between the 12-month pre- and postexclusivity period and a 9 percent increase for the pediatric population.

Cardiology was the most frequent prescriber specialty during the 12-month post-exclusivity period at 35 percent, compared to pediatrics at less than 1 percent.

Lastly, use among pediatric patients was too low to evaluate for an office-based physician carvedilol visits stratified by visit diagnosis codes.

On May 28th, 2003, the FDA issued a written request for studies of carvedilol in the treatment of heart failure in pediatric patients. The resulting pediatric studies included three trials: (1) an efficacy and safety study in a 161 pediatric patients 2 months to 17-years-old with congestive heart failure due to systemic ventricular systolic dysfunction, (2) a PK study in 80 pediatric patients and this was a substudy of the efficacy and safety study, and (3) a safety study in a 102 pediatric patients and in this

case, this was an extension study of the efficacy and safety study.

The efficacy and safety study was a multicenter randomized placebo-controlled double-blind parallel group eight-month study of low- and high-dose carvedilol added to standard treatment with an eight-week titration phase and a six-month maintenance phase.

Fifty-five patients received placebo, 53 patients were in the low-dose group in which patients less than 62.5 kilograms received 0.2 milligrams per kilogram BID or those greater than or equal to 62.5 kilograms received 12.5 milligrams BID, and 53 patients were in the high-dose group in which patients less than 62.5 kilograms received 0.4 milligrams per kilogram BID and those greater than or equal to 62.5 kilograms received 25 milligrams BID.

The primary efficacy endpoint was the CHF composite outcome response determined 12 hours after the last dose of steady medication. The three outcome response categories were worsened,

improved, and unchanged, as defined on this slide.

The efficacy analysis revealed that there were small irrelevant differences between placebo and the combined carvedilol group for the primary efficacy endpoint of CHF composite response. Thus, the medical reviewer concluded that there was no evidence that carvedilol is efficacious in children with heart failure in doses up to 25 milligrams BID.

For the safety analysis, there were no unexpected safety events. In addition, the number of patient deaths, non-fatal serious adverse events, and patient withdrawals were similar across the placebo and the carvedilol groups.

In total, there were 14 patient deaths, 62 patients with non-fatal serious adverse events, and 22 patient withdrawals due to an adverse event.

Out of the 14 patient deaths, five occurred during carvedilol treatment and nine occurred after treatment. Of note, each of these

cases is confounded by the patient having a complex cardiac condition.

There were six patient deaths in the placebo group, as described on this slide. The vast majority of these deaths were associated with cardiac-related events, such as ventricular fibrillation, asytole, worsening heart failure, or ventricular arrhythmia.

There were five patient deaths in the low-dose carvedilol group. The deaths in cases 3 and 4 were associated with cardiac events that included ventricular fibrillation or sudden cardiac arrest. Cases 1, 2, and 5 involved non-cardiac events, such as pneumonia, fungal infection, acute respiratory distress syndrome, renal failure, thrombocytopenia, subarachnoid hemorrhage, viral infection, or bone marrow failure.

Lastly, there were three patient deaths in the high-dose carvedilol group. All of these cases were associated with cardiac abnormalities, such as congestive heart failure,

dilated cardiomyopathy, or arrhythmia.

Please note that hypoglycemia is highlighted in case number 1 because there will be further discussion of this and other hypoglycemia cases later in the presentation.

With regards to serious adverse events, the medical reviewer concluded that there was no evidence of a clear association of any serious adverse event with carvedilol.

Out of the 62 patients having a serious adverse event, 24 were in the placebo group and there were 19 in each of the carvedilol groups. The most common events were reported by all groups and included worsening heart failure, viral infection and dehydration.

Out of the 109 serious adverse events, this slide lists in detail those reported by two or more carvedilol-treated patients. Worsening heart failure was the most frequently reported event by far with 10 reports in the placebo group and 14 in the combined carvedilol groups.

For viral infection, there were two reports in the placebo group and five in the combined carvedilol groups, and for dehydration, there was one report in the placebo group and five in the combined carvedilol groups.

Other serious adverse events, seen in two or more carvedilol-treated patients, and reported in all three treatment groups, included bronchiolitis, bradycardia, pyrexia, and failure to thrive.

Additional events, seen in two or more carvedilol-treated patients but reported in only the carvedilol groups, included upper respiratory tract infection, septic shock, anemia, pneumonia, and vomiting.

Patient withdrawals were considered treatment failures in this study. Out of the 22 patient withdrawals, worsening heart failure was the adverse event most frequently reported with six patient reports in each of the placebo and carvedilol groups.

Combining the carvedilol groups,

other reasons for withdrawal that were reported by one patient included congenital coronary artery malformation, respiratory tract infection, bradycardia, chest pain, fatigue, viral infection, muscle cramp, loss of consciousness, and exhertional dyspnea.

The pediatric exclusivity studies also included a population PK sampling employed in the efficacy and safety study. The PK results and conclusions were that (1) in pediatric and adult populations, age is a significant covariate for oral clearance for the R(+) carvedilol enantiomer, (2) in pediatric patients, weight has a significant impact on oral clearance for both the R(+) and the S(-) carvedilol enantiomers, and (3) pediatric patients have greater oral clearance and less exposure to carvedilol enantiomers than adults.

Lastly, the pediatric exclusivity studies included a safety study that was a multicenter open-label extension study of carvedilol dose BID with an eight-week titration

period and a six-month maintenance period.

The target dose for the maintenance period was the same as that for the high-dose in the efficacy and safety study.

For the safety analysis, there were seven patient deaths, 30 patients with non-fatal serious adverse events, and 11 patients withdrawing from the study due to an adverse event.

When considering the seven patient deaths, the medical reviewer concluded that it appears unlikely that carvedilol contributed to these deaths as each patient had complex medical histories, including severe congenital cardiac abnormalities, and each patient seemed to be able to tolerate long-term use of carvedilol.

The next two slides describe the seven patient deaths in the safety study. This slide describes death cases in which patients had left ventricular hypertrophy and endocardiac fibroelastosis, cardiac arrest, cardiomegaly, T wave abnormalities, dilated cardiomyopathy,

complex congenital heart disease, and asytole.

Case number 1 also was associated with thrombus and a pulmonary embolism or infarct.

In cases 1, 2 and 3, the patients had tolerated carvedilol treatment for four years, 40 days, or two years, respectively. In case number 4, the patient died two weeks after his last carvedilol dose.

This slide describes death cases in which patients had ventricular tachycardia and ventricular fibrillation, severe congenital heart disease, cardiac arrest, aortic coarctation, cardiomegaly, right ventricular dysfunction, and ST and T wave changes. Case number 5 also was associated with multiorgan failure.

In case number 5, the patient died one week after his last carvedilol dose and in cases 6 and 7, each patient had tolerated carvedilol treatment for 19 months.

Out of the 30 patients having serious adverse events, there were 59 total adverse event reports, including 13 reports for worsening heart

failure and three reports each for cardiomyopathy, pneumonia, and syncope.

Less frequently reported serious adverse events also are listed on this slide. Of note, there was one case of hypoglycemia that will be discussed later in this presentation.

The 11 patients withdrawing from the study reported 12 adverse events. Worsening heart failure was the adverse event most frequently reported with seven patient reports and one patient each reported ventricular fibrillation, arrhythmia, cardiomyopathy, fatigue, and nausea.

Based on the results from the pediatric exclusivity studies, the Pediatric Use Subsection of the drug labeling notes that the effectiveness of Coreg in patients younger than 18 years of age has not been established.

In addition, the efficacy, PK, and safety findings are described for the placebo-control pediatric exclusivity study.

Moving now from the exclusivity studies to postmarketing reporting, this table

describes the adverse event reports during the postexclusivity period.

For pediatric patients, there were two adverse event reports which comprised 0.1 percent of the total reports. Of these two reports, one was a U.S. case. One of the two reports was for a serious adverse event and this was a non-U.S. case. There were no death reports.

Since there were so few pediatric reports during the postexclusivity period, the safety reviewer also assessed the pediatric adverse events since marketing approval.

For pediatric patients, there were 21 adverse event reports which comprised 0.5 percent of the total reports. Of these 21 reports, six were U.S. cases. Of the 21 reports, 19 were for serious adverse events with four being U.S. cases. There were three death reports with one being a U.S. case.

Now looking at the 21 crude count pediatric adverse event cases identified since marketing approval, 11 of these cases were

excluded because they were duplicate or miscoded cases, were not a serious adverse event, or occurred during the pediatric clinical trials.

The 10 remaining cases involved three deaths and seven non-fatal serious adverse events. The three death cases were notable for complicated underlying medical conditions and/or insufficient details.

In the first case, a patient with congenital heart disease and heart failure on multiple cardiac medications died of shock, not responsive to IV hydration and glucose.

The second case involved a patient with a history of CHF and a cerebral vascular accident who died suddenly of unknown causes, and the third case involved a patient with an unknown past medical history who had vomiting, bradycardia, hypotension, pulmonary edema and death of unknown cause.

Please note that hypoglycemia is highlighted in the first case because there will be further discussion of this and other

hypoglycemia cases later.

The seven non-fatal serious adverse events included three cases of hypoglycemia, two cases of congenital anomalies and maternal exposure, one case of hypotension and renal failure, and one case of disturbed consciousness.

Now the next three slides will provide more details regarding these three postmarketing non-fatal hypoglycemia cases, all of which were from Japan.

The first case involved a 4-year-old male in Japan with congenital heart disease and heart failure who was started on carvedilol three milligrams per day for heart failure prophylaxis. Three months later, he developed flu symptoms with a sore throat, coughing and diarrhea, followed on the next day by an unarousable state.

On admission, his blood glucose was 21. Carvedilol was discontinued. His blood glucose increased to 90. Approximately one week after the admission, he was restarted on carvedilol at one milligram per day and there were

no further episodes of hypoglycemia. He was discharged three weeks later on carvedilol two milligrams per day.

The second postmarketing non-fatal hypoglycemia case involved a 4-year-old male in Japan with congenital heart disease. Bradycardia tachycardia syndrome, increased clotting time and growth retardation, who was on carvedilol, one milligram per kilogram per day, for heart failure.

Approximately six months after starting carvedilol, the patient experienced convulsions and developed respiratory arrest requiring intubation. Hypoglycemia with a blood glucose of 11 and acidosis were detected. He was transferred to another hospital and experienced another convulsion and was treated with anticonvulsants and an unspecified drug for brain edema.

Hypoglycemia resolved but neurological symptoms persisted. Treatment with carvedilol continued.

The last postmarketing non-fatal

hypoglycemia case involved a 7-year-old male in Japan with congenital heart disease, bigeminy, bradycardia, and pulmonary artery stenosis on carvedilol, five milligrams BID, for heart failure.

There was some inconsistency in the reports, so either three and a half years or eight months later, the patient experienced disturbed consciousness, coldness, and a blood glucose of 68, NPO prior to undergoing centigraphy.

Nine weeks later, he experienced disturbed consciousness, sweating, coldness, and a blood glucose of 24 after having little to eat for lunch that day. Both episodes required 20 percent glucose infusions. Treatment with carvedilol continued.

You will recall that there was one postmarketing death case associated with hypoglycemia that was presented earlier. This slide represents that case with additional details related to the hypoglycemia episode.

The case involved a 16-month-old male

in Japan with a history of congenital heart disease, open heart surgery, heart failure, and poor weight gain on carvedilol titrated to 0.4 milligrams per kilogram per day since the age of 6 months.

Five months after starting carvedilol, the patient experienced sweating, cyanosis, tachypnea, and hypoglycemia with a blood glucose of 18. He was hospitalized and intubated, carvedilol was discontinued, and the hypoglycemia improved.

Carvedilol later was restarted and titrated to 0.15 milligrams per kilogram per day. Three months later, the patient experienced bronchitis, poor oral intake, spasm, hypoglycemia with a blood glucose of 56, and shock that was not responsive to IV hydration and glucose. It is unclear if he was still receiving carvedilol at this time.

The identification of the three postmarketing non-fatal hypoglycemia cases and the one postmarketing death case that included two

episodes of hypoglycemia caused us to re-examine the pediatric exclusivity studies for hypoglycemia cases.

One of the death cases from the efficacy and safety study was associated with hypoglycemia and this slide represents that case with additional details related to the hypoglycemic episode.

The case involved a 28-month-old female with a history of sinus bradycardia. She had a loss of consciousness and sinus bradycardia and discontinued carvedilol on day 1. On day 106, she had decreased oral intake, respiratory distress, bradycardia, hypoglycemia with a blood glucose of 20, and chest x-ray abnormalities. She died later that day due to congestive heart failure and dilated cardiomyopathy associated with neonatal myocarditis and possibly due to a viral infection.

In addition, one of the serious adverse event cases from the pediatric exclusivity safety study involved hypoglycemia and this slide

presents that case in detail.

The case involved a 27-month-old male with chronic heart failure. Approximately 225 days after his first carvedilol dose, he had lethargy, hypothermia, hypoglycemia with a blood glucose of 29, hypotension, and hyponeutremia.

He was treated with IV fluids, glucose, antibiotics, sodium bicarbonate, potassium, and a dopamine drip. His symptoms resolved without further episodes of hypoglycemia and the final diagnosis was presumed sepsis.

Within the carvedilol labeling, hypoglycemia is broadly addressed in the Glycemic Control and Type 2 Diabetes Subsection within the Warnings and the Precautions Section. You will note that there's no pediatric-specific information in this subsection.

However, the propanolol labeling does have specific pediatric hypoglycemia language in its Diabetes and Hypoglycemia Subsection within the Warnings and the Precautions Section.

The pediatric-specific language

reads, "Propanolol therapy, particularly when given to infants and children, diabetic or not, has been associated with hypoglycemia, especially during fasting as in preparation for surgery."

This completes the one-year postexclusivity adverse event reporting. The safety review identified four postmarketing cases of young children with hypoglycemia which coincided with their carvedilol therapy.

Therefore, the related specific question for the advisory committee is does the carvedilol labeling adequately address the possible hypoglycemia risk for the pediatric population or is additional wording needed?

In addition, FDA recommends routine monitoring for carvedilol for adverse events in all populations, and the related question is does the advisory committee agree with this monitoring plan?

In closing, I'd like to acknowledge the assistance I received from numerous FDA staff in preparing for this presentation, from the

Office of Surveillance and Epidemiology, the Division of Cardiovascular and Renal Products, and the Office of Clinical Pharmacology.

Thank you.

Clarification Questions and Question to the Committee

DR. RAPPLEY: Thank you. This is now open for discussion and questions.

If I understand this correctly, there are two questions before the committee. The first is does the current language in the labeling adequately address the issue of hypoglycemia associated with this medication and if the implication of that is found to be negative would be that it should be changed, and second, do we accept the recommendation that this be moved to routine monitoring for children?

And Dr. Pena tells me that the sponsor's also here should we need to direct questions to the sponsor.

Discussion? Oh, and I might add that for our new people, our routine is to sort of

signal when you want to pose a question or make a comment, and we make a list and try to keep track of people that way.

Thank you. Dr. Bier?

DR. BIER: The issue of hypoglycemia in small infants with cyanotic and general heart disease has been around since at least the '60s when I'm aware of it and it occurs in the absence of any of these medications. So, I think it's very hard to know precisely that there's a relationship, even though it's reported, you know, with the use of the medication even in adults and so I think the labeling is adequate, in my estimation.

DR. WARD: I would maintain, though, that the warning about decreased intake would add, I think, to the clinician's caution about the need for monitoring.

I'm struck by the correlation between fasting or decreased intake associated with flu-like illnesses and the hypoglycemia.

DR. BIER: This is again another

longstanding issue, right? We had the disorder called ketotic hypoglycemia. That's pretty much passed out of the pediatric literature because we emphasized to all pediatricians that toddlers in particular require monitoring of their, you know, intake when they're ill.

So, I don't disagree with that. I just think it's something that's part of, you know, good pediatric practice, but I think if it helps, you know, that's fine.

DR. SABLE: Certainly propanolol, which is probably the most commonly used beta blocker in pediatrics, it's been observed, especially when initiating the drug, that hypoglycemia can occur and many clinicians actually routinely monitor it. So, I don't think it's unreasonable with carvedilol to consider similar-type labeling, especially in the initiation phase which many patients are already hospitalized or during acute events.

However, in patients undergoing severe events, like cardiac arrest, which are not

on these drugs, hypoglycemia is also very common. So, I agree that there are many confounding variables in all of these cases that make one wonder how critical the carvedilol was in these particular cases.

DR. WARD: I just want to make an observation about the issues around efficacy. It sort of looks like a settled issue, but we've got 30 percent less exposure, we've got a pediatric population of children whose congestive heart failure, as a non-cardiologist, neonatologist, appears to me to be more severe than that in adults, and I'm not sure we have the final word on efficacy with 30 percent less exposure in the pediatric population and a more severe underlying heart disease and the studies were conducted as adding carvedilol to current therapy.

So, we may have not been able to achieve anything better in these children, especially with a lower exposure.

DR. RAPPLEY: Dr. D'Angio?

DR. D'ANGIO: Just to go back for a

minute to the hypoglycemia. I agree that there are a lot of confounding variables here, but the experience in neonates at least is that with other beta blockers, given either to the mother or to the infant, that hypoglycemia is a risk.

So, I think that it's perfectly reasonable to expect that that might be the case with this beta blocker.

DR. RAPPLEY: Dr. Kocis?

DR. KOCIS: I think a couple things. I agree with everything everyone's said. I think specific to this drug, you know, labeling the hypoglycemia which is Type 2 diabetes is somewhat limiting. So, I think it is common practice. It's generally known. I think pediatricians know to recognize hypoglycemia and how to treat that under a variety of conditions and I think we should just be specific about stating that rather than leaving it to the general practice of pediatrics.

I think the second question would be should this be a class effect? Should it be only

unique to Coreg or all beta blockers? As we mentioned, it's listed. I didn't see propanolol labeling, but I would imagine this would be a class effect and we would want to consider it to the other beta blockers there.

And then third, as far as efficacy with these trials, heart failure in children is extremely complex. Doing studies in these patients is extremely complex. It's a mix of congenital defects that have gone awry and dilated hypertrophic and the like.

So, certainly these are difficult studies to perform to show effect and not showing effect means we can't show effect until we do larger, broader, more specific studies or consider different things, but there was no effect. So, we need to stay with that, too.

DR. RAPPLEY: Dr. Newman?

DR. NEWMAN: Well, I guess I would agree that it would make sense to me to have the labeling for hypoglycemia be similar to that for propanolol because I don't think there's a good

reason to think that it would be different and that would just be an extra caution.

I also want to come back to the last two points. I guess I am not sure I understand the results of the studies for exclusivity and wonder whether all the information that would be helpful to clinicians is being included in the label because when I first read it, I thought it looks like, oh, well, the exposure of the children was less because their clearance is higher, so we don't really know whether it works, but there's something in the labeling that says but actually they achieved beta blockade, their heart rates were five or six points lower, so that means actually they were getting enough.

I just want to ask some of the other people with more expertise than I do if you see a five or six point decrease in the heart rate, does that indicate adequate blockage or does that mean maybe the children are more sensitive to that effect of the medicine?

Just the way it is now, it says

efficacy hasn't been established, but it seems like there's a lot more information in the studies than is being captured in the label.

DR. WARD: In an earlier life in animal studies of beta blockade, there's a difference in concentration response for propanolol at least for inotrope and chronotrope. So, you can see a reduction in heart rate at a point where you may not have reduction of inotrope and so I don't think we can really judge that just from the reduction of heart rate, that we have achieved an effective beta blockage at that level.

So, I think, again as I said earlier, I think it's kind of unfortunate. I think that efficacy is not demonstrated, but we don't have equivalent exposure either and I think the court should still be out on its effectiveness for children.

DR. RAPPLEY: Tom?

DR. NEWMAN: Could I just then -- actually, I think what I saw written down here and what was on the slide are different because it

said some place in what we read that the PK data would not be included in the label, and I guess I don't understand that.

Actually, the whole sequence, it seems like if you're going to do a fairly expensive randomized double-blind study that's going to last eight months, why not first do the PK data and find out what doses you should use and then do that study?

It seems like what they did is they did the PK study as they were doing the other study and then they find out, well, it looks like we didn't give enough.

So, one comment would be why not do the PK study first, but the other one would be why not include the dose that was used in the label because that isn't included and include the PK data in the label?

DR. RAPPLEY: Yes, Dr. Sable?

DR. SABLE: I think trying to measure the effect of these drugs is very complex, as Dr. Kocis said.

A 3-year-old with congenital heart disease is dramatically different than a 13-year-old with dilated cardiomyopathy and the adult studies do demonstrate significant efficacy and maybe the latter group is really totally different and these studies certainly have a mixed bag and the theoretical effect of beta blockage is inhibition of intrinsic catecholamines, upregulation of beta receptors, which is very different than just looking for a decrease in heart rate.

So, I think that there are some earlier pediatric studies demonstrating some effect of metoprolol in cardiomyopathy but again it's a very difficult question to answer, and I think it would be premature to conclude from these studies that these drugs have no role in pediatric heart failure.

DR. RAPPLEY: Dr. Garofalo?

DR. GAROFALO: I'll just make a quick comment on sequencing. I mean, I don't know the details about this one, but I think it is ideal if

you can do the PK first, sometimes there's a time constraint. So, you get started with, you know, you extrapolate doses from adults and you get started with your controlled trials while you're obtaining your PK data, you don't have the luxury -- because even the PK trials are hard to do and they take a long time.

So, you know, I think it wouldn't be uncommon that we go into efficacy trials in children without knowing as much as we would like to know and we have to choose doses.

DR. RAPPLEY: More discussion on this?

(No response.)

DR. RAPPLEY: Okay. So, let's go back to the -- yes, Dr. Notterman?

DR. NOTTERMAN: I was just struck by the fact that this came from Japan and I wondered, was there a difference in marketing and surveillance or penetration of this drug there that accounts for that?

DR. RAPPLEY: Can the sponsor speak

to that?

DR. LUCAS: Do I have to turn this on? This is all right.

My name is Mariann Lucas. I'm here representing GlaxoSmithKline, the Clinical Group, but I can at least comment a little bit in terms of Japan marketing.

Japan has had carvedilol on the market as a drug called Artist since the early 1990s, not with a pediatric indication and with a different dosing and a different formulation than has been used either in Europe or in the United States.

So, it makes it perhaps even a little more complicated to translate what was seen in the couple of case reports from Japan versus the doses that we used in the carvedilol pediatric trials that we conducted here in the United States.

As far as safety surveillance in Japan, Missy, I don't know if you would want to comment on that at all.

As far as our arrangement with

Daiichi is that all adverse event reporting is shared but that we don't have a particular role, other than gathering the information that they send to us from Japan.

DR. RAPPLEY: Thank you.

DR. NOTTERMAN: Do you know if the studies, the efficacy studies that you conducted here contained representation of the Japanese ethnicity?

DR. LUCAS: In the trials, in the 161 patients that we included in the U.S. trials, it was about 15-16 centers in the United States. There were very few patients who were of Asian designation.

DR. NOTTERMAN: Thank you.

DR. RAPPLEY: Dr. Ward?

DR. WARD: Dan, I just want to observe that the patient number 2 with hypoglycemia is doses at 1 milligram per kilogram, at least as reported, two and a half times the upper limit of the dose here.

DR. RAPPLEY: Dr. Cnaan?

DR. CNAAN: I think that when we discussed Tamiflu, there was some discussion, and I'm not the regulatory expert, that in Japan, the reporting is mandatory of adverse events as opposed to here, that it is voluntary. Therefore, there is some difference in the overall reporting in Japan as compared to this country.

Can somebody add to that?

DR. MURPHY: There are differences in the systems, but I don't recall that that was the cut as far as that it's a mandatory system.

I think there are differences in the way, you know, the health care is delivered and the way the interactions with the reporting as far as the caretakers, but I don't think we could clearly say that it's required, but again I'd have to go back and check with our regulatory colleagues in Japan to verify that.

DR. RAPPLEY: Dr. Bier?

DR. BIER: Yes, I have the same recollection, but I'm having trouble sorting whether this had something to do with the flu or

with the drug.

DR. MURPHY: Right, right.

DR. BIER: That's where I'm having the problem with it.

DR. MURPHY: Right. So, I think it had to do with the fact that there was that severe encephalitis, necrotizing encephalitis in Japan and there were special circumstances surrounding Tamiflu and there was a lot of emphasis on reporting.

Just the word "mandatory" is -- but you're right. People were really emphasizing trying to get that required reporting because of this concern with the encephalitis, not just the drug but the disease itself, and then the drug.

DR. RAPPLEY: So, the first question that we spent most of our time on so far is whether or not the language is adequate, and if the answer to that is no, then should additional language be added?

Is the committee ready to move on that question? So, how many people are -- believe

that the current language is adequate just regarding hypoglycemia, yes.

(No response.)

DR. RAPPLEY: Then how many feel that the current language is not adequate?

(Show of hands.)

DR. RAPPLEY: Is that unanimous?

(No response.)

DR. RAPPLEY: Okay. So that's a unanimous -- no. I'm sorry. Did someone abstain or vote negatively? So that's a unanimous acceptance -- unanimous vote that the current language is not adequate regarding the hypoglycemia and we would like the agency to suggest some new language and talk with the sponsor about including that in the labeling, is that fair?

DR. MURPHY: And we'll come back and talk a little bit more about some of the other questions after you finish.

DR. RAPPLEY: So, but I think there still is -- there are a couple other things,

questions remaining or that surfaced.

One is does the label adequately address efficacy? Were you all suggesting that it was too strongly stating that the medication is not efficacious, that it should be indicated on the label that this question remains unresolved or that it is adequately described because it describes what we do know?

DR. WARD: I would suggest, as I think Tom indicated, that to omit the PK data and the lower exposure, I think, underrepresents what needs to be known, that efficacy was not demonstrated at those doses with 30 percent less exposure than that achieved in adults.

DR. RAPPLEY: So, we could further recommend that adding to the label, it should include the PK data and the exposure data.

DR. MURPHY: Could we talk about this for a second?

DR. RAPPLEY: Yes.

DR. MURPHY: Because I want to make sure that the committee is aware of a couple of

facts and this recommendation is fine. We just want to make sure we have everybody on the same information page.

As you all know and you're going to hear later today, the normal process under which this labeling was done, okay, at the agency is that if you have a negative study and particularly if the sponsor has not made that information public, that is considered, you know, confidential information and it doesn't go in the label at all now, whatever the reasons for failure.

What has happened with pediatrics is because there's so few studies, the agency has over the last 10 years, since the legislation has been in place, progressively included information in the label to make sure that the practitioner, because they aren't going to get -- and again this is in another publication. We looked at how much of this information actually gets into the peer-reviewed literature and you can guess that it's less than half.

So, certainly if it's a failed study,

it's even higher that it's not going to get into the peer-reviewed literature.

So, the agency has progressively over the last decade tried to provide information in the label when there is a negative study, meaning we weren't able to demonstrate efficacy for whatever reason.

As you heard earlier this morning, you know, there are times we know, we think these products ought to work but why aren't they, and we look at PK, we look at endpoint assessments, et. cetera, and we try to provide information to the practitioner about what we think the status of why they may fail, but sometimes we don't know.

Now, the new legislation has basically said, and you'll hear this, that this is a good idea and we ought to be putting that information in -- some information to help guide the practitioners as far as pediatric studies are concerned because you aren't going to get additional studies like you might with adults.

But we always walk a tightrope, and I

can tell you since this began in the very beginning within the agency, because marketing is an art form none of us are expert in, one word can give a sponsor an enormous advantage over their competitor. Okay?

So, every word that goes in that label is negotiated and, as I've told you guys before, at the table we've got all these scientists from FDA and then on the other side of the table from the sponsor we've got the scientists and then all their marketing people and so it's an unfair battle, I think. Of course, they think the opposite way.

But anyhow, getting in the label certain words actually then allows them to go out and market the product and what we may consider a fair -- what's the word -- revelation or fair exposure or explanation, they don't have to do all the time, you know, I mean, because we're not the marketing police, even though people think we are. It takes a fairly egregious marketing -- how shall we say -- I won't say malfunction,

dysfunction for us to get involved.

So, we have to be very careful about what we put in the label and what you do not want to do is give somebody a de facto claim because you've now said, well, here's the dosing. So that's where we have to be careful.

Now, what you all are saying is, well, this product may work, people may need to use it, but you didn't -- we weren't able to demonstrate efficacy and again we have to be very careful because that's a very slippery slope.

Once you say you haven't met our standards, and then you start putting in all this other information, we have to be very careful how we word that.

I think what the division and Dr. Karkowsky, you have to help me here, they've tried to indicate to the reader here that exposure appeared to be lower in pediatrics. It's in the label, subjects and adults. Under the Pediatric Use Section, Page 213, of your thing.

So, it says right in there, "exposure

trying to be flexible in the very beginning of this process, in trying to encourage, you know, different types of trial designs and best utilization in the pediatric population for studies, that probably the better part is to get your dose effect defined and then go forward with the efficacy trial. That has been explained always attention as to how to do that most effectively.

Lisa, did you want to say anything else about that?

DR. MATHIS: I would add that, you know, I think this really underscores the importance of the legislation that we have to obtain pediatric studies because we have learned a tremendous amount about the differences between adult and pediatric patients, and in that process of learning, as Dianne said, one of the things that we've also noted is how critical it is for us to get the dose right.

Metabolism in pediatric patients is different by different age group in ways that is

1 often unpredictable and so it is critical for us
2 to be able to get that dosing right in the first
3 place prior to going into Phase 3 studies.
4 As was mentioned earlier, there are
5 often tensions, such as the limited patient
6 populations or difficulties in getting PK studies
7 in patients that are separate from the other
8 clinical trials, but it certainly is where we are
9 moving when we're having the internal review
10 committee and looking over the written requests
11 and, of course, the review divisions having so
12 much experience in specific disease processes as
13 well.
14 We really are looking at obtaining
15 Phase 2 dose-ranging studies that are adequate
16 prior to moving into our Phase 3 trials.
17 Sometimes we're getting population PK in those
18 trials to try and confirm the data from the
19 smaller Phase 2 trials, but that definitely is the
20 direction we are moving in.
21 DR. RAPPLEY: Does the sponsor wish
22 to make a comment?

DR. LUCAS: Yes, thank you. I first wanted to thank the committee for all their comments on this trial program. It was quite a challenging undertaking for GlaxoSmithKline and to underscore and clarify just a few things.

Number 1. It did take us four years to enroll the 161 patients who were in this trial. So, it was very difficult and there were constraints certainly regarding trying to do PK data separately.

Number 2. We were very surprised perhaps that the data in this trial were not consistent with what has been shown in the adult population for many reasons, including the doses, the population, et. cetera, but wanted to make sure that it was clear, Number 1, that the full data from this study were in fact published by the lead investigator in the steering committee in the Journal of the American Medical Association the year after the study came out. So, at least the full data from the study are in the public domain.

The population PK data are also being

developed for use in an abstract and potentially publication. So, we are making every effort to make sure that these data are in the public domain, and lastly that none of the members of the Commercial Team from GlaxoSmithKline were involved in this label.

That's the only other comment I wanted to make.

DR. MURPHY: Thank you. I didn't mean to imply that your specific literature. I'm just saying in general that, you know, we've done that review and we're always delighted to find that it is in the literature.

DR. RAPPLEY: Thank you to the sponsor, and thank you, Dianne, for reminding us that sometimes the way we use language and information, we're not really aware of how it's used for other purposes, and it's both in giving an unfair advantage and also in the past, we've talked about certain words may actually encourage people to go to other medications that are in fact less well studied and we don't want to have an

unanticipated or secondary consequence of that nature for our decisions.

So, thank you for reminding us about that and I think we certainly support your efforts to walk that fine line and to determine what's the best way to over time, as we have over the last 10 years now or last few years, learn so much more about children than we knew 10 years ago. We expect that learning curve to be steep and there's a lot more to be shown, I think, through your efforts.

Yes, Lisa?

DR. KARKOWSKY: There are always problems in extrapolating an adult indication to a kid, to a children's indication.

First of all, the disease process, although it's heart failure, is dramatically different between adults and kids. In adults, it's usually hypertensive or ischemic. In kids, it's usually congenital, and the data on dose response in heart failure in adults is not really well known. All we know is that people will

titrate to tolerance to a maximum dose of, not that we know that a dose of half X is better than quarter X or that X is better than both of them.

So, I think the sponsor did a very credible job. My only recommendation would be to have larger dose ranges between doses, not factors of 2. We usually suggest factors of 3 or factors of 4, but aside from that, I think you got about as good as you can get. I think it was a well-done study and I compliment the sponsor for it.

DR. RAPPLEY: Thank you. Dr. Daum, did you have a question or comment?

DR. DAUM: I actually have two comments. The first one goes back to our discussion about the hypoglycemia and I think my sense was that people around the table voted unanimously that they were not happy with the current language, but I wondered if the agency would like our opinion as to what the new language should be or at least what the components of it should be or do you want to just leave it that we're unhappy with the present language?

DR. MURPHY: I think we're fine with what you told us because we already have some language that we can work with and we got the message from you all that you think it should be more similar to the propanolol type of beta blocker language and at least warn the physician that hypoglycemia is of concern, particularly in children.

So, I don't know that we need specific -- I mean, we'll always take any recommendations and consider them, Bob, Dr. Daum, if you all have them. I'm just saying we didn't ask you that just because we do have other language that we've been working with already for the other labels.

DR. RAPPLEY: Dr. Ward?

DR. DAUM: I had one more comment.

DR. RAPPLEY: I'm sorry.

DR. DAUM: Is that okay? Dr. Murphy, I'm not sure that we could sit here or you could sit where you sit when you're not here and control corporate excess by language that we put into

these statements that we're advising and you're writing.

I've seen companies detail things that never would have occurred to anybody and couldn't possibly have been routed out by the kind of approach you suggested, and I guess it's sort of a little bit -- I sort of feel like it's beyond us as our advisory committee's function to take into account how companies will use the language in these statements, and I think the best way that I would suggest we think about it, we think about it at least from our level, is that we apply, try to apply consistent and same standards to everything and be mindful of what you're saying but certainly not devoted to it and so I'm kind of comforted by this statement that it's the effectiveness in patients younger than 18 years has not been established and then I think it's appropriate to then give results of what seems like a well-done study and correctly to leave it at that, but I'm not sure that that's going to appease competitors who want to take that and run

with it, that, this is not an effective drug and you should use ours instead. I'm not sure we can control that.

DR. MURPHY: Again, I was just trying to make sure before we changed the language or you all made a recommendation on the language that we're aware of what's already in the label. That's all I was just trying to say, is that, Number 1, here's what happens, okay, so just be aware that when you're making these recommendations, that we then will be negotiating and we will be -- may or may not take the recommendation, but it has to be negotiated because of the issue. We don't want to give them a de facto, that we just don't want to be careless in how we do it and we aren't.

So, I just want to put that back on the table for everybody, but mostly, I just want to make sure everybody looked at what's in the language already before we proceeded with trying to add language there. So that was --

DR. DAUM: And with that, I heartily

agree.

DR. RAPPLEY: So, in the interest of staying on time, can we make further comments on this brief? We still have the remaining question.

Dr. Ward and then Dr. Kocis.

DR. WARD: The JAMA article doesn't mention exposure. It does mention half life. I just reread it.

DR. KOCIS: You know, I think through all the meetings I've been involved in the last year and a half and with the new pediatric labeling and the format and all that, I think the most important thing I've taken home was to provide factual information in the pediatric label.

We can't necessarily come to conclusions or to show, you know, you start using this drug or don't use this drug but to be as factual as we can and, you know, specific to this drug, you know, non-efficacy has -- they haven't shown it. So, we need to say that.

I think likewise, the dosing

limitation, the pharmacokinetics of that, should also be in there, but I don't think we should then say and therefore you should use it because it's going to show efficacy if you give them a third more.

I think practitioners will understand that if they're given that information and, you know, sort of going back and we mentioned this on the Toprol, I mean, I'm somewhat shocked to say that we showed it was efficacious in decreasing blood pressure by three to four millimeters of mercury and I'm sitting here thinking, well, maybe that's statistically true but clinically that's going to be an irrelevant use and so in an analogous way, I think providing information in the pediatric label, yes, it showed this to this degree and then let practitioners make the best decisions that they need to and particularly in this group of patients with the whole variety of patients that may or may not benefit from this drug in the future, I think we need to leave that open for practitioners to use.

And one final comment was just in the outcome study, when I was first a cardiology fellow looking at heart failure and stuff, we generally said a third died, a third stayed the same and a third got better, and if you look at just the group here, we've done better in the improved group. We're up to 55, almost 60 percent. Maybe or maybe not, the patients dying are less from a third down to 20-25 percent, but something we're doing over these years has made a difference. In some patients, this may or may not be beneficial.

DR. RAPPLEY: Is the agency satisfied with the recommendations from the committee regarding this?

DR. MURPHY: I guess what I would just like to clarify because I heard you wanted more PK information in the label and then I asked you to go back and look at Page 213 and make sure that even though we didn't give specific PK -- can you look at the PK Section 2?

We didn't give specific PK

information because we're trying to, if they don't reach efficacy, keep most of the information in the Pediatric Use Section. We did talk about the effect of the drug and we did talk about the exposure being lower in children.

So, what I'm asking is do you want more information? Is that what you're suggesting, is more information than what's in there right now?

DR. WARD: The exposure statement without the dose doesn't help you very much, you know. So, if I felt I had a patient that I wanted to treat with carvedilol and I knew that .4 milligrams per kilogram caused or led to a 30 percent lower exposure than in adults and then I would know that I wanted to push the dose higher and that would help me and would provide factual information that reflected the information in the study or from the study.

DR. MURPHY: Okay. So, you're saying that we should specify what that exposure was? Okay. Thank you.

DR. MATHIS: Could I just add one more thing, and that is we'll get to it later when we discuss the new changes in the new legislation, but of note is that the full clinical pharmacology review, not just a summary but the full review will now be posted publicly for both BPCA and PREA studies.

So that information will be widely available to the public outside of labeling as well in great detail about actually how we analyzed it.

DR. RAPPLEY: Very good. Dr. Sable?

DR. SABLE: I think the other thing to consider in this particular field is the good news and the bad news, is that there's really no drugs that treat heart failure effectively. So, the idea that there's competitors that are out there that have these great drugs that are going to look at this and say let's use something else, I think, is unfortunately decades away from being reality.

So, I think providing full

information to give someone the most information possible in using a drug that even has some chance of working in these patients is very important in this particular disease.

DR. RAPPLEY: So, if I'm correct in summarizing this, then we recommend that there be additions to the label that include language about hypoglycemia, about PK data, and about exposure, is that correct?

Okay. Second question regarding this medication then is are we accepting the recommendation that this be moved to routine monitoring?

Looks like a positive. Anyone opposed to that?

(No response.)

DR. RAPPLEY: Okay. So, we unanimously accept the recommendation to move this to routine monitoring.

Okay. Let's see. We have the next one up and then we're scheduled to have a break at 10:35, I think. Felicia is on again. Okay.

Thank you.

Eloxatin (oxaliplatin)

Standard Review of Adverse Events

DR. COLLINS: Okay. At this point now we will shift gears and I am pleased to be able to present to you the one-year postexclusivity adverse event review for oxaliplatin.

Eloxatin or oxaliplatin is an anti-cancer agent for which Sanofi-Aventis is the drug sponsor. Original market approval occurred on August 9th, 2002, and pediatric exclusivity was granted on September 27th, 2006.

Prior to the pediatric exclusivity studies, oxaliplatin was indicated for use in combination with infusional 5-FU/LV (1) for adjunctive treatment of Stage 3 colon cancer in patients who have undergone complete resection of the primary tumor and (2) for the treatment of advanced colorectal cancer.

The next two slides provide information about the drug use trends of

oxaliplatin. A projected 970,100 vials of oxaliplatin were sold in the U.S. for all age groups during the 12-month postexclusivity period. Seventy-five percent were sold to clinics and 20 percent were sold to non-federal hospitals.

Currently, the FDA does not have access to data describing the use of drug products in clinic settings. Therefore, the drug use reviewer was only able to examine oxaliplatin's utilization patterns within inpatient settings in non-federal hospitals.

An unprojected 7,064 discharges from acute care non-federal hospitals were associated with oxaliplatin for all age groups from October 2004 to September 2007. Pediatric use accounted for 0.4 percent of the total use during the 24-month preexclusivity period and 0.1 percent during the 12-month postexclusivity period. Most of the pediatric discharges were associated with the treatment of oncologic conditions.

On December 9th, 2004, the FDA issued a written request for studies of oxaliplatin in

the treatment of refractory or relapsed pediatric solid tumors. The resulting pediatric exclusivity studies included four trials, two Phase 1 dose-finding and safety studies and two Phase 2 activity and safety studies.

The studies utilized an open label non-comparative non-randomized design and a dosing regimen of two-hour IV infusions at doses ranging from 40 to 160 milligrams per meter squared. A 159 pediatric patients 7 months to 22 years of age participated in the studies.

The next six slides provide more details regarding the four individual studies. Study ARD5531 was one of the Phase 1 dose-finding and safety studies. It involved 43 pediatric patients 6 months to 21 years old with refractory or relapsed malignant solid tumors, and these patients had a life expectancy of more than six weeks.

This study included two dosing cohorts. Cohort 1 involved 28 patients who received six oxaliplatin dose levels of 40 to 110

milligrams per meter squared. For this part of the study, the dose-limiting toxicity was determined to be sensory neuropathy at a 110 milligrams per meter squared. Thus, the subsequent recommended dose was 90 milligrams per meter squared and 15 patients in the recommended dose cohort received oxaliplatin at this dose.

Study DFI7434 was the second Phase 1 dose-finding and safety study. It involved 26 pediatric patients, less than 21 years old, with metastatic or unresectable solid tumors, for which standard treatment did not exist or was no longer effective.

In this study, five dose levels were evaluated. Oxaliplatin 100, 130 and a 160 milligrams per meter square every three weeks for six cycles. Oxaliplatin 160 milligrams per meter squared and carbamazepine every three weeks for six cycles, and oxaliplatin 85 milligrams per meter squared every two weeks for nine doses.

The dose-limiting toxicity for oxaliplatin monotherapy was determined again to be

sensory neuropathy, this time at a dose of a 160 milligrams per meter squared. Thus, the recommended dose for the subsequent studies was a 130 milligrams per meter squared every three weeks.

Study ARD5021 was one of the Phase 2 activity and safety studies. It involved 43 pediatric patients less than or equal to 21 years old with recurrent or refractory embryonal CNS tumors.

Oxaliplatin 130 milligrams per meter squared was administered every three weeks for a maximum of 12 months, if there was no disease progression or unacceptable toxicity.

Study ARD5530 was the second Phase 2 activity and safety study. It involved 47 pediatric patients less than or equal to 21 years of age with recurrent solid tumors.

Oxaliplatin 130 milligrams per meter squared was administered every three weeks for a maximum of 12 months or 17 cycles.

Pharmacokinetic data were collected