prevention of CINV in children greater than 4 years of age.

The four primary endpoints were incidence of emesis, proportion of patients who received supplemental antiemetic medication during the 24-hour assessment phase, time to first rescue antiemetic medication and parent or guardian overall satisfaction.

The results of the CINV study were that, one, more than half of the patients had no emetic episodes. Two, more than half of the patients did not require rescue medications and, three, 80 percent of parents or guardians were satisfied with drug use.

The PONV PK study, the CINV efficacy and safety study and the PONV efficacy and safety study all combined to contribute to an integrated safety analysis with a total of 797 patients. This analysis did not identify any new safety concerns. There were no deaths and 1 percent of patients

had non-fatal serious adverse reactions in both the drug and placebo groups.

In the drug group, five patients had serious adverse reactions that included one case of convulsions, dehydration, respiratory depression and staphylococcal infection and one case of combined nodal arrhythmia, hypocapnia and hypoxia.

In the placebo group, three patients had serious adverse reactions that include tachycardia, bronchospasm and exacerbated pain.

Based on all of the pediatric exclusivity studies, four sections of the drug labeling were changed. The Clinical Pharmacology Section, Pharmacodynamics Subsection, noted the population PK analysis of the PK and CINV studies.

The Clinical Studies Section described the CINV and PONV studies. The Precautions Section, Pediatric Use Subsection, noted that there is little information about

the use of ondansetron in pediatric surgical patients less than 1 month-old and in pediatric cancer patients less than 6 months-old.

It also noted that there was a slower drug clearance and a half-life of, approximately, 2.5-fold longer in pediatric patients 1 to 4 months-old compared to older children greater than 4 months to 2 years-old.

And, lastly, the Dosage and Administration Section noted that for the prevention of CINV in 6 month to 4 year-old patients, three doses of 0.15 milligrams per kilogram IV should be administered.

And for the prevention of PONV in 1 month to 2 year-old patients, a single dose of 0.1 milligrams per kilogram IV should be administered for patients weighing 40 kilograms or less or a single 4 milligram dose should be administered for patients weighing more than 40 kilograms.

This table describes the Adverse

Event Reports associated with ondansetron and reported to the FDA's Adverse Event Reporting System since market approval of the drug and prior to pediatric exclusivity.

For pediatric patients, there were 204 reports which comprised 6 percent of the total reports. Of these, 148 were U.S. reports. There were 126 serious reports with 74 being U.S. reports and 18 death reports with one being a U.S. report.

Focusing on the pediatric deaths, of the 18 crude count reports, there were 14 unduplicated cases. Seven of these cases were excluded due to confounding or insufficient information.

There was one case of an erroneous classification of death, one case of an unspecified cause of death in an infant with in utero exposure, two cases with a significant time delay between symptoms and/or death and the last ondansetron use, and three cases complicated by underlying medical

conditions, some with concomitant medications, including stage 4 neuroblastoma with multi-organ failure in chemotherapy, medulloblastoma with radiation and chemotherapy and idiopathic pneumonitis with progressive germ cell disease.

Of the seven remaining cases, these also were confounded by complicated underlying medical conditions, concomitant medications and/or insufficient details.

Case 1 involved a 14 year-old female with asthma one day status/post scoliosis surgery who experienced decreased respiratory rate, blood pressure and oxygen saturation after morphine and one hour after 4 milligrams ondansetron IV for nausea.

Case 2 involved a 10 year-old male on chemotherapy for rhabdomyosarcoma who experienced dizziness and collapse after 0.15 milligrams per kilogram ondansetron IV for vomiting.

Case 3 involved a 9 month-old male

with bone marrow allografts who developed acidosis, bundle branch block and cardiac arrest with QT prolongation after cisapride and 6 milligrams ondansetron for nausea.

Case 4 involved a 16 year-old female with disseminated lupus who developed septic shock or cardiomyopathy three days after ondansetron IV to prevent nausea.

Case 5 involved a 6 year-old male with a history of renal failure and renal hypoplasia with an unknown cause of death after 17 days of 3 milligrams ondansetron PO for nausea and vomiting.

Case 6 involved an 11 year-old female with congenital heart disease on antibiotics who developed decreased oxygen saturation, headaches, dizziness and respiratory failure one hour after 4 milligrams ondansetron IV for nausea of unknown etiology.

And Case 7 involved a 16 year-old male with end stage cystic fibrosis who

developed decreased oxygen saturation and arrested minutes after 2 milligrams ondansetron IV for nausea.

This table describes the Adverse Event Reports during the post-exclusivity period. For pediatric reports, there were 20 reports that comprised 6 percent of the total reports. Of these, eight were U.S. reports. There were 16 serious reports with five being U.S. reports and one death report with no U.S. death reports.

With regard to the pediatric death, there was one case with insufficient information to assess causality involving a 3 year-old male with an unreported cause of death who received 4 milligrams ondansetron PO for an unknown indication and duration. Because this was a foreign case, the FDA has been unable to obtain additional information.

This slide lists the 16 serious adverse events reported to have occurred during the post-exclusivity period. You will

note that five of these cases were U.S. cases. Out of the 16, there was one respiratory case involving respiratory depression, which is an unlabeled event, two hepatic cases, one of which included ascites, which is an unlabeled event, three allergic reactions or anaphylaxis cases, five neurologic cases and five other types of cases, two of which involved birth defects that are not included in the drug labeling.

In summary, some of these cases provided very little information and, in general, most of the patients involved had underlying conditions and/or were receiving concomitant medications making it difficult to relate the outcomes to ondansetron use.

This slide provides more details regarding the four unlabeled serious adverse events. Case 1 involved a 1 year-old child with respiratory depression and bradycardia after receiving 2 milligrams ondansetron IV times one dose to treat an unknown condition.

This was a foreign case with very little information.

Case 2 involved a 9 year-old boy with neuroblastoma who developed increased alanine aminotransferase, ascites and pleural effusion after receiving several cancer chemotherapy agents and 4 milligrams ondansetron daily.

Case 3 involved an infant whose mother had used ondansetron during pregnancy who experienced a foot or limb malformation, and Case 4 involved an infant whose mother had used ondansetron during pregnancy and who experience tracheal malacia.

This completes the one year post-exclusivity Adverse Event Reporting as mandated by the Best Pharmaceuticals for Children's Act. FDA recommends routine monitoring of ondansetron for adverse events in all populations and seeks the Advisory Committee's concurrence.

And in closing, I just would like

to acknowledge the assistance I received from numerous FDA staff in the Office of Surveillance and Epidemiology, the Division of Gastroenterology Products and the Office of Clinical Pharmacology.

ACTING CHAIR WARD: Does anyone disagree with that recommendation?

DR. SASICH: Just one comment, and is the FDA looking at the extent of off-labeled use for hyperemesis gravidarum that is apparently associated with the use of this drug? Is this a concern to the Agency? And it is an off-labeled use for pregnant women and it looks like the use is fairly sizeable.

DR. MURPHY: I would lean toward the division and to OSE to ask and, at this point, it appears this is not an area in which they have started a review of off-label use or what the adverse events from that off-label use are.

DR. SASICH: Thank you.

DR. JOHANN-LIANG: I just want to

make a point that in order to look into the AERS data and just to give you a scope of what is involved, when you're looking at an off-label use of a drug, you know, to do it justice you really need to go in and actually take out all the reports that actually tell you what it was actually used for, which means you have to do a manual review of all the cases.

And then, in order to really understand, that's just the numerator, so we really need to go in now to drug use databases and try to get a sense of what indications, what the diagnosis for these prescriptions going out to the folks are, and for a drug like this again.

So in order to get all that together, we really do have to prioritize as to which ones we're going to be doing such investigation, what the sort of -- the level of concern of the hypothesis is. And, you know, if the Committee feels that this is

something we must do, then we really -- that is why we're here to ask.

But right now, at this time, that is not one of the projects that we're working on. We're really short of resources, so --

ACTING CHAIR WARD: I think it's time for a break, but in trying to get back on schedule, why don't we resume at 10:25? Is that okay?

DR. MURPHY: Okay. The only thing, Bob, is that we take it then that the Committee is in agreement with returning to routine monitoring. Okay. We just want it --

ACTING CHAIR WARD: Correct.

DR. MURPHY: I wanted it in the record that that's what you said. Okay.

ACTING CHAIR WARD: So I said it.

DR. MURPHY: Okay. Thank you very much.

(Whereupon, at 10:10 a.m. a recess until 10:23 a.m.)

ACTING CHAIR WARD: All right.

Lisa Mathis is going to return to the podium and discuss Celexa citalopram.

DR. MATHIS: And again, you will see Hari's name on the slide. Why not moving? Okay. I'm going to discuss Celexa or citalopram, which is an antidepressant by Forest Labs. It is indicated for major depressive disorder in adults and there are no approved pediatric indications. It received its original marketing approval in July of 1998 and was granted pediatric exclusivity in July of 2002.

This drug was presented at the 2004 Pediatric Advisory Committee and there were some outstanding issues that we promise to come back and update you on. The three outstanding issues were neonatal withdrawal, ophthalmologic malformation as well as QTc prolongation.

I'm going to cover the first two subjects and then once I'm done, Dr. Lisa Jones will come up to discuss the analysis of

the QTc prolongation.

Just updating the drug use trends for citalopram, pediatric patients account for, approximately, 3.3 percent of the total U.S. prescriptions of Celexa from 2002 until 2006. Adult and pediatric prescriptions have steadily decreased from 2002 through 2006.

Celexa does have some relevant safety labeling, including a boxed warning for suicidality in children and adolescents. It is a pregnancy Category C and under the pregnancy section of labeling in the precautions section of labeling, we do have a description about neonatal withdrawal and a warning about considerations that the physician should use while prescribing this drug to women in their third trimester of pregnancy.

The pediatric use subsection of the precaution section of labeling includes information from two placebo-controlled trials in 407 pediatric major depressive disorder

patients and that there was not sufficient information to support a claim for use.

The dosage and administration section of labeling echoes that neonates exposed to Celexa and other SSRIs and SNRIs in the late third trimester have developed complications requiring prolonged hospitalization, respiratory support and tube feeding, and that the physician should consider tapering Celexa in the third trimester.

In summary, there have been labeling changes since this drug first came to the Advisory Committee in February of 2004. These include the boxed warning for suicidality, as well as information in the pregnancy section about neonatal withdrawal. There have been no subsequent reports of ophthalmologic malformations and the ones that had been reported previously were not the same. Therefore, there was no pattern established.

And I will now turn this over to Dr. Lisa Jones, who will update you on the QTc issues. Okay. This is not good. Who is doing that?

DR. JONES: Thank you.

DR. PENA: I should mention Dr. Lisa Jones, she is board-certified in the field of preventive medicine and public health.

DR. JONES: Okay. Thank you for the introduction and as Dr. Mathis had noted, I would like to present the Committee with an update of the review of QT prolongation with citalopram and escitalopram that is ongoing within the Division of Psychiatry Products.

There it is. I would like to begin with a summary of the past review of this issue. In the initial citalopram NDA as well as the escitalopram NDA, New Drug Application, only a 3 to 4 millisecond prolongation of the QT interval was observed in the Phase 3 trials in the drug-treated

patient compared to the placebo-treated patients.

The AERS, the Adverse Event Report System, at that time, did find cases that were suggestive of a QT prolonging effect for citalopram. Also within the NDA was a small Phase 1 study which when corrected for heart rate using the Friderica method found it 7 to 9 millisecond prolongation.

And finally, there was a citalopram-pimozide interaction study which was difficult to interpret, because it was an interaction study, but did have some elements supportive of a connection between citalopram and QT prolongation.

The QT related labeling as it currently stands essentially describes the data from the Phase 3 studies of the NDA. However, based on the findings described in the previous slide, other than that in the NDA, in May of this year the division requested the addition of an expanded labeling

statement regarding QT interval prolongation.

Okay. I would like to for the remainder of the review, I would like to give the overview of the issues that are currently ongoing and that includes the sponsor's submissions subsequent to the letter sent in May of this year, which include a direct response to points in the letter as well as analyses in three new patient databases.

There has also been an updated AERS Search in pediatric patients and, finally, I would like to list additional points in which we're having other FDA review.

I mentioned that the citalopram-pimozide interaction study was difficult to interpret. And in their response to the vision, the sponsor reached some different conclusions than the division did in their labeling letter. In response the sponsor also reiterated their belief that the Study 92104 was unreliable due to the specifics of the QT data collection. And thirdly, they noted that

many of the post-marketing cases were confounded by concomitant drugs or medical conditions.

In the first of the three new database analyses, the sponsor examined TdP-related adverse events in the Medicaid claims database. And in doing so, they found similar rates of these adverse events for citalopram and escitalopram relative to other SSRI and SNRI antidepressants.

In the second of the three new database analyses, as you may know, the General Practice Research Database is a large scale database of outpatient records in the UK. Here the sponsor searched for QT-related events in depressed patients age 18 to 70 who were treated with at least one antidepressant. And here similar to the Medicaid analysis they found similar rate for citalopram as compared to other SSRI antidepressants.

Okay. The sponsor finally performed an analysis in the AERS database.

They searched the database for cases with QT-related MedDRA terms and in which an SSRI or SNRI was a suspect drug. In contrast to the two other database analyses here, they did find some elevated risk for citalopram with, approximately, 1.6 as compared to other SSRIs or SNRIs.

The sponsor did provide some evidence, however, that there may be preferentially use of citalopram in medically compromised patients which may increase their underlying risk.

The FDA has performed a number of searches of the AERS database in conjunction with the review of this issue. For this Committee, I would like to present the results of the most recent search in pediatric patients. The search criteria were for patients age 17 or younger and it covered a three year period from August '03 to August '06. A variety of QT-related preferred terms were used, only some of which are listed in

this slide. And these search criteria identified three cases.

The first case was a literature report of a 12 year-old female who concomitantly took an unknown dose of citalopram with 4 to 5 grams of diphenhydramine. She was treated in the ER for altered mental status, followed by bradycardia, a wide complex rhythm and cardiac arrest. And this patient unfortunately had a fatal outcome.

The second case involved a 17 year-old male who was hospitalized for seizures, intermittent tachyarrhythmias and wide QRS complex rhythms following an intentional overdose of 2400 milligrams of citalopram. This patient's symptoms resolved with supportive care and his past medical history was notable for asthma and marijuana use. There was no information in the report on concomitant drugs.

The third and the final case

involved a 14 year-old male who developed QT prolongation while taking citalopram 40 milligrams per day for depression and anxiety. He was diagnosed with prolonged QT or with QT prolongation by a cardiologist six months after beginning treatment with citalopram. When the patient's drugs, at the time, which were citalopram and atomoxetine, were discontinued, the QTc interval decreased from 445 milliseconds to 408 milliseconds.

I should add that this patient had a history of QT prolongation with other antidepressants, including while taking a combination of paroxetine and imipramine.

Okay. And I would like to conclude with a listing of some specific elements that are active at the moment. The division has already reviewed the Phase 1 studies previously mentioned, the Study 92104 and the Citalopram-Pimozide Interaction Study, however, we are now taking advantage of FDA expertise outside the division and requesting

additional input on these studies.

We are likewise requesting additional input on the sponsor's most recent database analyses. In addition, we have requested an AERS data mining analysis, which will compare citalopram and escitalopram to other antidepressants, with a particular interest in having a comparative group which is not an SSRI antidepressant.

This update, both this presentation and the presentation by Dr. Mathis on Celexa provides information on the recent pediatric-related labeling changes and on the ongoing analysis of QT interval data within the Division of Psychiatry Products. We will now ask if the Committee has any comments. In addition, the FDA suggests that this product return to routine monitoring. Does the Committee agree?

ACTING CHAIR WARD: Discussion? Yes?

DR. DURE: I would like to sort of

-- this is parallel to Larry's comment before. There are a lot of prescriptions being written for citalopram and it's off-label. And this may be more of strategy versus tactics, but is this something -- when you talk about devoting resources of the FDA, I mean, this seems to me like this would be one that you would want to devote some resources to to look at off-label use.

DR. LAUGHREN: What specifically would you like us to look at? I mean, since we know that physicians use drugs for other than the approved indications. Is there a particular concern that you want us to explore?

DR. DURE: Well, I guess, this is true. This is coming up with one of the anticonvulsants later, the use in bipolar disorder. And I guess the problem is is that should these drugs be studied more, since they are being used so frequently, because these are not necessarily -- this isn't the same

thing that we see with antibiotics or with anticonvulsants for refractory epilepsy where you don't have many choices or is that the case?

I mean, I think it's all -- we're, you know, hypothesizing. Should we do more to try to figure that out?

DR. LAUGHREN: Well, you know, we would like to have more studies. We do have some studies. Obviously, they did studies to gain exclusivity and those studies were not sufficient to support a pediatric indication. But we know that citalopram and other SSRIs and other antidepressants are being used in pediatric patients to treat not only depression, but various anxiety disorders and perhaps other disorders. And we would like to have more data.

The question is how do you get more data? You know, FDA doesn't have the authority to mandate companies to study or, you know, there are other Government agencies

that have some interest in this and I think NIMH has sponsored some trials of SSRIs and other antidepressants in children and adolescents, but it really isn't -- FDA doesn't have primary authority to mandate or even encourage trials.

ACTING CHAIR WARD: Could I raise the issue about pulmonary hypertension? Tina Chambers in this last year with Linda Van Marter reported in a case-controlled design an increase in pulmonary hypertension from SSRIs as a class. And it's clearly not at a level that you would refer to it as a public health problem, because it's a rare diagnosis, but it's a serious one. And is there any consideration for trying to incorporate information of that nature or confirm it either included in the label or confirm the finding?

DR. LAUGHREN: You know, this is an issue that has been around for a while. I don't think -- again, we didn't come prepared

to discuss this issue, but, you know, my impression is that we don't think that there is enough information to support a causal link to justify, you know, including that prominently in labeling.

DR. JOHANN-LIANG: Just in regards to off-label use and etcetera, it's, you know, our role to try to provide these updates and try to think about what we can study and how to go about doing that. But it's really also important, I think, for the various organizations, communities, you know, to take on the effort of educating prescribers regarding appropriate use of, you know, all drugs and what they are indicated for or not indicated, what information is available, obviously, and to try to encourage, you know, studies that would answer questions all around. So it's a group effort.

DR. MATHIS: I think, too, that it's really important. We have been working with NIH, specifically NICHD, with the BPCA

and it's one thing that has frequently, you know, come into our radar is that a lot of drugs are used off-label without a lot of evidence. And it's something that we have really focused on that the general medical community really needs to try and find some way and we're trying to find some way, but it would be helpful for others if they had suggestions.

We really need to find some way to better educate physicians and other prescribers about how important it is when they are prescribing a medication that they know what they are prescribing for and what evidence that's based on.

And I know Dr. Ward can tell you about medical schools that are cutting out pharmacology courses altogether. And so we're over time doing less to teach the people who are responsible for prescribing medication about how to do that. So it is a very important area that we would love to

collaborate with other people in trying to educate physicians.

DR. MURPHY: I would like to just remind particularly the new Committee Members, we didn't review all of this for you, because, you know, the whole BPCA legislation was to try to get at this issue of all of this off-label use in pediatrics and no data. Okay. And that's what the exclusivity has been doing. It has been trying to go out and get controlled trials.

And we can tell you when we do that one of the reasons you hear so much about the biopharm in these reviews is that a fourth or third of the time we had the dose wrong or we found a new safety signal or the drug didn't work, you know. And particularly in some of our oncology products, this has become really important that we got these trials in any of them.

The SSRIs being another one, at least the way the trials were studied, that

didn't work. So clearly, everyone agrees that there is enormous off-label use, that we are treating children without a fraction of the knowledge we demand for adults and that this is an effort to try to go forward and get some of this information.

And so in the process of what we're doing now, the mandate we have today is to look at when we have done that, are there any additional safety signals, because we do know that, as one of our classic examples previously, there was a lot of increased use after these products do get studied.

So that's what we are trying to do for the studies. However, what we are telling you is that AERS is hypothesis generating. It won't answer the question for us often. I mean, sometimes something is very peculiar or very rare or so dramatic that we do get the answer. And we are interested in your hypothesis that you think need further study, you know, out of this.

So I think Tom's question was well, we know there is off-label use, but what question are we going to ask about it? What would be our question to go back and look at or is there a study that would help us address the issue that is being -- that they are looking at right now?

ACTING CHAIR WARD: Larry?

DR. SASICH: Yes, kind of going to Dr. Dure's point about a large amount of off-label use. I think one of the enormous deficiencies of the antidepressant medication guide is the fact that there is no communication there of the large number of negative studies of the use of these drugs in the treatment of major depressive disorder.

It would be -- and I have always thought for a long, long time if we did have medication guides for every drug that consumers and parents of consumers would know which uses are approved and which uses are not approved. And that is the point at which the

parent of a patient or a patient can go and get into a discussion with the physician about the risks and benefits of an off-label use.

It may be perfectly appropriate, the physician may be doing research in that area and he has got a strong feeling. But here we have got a bunch of negative trials and I would like to suggest that for, I guess I would like to suggest it, every medication guide and I don't think it applies to every medication guide.

But for the antidepressant medication guides, that they need to reflect the fact that we have a whole bunch of negative studies using these drugs in major depressive disorder. So I think that would go a long ways in dealing with the issue of appropriate off-label use, if there is a discussion between the physician and the patient or a patient's parent.

DR. LAUGHREN: You know, I think it's important to distinguish between negative

trials and whether or not you have shown that a drug doesn't work. I mean, the implication of your question is that if you have a lot of negative trials, that that's evidence that the drug doesn't work and you should convey that information to patients.

And I don't think that's necessarily the case. And it's very difficult to convey this information in labeling. And, in fact, the labeling for all these products does state what the evidence is for that particular drug in pediatric patients. I'm sorry?

DR. SASICH: I am only talking about the medication guides.

DR. LAUGHREN: Right. But what I'm saying is that it's difficult enough to convey that message to clinicians let alone to try and convey it to patients, because I don't know. You know, we have like 15 trials of SSRIs in major depression in kids and only 3 of those 15, you know, were nominally

positive.

Does that mean that these drugs are useless in treating major depression in kids? I wouldn't reach that conclusion. FDA is not telling clinicians that they shouldn't use these drugs in treating major depression in children. And we say that in labeling.

DR. SASICH: That should be used in the medication guide, also.

DR. LAUGHREN: Well, you know, it's difficult. How would you want to convey that in the medication guide? What message would you want to tell a parent?

DR. SASICH: The particular drug for which has been studied and which is not shown to be effective in the treatment of major depressive disorder. There should be a brief statement in the medication guide to that effect.

DR. LAUGHREN: Well, it's something. We can take that back and see whether or not there is a way to do that in a

way that conveys that message, but also doesn't, you know, give the message that the drugs are of no value. That we have evidence to suggest that they are of no value, because that's a different message.

ACTING CHAIR WARD: All right. Let me move on to the last question on the slide. Does the Committee agree with returning to routine monitoring? And let me put it another way. Does anyone disagree with returning this to routine monitoring?

DR. NEWMAN: Is that a question?

ACTING CHAIR WARD: Yes, that is a question, Tom.

DR. NEWMAN: Yes, no, I just had a question then about the slides. I didn't -- I might have missed this, but I didn't know what the TdP-related adverse events were. What TdP stands for.

DR. JONES: Sorry. TdP is Torsades de Pointes. The cardiac rhythm associated with QT prolongation.

DR. NEWMAN: Okay. Thank you.

ACTING CHAIR WARD: V tac. Okay.

DR. NEWMAN: Can I just --

ACTING CHAIR WARD: Yes.

DR. NEWMAN: -- clarify this?

ACTING CHAIR WARD: Yes. Okay.

DR. NEWMAN: So the plan is still it will be routine monitoring, but you are continuing to investigate the QT prolongation?

ACTING CHAIR WARD: Yes.

DR. NEWMAN: And because, I mean, my thought would be that the analyses done by the sponsors of the Medicaid data and the GPRD are actually much stronger methodologically than AERS if they were done right. But I would want FDA to look them over very carefully and make sure that they, you know, were done right and can reach valid conclusions. But if they were, I think these confidence intervals are very narrow and quite convincing.

ACTING CHAIR WARD: All right.

DR. JONES: Yes, but those analyses are being reviewed currently.

ACTING CHAIR WARD: Yes. Right. So that it really is underway for the SSRIs as a class. Is that correct?

DR. LAUGHREN: Well, that's --

ACTING CHAIR WARD: Or it's still open.

DR. LAUGHREN: It's a very good question. You know, the fact that you find no difference between citalopram and other SSRIs doesn't necessarily reassure you that there is not a problem here.

ACTING CHAIR WARD: Right, right.

DR. LAUGHREN: But the difficulty is that these drugs, all the SSRIs, were developed roughly 20 years ago when we weren't looking as carefully as we are now at the issue of QT prolongation. And the fact that you don't find much of a signal in a Phase 3 trial doesn't really tell you very much, because those are not done optimally to look

at that.

Ideally, we would have thorough QT studies for all these drugs, which is something that we are asking for for all drugs that are coming through development now. The difficulty is in knowing how to get that study done for a class of drugs that is 20 years-old and that's the challenge. But I agree that having more specific thorough QT information would help to answer the question for the entire class.

ACTING CHAIR WARD: Where is the NIH?

DR. LAUGHREN: Good question.

ACTING CHAIR WARD: Unless somebody else expresses a concern, we'll consider that the Committee concurs with returning this to routine monitoring. Okay. Thank you. Dr. Collins, you want to come talk about Oxcarbazepine?

DR. COLLINS: I am pleased to be able to present to you the one year post-

exclusivity adverse event review for oxcarbazepine. Trileptal or oxcarbazepine is an anticonvulsant. Although its precise mechanism of action is unknown, it is thought that oxcarbazepine's anti-seizure effect is exerted primarily via its 10 monohydroxy metabolite or MHD.

This metabolite locks voltage sensitive sodium channels resulting in stabilization of hyper-excited neuro-firing and diminution of the propagation of synaptic impulses. The drug sponsor is Novartis and the original market approval occurred on January 14, 2000 and pediatric exclusivity was granted on March 2, 2005.

Prior to the pediatric studies, oxcarbazepine was indicated for monotherapy and adjunctive therapy in the treatment of partial seizures in adults and children 4 to 16 years-old with epilepsy. The next two slides provide information about the use of oxcarbazepine in the outpatient setting.

2.75 million oxcarbazepine prescriptions were dispensed for all age groups during the 12 month post-exclusivity period. 28 percent of these prescriptions were for the pediatric population. There was a 2 percent increase in outpatient prescriptions for all age groups between the pre- and post-exclusivity periods with a 1 percent increase for the pediatric population.

Neurology was the most frequent prescriber specialty during the 12 month post-exclusivity period at 26 percent compared to pediatrics at 3 percent. The diagnoses most frequently associated with oxcarbazepine use in the pediatric population were convulsions at 30 percent and bipolar effective disorder at 22 percent.

13 trials contributed to the pediatric exclusivity studies. There were four pharmacokinetics or PK studies in a total of 218 patients age 1 month to less than 17 years-old utilizing oxcarbazepine monotherapy

or adjunctive therapy. There was one monotherapy efficacy and safety study in 92 patients age 1 month to 16 years-old utilizing low and high dose drug for five days.

There was one adjunctive therapy efficacy and safety study in 128 patients age 1 month to less than 4 years-old utilizing low dose oxcarbazepine for nine days or high dose oxcarbazepine for 35 days. And there were seven safety studies in a total of 337 patients age 1 month to less than 17 years-old utilizing oxcarbazepine monotherapy or adjunctive therapy for four to five days, less than 30 days or six months.

The PD studies consisted of two open-label age-stratified, pilot studies and population PK sampling employed in the two efficacy and safety studies. The PK results were that, one, younger pediatric patients required a greater weight-based dose to produce the same concentration. Two, the proposed dosing regimens for the adjunctive

therapy were adequate. And three, data could not be interpreted for the proposed monotherapy dosing regimens.

The monotherapy study was a multi-center, parallel-group, rater-blinded, randomized comparison of low dose drug at 10 milligrams per kilogram per day versus high dose drug that was titrated from 60 milligrams per kilogram per day with a 2400 milligram per day maximum.

The primary and secondary endpoints utilized a time to failure design. The primary endpoint was the time to meet specified exit criteria based upon a central rater-blinded reading of a 72 hour video-EEG. The secondary endpoint was the percent of patients meeting the exit criteria and the number of partial seizures as determined by electrographic manifestations alone.

The two exit criteria incorporated into the endpoints were, one, three study seizures with or without secondarily

generalized seizures or, two, a prolonged study seizure with an electrographic manifestation of at least five minutes.

And, of note, here study seizure is defined as a partial seizure having an EEG finding for at least 20 seconds and a behavioral manifestation. When the monotherapy efficacy data were analyzed, there was no difference in the primary endpoint between the low and the high dose groups.

The adjunctive therapy study utilized the design that was a multi-center parallel-group, rater-blinded, randomized comparison of low dose drug at 10 milligrams per kilogram per day for six days versus high dose drug at 10 milligrams per kilogram per day with a slow upward titration to 60 milligrams per kilogram per day, as tolerated, for 32 days with a subsequent 72 hour inpatient video-EEG evaluation.

The study's primary endpoint was the absolute change in study seizure frequency

per 24 hours from baseline where, again, a study seizure was defined as a partial seizure having an EEG finding for at least 20 seconds and behavioral manifestation.

There were multiple secondary endpoints that included the percentage change and study seizure frequency for 24 hours from baseline, the absolute change in the frequency of all electrographic seizures compared to baseline and the response to treatment.

The efficacy results for this study included, one, a greater absolute reduction in the number of study seizures in the high versus the low dose group. Two, a greater reduction in the high dose group's percentage change in study seizure frequency and absolute change in electrographic seizures. And, three, for patients under 24 months of age, there was no therapeutic effects seen when baseline seizure frequency was considered.

And this last bullet is

particularly interesting for it shows how the pediatric studies revealed a difference in efficacy in different pediatric sub-populations.

Seven studies and 337 patients contributed to an integrated safety analysis since there was a similar safety profile seen across all of the studies. The studies included the two efficacy studies already described, the two pilot PK studies already described, four extension studies that were six month open-label extensions of the efficacy in the PK studies and one additional open-label, multi-center, active-control, flexible-dose monotherapy study.

There were five cases of deaths occurring in the exclusivity studies, but each case was confounded by medical conditions, that is respiratory pathology or the seizure disorder and/or concomitant medications.

Case 1 involved a 10 month-old male with encephalopathy and a history of lung

infections who died from pneumopathy secondary to an increase in seizures two days after discontinuing oxcarbazepine.

Case 2 involved a 22 month-old male with a history of influenza and oral candida who died due to pneumonia that led to sepsis while on oxcarbazepine monotherapy.

Case 3 involved a 13 month-old female with developmental delay and static encephalopathy who died due to a progression of her seizure disorder, approximately, eight and half months after discontinuing oxcarbazepine.

Case 4 involved a 10 month-old male with a history of bronchitis and cortical dysplasia who died of sudden death two and a half weeks after elective cortical resection surgery while on oxcarbazepine.

And Case 5 involved a 40 month-old female with developmental delay and cerebral infarction who died due to bronchoaspiration after a four hour seizure while on

oxcarbazepine.

With regard to non-fatal, serious adverse reactions seen during the studies, 18.4 percent or 62 out of the 337 patients experienced serious adverse events with the most common being convulsions at 5.9 percent, status epilepticus at 3.9 percent and pneumonia at 3 percent. These adverse events are expected for this population and are included in the drug labeling.

9.2 percent or 31 out of the 337 patients discontinued their participation in the studies due to adverse events. The most common reasons for discontinuation were nervous system disorders at 6.5 percent, such as seizure, tremor, somnolence and ataxia and non-serious skin and subcutaneous tissue disorders at 1.5 percent.

Rates of discontinuation due to these adverse events were no greater than those in prior studies and these events are also listed in the drug labeling.

Based on the PK studies, there was a labeling change in the clinical pharmacology section related to the decreased weight-adjusted clearance of the 10 monohydroxy metabolite or MHD as age and weight increases in children.

The monotherapy efficacy results were noted in the clinical study section of the drug labeling. The labeling also noted possible explanations for why the monotherapy trial failed to demonstrate efficacy, including, one, having a short treatment and assessment period, two, the absence of a true placebo and, three, the likely persistence of plasma levels of previously administered anti-epileptic drugs during the treatment period.

Please, note that oxcarbazepine maintained its indication for monotherapy treatment in pediatric patients 4 years and older based on pharmacokinetics and pharmacodynamic modeling that the sponsor submitted after the issuance of the written

request.

Based on the efficacy results of the adjunctive therapy study, labeling changes were made in the Clinical Studies and the Indications Sections of the labeling. The Clinical Studies section noted the efficacy of adjunctive treatment in children 2 years and above and such adjunctive therapy in these children is listen as an indication.

Based on the PK data, there were also four additions to the Dosage and Administration section of the labeling, Pediatric Patients Subsection, that included, one, in pediatric patients 2 to less than 4 years-old, treatment should be initiated at a daily dose of 8 to 10 milligrams per kilogram generally not to exceed 600 milligrams per day given in a BID regimen.

Two, for patients under 20 kilograms, a starting dose of 16 to 20 milligrams per kilogram may be considered. Three, children 2 to less than 4 years of age

may require up to twice the oxcarbazepine dose per body weight compared to adults and, four, children 4 to less than or equal to 12 years of age may require a 50 percent higher oxcarbazepine dose per body weight compared to adults.

The third and fourth bullets here, in particular, demonstrate the importance of the pediatric studies in determining appropriate drug dosing regimens in the pediatric population.

The next three slides list the three sections of the labeling that were changed to include new safety information. In the Precautions section, Pediatric Patients subsection, safety data were added from a prior pediatric study that had not been included in earlier labeling.

The labeling notes that in this study of pediatric patients 3 to 17 years-old with inadequately controlled seizures in which Trileptal was added to existing anti-epileptic

drugs, cognitive adverse events were seen in 5.8 percent of the drug group and in 3.1 percent of the placebo group with concentration impairment being the most commonly seen event in the drug group.

Somnolence was seen in 34.8 percent of the drug group and in 14 percent of the placebo group and ataxia or gait disturbances were seen in 23.2 percent of the drug group leading to a 1.4 percent discontinuation rate in this group, and ataxia and gait disturbances were seen in 7 percent of the placebo group leading to a 0.8 discontinuation rate in that group.

The Precautions section, Pediatric Use subsection, noted the increase in the number of pediatric patients involved in clinical trials to 898 with 332 patients receiving monotherapy treatment. This section also noted that the age range of these pediatric patients had expanded to 1 month until 17 years-old.

And the Adverse Reactions subsection titled Adjunctive Therapy or Monotherapy in Pediatric Patients 1 Month to Less than 4 Years Old Previous Treated or Not Previously Treated with other Anti-Epileptic Drugs noted that, one, the most commonly observed adverse experiences were similar to those seen in older children, except for infections and infestations.

And, two, 11 percent of the 241 patients in this study discontinued treatment due to an adverse experience with the most common events associated with discontinuation being convulsions at 3.7 percent, status epilepticus at 1.2 percent and ataxia at 1.2 percent.

This table describes the Adverse Event Report associated with oxcarbazepine and reported to the FDA's Adverse Event Reporting System since market approval of the drug.

For pediatric patients, there were 409 reports, which comprised 16.5 percent of

the total reports. Of these, 242 were U.S. reports. There were 344 serious reports with 177 being U.S. reports and 21 death reports with five being U.S. reports.

Focusing first on the pediatric deaths. Of the 21 crude count report, there were 13 unduplicated cases with four being U.S. cases. Of the 13 unduplicated cases, one case occurred during the post-exclusivity period and 12 cases occurred between market approval and the post-exclusivity period.

The case occurring during the post-exclusivity period involved a 6 year-old male who died in China due to rhabdomyolysis. The child was treated with oxcarbazepine for nine days prior at a dose of 150 milligrams daily titrated to 300 milligrams daily, and the child was hospitalized for fever and CPK of 100,000.

There was insufficient information to assess the possibility of drug causality, because the report lacked important details

regarding the patient's complaint of muscle weakness, the presence of myoglobinuria, the presence of renal failure and other factors preceding the rhabdomyolysis such as the occurrence of seizures.

The remaining 12 death cases occurred prior to the post-exclusivity period and are confounded by other suspect medications, underlying medical conditions, family history and/or insufficient details.

There was one suicide case of a U.S. male with a self-inflicted fatal gunshot wound after eight months of oxcarbazepine starting at 300 milligrams per day and titrated to 1,200 milligrams daily to treat complex partial seizures.

The patient developed psychosis described as periods of confusion prior to death. He had no prior history of suicide attempts and there were no concomitant drugs per autopsy. His family history was positive for depression, schizophrenia and drug abuse.

There were four seizure cases, including a case of an 11 year-old male with a history of nocturnal seizures who died due to asphyxiation when he became wedged between the bed and the nightstand during an evening seizure, a case of a 9 year-old patient who experienced status epilepticus during the night and died, a case of a 15 year-old female who died due to cardiac arrest after seizure activity had induced a comatose state, and a case of a 10 year-old male with multiple organ system disorders who experienced status epilepticus and subsequently died due to multiple organ system failure.

There were two cardiac cases, including a case of a 16 year-old patient who experienced fatal cardiac arrest nine days after an increased Lamictal dose, and a case of an 11 year-old female on multiple suspect medications who died due to myocarditis.

There were two unspecified deaths, including a case of an 11 year-old male who

had received Trileptal for five to six years without incident, had discontinued the drug when diagnosed with lupus without improvement and had restarted the drug for a year prior to death, and there was a case of a 2 day-old male whose mother had received multiple medications during pregnancy.

And there were three additional cases, including a case of a 15 year-old patient who died of hepatic failure after experiencing an inhalation pneumonia and subsequent hypoxemia, hypotension and compromised vascular circulation to the liver, a case of a 10 year-old female receiving oxcarbazepine for an unspecified disorder for one and a half years prior to developing nephrotic syndrome that did not improve with corticosteroids and the discontinuance of oxcarbazepine, and a case of a 4 year-old male with a history of congenital hydrocephalus who died due to infection peritonitis and septicemia after experiencing an intestinal

perforation associated with the placement of indwelling gastric catheter.

With regard to the non-fatal adverse events since market approval, there were seven cases of non-fatal hypersensitivity reactions.

There was one anaphylaxis case involving a 4 year-old male with progressive stridor, drooling and croupy cough that started 30 minutes after his first oxcarbazepine dose. The patient recovered after hospitalization and treatment with epinephrine, dexamethasone and diphenhydramine.

The anaphylaxis case prompted a focused review of all pediatric severe hypersensitivity reactions since market approval leading to the identification of the six non-fatal angioedema cases.

Case 1 involved a 5 year-old male with angioedema on 7 ml po oxcarbazepine every 12 hours with unclear timing of the reaction

relative to drug use, and there were multiple concomitant medications.

Case 2 involved a 5 year-old male with periauricular edema and an allergic exanthema occurring four days after starting 300 milligrams per day po oxcarbazepine. Symptoms resolved within seven days after oxcarbazepine discontinuance and the administration of IV corticosteroids.

Case 3 involved a 7 year-old female with an urticarial rash, facial edema and feeling of suffocation occurring one month after initiating 600 milligrams per day oxcarbazepine. Symptoms resolved with Urbason and it was unclear if the oxcarbazepine was discontinued.

Case 4 involved a 9 year-old female with a rash and eyelid edema three days after decreasing her oxcarbazepine dose to 300 milligrams per day after she had experienced dizziness and diplopia on 400 milligrams per day. The symptoms resolved after

oxcarbazepine discontinuance and corticosteroids.

Case 5 involved a 12 year-old male with facial edema, an allergic exanthema and conjunctivitis occurring three days after initiating 600 milligrams per day po oxcarbazepine. Symptoms resolved within five days after oxcarbazepine discontinuance and corticosteroids, and the case was assessed as probable oxcarbazepine causality.

Lastly, Case 6 involved a 16 year-old female with hand and eyelid edema and rash after eight doses of 3 milligrams BID po oxcarbazepine. The patient in this case was also taking isoniazid and there was no information available on symptom resolution and it was unclear if the oxcarbazepine had been discontinued.

Of note, there are two sections of the drug labeling related to hypersensitivity reactions. The Warnings section states that 25 to 30 percent of patients with

hypersensitivity reactions to carbamazepine will experience hypersensitivity reactions to Trileptal, and the Adverse Reactions section notes that angioedema has been observed in association with Trileptal.

This table describes the adverse events reported during the post-exclusivity period. For pediatric patients, there were 88 reports which comprise 18 percent of the total reports. Of these, 59 were U.S. reports. There were 82 serious reports with 53 being U.S. reports and one foreign death report that I have already described.

In order to better understand the context of the Adverse Event Reports during the post-exclusivity period, the next two slides list the indications and the outcomes associated with these reports.

There were 63 indications associated with the Adverse Event Reports that included seizure at 40, bipolar disorder at 6, affective disorder at 5, attention deficit

hyperactivity disorder at 4, no indication for fetus in utero with passive exposure at 4, abnormal behavior at 2, labile mood at 1 and opposition defiant disorder at 1.

There were 86 reported outcomes associated with the Adverse Event Reports with 67 being serious adverse events and 19 being non-serious. Out of the 88 crude count of pediatric Adverse Event Reports there were 84 actual unduplicated cases or reports and 83 total non-fatal cases that included serious and non-serious cases.

Of the 83 non-fatal cases, 52 were cases of unlabeled or unexpected events and 31 were cases of events that were listed or implied in the drug labeling. The 52 cases of unlabeled or unexpected events, including serious and non-serious cases, are categorized by organ system on this slide.

For these cases, the events were similar to those observed in adults excluding the in utero events. In addition, there were

no compelling cases that suggested a potential safety signal with the exception of the anaphylaxis case already described and is listed here as immunologic.

In order to demonstrate the overall confounding nature of these cases, the next four slides describe the neurologic and the psychiatric events since they were the two most frequently involved organ system.

For the neurologic, unlabeled adverse events, the 10 cases were confounded by insufficient details or alternative explanations for the adverse events. There was a case of a 13 month-old female with an unknown genetic disorder on oxcarbazepine and other drugs who experienced myoclonus without an EEG abnormality. The dose of oxcarbazepine was decreased and the myoclonus disappeared.

There were two seizure cases. One case was linked to an increased Wellbutrin dose and the other case lacked details or an outcome.

The seven other cases involved events that were explained by alternative etiology or that continued after oxcarbazepine was discontinued. These included two cases of sedation, one case of somnolence, one case of forceful eyelid closure, one case of dystonia, one case of depression and one case of mental retardation.

For the psychiatric unlabeled adverse events, the nine cases were confounded by underlying medical conditions and/or concomitant medications. For the three suicide attempts or suicidal ideation cases, there was a 14 year-old male with bipolar disorder who experienced suicidal and homicidal ideation that was not new behavior.

There was a 15 year-old female with a multiple drug overdose, including oxcarbazepine and it is unknown if she had been prescribed oxcarbazepine. And there was a patient with bipolar disorder on multiple medications who experienced anger, agitation

and frustration that continued after oxcarbazepine was discontinued, and this patient later attempted suicide by ingesting oxcarbazepine.

For the three hallucination cases, there was a 9 year-old female on 1,200 milligrams daily of oxcarbazepine for 16 days for seizures who experienced visual hallucinations and an increased number of seizures. Oxcarbazepine was discontinued and the patient recovered.

There was a 7 year-old male who experienced visual hallucinations of snakes following increased doses of oxcarbazepine to 1,500 milligrams and dexmethylphenidate. Oxcarbazepine was discontinued and the patient recovered.

And there was a patient on multiple drugs to treat attention deficit hyperactivity disorder who experienced hallucinations. An outcome was not reported for this patient.

Lastly, the three other psychiatric cases included a patient with epilepsy, an unknown duration of oxcarbazepine treatment who experienced attention deficit hyperactivity disorder.

There was a patient on oxcarbazepine concomitantly with Adderall who experienced tantrums, aggression and weight gain. Oxcarbazepine was discontinued and there was no outcome reported for this patient, and there was a 14 year-old boy with severe learning disabilities who experienced breath holding spells.

Of note, there is drug labeling related to cognitive or neuropsychiatric adverse events noting that the most common central nervous system adverse events are cognitive symptoms, including psychomotor slowing, difficulty with concentration and speech or language problems, somnolence or fatigue and coordination abnormalities, including ataxia and gait disturbances.

In summary, with regard to the exclusivity studies, the deaths were confounded by suspect medications, underlying medical conditions and/or insufficient details. And the most common adverse events seen in pediatric patients 1 month-old to less than 4 years-old were similar to those seen in older children and adults.

With regard to the adverse events seen since market approval, FDA's Division of Neurology Products is evaluating hypersensitivity reactions to further consider if there is an association with oxcarbazepine. And with this, I have now completed the one year post-exclusivity Adverse Event Reporting as mandated by the Best Pharmaceuticals for Children Act.

In a few moments, Dr. Evelyn Mentari from the Division of Neurology Products will present an update on the division's independent analysis of suicidality in controlled clinical trials in all anti-

epileptic drugs.

And after Dr. Mentari's presentation, the following questions will be posed to the Advisory Committee. Does the Advisory Committee concur with the Division's approach and does the Advisory Committee recommend routine monitoring of oxcarbazepine, at this point?

And in closing, again, I just would like to acknowledge the numerous folks that assisted with this presentation from the Office of Surveillance and Epidemiology, the Division of Neurology Products and the Office of Clinical Pharmacology.

ACTING CHAIR WARD: I think we are going to hold questions until after Dr. Mentari presents.

DR. PENA: Dr. Mentari is a medical officer on the Safety Team in the Division of Neurologic Drug Products. I should also mention that Dr. Russell Katz, the division representative here at the table, is

Division Director, Division of Neurology.

DR. MENTARI: Good morning and thank you for this opportunity to speak about our division's evaluation of suicidality and anti-epileptic drugs.

The Division of Neurology Products is analyzing the potential association between anti-epileptic drugs and suicidal thinking and behavior in placebo-controlled trials. The division's analysis is independent of the post-pediatric exclusivity post-marketing adverse event review, which Dr. Collins just presented.

Post-marketing cases of suicidal thinking and behavior are difficult to interpret. There are known limitations of post-marketing data due to their anecdotal and uncontrolled nature and patients with epilepsy and other illnesses for which anti-epileptic drugs are being prescribed have increased risks of suicide when compared to the general population.

An anti-epileptic drug sponsor approached the division with concern of a suicidality signal in their controlled clinical trial database. In response, the division initiated an analysis of suicidality events in controlled clinical trial databases of all anti-epileptic drugs. Sponsors were asked in March 2005 to provide data from their placebo-controlled trial experience and our division will conduct a meta-analysis of all data.

Our standardized approach is based on previous FDA analysis of suicidality in children and adolescents treated with anti-depressants. In this analysis, pediatric patients treated with anti-depressants were found to have an increased risk of suicidality compared to those treated with placebo.

Our analysis includes parallel-arm, placebo-controlled trials with at least 20 subjects in each treatment arm. A search for events related to suicidal behavior or

possibly related to suicidal behavior was performed by the sponsors using search terms specified by FDA.

Our search terms include the following, preferred terms with the text strings "suic" or "overdos," including all events coded as "accidental overdose," verbatim terms with the text strings "attempt," "cut," "gas," "hang," "hung," "jump," "mutilat-," "overdos," "self damag-," "self harm," "self inflict," "self injur-," "shoot," "slash," "suic," "poison," "asphyxiation," "suffocation," "firearm," and these events were screened for false positives.

Our search terms also include all deaths and other serious adverse events and all adverse events coded as accidental injury.

After events were found using this search strategy, structured narratives were prepared. Based on these narratives, events were classified into seven categories and

classification was done by raters blinded to treatment.

This is a list of our seven suicidality event categories and they include completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, suicidal ideation, self injurious behavior, intent unknown, not enough information, fatal, and not enough information, non-fatal. And this is a list of the drugs to be evaluated.

At this time, nine sponsors have submitted data and the data received so far includes 36,290 subjects from 170 trials. The oxcarbazepine data has been submitted.

Of the nine submissions received so far, this chart represents the age distribution and of the nine submissions received so far, 29.4 percent of trials have a trial indication of epilepsy. 34.6 percent of trials have a trial indication related to a psychiatric diagnosis and 34.6 percent of

trials have another trial indication.

As for the oxcarbazepine submission, there are 12 trials which include a total of 2,370 subjects and 1,470 of those subjects were treated with the Trileptal. And, again, this chart represents the age distribution of the data received.

In the oxcarbazepine submission, 55.3 percent of the trials had a trial indication of epilepsy. 4.9 percent of trials had a trial indication related to psychiatric diagnoses and 39.8 percent of trials had indications related to other etiologies.

In terms of our future plans, our meta-analysis will proceed once all sponsor submissions are received and, depending on results of the analysis, data may be presented at an advisory committee meeting and/or regulatory action may be indicated. This concludes my talk. Thank you very much.

ACTING CHAIR WARD: Very good. I believe the questions before the Committee

then are whether routine monitoring is appropriate from this point forward.

MS. DOKKEN: I have a question.

ACTING CHAIR WARD: Okay. Debbie?

MS. DOKKEN: I guess this is more a process or clarification question, but the recommendation is for "routine monitoring," yet we heard about ongoing investigation of hypersensitivity reactions and independent analysis of suicidality.

And there is a part of my brain that can't quite say this is routine if these other analyses are going on independently, and there is a part of, you know, sort of thinking about the public that routine doesn't seem the appropriate word either.

So could someone clarify? Is this a process question, a clarification question or just me?

DR. MURPHY: No, we -- because this is an active process that is ongoing right now, we did not want to indicate that we

thought any other adverse event searching was going to in the AERS database.

You know, in other words, if we come back in another year with more AERS data or two years, that is why that question was phrased the way it was, because we think we have the best possible process which is the re-analysis of 170 trials going on right now.

So it does seem a little disconnected, I agree, but that is what we're trying to say. As far as our just coming back and giving you another follow-up on adverse event report, we don't know that that is, you know, going to be very helpful.

ACTING CHAIR WARD: Yes. It seems to me that part of the issue is have we adequately fulfilled the mandate under BPCA at this point in time. It clearly has identified additional areas of concern that the Agency is undertaking, but it's beyond the scope, I think, of BPCA.

DR. MURPHY: The Committee can say

that you think the division should complete their review, decide whether they want to change labeling or not or bring it to another advisory committee, and that's fine. You could say we want you to give us outcomes, you know, of what the division finds.

You know, there are a number of options. I don't want to be putting words in your mouth, because the division basically has outlined, you know, we have a huge task before us. I think anybody would agree with that and we're not sure where it's going to come out yet, but that we're trying to tell you that we are being very attentive to making sure that this issue is addressed.

So without being any more directive, it's up for discussion by the Committee for what other comments that you may have or suggestions or requests.

ACTING CHAIR WARD: Rich and then Tom.

DR. GORMAN: I am probably having

less trouble with dichotomous statements than some people, I would be comfortable, even though I'm not voting, for a routine continued analysis, but with the assurance from the Agency that any pediatric relevant results from the independent analysis for suicidality and the hypersensitivity get reported to this Committee.

DR. CNAAN: Along the same lines, for the 170 trials, are you receiving actual raw data or only the results to combine in a meta-analysis?

DR. MENTARI: We have the raw data.

DR. CNAAN: Okay.

DR. MENTARI: We actually had a data request that was standardized for all sponsors.

DR. CNAAN: Because in looking at these 36,000 and whatever subjects, there are maybe 2,000 subjects under the age of 17, about pediatric subjects, and I think I would

like to request a sub-analysis or something focusing on that group.

DR. MENTARI: That is certainly part of our plan, yes.

ACTING CHAIR WARD: Okay. Can I ask a more technical question? The infants under 24 months for whom efficacy was not demonstrated, do we know that they had -- since the clearance seems to increase at that younger age, do we know that they had comparable AUC exposure to the group that demonstrated efficacy?

DR. KATZ: I don't know the answer to that off the top of my head, but I do know that I believe we knew about the clearance differences when the doses were determined for the study, but I don't recall. Maybe there is somebody else in the room who recalls whether or not we had the exposure data specifically. I doubt we did in the trial but, yeah, I don't -- I mean, there is no way it would be --

ACTING CHAIR WARD: When I skimmed back through, I didn't see any reference to pharmacokinetics in the analysis, as opposed to just efficacy.

DR. KATZ: Yes, but, again, I don't think we had plasma level data in the trial.

ACTING CHAIR WARD: Other questions, comments? Sorry. Hi, Tom.

DR. NEWMAN: Hi. Yes, two things. One, you know, as I seem to keep pointing out, it is dismaying that they got the exclusivity when one of the trials they did, the FDA felt was not adequately designed or controlled and the results were uninterpretable. That is the monotherapy study and so I guess just to try to figure out how that happened and keep that from happening in the future.

And then a general comment about how adverse events are reported. This is true for many, maybe most drugs, maybe all drugs,

that the way FDA reports these is just giving a table of which ones occurred in more than 5 percent of the subjects, but without anything that will help the user of the label to tell whether this is a causal relationship and whether it's statistically significant.

And so reporting, for example, that the adverse events are similar to those that were reported in adults, except that there were more infections and infestations, seems to me kind of silly because, of course, children get more infections.

And so unless there is some thought there that what you are reporting relates to something that is causally related to the drug, I don't understand what the point is of reporting it and would urge that these tables of adverse events include, you know, the difference and whether it's statistically significant between drug and placebo or between the various drugs, so that the person reading the label will know which ones are

actually important and which ones are just the fact that these are children and they get infections.

ACTING CHAIR WARD: But in some of these tables, they are describing simply children or only children and they do have the placebo group side-by-side. I think what is missing is the statistical analysis of those two frequencies.

DR. NEWMAN: Yes, that's missing.

DR. KATZ: A couple of things. Yes, first of all, the second point about the incidence of -- it's hard to know exactly how to apply statistics to those sorts of things and we typically don't. We just sort of present what happened more often on drug and placebo, and sometimes we even say in a sort of footnote of the table what happened more often on placebo than on drugs to give an idea of what sort of things happen in these populations.

But we don't typically subject

these sorts of things and there are, of course, many, many, many comparisons to formal statistical, you know, inferential statistics. It's hard to know what that would mean.

We just believe it's -- and, again, it's done differently across probably different groups, some tables of incidence of 5 percent and at least twice as great on drug compared to placebo. So I'm not sure it's immediately obvious how to figure out which ones are drug-related other just to say this happened more on drug than on placebo.

The other thing about the monotherapy and granting exclusivity on the basis of a negative study, I don't think we thought that the study -- well, certainly, going into it we didn't think that the study was poorly designed.

I think it was high dose versus low dose, which is -- it's very, very difficult to do monotherapy studies in epilepsy, placebo-controlled monotherapy

studies, and so high dose versus low dose is-- you hope you pick a range of doses that will allow you to demonstrate a difference, so that the study would be interpretable.

And, as it turned out for various reasons, we didn't think it was interpretable and that happens, but I think the intention going in was to design a study that looked on face anyway as one that could show a difference and that was the goal. It just didn't work out.

DR. MURPHY: Tom, this is a problem. It gets to when you can't do placebos or you're doing add-on trials and you have an option sometime of doing a dose control and if you don't pick the right doses, even though on face they ought to be high and low enough that you would be able to see a dose response, sometimes you don't.

And, actually, in our anti-hypertensives we have seen this happen a couple of times now, but the whole -- it

doesn't mean -- I guess that we're trying to say it doesn't mean that they were poorly designed. It meant that, yes, they didn't get the right dose range and you could say we should learn from that. But, clearly, people who get exclusivity fail trials. That's the way the law is written.

DR. NEWMAN: I think the point is that it wasn't just a negative trial. Just reading from the executive summary, it says comparison of results across trials indicated strongly that the Monotherapy Study 2339 was not adequately designed and conducted. The major deficiencies include the short duration of the study and lack of documentation of seizure rate at baseline. These deficiencies render the study results uninterpretable.

So it's not just a study that wasn't successful and, you know, had a negative result, which is what you expect. It was a study that FDA concluded generated results which were uninterpretable. That

concerns me.

DR. MURPHY: That is the second part. Okay. I just want to make sure we got out that the dose design is an issue and sometimes you pick them wrong.

The other question of when you actually get all the way into the data and you find out that people didn't do what they were supposed to do and they still have gotten exclusivity, because you hadn't gotten that far into the data when you grant exclusivity, is something the Agency has articulated as a problem we have and we would rather be making that determination.

Again, it doesn't have to succeed, but we would rather be making that determination after we have had sufficient time to get into all of the data. So we're in agreement with you on that point.

DR. JOHANN-LIANG: I just wanted to -- if it's okay, I just wanted to add a little bit about the causality of the adverse

event issue.

Figuring out what the safety issues actually do to the drug is sort of a moving target. I mean, at the time of clinical trials coming in, the hypothesis there is to -- is an efficacy endpoint and, you know, you get a whole slew of different adverse events and the two arms coming in.

It's very hard for us at that time to say much of anything, unless something really strikes out and if something is -- so it's hard to sort of tease out what we think will be drug causal, what we think will not be drug causal at that point and sometimes, you know, it's important to have a listing of what went on, so that as the body of evidence grows, you can grow with the data coming in, look at the aggregate of the integrated safety.

And so there is some time. There are inconsistencies in how we do this and how we put it into tables, but there are some

rationales as to why things are projected this way.

DR. NEWMAN: Yes, I do think, I mean, what Dr. Katz said, that, I mean, having that list of tables and showing the ones that are more often with drug than placebo or more often, you know, that's helpful.

But, again, as the consumer of that information, the question is, well, was this more than what would have been expected by chance, and so the two things that you can do to look at that or one are what are the confidence intervals around the estimates.

And then you can just sort of see, okay, well, there were four things where a drug was significantly worse, yet there is also four things where placebo was significantly worse. You sort of go -- you know, when you looked at 100 different things, you're not impressed, but if all of the bad things are on the drug side rather than on the placebo side, that is a little bit more

impressive and that is information which currently isn't always available.

DR. JOHANN-LIANG: And I think we would love to have that kind of more of a quantitative, you know, more of a scientific-driven look, but it's not always so easy to be able to do that. And we really do try to be balanced in how we present it. And, again, as more data comes in and we're able to -- you know, it is a safety analysis, so we're trying to aggregate on it.

We can go to that type of more quantitative risk-benefit ratio and even an adverse, you know, one arm to the other statistical analysis.

ACTING CHAIR WARD: Yes, Dr. Cnaan?

DR. CNAAN: There is one risk in doing all of this significance testing is that quite a few of these exclusivity studies are not large, are not powered to begin with to look at any adverse event whose incidence is

on the low side, let's say anything less than 10 percent.

And if we go to the trouble or the FDA goes to the trouble or the sponsor goes to the trouble of doing all of these significance testing, we might end up sending the wrong message by saying it wasn't significant and to begin with, it wasn't even powered to do it, so we had better proceed with caution there.

DR. KATZ: You know, and not only that, something I said earlier, that there is untold numbers of these events and it's hard to know how to apply statistics. I mean, what do we call a different -- what do we call statistically significant, a nominal significance, a .05 even though you have made 100 comparisons. Does it have to be adjusted for multiple looks? I don't think it's, again, immediately obvious what the best way is to present it.

I agree, there's lots of things that happen that are more often on drug than

placebo and there are some things that happen more often on placebo than drug and it is hard to know how to balance those two, how to decide which one is real and which ones are a chance finding. We don't have a perfect solution.

DR. MURPHY: And I would say that, at this point, our solution is try to give you the placebo versus the other at least and right to the point that was just made.

These studies often are small and we don't want to actually send a more reassuring message than is there, and that is why the subsequent follow-up in the post-marketing, as has been pointed out, as flawed as our data collection system is, post-marketing, once you get out into large numbers, is where you're going to see what really happens, and that we try to use that data to change things as we learn.

ACTING CHAIR WARD: All right. Let me bring the Committee's attention back to

the two questions. Does the Advisory Committee concur with the Division's approach? Anyone not concur with the Division's approach? Let's put it that way. Okay.

Does the Advisory Committee recommend routine monitoring of oxcarbazepine, at this point? Does anyone not? Okay. Larry, what is your comment?

DR. SASICH: I like Richard's statement. Can that be part of our recommendation, that the ongoing monitoring about the suicide risk does, in fact, come back to this Committee for review?

ACTING CHAIR WARD: I think both points that is once the meta-analysis is conducted that it would be helpful for this Committee to hear those results, especially focus on the pediatric sub-population. Yes.

DR. SASICH: Thank you.

DR. MURPHY: Okay. So particularly this Committee wants to see those 2,000 and some. At minimum now, we have

patients that are classified as pediatric, have that data analysis re-presented to them whenever the division has completed that review. And was there --

PARTICIPANT: The hypersensitivity.

DR. MURPHY: And the hypersensitivity. Okay. Thank you. Oh, you want to say something?

DR. KATZ: Just about the hypersensitivity. That's a much more routine sort of thing that we do. If we believe there is a signal from the post-marketing, we go and look at the data and make a decision as to whether or not the labeling ought to be changed.

Again, that is sort of -- that is different, sort of qualitatively, from this suicidality analysis, which is a much more formal, much more major, so I'm not exactly clear from our procedure.

Does that mean the next time if

and when we decide, for example, to make a labeling change, we have to come back and tell the Committee or how does it -- I'm just trying to learn the process.

ACTING CHAIR WARD: Let me just try to clarify with the Committee. The label as written contains an extensive list of multi-organ hypersensitivity reactions that seems to me to comprise or to contain all the events that have been mentioned today as occurring.

Is there concern that pediatrics is at increased risk? Is there a specific issue about hypersensitivity that we think needs to be addressed?

DR. KATZ: Well, again, what was presented here is something that the division is still looking at is specifically the question of anaphylaxis and angioedema. And, again, we may, after having looked at the data, decide just hypothetically that the labeling needs to be changed. I think

angioedema or anaphylaxis is in sort of what we call the laundry list at the end, but it's possible that we might make that more prominent just hypothetically.

So that is something we sort of do in the routine course of our work. Assuming we did that just for argument sake, what is the process? Do you want to hear about that? Do we need another presentation of that or what is -- I'm just trying to figure out the process at this point.

ACTING CHAIR WARD: Let me pose that question to the Committee. Do you want to hear about the outcome of their analysis of hypersensitivity, especially with respect to angioedema and anaphylaxis?

DR. GORMAN: Both the outcome and the determination by the Agency of what their recommendation based on that data would be.

So if you say that you have come, you have analyzed the data and the labeling is adequate in your opinion, we would like to

hear that. And if it's not adequate and you want to change it, we can either support or help you phrase it in a way that will make it move faster through the Agency after it comes from an advisory committee.

ACTING CHAIR WARD: Is that okay?

DR. MURPHY: I think what we're just -- fundamentally, you want to hear the outcome whether it's nothing and if it's something, they can come back and say it was something. The sponsor agreed with us. We got it in the label. Are they going to come back and say we think it's something, we're still in negotiation, here is what the issues are.

ACTING CHAIR WARD: Yes.

DR. MURPHY: That's what --

ACTING CHAIR WARD: And I would maintain if it's no change and it's adequately covered, that that doesn't even require presentation, but could be covered in written documentation to the Committee. Why waste

your time and ours in a presentation? I mean, yes, I agree. I'm speaking on behalf of the Committee. Is that okay? All right.

We are moving ahead. I thought we were going to just not talk about the next one. Is that right? Okay. So, Dr. Johann-Liang, do you want to deal with oseltamivir?

DR. PENA: I should also mention that at the table we have Dr. Deborah Birnkrant, Division Director, Division of Antiviral Drug Products.

DR. JOHANN-LIANG: I'm going to ask Dr. Mosholder to sit at the table as well. We're going to be tag teaming this talk, just logistically it came out better this way. I'm going to sort of give you an update, bring you to where we are, a little bit of history, especially for the new Members and then Dr. Mosholder, who is our divisional, you know, psychiatric expert and our epidemiologist, will walk through with you our most latest review, another one. We have done a series of

these on Tamiflu and neuropsychiatric events.

Okay. So I'll go through some of the background and then go over with you a little bit more in detail what happened last year in November regarding this drug and then give you the safety update. You wanted to hear about what happened with the skin and hypersensitivity that was discussed last year. I'll give you some update on drug use data to put things in perspective.

I am going to touch upon the pediatric death and then Dr. Mosholder will follow me with a more substantial discussion on the update in neuropsychiatric events.

The drug is oseltamivir. The dosage form are capsules and oral suspension. It is an antiviral, a neuraminidase inhibitor. The sponsor is Roche and the current indications are the treatment and prophylaxis of influenza for, you know, patients greater than 1 years of age.

It was first approved in 1999 with

the capsules in adults and then the prophylaxis indication was added and went down to the age of 13 and above in 2000. The suspension was approved also later that year. And then last year, we presented the pediatric exclusivity, the BPCA Section 17 review, in November.

That presentation was basically based upon the March 2004, one year following that cutoff. So it was really June/July that the initial review was done. That review was followed-up with a formal review from OSE in December. So there was a review done in December. And then that was around the same time that the prophylaxis of influenza for pediatrics 1 to 12 was approved.

That's also the time when the skin labeling went into, you know, the current label. And then this year, because of the Committee's charge, we came back with another year's review of neuropsychiatric events that takes account the 2005/2006 flu season and

that is what's going to be presented today.

So going back to last year in November when you all were here, there was a long discussion actually on this drug. The FDA presentations included clinical trial safety data by Dr. Linda Lewis. There was also pediatric post-marketing adverse event review by Melissa Truffa and literature review as well.

Presentations from CDC and Roche were also done at that time. The consensus in the room was that it was really unclear if these neuropsychiatric adverse events represented a safety signal specific to the drug or a drug overlay on top of the disease manifestation.

And there was a lot of discussion regarding this issue of the Japanese reporting. Most of the events were from Japan and the drug, you know, for whatever reason is used in a tremendous amount in Japan. And there was also a lot of discussion about

whether there were some specific flu disease manifestations to the Japanese that's different than the rest of the world.

There was a discussion about the severe skin reactions and that was thought by the Committee to be more likely drug-related than the neuropsychiatric discussions that were ongoing.

So the charge last year was that we, the FDA should come back after an extra flu season and just to give you guys an update. I mean, it was kind of like the discussion that went on right now. If there wasn't much to update, then we can just kind of say that or if there was something to update, then you wanted to hear it.

But what you really wanted was after two years of flu season to really come back to this Committee and give an accounting for what has happened. And you also asked that the company who has a variety of other studies ongoing come back as well and present

to the Committee with an update on the safety. And if there are other efficacy studies being done.

Okay. So to start off with to give you an update on the drug use data for this drug, this is our assessment done by the DCRCUS folks with us using that Verispan that I talked about earlier. And this looks at sort of the flu season one year span. So you can see that. You saw this data last year for 2005 after the end of the 2004 flu season and that's sort of the blue bar is the total market use and then the pink, you know, the dark pink bar is the pediatric use in this country.

The last set of bars is, obviously, our update to you from the finishing of 2005 flu season. And basically, I think, the take-home message is that there is a slight, maybe tiny increase, you know, for both the total and the pediatrics. And maybe that probably has to do with the concern