clearly stated but then to speak specifically to the second part of the question, and does the MedGuide clearly communicate that, "there's no clear evidence that ICS mitigates the risk of asthma related deaths", blah, blah, blah, it's really silent to the issue which I don't have a problem with because it doesn't imply one way or another that the risk of death could be mitigated by having combination therapy. So I just wanted to address that specifically.

I believe today the MedGuide is silent to that issue and I don't have a problem with that, but I don't know if anybody else does.

DR. RAPPLEY: Further discussion? Is the committee satisfied, then, that you've had a chance to review the correct package insert? And the agency is satisfied with the current recommendations? Okay, go ahead.

DR. MURPHY: Thank you for your

lunchtime reading.

DR. RAPPLEY: Okay, I think, then, we will shift gears and move to the next medication that we are to review which is modafinil and that presentation -- I've lost my agenda, oh, Dr. Mannheim, yes, thank you.

DR. MANNHEIM: Good afternoon. My name is Glenn Mannheim. I'm a Medical Officer in the Division of Psychiatry Products at FDA. I reviewed the initial submission of modafinil for the indication of pediatric ADHD in 2005. I previously presented the data for modafinil for ADHD with special emphasis on safety to the Psychopharmacological Drug Advisory Committee in 2006, the minutes of which and the briefing document, responses and slides from that meeting are still available on the Web. I've now been asked to present a modified version to the committee to help you form a complete assessment of the safety of modafinil in children and adolescents.

My review will be followed by

reviews by Dr. Farkas of Neurology on the pediatric narcolepsy, BPCA, that will be followed by Dr. Lourdes Villalba, from the Neurology Safety Group who will talk about a safety review of the skin reactions which were identified in my review and Charlene Flowers of the Division of Drug Risk Evaluation will talk about the one-year pediatric exclusivity review. Here's an outline of what I will be covering today. I'll be reviewing the background, the safety database, in the ADHD clinical trial, common adverse events, psychiatric adverse events, other adverse events of note, the rashes, what was discussed at the previous meeting, the potential public health impact, and then some closing comments.

Modafinil goes by the trade name Provigil. It is a central nervous system stimulant. It is manufactured by Cephalon. In 1998 it was approved as a awakefullness promoting agent for adults with excessive daytime sleepiness associated with narcolepsy.

In 2003 it was approved for excessive daytime sleep associated with obstructive sleep apnea, hypopnea syndrome and shift wake/sleep disorder.

In 2006, pediatric exclusivity was granted. In 2006, it was not approved for children and adolescents based on serious skin reactions. And also in 2006, it was not approved for narcolepsy and obstructive sleep apnea hypopnea syndrome in children and adolescents under the Best Pharmaceutical Children's Act based upon lack of efficacy.

The recommended dosing for the adult indication is 200 milligrams once a day. I put in the brackets 2.67 milligrams which is based on a 70-kilogram body mass and I did that to allow comparison with the doses that were used in the pediatric exposures in an ADHD trial.

The ADHD submission was not conducted under the Best Pharmaceutical Act. Children with ADHD six to 11 years of age and

adolescents up to and including 17 years of age were studied. Two doses were studied. Children less than 65 pounds or 30 kilograms got 340 milligrams. Those greater than 65 pounds or 30 kilograms got 425 milligrams. The important thing to note is that, on a milligram per kilogram basis, the highest dose in children less than 65 pounds was 21 milligrams per kilogram compared to the 2.67 milligram per kilogram in adults or about eight times higher than the adult dose.

In children who weighed more than 65 pounds, the highest dose was 14 milligrams per kilogram or about 5.3 times higher than the adult dose. The population which the sponsor studied were children and adolescents with DSM-IV diagnosed ADHD going full-time school. They were based on the CGIS score of greater than four, they were moderately to severely ill. There was minimal comorbid learning differences. IQs had to be greater than 80 and, to note, for the purposes of the

adverse events which occurred, the population was clean in that they excluded psychiatric comorbidities, children and adolescents with psychotic disorder, suicide risk, depression mood, anxiety disorder, substance abuse, stimulant non-responders, those with abnormal labs and those with clinically significant illnesses. There were three Phase 3 studies, two flexible dose studies which were nine weeks in duration, which are Studies 309 and 311 and there was one fixed dose study which was seven weeks in duration which also had a two-week randomized withdrawal which was Study 310.

This slide shows the total number of subjects and doses used in the Phase 3 double-blind placebo-controlled trials. Four hundred and twenty subjects were treated with modafinil and 213 subjects were treated with placebo. Only 358 subjects received the proposed dose of 340 or 425 milligrams.

This slide is a bit busy, but it

shows exposure to modafinil and modafinil metabolized and compares to what one sees in practice with clinical-use doses in adults. What I want to bring your attention to is the exposure to the modafinil sulfone over them as mentioned by the total exposure or AUC. In adults receiving a clinical dose of 200 milligrams, the average AUC is around 40. Going to the higher child receiving 425 milligrams, the AUC of the sulfone is about 250 or 6.5 times higher than exposure seen in adults. Going to the lowest weight child receiving 340 milligrams, the AUC of the sulfone is about 630, or about 16 times higher than that seen in adults with clinical dosing. This cannot be explained by differences in dosing on a milligram-per-kilogram basis. Now, I'd like to look at some of the adverse event date which was seen in my review.

This shows the incidence of two percent of common treatment emerging adverse events in the Phase 3 double-blind placebo-

controlled trials. Insomnia occurred in 27 percent of subjects on drug and four percent of subjects on placebo. Anorexia occurred in 16 percent of subjects on drugs and three percent of the subjects on placebo. Weight loss occurred in four percent of the subjects on drug and one percent on placebo. And skin rashes occurred in four percent of the subjects on drug and two percent on placebo.

Now I want to go over some notable psychiatric adverse events -- included psychosis was seen in five subjects out of -- including the adult wide and open label. The total exposure which I reviewed was 933. There were five subjects who had psychoses. One subject had formication or the ants were crawling all over the skin. And it occurred one day after stopping the drug. There was one subject with command auditory hallucinations with suicidal ideations who had to be hospitalized, with two other cases of hallucinations.

There was one case of -- who had ideas of referential control. There was -- in terms of suicidal events, there were six cases of suicidal events, four occurred during the double-blind placebo-controlled trial. There were no events in the placebo. You'll note that the denominator is a little different here. This is from a separate review of suicidal events done by Dr. Mosholder and he had more data available. There were five people with -- children with ideation and there was one attempt and there were no completions.

Other clinically significant adverse events present; there were two subjects with gastric duodenal ulcers. One occurred in a nine-year old child in open label who developed a severe dehydration with a metabolic acidosis and was found to have extensive ulcerations with a gastritis and was found to have H pylori. The other occurred in an eight-year old in the double-blind who had

nausea and abdominal pain and rash and was found to have a peptic ulcer with duodinitis.

I'm not an expert but it's my understanding it's a little unusual to find this in children less than 12 years of age. There were nine case of syncope seen. One child, eight days after starting the drug -- one week -- there was one child who, a week after having a brachycardia hypertensive syncopal episode had an ECG done which showed AV dissociation with junctural rhythm. There were 24 cases of asthma. There was one subject who was started on the drug and eight days later collapsed at school during gym, stopped breathing momentarily, was given an inhaler and began breathing normally and who was diagnosed as having an acute asthma attack.

There was three subjects who had dehydration. One subject was hospitalized with severe dehydration and a mauricio acidosis with hypoglycemia starting with a

strep throat and there were 16 subjects with evidence of hepato-cellular injury greater than three times upper limit of normal on ALT, AST, or GGT. There were no cases of jaundice or liver failure and there was no significant bilirubin elevation.

I'm now going to talk about the rashes, but keep in mind I'm not a dermatologist. When you look at all the subjects exposed, the rashes were present in five percent of all subjects compared to four percent on modafinil versus two percent on placebo in the Phase 3 placebo-controlled trials. Only one subject dropped out in the double blind placebo-controlled trials which was an eight week study, because of the rash and we'll talk about that case a little more, in a little bit. There were 13 subjects who had rashes which were listed as a reason for discontinuation.

Rashes varied in severity and type. Eight children with rash also had fever. Two

with rash also had elevated liver function tests. Other skin events consisted of possible allergic events in about 22 subjects or 2.4 percent of the patients and consisted of hives, urticaria, facial edema, pruritis, allergic reactions, red lips, eczema with increased LFTs.

I'm now going to talk about some serious skin reaction, primarily erythemus multiforme Steven-Johnson which are usually hypersensitivity reactions to drugs. At the time of the advisory committee, there were two cases which were thought to possibly be EM/SJS. One subject had peeling and blistering over the entire body with lips and urinary tract involvement. The drug was stopped but the rash progressed to peeling, blistering, mucosal involvement over days.

Another child had a maculopapular morbilliform pruritic rash. Again, of note, the drug was stopped and the rash progressed. The child was hospitalized. Other rashes

present -- some of the other rashes; one child had vesicular bullous cheeks with severe lip blisters. There was an unspecified rash in a seven-year old with a positive rechallenge treated with prednisone and benadryl.

Now, I'd like to give you more details about the index case, the child who was thought to have Steven-Johnson. This was a seven-year old Asian male with ADHD treated with modafinil, 425 milligrams over two weeks, developed a fever of 101.9. At day 16 had a sore throat, mild rash. On day 17 the child received one single dose of amoxycillin. By day 18 the drug was stopped. Over the next four days the rash worsened and progressed. On day 19 there were multiple pruritic areas over the stomach and face. By day 23 there was mucosal involvement in two areas, the urethral meatus and the lips which was followed by extensive skin peeling.

On day 30 no new lesions were seen and events resolved. On day 31 the child was

given one dose of modafinil and the itching worsened. On day 44, the child was withdrawn from the study and the rash resolved. This picture -- the photo was not available at the previous Advisory Committee meeting. I'm not a dermatologist but you know, one can see that, you know, the lesions are generalized. They're fairly well circumscribed. There's erythema at the edge. I was told, you know, that some people see blisters, but I can't really appreciate that.

Another subject was a 11-year old female with attention deficit disorder, Turner Syndrome, and nocturnal enuresis who was started on modafinil and developed a fever, abdominal pain, diarrhea and, by day 14, developed a pruritic rash involving the face and chest. The drug was stopped and treated with diphenhydramine. The rash worsened on day 15 and the child was hospitalized for possible SJS. There was no mucosal involvement and the child was diagnosed as

moderate morbiliform rash and treated with hydroxyzine.

What's clear with many of these rashes is there's significant rashes and there's a lot of disagreement among dermatologists what to call them. In this child, this is an eight-year old child with attention deficit/hyperactivity disorder treated with modafinil, developed a fever, rash on cheeks. The rash progressed again. There was severe blistering on the lips. The rash was described as vesicular bullous. The drug was stopped. The child recovered. The time course isn't specified. The child was treated with cephalexin and acetaminophen with codeine.

The Dermatology Division at FDA at the time we did this review, reviewed all the cases of possible rash in this submission and identified 12 cases of concern, or 12 out of 933, with definite -- which they thought were definite or possible erythemus multiforme

Steven-Johnson. Dr. Poris, a reviewer, classified -- said there were two cases of definite EM/SJS, three cases which were consistent with early prodromal EM/SJS and seven cases consistent with -- where there was insufficient information but the history was suggestive of prodromal EM/SJS. Now erythemus multiforme Steven-Johnson is generally thought to be a hypersensitivity reaction and the drugs are generally thought to cause -- the drugs are generally thought to cause SJS can cause other hypersensitivity reactions. Hence, we looked at -- looked for other cases of possible hypersensitivity reaction. And this is the theme which Dr. Villalba will present further when she presents.

One of the cases of interest suggesting a possible hypersensitivity involved a nine-year old boy with a history of sulfamethoxazole trimethoprim allergy who had normal labs and physical at baseline and during the double blind placebo portion of the

trial. The child was rolled into the open label modafinil and after 10 days developed urticaria, facial edema, fever of 99.6 and vomiting. After 14 days there was an elevated ALT up to 17 times the upper limit of normal and an AST up to 10 times the upper limit of normal. After stopping the drug and supportive treatment, the child recovered. As Dr. Villalba will show in the cases she's going to review, there were about 13 cases of hypersensitivity reactions and the mean age of all those children is about 8.6, which is a group with a larger milligram-per-kilogram dose and sulfone metabolite.

You know, of note in going over the rashes, there was also another case -- there was another child with a rash who had a history of sulfamethoxazole allergy and there was another child with transaminase elevation who had a history of sulfamethoxazole allergy. So you know, is cross-sensitivity possible? Maybe.

At the last meeting, we opined what's the potential public health impact if the drug was approved. We -- based on the background rate of one to two per million per year of SJS in the cases which were observed here, which were anywhere from one -- you know, anywhere from one to 12 and there was a range of risks which was possible from .2 to 1.3 percent. And we estimated what the usage would be based on the number of children who take ADHD medications which is about 2.5 million, based on the 2003 CDC study and we estimated a projected market share of modafinil Provigil of 10 percent. And we then tried to estimate what the cases of SJS would occur if this drug was approved.

We estimate that there would be a range, you know, assuming a quarter of a million children switched to modafinil, you know, based on the 10 percent market share, between 500 and 3200 cases based on the incidence of .2 to 1.3 percent and if we took

the mortality associated with Steven-Johnson, you know, in published literature, is anywhere from five to 15 percent, if you take the five percent, I mean, you know, you're talking at least 25 and it can go all the way up to, you know, 162 deaths which are possible, some time post-approval. So the question which we asked was, will labeling work. Dr. La Grenade and co-authors in Food and Drug Administration published a paper in 2005 which related to Cox-2 inhibition, and associated Steven-Johnson epidermal necrolysis and I quote from that paper since I thought it was relevant then and I think it's relevant now. "There is no satisfactory method for determining who is at greatest risk for developing drug-associated SJS and TEN and hence, preventing it, short of avoiding drugs altogether. There has been a single study suggesting that early withdrawal of the agent at the first sign of the illness may improve the outcome. Although this intuitively makes sense, the study needs

to be replicated. Even if it is proven to be correct, in practical applications, will be limited because it is very difficult to identify the very earliest lesion in a timely manner because of the rapidly progressing nature of this illness and the non-specific features of its prodrome".

In the cases we observed with modafinil in this experience, no deaths occurred. In two of the four cases which we discussed, a rash progressed, there was progression of the rash after the drug was stopped. Whether stopping the drug at the first sign of a rash, whether that will always work is speculative and, you know, it may be a gamble.

Okay, so this was taken to the previous Psychopharmacology Advisory Committee on March 23rd, 2006 and we asked them to review and discuss the safety and efficacy of modafinil in the treatment of attention deficit/hyperactivity disorder in children. I

think Dr. Rappley was there at the time and the committee voted at that time that modafinil was shown to be effective in the treatment of attention deficit/hyperactivity in children; however, it did not have the same effect size as with other stimulants.

On the question of safety, the committee voted 12 to one that modafinil was not safe, based on the available information and they concluded that at least one of the cases was definitely SJS. There was discussion of the risk -- I'm not good at this. There was discussion of the risk and there was a suggestion at the meeting to try to cap the risk at 3,000 using -- 3,000 at one to -- 1,000 using a 3,000 patient study.

There was discussion of a box and then afterwards, the FDA requested updated information on all skin and multi-organ hypersensitivity reactions in children and adult clinical trials and post-marketing experiences with modafinil and this

information was updated in labeling and Dr. Villalba will talk about the bolded warning in the labeling and that's it. Thank you.

DR. RAPPLEY: Thank you, Dr. Mannheim. Dr. Farkas?

DR. FARKAS: Hello, I'm Ronald Farkas from the Division of Neurology Products. I'm going to be talking about the pediatric exclusivity studies. There was one placebo-controlled trial conducted. It was a narcolepsy trial in patients age five to 17 years old. It had 165 patients with narcolepsy on modafinil or placebo, for six weeks. There was also a 12-month open-label extension to that study.

There was a study planned in obstructive sleep apnea hypopnea syndrome. That study was aborted due to low enrollment. Twenty-six patients were enrolled in that study on modafinil or placebo for six weeks, 26 patients on modafinil and then additional patients on placebo, plus 12-month open-label

extension.

There were also two open-label studies, a 12-month open label study with 148 patients, with 132 with narcolepsy and 16 with obstructive sleep apnea and a six-month open label study with 91 patients with narcolepsy and -- or obstructive sleep apnea. The placebo-controlled narcolepsy study was a multi-center, double-blind, placebo-controlled randomized study of modafinil at three different doses, 100, 200 and 400 milligrams per day. The 100 milligram per day corresponds roughly to the adult dose, to the approved adult dose and then we just heard about the ADHD study which was about 400 milligrams, a little bit more complicated dosing scheme for the ADHD study but basically there were 40 patients in this controlled study who were on doses that were similar in the control trial period to the ADHD study.

There were 123 modafinil patients in total and 42 placebo patients. The co-

primary efficacy endpoints were change from baseline to final visit and multiple sleep latency tests and proportion of patients with improvement on a seven point clinical global impression of change scale. The efficacy outcomes were negative. There was no statistically significant differences favoring modafinil in prolonging sleep latency really MSLT or in perceptions of sleepiness, the DCIC endpoint. The aborted obstructive sleep apnea study was also multi-centered, double-blind, placebo-controlled, randomized, parallel group study of modafinil with the same doses, 100, 200 and 400 milligrams per day.

The study was aborted because the sponsor demonstrated that not enough patients could reasonably be enrolled. The study is not in the final written request but the patients who were enrolled, who were evaluated for safety only and the results were included in the supplement.

The labeling that resulted from the

exclusivity studies is shown here. Under indications and usage, the label states that there are no pediatric indications and, in the pediatric use section, the label states that safety and effectiveness in pediatric patients below age 16 have not been established and then it describes the studies. In the controlled six-week study, 165 pediatric patients, age 5 to 17 years, with narcolepsy, were treated with modafinil or placebo. There were no statistically significant differences favoring modafinil over placebo in prolonging sleep latency as measured by MSLT or in perceptions of sleepiness as determined by the clinical global impression clinician scale.

These are the safety results. For the exclusivity studies, there were 270 exposed patients. There were no deaths. Serious adverse events in the control trial, in the narcolepsy trial, were one case of viral encephalitis in a patient on 400 milligrams per day and a case of appendicitis

in a patient on placebo.

In the open label studies, which included mostly narcolepsy patients and then a few patients with obstructive sleep apnea, there was one patient with a suicide gesture who was taking 400 milligrams per day and one patient with weight loss, who was on 100 milligrams per day. These are the adverse events, the non-serious adverse events that were more common in the drug arm in the controlled study; insomnia, six percent versus two percent, abdominal pain, seven percent versus zero percent, pharyngitis, sinusitis, three to four percent versus zero percent, dysmenorrhea, five percent versus zero and also included here is hostility, irritability even though these were about equal in the control trial, in the open label study, there were more cases seemingly of irritability and hostility -- there were 13 cases -- than might be expected in this population, but it was difficult to clearly ascribe that to drug.

Other psychiatric adverse events that occurred were abnormal thinking, hallucinations, agitation, emotion ability and hypomania. This is a case of hostility. An eight-year old girl with narcolepsy. She was on 200 milligrams titrated to 400 milligrams per day. On day 55 she had behavior outbursts, coded as hostility. The modafinil dose was halved on day 56 and then eliminated on day 69 and the event resolved on day 88.

This is the case of suicidal ideation. It's a patient who didn't previously have psychiatric background. It's a 10-year old girl with narcolepsy treated with 100 milligrams per day titrated to 400 milligrams per day. She threatened to cut her wrists on day 75. No psychiatric treatment was given. Modafinil was continued first, then withdrawn on day 144.

Safety concerns that were placed on the modafinil label in the pediatric use section for psychiatric and nervous system

include possible worsening of Tourette syndrome, insomnia, hostility, increased cataplexy increased hypnogogic hallucinations and suicidal ideation. In the pediatric use section, it states, "Safety and effectiveness in pediatric patients below age 16 have not been established. Serious skin rashes, including erythemus multiforme major and Stevens-Johnson syndrome have been associated with modafinil use in pediatric patients." And then it refers to warnings which Dr. Villabla will talk about in more detail.

These are additional safety concerns in the pediatric use section. In the controlled and open label clinical studies, treatment-emergent adverse events of the psychiatric and nervous system included Tourette syndrome, insomnia, hostility, increased cataplexy, hypnogogic hallucinations and suicidal ideation. Then, in addition, there was a case of transient leukopenia which resolved without medical intervention and then

describing the cases of dysmenorrhea in more detail and that was a greater number in the control trials. And that's all.

I believe we're going to take clarification questions now.

DR. RAPPLEY: Thank you. So we are open to clarification questions for Dr. Farkas and Dr. Mannheim. Dr. Daum?

DR. DAUM: The patient with viral encephalitis, can you be more specific as to what virus and how that was proven?

DR. FARKAS: Yes, that was a not completely clear case. Let me read you a little bit of it. I think that would be the best. This is a six-year old patient titrated to 400 milligrams of modafinil by study day five. "On day 12 he had nausea and vomiting in association with fever. He had pharyngitis on day 13, received Amoxycillin, throat cultures were negative. On day 16 he was hospitalized due to somnolence and confusion. He had elevated ammonia, hypophosphatemia.

On day 17 he had seizures, delirium and hallucinations. He had extensive work-ups, cerebral spinal fluid, neurological exams, serum chemistries, et cetera, CT of head and there were no positive findings."

There were also no outbreaks in the community of varicella or influenza. The only -- ultimately, the only abnormal hematological finding was borderline low hematocrit. The case was carefully reviewed and consultants, specialists concluded that this was a case of viral encephalitis.

DR. DAUM: Any idea what the basis was? I mean, it doesn't come over from this --

DR. FARKAS: Yes, I don't think I can add anything more.

DR. McNEIL: We don't have any additional information on that. Unfortunately, that's the information we were given. The sponsor was concerned at the time and called multiple consultants and at this

time, we also had some concern about the sulfone metabolite, so there was an issue of whether this was a drug reaction or a viral encephalitis. I think we've got some representatives, if you guys would like to chime in from Cephalon.

CEPHALON REP: No, I really can't add very much else except to say this case was extensively reviewed. I think of note there were no liver function abnormalities which was carefully looked at too, and that excluded some diagnoses and the final diagnoses by the consulting physicians in the hospital was a viral encephalitis. I really can't add much more than that.

DR. RAPPLEY: Thank you.

DR. MANNHEIM: I mean, I remember looking at it myself and I remember there was a question of aspirin prior to that and the question of rye syndrome was raised with this case.

CEPHALON REP: Rye was raised by

with normal liver function tests it was ruled out.

DR. RAPPLEY: Dr. Gorman and --

DR. DAUM: I guess just a final comment, I'm not going to take away from this that the drug causes viral encephalitis from this case. I mean, I'm not impressed that there's any viruses around and it doesn't have a biologic plausibility piece for me anyway. Surely, the child was encephalopathic from something but to say it was a virus doesn't -- I didn't hear that from anything that was said.

DR. RAPPLEY: Dr. Gorman?

DR. GORMAN: In a study of narcolepsy I was a little confused by seeing insomnia as an adverse event. How is that coded versus a super-therapeutic event? I just -- I'm having trouble with that as an adverse event.

DR. FARKAS: Right. Well, I think that it's a difference between the -- I

suppose when the patient is insomniac. Since it's increased in the drug arm, it's likely the result of the drug. And we have indication that, you know, potentially the drug could be doing something. Also, it didn't have proven efficacy.

DR. GORMAN: So that I understand, so you're telling me, when their insomniac they want to sleep but they can't, as opposed to keeping them awake when they want to stay awake.

DR. FARKAS: That's correct. I mean, I think that you're right, that that adverse event could be, if you will, a sign of possible efficacy.

DR. RAPPLEY: Dr. Hudson?

DR. HUDSON: In the randomized exclusivity study that was aborted, what were the issues about not being able to enroll? Was it patient or potential participant or was it provider-related? Do you have the details?

DR. FARKAS: It's the obstructed

sleep apnea condition is rare in the pediatric age group and so they couldn't enroll enough patients.

DR. RAPPLEY: Dr. Malone?

DR. MALONE: I wanted to ask for some clarification of Steven-Johnson. At the ADHD Advisory Committee there was a slide where it said there were two cases, then there were all these possible cases. But it looks like this has been changed to one case or -- I don't know what's happened to the cases of Stevens-Johnson, how many they think there are now and how many possible ones there might be.

DR. FARKAS: Well, I think one thing, too, is that you'll hear more about that from Dr. Villalba.

DR. MANNHEIM: The briefing package which was -- which I remember suggested there were two cases. I understand that there's a lot of disagreement about what actually -- there's been a lot of arguing about the numerator, what is actually a case, what is

not actually a case. After the meeting, everybody agreed that there was one definite case. And the other case, it was uncertain from what I recollect.

DR. RAPPLEY: Dr. Ward?

DR. WARD: My question had to do with the same issue. I'm not a dermatologist and it's been a while since I looked up a definition of Stevens-Johnson, but what I found was people recommending having two mucosal areas involved with lesions, not just one, but it does seem to be pretty specific for hypersensitivity reactions manifested in the skin and I guess what I'd really like would be for those at the Agency to give us some evaluation of how they view the occurrence of Stevens-Johnson syndrome after these drug exposures: about its linkage to the specific drug, is it considered absolutely hypersensitivity reactions to the drug and so on. By the way, it's interesting the sulfone reaction because its structure has the sulfone

group and then a little short side chain and then another nitrogen, looking actually relatively similar to sulfonamides.

DR. RAPPLEY: And that was the basis of our discussion at the last meeting about this, yes. Maybe we should listen to the next presentation and then go back to the skin reactions. I think because Dr. Farkas and Mannheim will still be here. So why don't we do that?

Could I just ask one question about the efficacy study since we last met? Am I clear that there have been additional studies for efficacy on narcolepsy and they have shown no benefit from the medication?

DR. McNEIL: Since the pediatric -- the psychopharmacology is the one I last remember you being at, that the narcolepsy study was being reviewed at that time.

DR. RAPPLEY: And so that's the only additional information we have about efficacy, whether narcolepsy or ADHD or

anything else? Our new information since that point in time is about narcolepsy and it is that it has no clear evidence of benefit.

DR. McNEIL: That is correct.

DR. RAPPLEY: Okay, thank you. Dr. Joad.

DR. JOAD: Yes, as I recall reading the background material, the significance was very close to significant in that efficacy part, if I'm remembering it right. Is that right, and what do you think about the power of the study? Was it just underpowered or --

DR. McNEIL: For the narcolepsy trial?

DR. JOAD: Maybe I'm remembering it wrong, but I thought the P values were like .053 or something. They weren't officially statistically significant, but they were suggestive.

DR. McNEIL: I believe they were suggestive. I don't remember the exact number, ma'am.

DR. RAPPLEY: Okay, Dr. Newman, did you have a question?

DR. NEWMAN: I just -- I was going to bring this up later but since Dr. Joad brought it up, just it would be much more informative when the FDA adds labeling about an ineffective study, to not just say it wasn't statistically significant, but actually provide the point estimate and the confidence interval for the effect, so that we can see what happened because it just throws away a lot of information just to say, you know, it was not statistically significant.

DR. RAPPLEY: When we look at our material in our packet, there was a review done by Dr. Katz which shows significant P value of .06 for trend test of MSLT, I'd like to know that that means, and with the CGIC of 0.052. Any other questions about efficacy before we continue with the presentation about the skin conditions? Okay, Dr. Villalba?

DR. VILLALBA: Yes. I'm here. My

name is Lourdes Villalba. I am a Medical Officer in the Safety Team in the Division of Neurology Products and I'm going to give you a follow-up on the serious skin reactions and hypersensitivity reactions with modafinil. This is an overview of my presentation. First of all, I will go very briefly over what Dr. Mannheim has presented and then I'm going to show you an analysis of updated clinical trial data from pediatric and adult patients and also the analysis we did with the post-marketing data and what we did with all this information.

DR. DAUM: Dr. Villalba, could you adjust the microphone?

DR. VILLALBA: Oh, yes, I'm sorry. You didn't hear me? Is this okay now? Oh, okay. Is this good? Oh, okay, thank you.

Okay, this is what was presented at the Advisory Committee meeting in March 2006 and there were three cases of serious rash and one multi-organ or systemic hypersensitivity

reaction. Because of these findings in the ADHD database by Dr. Mannheim, a dermatologist did an evaluation of all cases that could be Steven-Johnson syndrome or erythema multiforme in the available database. And he found two cases of definite either Steven-Johnson syndrome or erythema multiforme. That's why you have two cases there. One was Steven-Johnson, because he looked at EM or SJS the same thing. And because as you know, these many experts considered these the same manifestation of a spectrum of diseases that go from erythema multiforme from a minor, major Steven-Johnson syndrome and necrolyzes and while other experts think that there is a difference between Steven -- I mean, erythema multiforme and Stevens-Johnson and toxics necrolyzes.

In any case, there were two definite cases but there were 10 additional cases that could be early prodromal EM or SJS and there wasn't sufficient information but

the history was suggestive of prodromal EM or SJS in seven patients. And there were no cases on placebo. And we have to point out that many of these cases have very little information to work with. And so you have to -- and even having full information, sometimes people don't get to agree that it's definite case or not. But particularly working with little information, it's hard.

And the following slides are actually the same slides that Dr. Mannheim showed to you. These are the three cases of this year's rashes. The first case in the seven-year old Asian male that he showed the picture, that was consensus that this was a definite case of Steven-Johnson syndrome. The other two cases, the diagnosis was controversial. It was thought that it could be morbilliform rash or erythema multiforme in the following case. The point here is that, even if they are difficult to distinguish or make the definite diagnosis, these were

serious rashes, they were nasty rashes and a couple of them required hospitalization.

The other case here is the case with the nine-year old who had a history of sulfonamide allergy and developed a rash and increased LFTs and was considered to be consistent with a multi-organ hypersensitivity reaction. And I want to point out that, yes, this patient had an allergy to sulfa, but we are not sure of the role of the sulfone metabolite in these rashes and hypersensitivity. It's a sulfone, it's not a sulfonamide and also there are certain patients that have a genetic predisposition to have reactions to many drugs. So not necessarily it implies that there is cross-reactivity, but we don't know. And another point with these cases is that all of them continue to progress despite stopping the drug, at least for a few days. So this is not something that you stop the drug and the rash goes away immediately and there is no well-

known risk factors for developing rash at least for the evaluation of these cases. Therefore, this data was extensively discussed and there was again, an agreement that one of the cases was definitely Steven-Johnson syndrome but there were other serious rashes and some rashes that were -- could not be defined because of insufficient information. But there were no cases on placebo. And based on the background rate of Steven-Johnson syndrome which is very low, one or two per million patient-years in the high mortality rate which is five to 15 percent, the panel voted against approval of modafinil in ADHD and recommended a large study to quantify the risk in the pediatric population.

Now, I spoke about all -- what was already presented by Dr. Mannheim. Now, I'm going to show you the other analysis that we did and because we requested the sponsor to submit updated trial data, clinical trial data, on all skin and multi-organ

hypersensitivity reactions in all pediatric and adult clinical trials of modafinil and also from adult clinical trials with R modafinil. R modafinil is the R-enantiomer of modafinil and has been recently approved for the adult indication but we do not have any data from pediatric patients. And we also looked at post-marketing data. We looked at the FDA adverse event reporting system. We asked the Office of Surveillance and Epidemiology to look at these cases of serious hypersensitivity reactions in -- skin reactions for both children and adults and we also asked the sponsor to provide post-marketing data from their database and also from some European epidemiologic studies on severe cutaneous adverse reactions.

Now, I'm going to discuss the clinical trial data from pediatric and adult patients. This is the updated exposure and this table shows on the left-hand side the different ages, zero to 16 for pediatric age

and 16 and above for adults and these 16 and above include some patients for whom we didn't have the age and it shows the exposure in placebo controls trials in all modafinil trials. That includes the patients on placebo control. And I want to point out to the denominator that we are working with here is 1585 patients.

Sorry. I also want to mention that these updated exposures includes all indications ADHD, narcolepsy, and obstructed sleep apnea and the doses involved are 100 to 425 milligrams a day. This is a summary of the skin reactions in pediatric trials. There were no deaths. There were three serious reactions, the ones that we already discussed earlier and we specifically looked at cases of rash that led to these continuation. There were 13 cases in which rash led to this continuation. That makes .8 percent but roughly one percent of the patients because most of these cases came from the placebo

control studies.

This is not unexpected in the way most of these open label were extensions to the placebo control and Stevens-Johnson is expected to occur within the first weeks of treatment. These tables -- I need to clarify that every time -- this table, every time that I say "rash" in all these slides, I'm referring to skin reactions that may represent drug hypersensitivity reactions. I'm not including skin reactions like dermatitis or chronic eczema and I am not including patients who had some other adverse event and also had a rash but discontinued because of something else like a duodenal ulcer.

Therefore, this is a summary of the 13 patients in whom rash led to discontinuation. There were nine male, four female, ages six to 12 with a mean of 8.6 years and I want to emphasize that these trials were -- included patients up to 17 years of age but the reactions all appear in

the six to 12 group.

The doses were 100 to 425 with a mean of 250 milligrams a day and the relative data form set was 13 days with a range of four to 24. This is a summary table of the cases of rash. At least there were no reports of other involvement or fever in these cases. There are six cases. I am not going to go into detail but if you have any questions. On the left-hand side you have the patient ID. In the second column is a description of the demographics in the case.

In the third column, you have the milligrams -- the dose by day and the last one is the onset of the event. None of them were serious but they required discontinuation in treatment in most cases. And this is the table that includes the other seven patients and these patients have rash and something else. Actually all of them had fever. Two had leukopenia and one had the increased transaminases and this was the case consistent

with the multi-organ hypersensitivity.

The cases in yellow are the ones that were included already in the previous slides, and the last one, the bottom one, is the index case that was agreed at the Advisory Committee that it was Stevens-Johnson syndrome. Now, I'm going to show you the data from the adult clinical trials. We looked at modafinil trial and R-modafinil trials and as you can see, there is no difference between modafinil and placebo and the incidents rate is very low. In our modafinil, again there is no difference between the rate of reactions that led to discontinuation between modafinil and placebo, although they are higher than in the modafinil trial. So we cannot conclude anything -- we cannot make comparisons of to modafinil from this data.

In summary, in the pediatric population, there was a higher rate of discontinuation due to skin reactions in

modafinil, including three cases of serious rash, none in placebo. In the adult population, there were similar, the rate of discontinuation for modafinil and versus placebo and there were no cases of serious rash and so it is -- we need to be cautious in comparing trials and cross comparing but the data suggests that there is a real signal for pediatric -- for the pediatric population, while in the adult population, it's not serious.

Now, I'm going to show you the post-marketing data. We asked the Office of Surveillance and Epidemiology to look at cases of serious skin reactions and they found one case of Stevens-Johnson syndrome, but this was the case that had already been reported from the clinical trial, so we usually would not consider this case as a spontaneous report.

And there was also a case of DRESS syndrome, Drug Reaction with Eosinophilia Systemic Symptoms in a 15-year old patient.

And I'm going to talk about it in a minute. In the adult group, there were four cases of SJS including one case in a 17-year old female. And actually this analysis for the potential multi-organ hypersensitivity reactions we looked at the data provided by the sponsor because we asked them specifically to look at potential reactions like these and it's hard to look -- to do an eye and ears search of these reactions because there is no one term for them and these usually have fever, rash and some major organ involvement like lymphangiopathy, I mean, lymphangiopathy is also very common in major organ like nephritis, pneumonitis, myocarditis, et cetera.

So based on the information that the sponsor had provided that were like probably 15 cases that fulfilled this case definition, we found seven that could be consistent with a multi-organ hypersensitivity reaction and one of those reactions was a

fatal as in a myocarditis. Actually, this case was recently published in the New England Journal of Medicine in the last issue.

Also, we asked the Office of Surveillance and Epidemiology to look at cases of angioedema because I forgot to mention but in the clinical trial data for armodafinil there was one case of angioedema and one hypersensitivity and one anaphylactoid reaction. So we thought that we wanted to see if there was anything for modafinil. And there were two cases, actually this is low exposure of this drug.

I'm going to talk a little bit about the DRESS syndrome and then I'm going to go back to the reporting rate of Stevens-Johnson syndrome and I know there is not -- it's kind of in the way, but I would like to mention this case in particular because it's a typical case of DRESS.

This was a 15-year old male who received modafinil for five weeks up to 400

milligrams a day for treatment of ADHD. And he developed a maculopapular rash with fever, myalgia, received some ibuprofen and soon after he developed multi-organ failure with the eosinophilia, so the same person, had a skin biopsy and the patients was considered with DRESS syndrome. He ended up in the ICU, requiring mechanical ventilation and cardiovascular support but the good thing is that improved. He was treated with IVIG corticosteroids and GI support and he improved and was extubated and everything came down to normal. But this is a typical case; however, there is one confounding factor here that is the use of ibuprofen that has been addressed too.

Now, going back to the reporting rates, this is a BC table. Let me orient you a little bit here. On the left column we have the pediatric age or adult age and overall which includes both, plus the patients for whom we don't have the age. And the second

column is the number of events and in parenthesis you have the case that was found in the clinical trial.

The third column is the number of prescriptions from the period of January 2002 through December 2006. The next column is the patient exposure in patient years and the last one is the reporting rate per median patient years.

And I want to point out how small is the exposure here in the pediatric populations; 1.8 percent of the total prescription and I mean that's good because this is not approved in pediatric patients, so there is a limitation for these database that there are very little exposure to the pediatric population.

And the reporting rate is either zero or 82 per million patient years if we include that patient from the clinical trial. However, in adults, the rate is 6.1 per million patient years which is above the

background rate of one to two per million patient years.

And the overall rate is above and it's driven by the adult data. So we do have kind of a contradiction here from the clinical trials. We saw a strong signal in the pediatric clinical trials, nothing in the adult trials. Here we have this mild signal, I would say in the post-marketing adult data and no signal in the pediatric age. But in this case we need to put more weight on the clinical trial data.

And there is also some post-marketing epidemiologic data from Europe and this is coming from the sponsor data from three studies. For severe cutaneous adverse reactions, they involve approximately 60,000 patients and the -- actually we didn't get the exact exposure by age, but the sponsor estimated that approximately three percent of these patients were younger than 19 years. And this is extrapolated from US usage data.

In any case, there were no cases of severe cutaneous reactions in these trials, but again, because of the small exposure, we cannot rule out an increase of Stevens-Johnson syndrome in the pediatric population.

So this is a summary of what I just said, that in clinical trial data, there is a difference between modafinil and placebo for the pediatric age, not for the adult age. The post-marketing data there seems to be an increase rate over background for the adult population.

But actually, if you remember, there was one patient with Stevens-Johnson who was 17, so if we use a different cutoff date, if we include this patient in the pediatric population, that will increase the rate to very much above normal. So with this information what we did is we did request the sponsor to conduct a large study to further evaluate the risk of serious reactions. However, this is not a mandatory study. If

they want to pursue the pediatric indication, yes, we do have authority to mandate these to be conducted, otherwise, we can't. But most importantly, we ask for -- we updated the label and we are working with the sponsor in developing a risk minimization action plan. And these are the highlights of the new labeling that was approved in August 2007 and it specifically mentions that serious rash, including Stevens-Johnson syndrome occur, can occur with modafinil. It's a bolded warning and also includes data from the pediatric and adult clinical trials and post-marketing experience and it specifically mentions that Provigil is not approved for any pediatric indication.

The risk of angioedema and anaphylactoid reactions and multi-organ hypersensitivity reactions have also been included and these are parts of the label that I'm not going to read all of it but I just want to show you what I highlighted, the

serious reactions, including Stevens-Johnson. Modafinil is not approved for use in pediatric patients. The description in the clinical trial data, post-marketing data, and that there is no reliable way to predict when this can occur, therefore, discontinue modafinil at the first sign of rash unless the rash is clearly not drug related. And also I think this is a very important part of the actions taken by the FDA is working, developing a risk immunization action plan. We have asked for a 15-day expedited reports of serious skin and hypersensitivity reactions and this is important because now that these events are labeled, the sponsor doesn't need to submit them right away. They can come with periodic reports or annual reports, so if we see that this is being used off-label in the pediatric population, then we are starting to see many of these reports, that is a concern that we can catch earlier then in the annual reports.

We have also requested improvement in the reporting and follow-up of all these cases. A letter has been already sent to many physicians and they specifically highlight the serious skin reaction including Stevens-Johnson and multi-organ hypersensitivity. Provigil is not approved in the pediatric population, stop Provigil if rash or hypersensitivity develop and it is also important that there are patient and physician education on materials and regular monitoring of the -- and evaluation of the RiskMap. Also the first FDA drug safety newsletter of September 2007 features the issue of serious skin reaction with Provigil and here is the website.

In summary, Dr. Mannheim raised the issue of serious skin reactions including SJS in the pediatric population. That was taken to an advisory committee, that was followed by additional analysis of serious skin reactions in trials and post-marketing data. We -- to

date, modafinil is not approved for any pediatric indication and the label was updated and a RiskMap is under development. This is it.

DR. RAPPLEY: Thank you very much. Open for clarifying questions? I'm sorry, not reading my agenda again. Dr. Flowers, thank you. Dr. Malone?

DR. MALONE: I still have some question about clarifying Stevens-Johnson. At the previous advisory committee slide, there were two definite cases. Then somehow, I guess in one of the letters here, there was one definite case and then when you look at the labeling, there is one possible case. So it somehow changed from two definite to one possible over time and I don't know, how would that happen?

DR. VILLALBA: At the advisory committee there was one -- I mean, the FDA dermatologist thought that there were two definite cases of EM or SJS and I think that's

the confusion. But the advisory committee after discussion there was agreement on one case and the other two were controversial.

DR. MALONE: It says possible.

DR. VILLALBA: In the labeling.

DR. MALONE: Yes, in the labeling it says possible.

DR. VILLALBA: Well, because after the advisory committee there were additional discussions with the sponsor and the sponsor has provided expert data supporting that this is not true Stevens-Johnson syndrome, but erythema multiforme major, atypical erythema multiforme major which is slightly different, maybe some kind of symptom distinction although erythema multiforme major is -- there is more chance that this could not be associated with the drug because -- but still 30 percent of the cases could be drug related. So --

DR. RAPPLEY: I read here, though, on the new Provigil labeling under warnings,

"serious rash requiring hospitalization and discontinuation of treatment has been reported in adults and children in association with the use of modafinil". And the warning is serious rash including Stevens-Johnson. Are you looking at a different --

DR. VILLALBA: Yes, I think he's referring to the description of the clinical trial, but --

DR. MALONE: Down below in the paragraph.

DR. RAPPLEY: In the paragraph below, okay. Dr. Flowers, thank you.

DR. FLOWERS: Okay, I'm the final talk of the day and we can get through this. My name is Charlene Flowers. I'm a safety evaluator in the Office of Surveillance and Epidemiology or OSC in the Division of Drug Risk Evaluation or DDRE and the primary objective of my talk is to summarize the case reports from the Provigil one-year post-exclusivity adverse event review.

You've just listened to several talks from the speakers about the pre-marketing clinical trial data but my talk is mostly focused on the post-marketing spontaneous data from the Adverse Event Reporting System database or the AERS database. In my overview, I will cover a summary of the adverse event reports from the -- that were completed by the Office of Surveillance and Epidemiology for Provigil from its marketing date in December 1998 through April 2007 and following that I will summarize case reports from the pediatric post-exclusivity review.

First off, I will summarize the adverse event reviews for Provigil that were completed by the Office of Surveillance and Epidemiology and these reviews are based on spontaneous reports from the AERS database. And for this review -- for these reviews primarily, the request for the reviews were from the Office of New Drugs or OND or either

they were reviews that were generated from routine post-marketing surveillance of the Adverse Event Reports from the AERS database by the safety evaluators in the Office of Surveillance and Epidemiology.

This is a list of the categories of the adverse event reviews by the Office of Surveillance and Epidemiology for Provigil since its approval and they were the reviews in the categories of dermatology, hematology, hepatology, psychiatry, maternal exposure, drug abuse, angioedema and anaphylaxis.

So we'll start off with the skin, the dermatology reviews. And because the OND, the Office of New Drug identified a case of Stevens-Johnson in the clinical trials, they requested that the Office of Surveillance and Epidemiology review the spontaneous database for additional post-marketing cases of Stevens-Johnson syndrome in all age groups.

So the initial review was done in September of 2005. At that time we identified

four cases of Stevens-Johnson syndrome and that included the seven-year old Asian patient that you've heard lots about today and in addition, the other three cases were not very well documented. Because there was so much discussion around that seven-year old Asian patient, subsequent updates were requested and the first update was done in July of 2006. At that time, there were no new cases of Stevens-Johnson in the database. We did an additional update in February of 2007. At that time, we identified two cases; one case of drug rash with eosinophilia and systemic symptoms and a case of Stevens-Johnson syndrome. And this case happened to be in an adult female. Now, I'll come back and I'll talk about the EuroSCAR study but first I'll show you; this is the same picture that you've seen before of this Asian young boy, the seven-year old boy who experienced Provigil associated Stevens-Johnson syndrome and I put it here because it was also described in the OSC review.

In addition, I put a picture of the 49-year old female that we received that experienced Stevens-Johnson during her course on Provigil. So continuing with the dermatology reviews for serious skin, the Office of New Drugs asked our epidemiologist to review the EuroSCAR study and I think that you heard a little bit about that earlier and the epidemiologist concluded that the study was under-powered to identify any cases of serious skin events, including Stevens-Johnson syndrome.

As a result of the clinical trial data as well as the post-marketing data, the Provigil labeling was modified to include warnings, bolded warnings, of serious skin reactions, including Stevens-Johnson, toxic epidermal necrolysis or TEN, and multi-organ system hypersensitivity reaction, such as DRESS. In addition, this labeling was extended to a similar product the R enantiomer of modafinil which the brand name is Nuvigil

or Armodafinil, has the same labeling.

When we move to hematology reviews, again, there was a request from the Office of New Drugs, because during clinical trials, they identified a case of neutropenia and so there was a suspicion that -- for this event and so they asked that we search the AERS database for additional cases. The first review was done in October of 2000. At that time we identified only a few cases in adults and no cases in children.

Because of the nature of this event, there were several updates requested, again in August of 2003 and then again in August of 2005. At that time, we identified no new cases and still no cases in children. And the current Provigil product labeling is -- has a list in the adverse event section for agranulocytosis.

Again the Office of OSE received a request from OND because they wanted our comment on a case of what they thought was

potentially a case of hepatotoxicity in a six-year old boy who had vomiting and convulsions. However, the reviewer concluded that the event was likely related to viral etiology so there was no regulatory action and no recommendations for label changes.

We move to the category of psychiatric reviews. And actually, the impetus for these two big major reviews, I'll have to give you a little bit of background on this. In early 2005, there was a pediatric exclusivity review -- well, actually before that. During routine post-marketing the surveillance, one of the safety evaluators in the Office of Surveillance and Epidemiology identified cases of potentially psychiatric events with Ritalin and at the same time there was a pediatric exclusivity review that we were completing for Ritalin and at that time, those same psychiatric events came up. And then later on in the year, in June of `05, that pediatric review was discussed at the

pediatric AC at that time and maybe some of you are familiar with that and at that time, the committee recommended that the entire class of products to treat attention deficit/hyperactivity disorder be systematically reviewed for psychiatric events. As a result of that, we completed -- and in March of 2006 there were two major reviews conducted by the Office of Surveillance and Epidemiology, well not conducted but the first review was done utilizing the adverse event or the spontaneous data from the AERS post-marketing data and the other was a review of clinical trial data by Dr. Andy Mosholder. And both of these reviews systematically looked at the entire class of drugs to treat ADHD including Provigil, because it was believed that the drug would be useful in the treatment of ADHD.

As a result of the clinical trial data and the post-marketing data, the psychiatric events including things like

psychosis, mania, suicidal events, and aggression, were put into warnings in the Provigil as well as Nuvigil labeling and also extended to warnings in six other ADHD products.

The Office of New Drugs identified during a clinical trial review, a case of -- a fatal case of intrauterine growth retardation and asked that we look for additional post-marketing cases in the AERS database. And the case that we identified was the same case that was identified in the clinical trial data. And a case identified at birth a child who had the femur lymph measurement was less than the stated gestational age and the head circumference was in the fifth percentile. The baby later died because of respiratory distress and severe intrauterine growth retardation related to prematurity.

As a result of the reviews both the clinical trial reviews and post-marketing reviews, the Provigil and Nuvigil product

labeling characterizes this case of growth retardation in the pregnancy sections of the labeling. The FDA controlled substance staff requested that we again look in our database for reports of potential drug diversion because Provigil is a Schedule 4 category drug according to the Federal Controlled Substance Act and they suspected cases of drug diversion. So they asked that we look through the database for cases of all ages for any misuse or drug abuse potential with Provigil. There were no cases identified of drug abuse, misuse or addiction, and so, therefore, there was no regulatory action.

From the clinical trial data, during the review for Nuvigil which was approved earlier this year, I think it was in June of 2007, the Office of New Drug identified cases of angioedema and anaphylactoid reactions during that trial and extended a request to the Office of Surveillance and Epidemiology to look at

spontaneous reports for all ages for these hypersensitivity reactions. In fact, we identified cases of angioedema, a few cases of angioedema but no cases of anaphylaxis. So based on the clinical trial data and the post-marketing data, the Provigil and Nuvigil labelings were modified to include warnings for angioedema and anaphylactoid reactions and you've heard that prior.

So actually, that concludes the summary of the adverse event reviews that we've done since market approval of Provigil, so now I'll move to summarize case reports from the Provigil pediatric exclusivity review of adverse event reports that have been received at the FDA since exclusivity was granted to Provigil as of March 21st, 2006 through April 21st, 2007. But before I summarize the cases I'll give you a little background of the Provigil drug use and that gives you some perspective concerning the population that's prescribed Provigil.

Approximately 2.3 million prescriptions are dispensed or nearly 600,000 patients received a prescription during April 2006 through March 2007. Children ages 17 years and less accounted for approximately two percent of that, and that being nearly 51,000 prescriptions or 15,000 patients of total use.

In terms of prescribers during the exclusivity period, psychiatrists were the most common prescribers with 27 percent of dispensed prescriptions followed by general practitioners, family medicine and DO's with 17 percent and neurologists about 15 percent. Pediatricians accounted for less than one percent of the total prescribing for Provigil. And there was no use recorded for pediatric patients during the post-exclusivity period, that being April 2006 through March 2007 from office-based physicians that were surveyed. In terms of the indications, the most common indications for use in the office-based practice settings for pediatric patients, ages

newborn through 17 years during the post-exclusivity period, April 2005 through March 2006, were attention deficit disorder, cataplexy and narcolepsy, major depressive disorder, a single episode and in parenthesis, the ICD-9 code was how they captured the indication.

In contrast, the most common indications for use recorded for adult patients, those patients greater than 18 years old during the post-exclusivity period, April 2006 through March 2007, were malaise and fatigue, sleep disturbances, cataplexy and narcolepsy, again the ICD-9 code enabled them to capture these indications. And now, I can talk about the case reports from the pediatric -- the Provigil post-exclusivity review of adverse events that were captured from the AERS database and in this review we cover raw counts of data from the database as well as an in-depth review of some reports.

The raw counts of the adverse

events from Provigil's market approval in December of 1998 through April of 2007 were the first raw counts and then we did -- we provided raw counts of the adverse event during the exclusivity period. And then we did an in-depth review of the unduplicated reports for children, newborn through 16 years of age during the one-year, post-exclusivity period. So this is the first table that shows the raw counts of adverse event reports to Provigil since its marketing in 1998 through April 2007. And if I can direct your attention to the last row of the pediatric population, for all reports, that's foreign and domestic reports, totaled 42 reports and of those 40 were from a domestic or a US source. And of those 42, 21 were serious reports of which 19 were US reports and then there was one death from -- a US death.

This illustration just shows a distribution of the pediatric reports since marketing of Provigil in 1998 and you see I've

marked the year 2006 when pediatric exclusivity was granted. In that time, there are a total of nine reports. Now, this table may confuse you a little because it's the raw counts again, but if I direct your attention to the last row of the pediatric population, it says 10 but actually, when we did an in-depth review of those reports, it's actually a total of nine as I've mentioned before and of those nine, eight are US reports. And of the nine, five were serious, four coming from the United States and that same one death shows up in the exclusivity period. So these are the raw count. I don't think I said that but this is the raw count data during the exclusivity period.

Of the nine cases that we captured in the one-year post-exclusivity, these were the outcomes. Now the outcomes are not mutually exclusive but the outcomes included death and there was just one death case. Hospitalization, life threatening events,

disability, congenital anomaly or the events were considered medically important.

Of those nine cases, this -- these were the indications for prescribing Provigil to the pediatric population and the first four cases the patients were prescribed Provigil for the treatment of attention deficit, hyperactivity disorder and two of those four also received the product to treat bipolar disease and anxiety. Four others were treated with Provigil for sleep disorders including narcolepsy. There was one report that the indication for Provigil therapy was not reported.

On this slide, I just -- I give you a summary of the US death case. It was a completed suicide in a 15-year old female with a history of depression. The patient received Provigil for an unknown indication and she received initially a 50 milligram does that was titrated to 100 milligrams. The patient died by strangulation seven days after a dose

increase. Concomitant medications included duloxetine, dicyclomine -- and dicyclomine. Before -- at the time of the event, the patient's family described her as being recently upbeat. Of the remaining -- this is a list of the categories of the remaining non-fatal cases that we reviewed and these are the categories. There were -- and the category psych adverse reactions, we identified three cases. In the dermatology category there were two cases and then there was one case each in the category of congenital anomaly, drug interaction or neurology.

Now, this slide just is -- this is a slide that shows the base -- the basis for our review. Our review is based on the adverse events signs or symptoms as compared to the current Provigil product labeling. Now, an adverse event is considered labeled if it has the exact wording or some similar wording to the adverse event. And an unlabeled event is the adverse event is not

mentioned in the labeling.

Now, if the adverse event or symptom is open to interpretation, the reviewer relies on the clinical expertise to determine whether the event is a labeled event or an unlabeled event.

So the first category we identified three cases, three psychiatric cases. The first case, the patient's behavior was defined as being angry, defiant and irrational and the patient also exhibited behavioral problems in school. Therapy with Provigil was discontinued and the events resolved.

The second patient was diagnosed with oppositional defiant behavior and in the third case the patient exhibited suicidal thoughts. We considered all these events labeled events as the Provigil product labeling, the current labeling has warnings for psychiatric symptoms that include those events. Then we moved to the category of dermatology and in this review we captured two

cases; one case of Stevens-Johnson syndrome and one case of DRESS. However, both these cases were previously identified with the serious skin event and they -- that Stevens-Johnson case was the seven-year old boy again, and the reason we captured it in our search for this exclusivity review was because the sponsor sent in the reports with minor follow-up.

There was one case of phimosis and this is an unlabeled event, however, it's a very common event, so there was no FDA regulatory action and no recommendations for labeling changes. There was one case of a drug interaction between Provigil and valproic acid in which the valproic acid serum level was lowered. Now, this is an unlabeled event; however, it's one case and based on one case, no labeling recommendations were made.

We identified one case of seizure and the patient was rechallenged with Provigil at some point and there was no recurrence of

seizure. Seizure is an unlabeled adverse event in the product labeling; however, based on one case, there were no labeling recommendations for this.

In summary, we identified during the post-exclusivity review, nine unduplicated pediatric reports and what was outstanding is the indications for the use of Provigil included four patients received Provigil to treat attention deficit disorders and four for sleep disorders, and one received the product for an unknown indication. However of note, all of these indications are unapproved in the pediatric population. So overall, there were no new serious unexpected safety signals for the pediatric population that were noted and so the FDA recommendation is to continue routine monitoring of Provigil for adverse events in all patient populations and in addition, there's a risk management action plan in development to capture reports of serious skin events.

And so our question to the advisory committee is that do you concur with the FDA recommendations?

DR. RAPPLEY: Thank you, Dr. Flowers.

DR. FLOWERS: And sorry, this is just an acknowledgment to the OSC staff.

DR. RAPPLEY: Thank you. At this point in time, I'd like to ask if anybody requests to speak at the open public hearing. I suggest then that we break. We resume right at 3:15. At that time, we'll take questions for our presenters and then begin the deliberations. Okay, so we'll meet back at 3:15. Thank you.

(Whereupon, a brief recess was taken.)

DR. RAPPLEY: Okay, Diane?

DR. MURPHY: Marsha, somebody left me $1.35 and whoever it was, I can't be bought for that.

(Laughter)

DR. PENA: Thank you for disclosing your financial --

DR. RAPPLEY: Okay, so we'd like to open then for clarifying questions to Dr. Mannheim, Dr. Farkas, Dr. Villalba and Dr. Flowers. It looks like Dr. Ward is eating a cookie but he's ready with a question.

DR. WARD: I can lay the cookie down. Could you provide a few more details, one of you about the child who had intrauterine growth retardation? What was the birth weight and what attempts were made at a diagnosis because what you describe in a child that doesn't survive sounds like it may have been a specific syndrome associated with under-development of the chest and lungs, et cetera. DR. FARKAS: With that case, we didn't have very much information. The information that we did have was not particularly reassuring that the case was what it was potentially -- you know, had potential implications. So there were pieces of

information but there was enough also pieces of missing information that we weren't really sure what to make out of it. I mean, for example, we didn't really have certainty that it really was intrauterine growth retardation, you know, confirmation that the dates were measured accurately, even the very basic things.

DR. RAPPLEY: I'd like to ask clarification on what specific things the committee should deliberate on in regard to modafinil. So if I understand this correctly, the medication continues to be not approved for use in children or any indication; is that correct? And that is not subject to discussion or change at this point in time. We just -- it continues to be not approved for use in children.

And the label was changed recently in August of `07, so you wish to report to us those changes that were made and link them to the concerns we had expressed at previous

meetings; is that correct?

DR. MURPHY: Well, I think the effort here was to make sure that the committee, and we may have done this in more excruciating detail than you need to have or we intended. We wanted you to be aware there had been extensive safety evaluations for this product. We also wanted you to be aware of the in-depth cutaneous analysis that had gone on and we also wanted you to be aware that all of this had culminated in some recent labeling changes. And I think the question relates to the fact that we don't think that there's any other additional safety signal that hasn't been looked at that we're worried about and we would like to go back to routine monitoring.

Having said that, you could see the product still out there being used. If you have any other thoughts you want to convey to us, we're always glad to hear that but our question really was do you agree that we can go back to routine monitoring?

DR. RAPPLEY: Dr. Rosenthal?

DR. ROSENTHAL: Just in reading the warning section on the label, there is a single sentence. There really is no reference to the age rate -- to the age ranges of patients in studies anywhere in the label or well, through most of it anyway. But there is a sentence that says modafinil is not approved for use in pediatric patients for any indication and I'm just wondering, you know, getting back to the point that Dr. Kocis made yesterday, regarding our definition and actually it's come up again today, regarding our definition of ages, I wonder whether it isn't being used in patients that we would consider pediatric because there's not more clarity as to what defines a pediatric patient. If family practitioners or psychiatrists are treating you know, 12-year old kids, it makes -- oh, you know, that's not a pediatric patient. And maybe clarification of that point somewhere would help to dissuade

off-label use.

DR. MURPHY: So if I'm understanding, you want us to put the age groups that we don't -- you think it would be helpful to specify that this product has been studied and is not indicated from zero to 16. Is that what you're saying?

DR. ROSENTHAL: Yes, yes, I'm saying that I think it's reasonable to consider specifying an age below which it shouldn't be used. And you know, the term "pediatric" is just vague and it's been used invariably by, you know, many people around the table and in other contexts during this meeting. So I think if you're looking for ways to try and dissuade its use in what we consider the pediatric population, then specifying what we consider the pediatric population would be one way to try and achieve that.

DR. RAPPLEY: Dr. Villalba would like to add to that.

DR. VILLALBA: Yes. Thank you. We do mention the age group in the warning section under the description of the clinical trials in pediatric patients under 17 years of age, but maybe they should be mentioned in some other place -- part of the label, but it is there.

DR. RAPPLEY: Dr. Rosenthal? Oh, you just spoke, sorry, Dr. Fant.

DR. FANT: I had one question about the possible drug interaction. The way it was presented suggested that Provigil, the way it was written on the slide, it lowered valproic acid serum levels and that was an unlabel thing. Was that an association or -- I mean, if that's a real interaction that was unappreciated, I mean, I would think that practitioners may want to know about that but I mean, how did the agency kind of synthesize that observation and --

DR. FLOWERS: Well, that was the information on the report and there was only

one report and the outcome for that event was a non-serious outcome. It was just a lowered serum level and actually valproic acid is an enzyme inducer as well as Provigil. But the Provigil may have more affinity at the -- in that patient so it's undefined at this point, so we would like to probably see more reports for that.

DR. FANT: So I guess my question is based on everything that you, you know, considered, you know, it would sort of fall into one of two categories. Let's wait and see if we hear some more about this, or we can just sort of mention it and say --

DR. FLOWERS: Well, you can't make much out of one report. So, I mean, we would either like to see more reports or see something studied about it that proves it. It remains unproven at this point, I think.

DR. FANT: Okay.

DR. RAPPLEY: Other questions or comments? Dr. Rosenthal?

DR. ROSENTHAL: Just real quick, is it true that the labeling for armodafinil also has a sentence regarding not using in pediatrics? We didn't really talk about that but I mean, a comment was made that the labeling -- that the pediatric warning was extended to the other formulation, so I'm wondering -- I just want clarification on that point.

DR. McNEIL: The armodafinil label states that -- does carry the same warning but armodafinil has never been studied in the pediatric population. So it's safety and effectiveness has not been demonstrated.

DR. RAPPLEY: So in the pediatric section, it wouldn't have the same statement then, would not have the same type of statement; is that correct? It would just say it hasn't been studied.

DR. McNEIL: If I remember correctly, it says safety and effectiveness has not been demonstrated in patients under 18

because it's never been studied, armodafinil has not been studied in pediatric patients.

DR. RAPPLEY: Right, right.

DR. McNEIL: Modafinil has.

DR. RAPPLEY: Okay.

DR. McNEIL: But the rest of the warnings, the Stevens-Johnson and all those are in the armodafinil label.

DR. RAPPLEY: We will Google the pediatric section of -- and did you look at -- do you have -- okay, but what we're telling yo is that from memory and our usual practice would be that they wouldn't be exactly the same because you would hope that when something had been studied it would be more definitive that it had been studied and efficacy hadn't been -- we've got it, great. Do you want to read it to us, please?

DR. FLOWERS: We do have the product labeling for armodafinil and in the warnings, bolded warnings section, it says, "Armodafinil has not been studied in pediatric

patients in any setting and is not approved for use in pediatric patients for any indication".

DR. MURPHY: In the pediatric subsection what does it was?

DR. FLOWERS: No, it's actually a statement in the warning section.

DR. MURPHY: Yes, I know. Could you look in the label in the pediatric subsection and just tell us what it says there. I think that's what the question was. I think you said --

DR. KOCIS: Just following up on that point while we're waiting, the patient information says it is not known if Provigil is right for children under the age of 16 and the parent -- I'm still trying to find the table that you referred to about age and I can't find it at least in the approved labeling as of January 23, 2004 which is in the --

DR. MURPHY: We will follow up on

that one, okay?

DR. FLOWERS: Yes, it does appear in the pediatric use section, "Safety and effectiveness of armodafinil use in individuals below 17 years of age have not been established. Serious rash has been seen in pediatric patients receiving modafinil," and it refers you to the warning section as well.

DR. RAPPLEY: Okay, thank you. Did you have other comments, Dr. Kocis?

DR. KOCIS: No.

DR. RAPPLEY: Okay, Dr. Daum?

DR. DAUM: So I was just going to ask for some quick guidance. As I understood what was presented this afternoon, the skin reactions occurred in the trials in children and minimally, if at all, in adults. And the post-marketing studies suggested that the skin problems did not occur in children but did occur in adults. So these results to the novice, like me, seemed diametrically opposed. Rare events are funny. They sort out in

weird ways in small numbers. These are pretty small numbers. Can the agency supply us at least with their experience with a role reversal like this, where the post-marketing studies seem diametrically opposed to what was found previously?

DR. MURPHY: I want to ask a question of the division. On that post-marketing adverse event, wasn't that one patient, adult patient 17 or was that the 49-year old?

DR. RAPPLEY: 49-year old.

DR. MURPHY: It was the 49-year old. I wanted to make sure that it was the 49-year old, okay. Do we have -- what do we do when we have clinical trial data versus AERS data? We tend to rely on clinical trial data. We use the AERS data as hypothesis generating more than anything else. I guess one could say that the division has been alert all along to the concern about cutaneous reactions and has continued to monitor it. So

it's not like we're going to stop looking for it in adults in the adverse event report.

DR. RAPPLEY: Would it be fair to say that the clinical trials confirmed our earlier concerns about serious skin reactions including -- from the spectrum of hypersensitivity to Stevens-Johnson in children treated with modafinil?

DR. MURPHY: Yes, I think the other thing though, Bob, just to go back is you have, you know, theoretically, this product shouldn't be used in kids, so if the use is an adult, you would expect that's what the adverse event reporting would come in as. Even though the clinical trial data said that it appears pediatric patients are at a higher risk. Then if you don't have much use in it, you're just not going to get the cases. But we won't stop looking if that's sort of the underlying question for pediatric cases or adult cases.

DR. DAUM: We'd be pleased if you'd

stop looking. I'm just trying to come to -- I'm just trying to come to grips with the data. So thanks for the help.

DR. CNAAN: I think there is a fairly easy explanation to the data. We started by looking at the pk data, and the pk data showed that, on average, in gross terms, what you need to give to children is about 100 milligrams per day. If we go to the presentation about the 13 pediatric cases with rash, there was only one, and that was a case of hives with 100 milligrams. The 12 other cases were at least 200 going as far as 425 milligrams. My guess is that, in the off-label usage that is now out there, seeing that the adult dose is 200 milligrams, I doubt that even off-label anybody is using these very high doses from the clinical trials that produce these adverse effects. That would be my guess for the explanation.

DR. MURPHY: I think that was one of the things Dr. Mannheim was trying to point

out, too, when he presented as far as the exposures. That's a good point, thank you.

DR. RAPPLEY: Dr. Ward, and then Dr. Malone.

DR. WARD: Do we really think, though, that the label gets to that point, because I don't, and I thought the data were quite revealing with AUCs that were two and a half to three fold greater than adult exposures, and if somebody picks it up to use it, let's say they're an adolescent and they think, "Well, fine, we'll give the adult dose," and the AUC may be dramatically higher, and I don't know how you address that when you don't want to tell them how to use the drug in pediatrics.

DR. MURPHY: I don't know what you would say except to strongly somehow word it that, unless you could say something about, and I'll look to Dr. Villalba since you did these cutaneous, we didn't have a dose breakout for who we did.

DR. WARD: Could you cover it in the precaution section of saying that doses above 100 milligrams in children produce exposures that were two and a half to three-fold higher than in adults, or is that giving too much information?

DR. MURPHY: I don't know, Bob. I just think it's very dangerous when we start putting things into the label, when we're particularly concerned about the use in the pediatric population. I would be very concerned about that.

DR. RAPPLEY: I hear you saying that the label already says, do not use in children and -- not that clear. Okay, it says not approved for use in children. Is there another way for us to let the prescribing physicians know that we have once again reviewed this data, and we affirm, in fact, we have additional information which further confirms our concerns that this medication should not be prescribed in children? I guess

we're all concerned about, one, the downward drift to unapproved use, and also the drift to other products, which I think is behind the question about armodafinil. Tom?

DR. NEWMAN: I think there is a big difference between saying it is not approved for any indication in children and saying do not use in children under 17 or under 16, and I think, if you combined the -- you know, that levels in children are much higher and the drug should not be used or do not use, that I think provides more information than just saying it is not approved, because drugs are used off label all the time, so I think that could be more explicit.

DR. RAPPLEY: DR. Kocis?

DR. KOCIS: Just two things because, when we were first starting on the dosing, again, it struck me odd. I had never been involved in a clinical trial where we dosed children, I mean, two times, three times, four times adult doses. Usually we use

the adult, particularly in early studies, as the ceiling, and so I don't know who figured that out or if there's a reason for that. But that certainly struck me as very odd in the study design part, but Stevens-Johnson syndrome, at least that spectrum as I view it, and erythema multiforme, often times usually is not dose dependent. It's just the exposure, regardless of dose, so that wouldn't prevent that. And then just finishing up with kids, and what we've said in this label here is in tiny print.

So on the pediatric use it says here safety and effectiveness in pediatric patients below age 16, and then they talk about the trial from ages five to 17, but they don't talk at all about the Stevens-Johnson underneath that to highlight that's what our concern is. And then the stronger labeling for, not that it isn't approved for children, but don't use in children, we're still going to have to figure out what that is and, you

know, in the patient information on this one, it just says Provigil is not approved for use in children. And if I were a layperson, I'm not sure I would consider an adolescent a child, you know, and we have those disputes.

DR. RAPPLEY: DR. Malone, did you have a question?

DR. MALONE: I was just going to respond to what I think Dr. Daum brought up that the AERS data didn't show the same effect as the clinical trial, but there was a lot of discussion about rare events at the last meeting that, in order to find a rare event, you have to have a lot of exposures, and if you have it in one clinical trial, what would that mean? And I think the decision was that you might have to see close to 3,000 patients to start assuring yourself it wasn't a random event. So that if you had AERS data with little exposure, it may not really give you much assurance that the clinical trial data was not correct.

DR. MURPHY: I want to try to go back to the question about why the high dose, so Glenn, do you want to address that, please, because remember there was the study for the narcolepsy which had different dosing than the other ADHD which had the lower dose.

DR. MANNHEIM: My understanding is that ADHD trial, in order to achieve efficacy, they really had to shoot the dose really -- they had to go up in the dose on a milligram per milligram basis in order to get efficacy in ADHD.

DR. NEWMAN: But they would do that before they'd shown safety? You know, you'd normally show safety in dosing trials and, of course, we'd like to show efficacy at the same thing, but before we ramp up or, you know, you arm it into a low and high and --

DR. MANNHEIM: Maybe the company wants to respond.

DR. MURPHY: I wasn't there. I'm just saying you can -- we do a number of

trials where you, if you pk -- do a very limited pk study, you're not going to get much of a safety signal with a limited pk, and as long as you show that you're not outside some boundary, you could justify doing a trial with different dosing to look for efficacy. So what I'm saying is that you're not going to have -- typically, we don't have much safety data -- large safety data base when we go into doing our efficacy trial, and one way you can demonstrate efficacy is at dose range and study.

DR. KOCIS: But dosing it above the adult dose?

DR. MURPHY: If you thought that was -- because we have a couple products now that we know that the kids are clearing it faster, and so, you know, that's what you would do. I mean, his answer was that's what somebody thought, but my point being, you don't have much safety when you begin your efficacy studies and fortunately, in

pediatrics, we've actually been using adults as our first screen, if you will, and often we have that information. So and we -- but just in a general term, one can use a dose ranging study to demonstrate efficacy. Certainly some of our anti-hypertensive drugs, that's the way they have chosen to try to demonstrate efficacy.

DR. FLOWERS: (Off-mike comment.)

DR. RAPPLEY: Could you come to the microphone? She was just mentioning gentamicin.

DR. KOCIS: Gentamicin though, I'm sure the first time we used gentamicin in clinical trials they didn't start out with dosing greater than the adult dose or per kilo -- I mean, when you extrapolate for pediatric use, you usually use 70 kilos in the adult dose, and that's where you start from until you either have pk data to show their rapid metabolizer or something different, you know, clearly there is children in pharmacokinetics

that drive higher dosing on a per kilo basis for children, but that's after demonstrated safety first, then usually efficacy, and then figuring out the dosing all the time.

DR. RAPPLEY: If I might pose a question in a different way, just sort of a variation on that. In our last meeting, we made a recommendation that there should be a large scale study done to look for these rare events. Based now on what we know from clinical trials, would we still think that there should be any kind of large scale study done in children with this medication?

DR. MALONE: I think rare events could go both ways. They could have been unfortunate and have one or two rare events in a smallish sample. And you could do a larger study and not find that rare event occurring. I don't know that I would say it would mean you shouldn't do larger studies, but I think it does mean it would require larger studies to assess the meaning of that rare event.

DR. RAPPLEY: Dr. Cnaan.

DR. CNAAN: The pediatric use section, short as it is, says safety and effectiveness under 16 have not been established. I think -- and that's the same statement as in the other product, but I think that there is a difference. Either we say there have been studies in children under 16, and they did not show either effectiveness or safety, or we go ahead and do some studies because, according to Dr. Kass' memo, it might be that the 100-milligram dose is effective, but it hasn't been studied extensively enough. But right now, I think it's a little unsatisfying because it makes it look like nothing happened, and something did happen.

DR. RAPPLEY: DR. Hudson?

DR. HUDSON: Well, couldn't -- in that same section, couldn't you add a subsequent sentence that says, "Notably, drug distribution was remarkably different," and give the information about the area under the

carbs there, so that would be a place to alert them that there needs to be a dose adjustment if they're creeping down into the pediatric age range?

DR. RAPPLEY: DR. Malone?

DR. MALONE: As I recall, the data for modafinil in ADHD was that it was effective. It was a safety concern that got it voted down. So I don't know whether you'd want to be labeling that you have efficacy data but we don't recommend you use it. It would be kind of a mixed message. I don't know how you would do that.

DR. MURPHY: We're passing out what we hope is a more current -- yes, August 2007, wording and since I don't have it, somebody is going to have to read the exact statement. Would you, Marsha? Again, the pediatric use section, what does it say under precautions? Oh, it's in a new format? Okay.

DR. RAPPLEY: It's on the third page, Pediatric Use, "Safety and effectiveness

in pediatric patients below age 16 have not been established. Serious skin rashes, including erythema multiforme major and Stevens-Johnson syndrome have been associated with modafinil use in pediatric patients. See warning, serious rash, including Stevens-Johnson syndrome.

In a controlled six-week study, 165 pediatric patients, age five to 17 years with narcolepsy were treated with modafinil., N equals 123 or placebo, N equals 42. There were no statistically significant differences favoring modafinil over placebo in prolonging sleep latency as measured by MSLT or in perceptions of sleepiness as determined by the clinical global impression on the clinician's scale, CGIC. In the controlled and open label clinical studies, treatment emergent adverse events of the psychiatric and nervous system included Tourette's syndrome, insomnia, hostility, increased cataplexy, increased hypnagogue, hallucinations and suicidal

ideation. Transient leukopenia which resulted without medication intervention was also observed in the controlled clinical study." That's a new sentence. "In the controlled clinical study, three of 38 girls ages 12 or older treated with modafinil experienced dysmenteria, compared to zero of 10 girls who received placebo."

DR. MURPHY: So the pediatric use statement has an age in it but it does not say do not use which is, I guess, the question that the committee is asking. Are you -- you can make your recommendations. We didn't bring a labeling question but you can always bring a labeling question to us.

DR. RAPPLEY: If I might add to what Carlos has pointed out, there was a Dear Health Professional letter sent -- when was it sent, Carlos, can you tell? The date for the healthcare professional letter, it was sent this summer? Okay, and I can read what it says. I won't read the entire letter but it

says that, "Cephalon would like to inform you of the following new warnings of important safety information for Provigil (modafinil) tablets. Provigil can cause life-threatening skin and other serious hypersensitivity reactions. You should instruct your patients that if this occurs, they should discontinue the use of Provigil and contact you immediately. If you receive a report of a rash or other potential hypersensitivity reaction", then it gives phone numbers. "Provigil is not approved for use in pediatric patients for any indication. Provigil can cause psychiatric symptoms".

And those statements I just read are indented, so they're very prominent in the letter. And then it goes on to describe the studies in more detail. So in addition to the label change in August, this letter was sent to all physicians in the country in the summer of `07. DR. Fant?

DR. FANT: Just a point of

information. Could somebody -- I may have missed this but could somebody speak to the conditions that are driving the off-label use? I mean, what's the perception out there? Why is it being prescribed for kids, for what uses?

DR. RAPPLEY: Dr. Malone?

DR. MALONE: The drugs that are used to treat narcolepsy were the stimulants, so as soon as this drug came out, I can tell you people came to me, they were adults, and said, "Can you prescribe me modafinil because I don't want to take stimulants and if it works in narcolepsy, it must be like a stimulant". So I think that it was the thinking that a drug usually was a stimulant if it worked in this condition.

DR. FANT: So is it being used in kids mostly for narcolepsy or for ADHD or --

DR. MALONE: I think the data we saw was that it was half and half. It was preventative then.

DR. RAPPLEY: Dr. Flowers?

DR. FLOWERS: Can we take my presentation back to -- there's some drug use data on in Slide Number -- with indications in Slide Number 24. In this slide you can see the indications were captured by the ICD-9 codes and is that in order of most frequently reported? Okay, so attention deficit would be the most frequently reported indication followed by cataplexy and narcolepsy and major depressant disorder, a single episode. So those are in descending order of -- but it's no breakdown?

DR. DAUM: So we don't know if it's 80, 15 or five.

DR. FLOWERS: Well, somebody's going to -- I mean, Lauren knows a little bit more about the use data.

PARTICIPANT: The indications for use was captured from the Office Based Physician's Survey and those were the only indications for use captured for the pediatric

population during the pre-exclusivity period. Now, if you'll recall, the physician's survey data is coming from approximately 3100 office based physicians and this is projected to the national level, so because we're working with a small sample size of physicians, those were the only indications that were captured at this time.

DR. MURPHY: The question was, do we have any breakdown like this was evenly distributed or that you have attention deficit up there not because it starts with A but because it was the most --

PARTICIPANT: We do have a breakdown of the frequency but because of the small sample size, Verispan who is the data vendor, does not recommend putting so much weight behind the numbers. It is also included in the background package, so based on the data that was provided, attention deficit disorder was the most frequently reported indication.

DR. RAPPLEY: So then I think that at this point in time, there's been discussion about whether there needs to be some stronger message sent to prescribing physicians. Since that suggestion was made, we reviewed the package insert that went into effect as of August and we reviewed the letter that was sent to physicians in the country in the summer of `07. Is there still a sense that something more needs to be done to communicate this concern? Ms. Celento and then Dr. Fant.

MS. CELENTO: Just if we're looking at the label, we don't need to see the MedGuide here but I believe it should also be reflected in the MedGuide that this is not approved for use, pediatric use under the age of 16. Again, I think that's what the parents or patients will be looking at.

DR. RAPPLEY: Dr. Daum? Or, Dr. Fant, I'm sorry.

DR. FANT: Yes, the reason I asked is because in the label, you know, it refers

specifically to the lack of efficacy that was shown with narcolepsy and it mentioned that specific case in the context it's not indicated in pediatrics in general and I can see where somebody who sort of is kind of motivated to use it for something and say, "Well, my ADHD is not mentioned in this so maybe I can get away with it here or maybe my depressive disorder is not mentioned here, so maybe I can get away with it here".

And I mean, there are a lot of things that drive off-label use and something is clearly driving it. So that was, you know, the reason for the question and following that, would broader inclusion in this section of the label, be worth considering?

DR. MURPHY: Can I ask, Dr. Fant, when you say broader inclusion, are you saying that --

DR. FANT: To include somewhere some type of reference to the things that we know are driving the off-label use. I mean,

you know, we know in fact it's being used off-label.

DR. MURPHY: So we know that we have a study for ADHD which was effective, right? Yes? But the committee voted because of the risk benefit, could not approve it; is that correct? Right? So at this point, are you suggesting that we need to put that information in there, that in other words, this product has been studied for ADHD and was reviewed for its risk benefits and was -- it was recommended it not be used in that context? We don't have to say it proved to be effective but the safety profile was considered to outweigh the benefit. We could put it in different -- you're saying something like that needs to be added to the label or am I missing it?

DR. FANT: No, I haven't gotten to the point of taking a strong position, but, you know, I'm just putting the question on the table because it seems we have a drug out

there that's being used off-label for at least three different conditions. And the only one that we specifically mention in the pediatric section, you know, is not the -- at least the information that we have is not the predominant indication that it's being used for, you know, the predominant use that it's being used for. Are we sort of sending -- should the wording be altered to just sort of more generally dissuade all off-label use or somehow bring all of the uses under the same umbrella or speak to them in some way?

DR. RAPPLEY: Dr. Ward.

DR. FANT: So, I don't know, I'm putting the question on the table.

DR. RAPPLEY: Dr. Ward, then Dr. Bier.

DR. WARD: In the background information in `06, April `06 to March `07, there 2.3 million prescriptions for ADHD. No, I take it back, yes, for modafinil and the selected ADHD market. So I would suspect that

the ADHD usage is predominant and in another area in here it suggests that it's 15 percent of the ADHD market share, and so I think if we were to say that it has been discussed and felt that the risk outweigh the benefits for ADHD, that that would serve -- send a pretty strong message to prescribers and to families that this drug carries more risk than, we think, benefits for this particular population.

DR. RAPPLEY: And then understanding what's required for a label change, do we feel that should go into the label or do we feel that there's another mechanism to do that health profession letter? Respond there?

DR. WARD: I would support it being in the label.

DR. RAPPLEY: Dr. Bier, did you have something to add?

DR. BIER: Well, no, I guess, I'm, you know, confused about what it is about do

not use in children that we don't understand. I mean, if we say do not use in children for the following reasons, you know, I mean there are reasons why that exists and that's, what it seems to me, we need to explain, period. Once we start talking about all of the studies that may or may not have done something, it's, "Don't use in children but, you know, maybe if you'd get by here and do it". You know, I just don't think that's appropriate. "Do not use in children for the following reasons".

DR. RAPPLEY: So there have been two suggestions to change the label. One is to include the information that the risk benefit for using ADHD has been reviewed by the agency and by the Pediatric Advisory Committee and it's found that the risks do not support use in ADHD. And the second suggestion is that there be a statement that explicitly says, "Do not use in children".

DR. WARD: I have concerns about the liability for a prescribing physician to

make it a do not use for -- the skin reactions certainly are severe and there's some other -- some significant adverse effects, but I hate to be quite that explicit on this level of data.

DR. RAPPLEY: Dr. Malone?

DR. MALONE: Yes, I'm not sure I would say to say "do not use". In fact, I don't know if the FDA ever writes, "do not use in children", but if they did write that would it be illegal to use it in children? I don't know what happens with that.

DR. MURPHY: If this committee, if that was your recommendation that that's what we should say, we'd have to go back and look but I'm sitting here having the same concern because normally if we say something on the label it's based on data and so you know, just to sort of globally say, "don't ever use it" might be difficult from --

DR. BIER: Yes, but you didn't give it an indication for use so you had a reason

for that. Presumably, there's a reason.

DR. MURPHY: Well, we can say that it's been studied and it shouldn't be used because of the risk. I mean, we can --

DR. RAPPLEY: Dr. Hudson?

DR. HUDSON: I think we should make a statement similar to what you've just suggested that says more benefits have not been established and there are still specific concerns about risk and then elaborate on that. I don't like this idea of saying "do not use". I don't think there's enough data at this point, and I think you should just describe what the data shows at this point as succinctly as possible.

DR. FANT: Yes, I would be in agreement with wording it that way. The only caveat would be, it seems like when we start mentioning individual conditions, like when we put in the data about narcolepsy by itself, and then leave the others out, it's almost like inclusion by exclusion and if you make a

blanket statement saying, "Either because of lack of efficacy or specific safety concerns where the risks outweigh the benefits, you know, that this drug is not indicated for any use in kids and I think that just sort of captures everything and sends a message as strong as it can be sent.

DR. RAPPLEY: Dr. Malone?

DR. MALONE: I mean, I would have to say, having been on that psychopharm committee, it was a risk/benefit ratio in general that was not a good ratio. I don't know that there might not be some children out there that a clinician might think we've done everything and it might make sense to try this and that's a different risk/benefit ratio. So I don't know about you know, essentially banning this. I still think there could be a clinical judgment in using drugs off-label and we do it all the time.

DR. RAPPLEY: So is there a way to send yet another message to the prescribers

that we feel strongly about -- well, that we reaffirm it should not be used in children in a way that doesn't compromise some of these other issues, that doesn't compromise the ability of the physician to exercise his or her own judgment with a particular patient?

DR. MURPHY: I think it will -- the divisions are very good that coming up with wording and I think it would come out somewhere along the lines of discussing the fact that it has been studied. I think that's the point you all want. It's been studied and that the risk/benefit is -- we have to come up with a way to say that it's not there to warrant its use. It's not recommended because of the safety profile, something like that. That seems to be what I'm hearing from the committee at this point.

DR. RAPPLEY: Dr. Kocis?

DR. KOCIS: Just taking this to the next step, if we say don't use in children, it's going to be real difficult to do the next

randomized clinical trial at a certain dose looking at safety and efficacy to see if it does have a role. You know, I think trying to get that through an IRB or getting a parent to sign it with explicit things as that, but on the other hand, we shouldn't -- we can't swing the pendulum the other way which is it hasn't been -- you know, it's the usual we haven't -- you know, whatever the wording we usually use that's so nebulous that everyone uses it anyway. So I'm looking for balance.

DR. RAPPLEY: Okay, so is there -- is it possible, do you think for us to have some consensus about the statement you just made, Diane? Would you repeat that? Just in general, how that wording might be added?

DR. MURPHY: The wording, is the committee recommending that we have something in the label along the following lines; "that this product has been studied in children and its risk/benefit profile has been assessed and it is not recommended that it be used in

children because of safety issues", something along that line.

DR. RAPPLEY: Are people in general agreement with that? I see that's a thumbs up. Okay. Let's take a vote about that, because if we can arrive at a consensus, this is a strong statement, I think, for the agency to hear. How many people would support that? That looks unanimous. Any opposed? Okay, Dr. Kosic?

DR. KOCIS: Just, we came back early on. Just putting actual ages in there, just to get by that --

DR. RAPPLEY: He can't let it go, he can't let it go.

DR. JOAD: It's been studied in patients 17.

DR. RAPPLEY: Dr. Hudson, do you want to add that?

DR. HUDSON; It's been studied in what specific clinical conditions and that will address Michael's concern that it will be

ADHD, narcolepsy, whatever.

DR. RAPPLEY: Dr. Rosenthal?

DR. ROSENTHAL: I'm just looking at the patient information part of the label that's -- it says FDA approved labeling August 17th, is the version I'm looking at and I've got it online, but back in the patient information, it's really very vague -- well, it's very sort of confusing about do not use in pediatrics. That sentence just sort of appears at random in different -- it says Provigil is not approved for use in children and it's just kind of out of the blue and then it actually comes up again like on what is for me the next page and again, it's not really supported by anything. So I'm wondering whether there isn't an editorial opportunity and also maybe and opportunity to add some of this information regarding supporting evidence in this section.

DR. McNEIL: You didn't want this in the patient information section. This

product doesn't have a MedGuide. It only has the patient information section. So that's where you'd like it?

DR. ROSENTHAL: It just occurs to me that that needs to be cleaned up and that that might be a good place for this info as well.

DR. RAPPLEY: That it should go in both places so that it will be seen. Okay, any other comment or question about modafinil? Is the agency satisfied with recommendations?

DR. MURPHY: I'm looking all around. Anybody have anything else they want to say to the committee? Okay. Thank you all very much.

DR. RAPPLEY: Okay, so we'll move on in the agenda then to global pediatric drug development.

DR. MURPHY: Well, ethics always takes precedence, so Dr. Nelson was going to have a few statements for the committee.

And Skip points out that we never

heard from you that you did not want us to come back again. Did you agree with our routine monitoring? I thought Dr. Daum implied that but there was not a general final statement on that Dr. Rappley.

DR. DAUM: Well, I'll make my statement. I would be happy with routine monitoring and come back if you think there's a problem.

DR. RAPPLEY: I take that as a motion. Second?

PARTICIPANT: Second.

DR. RAPPLEY: Okay. Support for that motion?

DR. MURPHY: Okay, thank you.

DR. RAPPLEY: Opposition to that motion, just to be thorough? Okay.

DR. NELSON: Very quickly, I'm just going to take a few minutes and introduce myself to those who don't know me. I'm Skip Nelson. I go by Robert officially and I'm the Pediatric Ethicist with the Office of

Pediatric Therapeutics. I'm formerly involved with this committee in another role. I might say, I just want to introduce a few things that are on the horizon. One of the reasons you're being asked for availability in March is we do also have a referral from an IRB for a review under 21 CFR 50.54 and so we would be having the Pediatric Ethics Subcommittee meeting prior to the Advisory Committee meeting in order to advise that particular IRB.

For those of you who are new, you may not realize that there is actually a formal Pediatrics Ethics Subcommittee that's chartered under the Pediatric Advisory Committee. I won't go into that but you can get that if you just to the website and read it.

What's important about that is to meet we need two members of the Pediatric Advisory Committee to be there. So we would then be looking for volunteers who would want

to be there and barring that, would look for individual who we could encourage to come.

The other two things that are on the planning horizon at this point but have not really been formulated to be concrete enough to talk about dates is one of the ideas that I'd like to have the Pediatric Ethics Subcommittee explore is the application of Subpart D to pediatric FDA regulated research and in particular provide advice about that application around different areas such as minimal risk, prospect of direct benefit, interpretation of these categories, the application to FDA regulated research. Those meetings would not need to be linked with an actual meeting of the Advisory Committee, so at this point, I would imagine them to be separate.

But again, we would still need to have at least two members participating. That's on the horizon. We have no particular dates for that. We're working on the ideas

and formulating those meetings at this point. So I just want to put that on your horizon. I'm happy to answer any quick questions because I know Diane's got a much more extensive presentation she'd like to give.

DR. WARD: Skip, I thought that was already accomplished, that is comparable FDA regs to Subpart D.

DR. NELSON: Well, I'm not talking about the regulations themselves. I'm talking about issues in the application of the regulations. As you know, when you take a general principle and you try to bring it down to a case-based discussion, there can be a range of different opinions and at times, there are protocols that engender that kind of discussion. So the idea would be to bring that discussion to the Ethics Subcommittee.

DR. BIER: But aren't the regs written in this, you know, somewhat less than specific way precisely because there are these different approaches and it's a case-by-case,

you know --

DR. NELSON: There is what I would call justified variability and what I would call unjustified variability and part of the challenge is seeing the difference between the two.

DR. BIER: And is that likely to be uniform among ethicists much less among the biologists?

DR. NELSON: I think there can be more uniformity in the field than currently exists, yes, but I'm not going for uniformity. But I think that would be precisely the point of the discussion, where can you find points of commonality, where can you not.

DR. ROSENTHAL: You know, I think if you're not going for uniformity, you've come to the right place.

(Laughter)

DR. NELSON: So I just wanted to introduce those. The idea was just to get you sort of an appetizer to know what's on the

horizon and to not take up any more of your time.

DR. RAPPLEY: Thank you, Skip.

DR. MURPHY: You're welcome to discuss this but there will be no questions. We don't have to take a vote and this is strictly FYI. We had a choice of trying to update you on all the new legislation and the international and we ended up with about 15 minutes. That's all we had time for. What we -- I'm going to do in the next 10, 15 minutes is review for you some really important activities that have been going on in Europe for the last couple of years, and you're saying why am I bothering to tell you this? Because you all know probably as well as anybody, pediatric studies involve often small populations. The trials often are global, international and we find that we need to coordinate with our colleagues in Europe extensively.

We have had the benefit now for a

decade of legislation that has helped propel getting studies done and many of you are very familiar with that. What the Europeans have been doing is been trying to do that same thing for the last decade and today, I'm going to quickly tell you what has happened and how we're trying to coordinate with them.

We hope to have a more -- which one do I do forward? Okay, hope to have a more extensive update for you with some scientific issues because you'll see that we're already -- we've just begun and we already know we have scientific issues that we're all beginning to discuss.

So what is the European regulatory framework? I'm going to try to explain it to you and Dr. Julia Dunn as I introduced the other day, is here and she has been very active in this area and she can stand up and correct me and I won't be at all offended because I am merely stealing many of their slides, as you'll notice by the spelling on

many of these slides.

So basically, we have now 27 member states and there are a number of -- these are economic groups, the EEA, I think what's what it stands for, is that right, that are also associated with the European regulatory framework. They have observers and this is a free trade something, right, the European Free Trade is with Switzerland, but it doesn't matter. They all have some status one way or another in this European framework.

They work in 23 languages. So I think one thing we have to do is admire their ability to do this. It is not an FDA for Europe. I wanted to make sure everybody understood what it is that they do. Their member states have pooled their sovereignty for authorization of medicines. And that the EMEA coordinates the existing scientific resources of the member states.

And they interface in a very different way than we do and I'm not going to

spend this talk talking about that, but there are differences and that's really what this slide is supposed to say. But for the activities involving approval of authority of medicines, they have this process which is coordinated across Europe.

You can still do regional authorizations but Julie was telling me, it's become more and more limited. They also have the all parties are linked by an IT network, EudraNet which I just think is incredible considering we are lucky to stay connected within the FDA all the time. So this is -- they have a single authorization is what the sponsor can -- where it's optional can elect either do country by country or a single authorization and they have a scientific evaluation by committee, the CHMP, and then they get one product authorization in 23 languages. So that's the process.

I'm not going to go through the whole organizational activity but to show you

the important part is they now have new legislation that we'll go over in a minute, that has established a pediatric committee and that this pediatric committee is actually very -- going to be very, very important and has a significant amount of influence as you will see, which is unusual but in any institution with pediatrics we often don't seem to have that sort or authority. So I'm impressed with this fact.

They also have a -- it will be coordinating all of their pediatric activities and as you all know, we've had a rather separate parallel tracks for ours which under the new legislation is trying to better coordinate that. We do have an internal committee now within FDA to better coordinate ours but the Europeans sort of beat us to the punch on this.

And Dr. Elise Mathis is the Chair of that Committee, so we hope to be able to catch up with them as far as better

coordination of all pediatric drug development. This is to let you know that they have been working on this since 1997. It's very complicated. They have to go to the Parliament and they have a commission and whatever but they've sent people over here to work with us and see what we've been doing and they've -- and I presented to you all before, they've taken some of our ideas and they've really improved upon a lot of them.

And they -- that was just to show you they have to go through all these people besides the 23 languages, that's why it took them 10 years to get this legislation for the first time and it went into effect this January. That's a key thing. And what -- I'm not going to walk you through the time lines, just to say different parts -- what parts happened over time.

The main thing for you to know is that this effects every product that comes in for an authorization through this process.

And what does that legislation do? It basically has measures that for every patented product, that they must have a plan, a pediatric plan, in place when they submit their product, and we'll talk more about that plan, or it's not accepted fundamentally. They don't even accept it to review it. So that's a very powerful tool.

And so the pediatric plan has to be evolved and developed before they will have a -- what is -- it's not a complete package but there's a word for it. Julia, what is it?

DR. DUNNE: It's the application.

DR. MURPHY: Yes, and it's incomplete or what if they --

DR. DUNNE: It's not valid.

DR. MURPHY: Not valid, it's not valid if it doesn't have a pediatric investigational plan it in. They also have measures like we do for the off-patent process and they have this, noted, a standing Pediatric Committee that will review the plan.

And it's required by law for all applications. This is like wow, very impressive.

They have other measures that are also very interesting and again, something we admire in that they're developing extensive networks. They have regulation, law, about the transparency of this process and they provide free scientific advice, pediatric advice. Let's see here. So this is the committee that's now in place. They -- the committee reviews all of these PIPs. It also determined whether you can -- whether you will have a waiver or not because that means you're not going to study it or whether you have a deferral.

So it's going to look at the PIP, look -- determine whether you have a waiver or a deferral and provide you advice if they think you need it or you're welcome to have it. And I think the other important thing here that you need to know is that this PIP is

key to their obtaining their exclusivity because that's what is driving this also is that they now get six months of additional marketing authority if they have fulfilled this PIP, but the PIP has to be approved by that committee.

And again, the transparency in that these trials will go up on their EudraNet, so unlike the rest of the adult trials which are not public, it will be planned that the pediatric trials will be. Let's see, oh, and we've got funding, that's always important. So we've got networks and we've got funding and we'll talk about that in a minute here.

What is the PIP? It's -- this is their Pediatric Implementation Plan and it must be -- or it is supposed to be developed at the end of Phase I. Now that is quite early and some people have said that's too early, how do you know? Well, again, remember a lot of pediatric drug development is now based on products that are already out there

for adults so we often do have a lot of information and so it's not really Phase I. But for a new product that is coming along the line that is being developed, they have to think about children and they have to start thinking about whether they want to study it and how they want to study it.

It has to get approved by the committee and -- oh, here is it, application is not valid without the approved PIP and it is required if you want your exclusivity and that Europe does not want to subject children to trials for indications already studied in the US because you can imagine, you know, you've studied the product in the US, you've gotten your exclusivity. It might be tempting to say, "Oh, I'm going to go to Europe now and study it again".

And so there's been a real concern that that not happen and there's been a lot of communication and work to try to insure that we do share information so that does not

happen. So we are in the process of implementing monthly -- well, we have implemented monthly communications on what are the PIPs, what are the written requests and what are we all doing?

This is just a graphic to show you how early on they get involved. Their Pediatric Committee gets this PIP somewhere along in here as compared to what happens in the United States, skip this slide, it's too fancy for me. Let's get it all in there. Okay, so there's the EC/EMEA. There they are with their PIP and here we are coming in with our PREAs and written requests later compared to them and also post-marketing.

So there really is a difference in timing between these and I only bring that up because I think as we go into the future, we may see that we're actually getting the Europeans sending us what's going on in Europe and we'll be trying to develop our trials knowing what they have done or are doing. Or

some of you in academic medicine may see that the trials are beginning to be developed in Europe before they are here or at least the protocols and the plans are.

For the patent protected products, I mentioned that there will be an incentive, a reward, a six-month incentive and this is supposed to be -- I put a question mark here, because Julia told me that they had planned to put this on the product so the parents would know that the product had been studied in children. But once they started looking at 23 languages and what symbols mean, they actually have not been able to come up with what that is going to be at this point, so that's why we have a question mark. I think it will be fascinating to see what effect something like that might have. So I wish they'd come up with a symbol that they could think would be safe, but that was the original plan so that these products that are studied would have some indicating -- indicator on them.

The absence of an agreed PIP or waiver is an invalid application and that just tells you that they can -- pediatric study results can be submitted either with the marketing authorization or later if they have a deferral. Old products, what do they do about off-patent products that are not covered? There's a new -- they have a very different approach to this. It's called a Pediatric Use Marketing Authorization. It's a new marketing authorization. It's covering exclusively therapeutic indications for use relevant in use in pediatric population and it could be including appropriate strengths or routes and what they get is 10 years of data protection and use of existing brand name, so they get to keep the recognition, the brand name that's recognized. Again, we don't know what's going to happen with this, and they get to refer to data in other packages without company permission. So that's again, these older products there's often data out in other

applications. So if you'll develop this product, these older products, if you don't have an incentive to do, these are ways they're trying to incentivize them, if you will.

This is just to show you what that committee must look like, that they have somebody with the CHMP which is a final authorizing entity, they have patient family health professionals, and then they have representatives from all of the -- I don't think I added in the extra two here because this is their slide when they had 25, from each of the participating countries.

They're meeting monthly now and they are inundated with applications already and we're inundated now with their PIPs. That committee has to look at the PIP, the waivers, the compliance with the PIP and they have to support the -- helping support the establishment of the European network. I'm not going to go through everything they do but

to let you know that their pediatric investigational plan requires the company to submit an enormous amount of information that we at FDA don't routinely require and it's just a wealth of information. It's wonderful. You know, when you get the -- I think the first one we got was 500 pages and it was just like all the studies that had ever been done. It's really quite extensive background information I think people are going to find very useful in the future.

Other things that we mentioned earlier were transparency. There's going to be public access to pediatric information in the European database of clinical trials and that they are developing the European networks and there's funding. I was going to get to the good part last here for -- oh, this is about the transparency and I'm not going to go through this except the goals.

Right now they're working out the details of how they're going to do this, you

know, developing how they're going to open up part of a system so that part of it will be public and what fields will be available. But this is just a quick review, the fact that they have had preliminary discussions about their networks and the countries -- many of the countries are very eager to develop this network, and I think it's going to be very interesting to see how they utilize this and I think it's going to be interesting if they're able to develop some of the sub-networks that we haven't been able to do that well in this country.

This is the money that has actually -- you know, we had money that was identified that we never got for development of pediatric programs. They actually got under what's called their Seventh Framework Program, 30 million Euros for development of off-patent products. And I know that doesn't sound like a lot but that's every year, isn't it? That's every year that they're going to get 30

million Euros for development of the products that aren't going to be studied via the patented or the off-patent way and that will link with identify priorities for research into the off-patent medicines which will be on the EMEA website.

So there's a need for global development for children for efficacy and ethical reasons we think. We are now having monthly FDA teleconferences. We have already received over 30 PIPs from them and we've already had scientific exchanges, some rather extensive, meaning we've had experts on one end of the phone and groups of experts get together and discuss why one side is not studying it in a certain population and then why the other side is, or what -- we've had discussions about what were the safety issues that we found that they didn't have all that information. And it's been really very interesting to see how these issues are going to be developed. And certainly we plan to

have a future forum on what some of the issue on how you learn from each other, how do they learn from the trials we've already conducted, use that information, design a better trial and how are we going to learn from what they have and to make sure the kids aren't enrolled in trials that either aren't very scientifically robust or just is unethical.

We actually found one company that failed to tell them that they had a written request that was turned down and way. So we're already finding out that this exchange of information is important. So, it's very exciting and I think it's going to really enhance pediatric information in the next decade. And so in the future you may be hearing more about the safety data that came out of some of the European trials in addition, too. Thank you all very much and if you have any questions, I'll try to answer them, but otherwise, I know you must be eager to end this day.

DR. RAPPLEY: Questions for Dr. Murphy? DR. Daum?

DR. DAUM: I apologize. Where do you think the funding might come from? I apologize. Where do you think the funding might come from and can we get started on that now, because it's probably the rate limiting step? It seems to me 30 million Euros is a lot of money and in US dollars it's growing everyday.

DR. MURPHY: Yes, it is, isn't it?

DR. DAUM: So it might be -- the first effort might be to think about how to get this and a similar effort into Congress to get funding for this. I don't think we're going to get too far without that.

DR. MURPHY: Well, Bob, I can tell you people have been trying. They supposedly had 225 -- Congress said we would get $225.00 -- million dollars, but then they did not fund it. They said, "This is a great idea, you ought to have it", but then they didn't fund

it. What NIH has done, NICHD has basically been able to extract is the right word, extract around 25 million from other entities within NIH for development of products, and that's on an annual basis, right? So we do have some pediatric funding but I think the Academy of Pediatrics has done -- and I know Mark Delmonte is here, Dr. Gorman, Bob Ward, all of them have worked trying to get Congress to give us money for this and I don't know if they have any insights you'd like to share with Dr. Daum.

DR. NELSON: I think it's approved but not funded.

DR. MURPHY: Yes.

DR. GORMAN: And we're always looking for another ally in this particular fight, so we'll be glad to put you as a new enlistee to speak to your local congressional individuals.

DR. DAUM: Well, all kidding aside, I just finished making the rounds on behalf of

INSA. I'm stuck on one of their anti-microbial resistance working committees and had a session. I testified in front of Congress last week and went around to a lot of Congressmen. We could talk about maybe --

DR. WARD: That's actually what it takes. It really is and --

DR. MURPHY: FDA is not supporting this lobbying effort at the moment. This is a spontaneous conversation between these -- okay. Okay, well, I want to thank you all very much for lots of thoughtful advice and we will see you tomorrow. Marsha, did you have anything you need to say or Carlos?

DR. RAPPLEY: Just as we're ending here, please make sure that you leave your binder, this one right here. We need to collect all of these. Can people leave these at their places? Is that adequate? Yes, okay, thank you. See you tomorrow, 8:00 a.m.

(Whereupon, at 4:33 a.m. the hearing in the above-entitled matter recessed

to reconvene at 8:00 a.m. on November 29, 2007.)