have--and I know it's difficult. I know it's difficult. But just looking at that list without the context, it leaves me like, yes, I'm not surprised that this is happening, this is happening in adults 10 times more or 20 times more.

DR. IYASU: I think you make an important point there, and we just have to live with the limitations of the data. What we can do, when it's an important issue, serious adverse event, we can go out on a limb and go to other databases like Claims database, which has its own set of limitations and caveats. So there are many avenues that you can go, but reporting rates or relative reporting rates are the best that we can do with this limited data set. We have refrained from doing that because of the limitations in terms of defining the actual numerator that you use, and also the denominator, especially for pediatric. So we may--we're concerned about sending the wrong signal as to the relative safety of certain drugs if we don't have--if we're dealing with uncertain denominators and uncertain numerators. So that's

where, I think, the problem is in trying to assess it.

So what we've done is if there is really an issue, then our best resource is really the clinical trial data. And what we've done is the initial sets of presentations that we've done for adverse events for these drugs did not include a review of what was actually in the clinical trials done for exclusivity. Now all our reviews include summaries of the exclusivity trials and what kind of safety signal this might have resulted that may be similar or been supported by the adverse event reports.

So we're trying to strike a balance here and trying to give you the best information that we have with all the limitations for interpretation. So I can't say anything more than that. If there are other suggestions from the committee, we'll be very glad to consider them to improve the system.

Thank you.

DR. CHESNEY: I think it also doesn't address the issue of the drugs that didn't go

through exclusivity. But I think in your spare time, if you could develop a national database that would capture this inform for us.

[Laughter.]

DR. CHESNEY: Dr. O'Fallon?

DR. O'FALLON: This brings us back to the problem--clinical trials provides the very best data we have, no question about it. You know, I'm a lover of clinical trials. But there's all those comorbidities that are excluded that are encountered, and a good chunk of the patient population are excluded often from these clinical trials. And so the question is: If there are a lot of adverse events being encountered by kids being treated with these things but they're not in clinical trials because they keep getting ruled out due to the exclusion criteria, does the adverse events--the MedWatch, does that capture those? If the parents are screaming, do those--like those people that were the public presenters on Monday, are their cases ending up in MedWatch?

DR. IYASU: Well, consumers also, you

know, send their reports through the MedWatch program. Health professionals do. But as I said before, 80 percent--or more than 80 percent or 90 percent of the reports are actually from manufacturers. Some of them may actually have been reported directly to manufacturers from health professionals, and then they are transferred to us.

The extent of the reports of adverse events or experiences of adverse events by patients directly is variable. It's small, actually. Probably it's very underreported.

DR. O'FALLON: Yes.

DR. IYASU: So we really don't have a way of capturing that through a passive system such as AERS, unless you go and do an active surveillance system, which is a resource issue.

DR. O'FALLON: Yes.

DR. CHESNEY: I think unless there are any other pressing questions--we're about a half-hour behind, so maybe we need to move ahead. Dr. Iyasu is going to introduce our next speaker.

DR. IYASU: Thank you. Our first speaker

for this section of adverse events is Dr. Hari Sachs. Hari is a professor of pediatrics with over 15 years of experience in private practice. She also served on the FDA Non-Prescription Drug Advisory Committee and is one of the FDA liaisons to the American Academy of Pediatrics Committee on Drugs. She will be presenting the adverse events for ofloxacin and alendronate.

Dr. Sachs?

x

DR. SACHS: Thanks again for that kind introduction. Forgive me, I'm a little mechanically challenged, so if I screw up this presentation, at least the mechanics of it, bear with me.

I'll be discussing the adverse events for ofloxacin, trade name Ocuflox, which is an ophthalmic anti-infective that was approved in July 1993 for the treatment of conjunctivitis and corneal ulcers due to susceptible bacteria in both children and adults over one year of age. Depending on the condition, one to two drops of ofloxacin applied to the eye at frequent intervals.

The exclusivity was granted in March 2003 based on studies of neonatal conjunctivitis, although ofloxacin is not approved for that purpose.

As you can see from these statistics, millions of prescriptions for ofloxacin were written for both adults and children during the one-year exclusivity period. Pediatric patients accounted for almost one-third of these prescriptions. And, in fact, pediatricians prescribe almost as much ofloxacin as ophthalmologists, and not surprisingly, the most common indication is conjunctivitis.

Now I'll look briefly at the studies performed for exclusivity, and as you can see, they are posted on the Web.

The pivotal study was a one-week, active control trial which compared ofloxacin and trimethoprim sulfate treatment of conjunctivitis in infants less than one month of age. The clinical cure was based both on resolution of discharge and erythema by (?) lamp exam and microbiology cure. The safety of ofloxacin is comparable to that which

is seen in older patients in previous trials. But although the clinical cure rate for ofloxacin exceeded the active control, neither of the two drugs exceeded the historical control, and, therefore, the study was--it was deemed that this was not an approvable indication.

Note that the vehicle that's used that's the historical control does contain benzyl chromium, which has antibacterial properties.

The submitted data from this trial doesn't really allow us to figure out why the cure rate was low, why this study didn't seem to work. But potentially there are factors related to the design or conduct of the trial, the bacteriology of neonatal conjunctivitis, or perhaps the time course of it, or maybe a combination of all these factors.

In discussing the relevant safety labeling, I'm going to highlight information that's either pertinent to pediatrics or the adverse events. Ofloxacin is a Pregnancy Category C drug since there are no studies in pregnant women and there are some effects on animals. It is

potentially excreted in breast milk. Under the Pediatric Use section in precautions, there's a statement that although the oral form of ofloxacin has been associated with arthropathy in juvenile animals, there is not an association for the topical form.

There is a warning about allergic reactions, including anaphylaxis, which details a case report of Stevens-Johnson syndrome from the topical preparation. Most adverse reactions to ofloxacin, however, are really mild and include ocular burning or discomfort and, very rarely, visual changes such as photophobia or blurriness or systemic symptoms may occur.

Now that you're familiar with the label, let's look at the adverse events. As you can see, there really are very few reported adverse events for ofloxacin in all ages. And during the one-year post-exclusivity period, there were only three reports--or three events, actually, all unlabeled, two of which occurred in one adult and one that occurred in a pediatric patient.

The pediatric event was a foreign report that is also found in the literature of corneal deposits in a 6-year-old who was receiving the ointment. That's not available in the U.S. And, in general, these types of corneal deposits actually resolved by themselves and are thought to be benign. This patient was actually treated with scraping fairly early in the course. The natural history actually is that it should have resolved.

With such few events, we really can't draw a meaningful conclusion, and while this completes the one-year post-exclusivity adverse event monitoring, as mandated, we will continue our routine monitoring of adverse events for this drug.

Are there any questions?

DR. NELSON: Just to repeat what I think I--you're unable to tell the ages of the pediatric use. You can't tell how old the conjunctivitis prescriptions were? In other words, is it being used on-label above one year of age, or is there any off-label use--

DR. SACHS: Most of the use was on-label.

There's one database that captured some of the use in kids under two, but it didn't separate out which were under one. So it didn't help. It is approximately 20 percent of the pediatric use for that, the lower age group.

DR. CHESNEY: Thank you very much.

x DR. SACHS: Switching gears from one system to another, I will now discuss the adverse events that occurred during the post exclusivity period for alendronate.

Alendronate, or trade name Fosamax, is a biphosphonate which inhibits bone resorption by osteoclast, and it was originally approved in September 1995 for the treatment of osteoporosis in adult women. Pediatric exclusivity was granted in April 2003 based on studies of children with osteogenesis imperfecta.

Currently, alendronate is approved only in adults, and it's for the treatment of osteoporosis for both men and women, its prevention in women, and for Paget's disease. The dosage varies from indication, and there are really no pediatric

indications.

As you can see from these numbers, although Fosamax is widely prescribed in the U.S. for adults, and the use is increasing, the use in pediatrics is really minimal. There's like 10,000 prescriptions in pediatrics compared to 22 million for adults. Alendronate is primarily used in the outpatient setting with the lion's share of prescriptions from internists, OB-GYNs, and family practitioners. Pediatricians write very few of these.

Osteoporosis and osteopenia were the primary indications for therapy in adults, but in pediatrics alendronate is used off-label for treatment of osteoporosis and osteopenia either due to underlying disease, such as renal or connective tissue disease, or for its therapy, glucocorticoid therapy, for example,, fibrous dysplasia, and as you will see, osteogenesis imperfecta.

I'll briefly discuss the results of the studies that were performed for exclusivity.

Both pharmacokinetic and safety and

efficacy and safety studies were performed to evaluate the treatment of severe osteogenesis imperfects, or OI, in pediatric patients ages 4 to 18. The PK studies found that the oral bioavailability of alendronate relative to the IV dose was really similar in both children and adults. Exclusivity was granted based on submission of the 12-month analysis of this trial in pediatric patients with OI, and both doses that were used in the trial did significantly increase lumbar spine bone marrow density, which was the primary endpoint. But, unfortunately, a key secondary endpoint was not reached, and that was actually the occurrence of fractures either by report or by x-ray.

The adverse events in the one-year analysis appear comparable to those seen in adults, and it's hopeful that this trial--there's going to be more data coming in on a one-year extension of this trial.

Once again, I'd like to highlight the relevant safety labeling for pediatric patients.

Alendronate is considered a Pregnancy Category C drug, with animal studies that have shown maternal hypocalcemia that sometimes leads to early delivery, and although there's no human data, theoretically there can be an effect on the fetal skeleton.

Due to significant gastrointestinal irritation, alendronate is contraindicated in patients who have a risk of esophageal emptying--excuse me, have a delay in esophageal emptying or risk of aspiration or cannot stand upright. And patients with hypocalcemia or allergy are told not to take the drug. Esophageal perforation, including ulcerations or erosions, are also described in the warning section of the label.

Precautions include the recommendation to monitor calcium and vitamin D status. And gastrointestinal symptoms, such as abdominal pain or nausea, musculoskeletal pain, headache, dizziness, and taste perversion are the more common side effects that are seen.

Now, since alendronate approval,

paralleling the relatively small percent of pediatric use, pediatric adverse events really represent only a very small percent of adverse events. There were 17 total reports for pediatrics out of 18,000 total reports. And this is kind of indicated in the post exclusivity period as well, with only four pediatric case reports that were unduplicated. And there were no deaths.

The four reports include two cases of hepatocellular injury, one patient that suffered a drug-drug interaction potentially, and one infant that had hypocalcemia and prematurity.

Hepatotoxicity was noted in two children that were treated for steroid-induced osteoporosis, and the details of their cases are reported on this slide. But, briefly, liver dysfunction was temporarily associated with the onset of alendronate therapy and resolved after its discontinuation and treatment with pulse steroids in both patients. One patient did have underlying liver dysfunction, and the other patient was on methotrexate.

The drug interaction occurred in a 7-year-old with JRA who was taking cyclosporine, and after starting alendronate, the cyclosporine levels decreased, and his disease flared. Once the alendronate was stopped, the cyclosporine levels returned to normal. There was some fluctuation in baseline levels, so the exact interaction is unclear--I mean baseline levels of the cyclosporine, that is, before the alendronate was started.

The last case was the prenatal exposure which describes hypocalcemia, hypocortisolism, and prematurity in a male infant that was born to a woman with multiple medical problems, including gestational diabetes, and who was on multiple medicines. Hypocalcemia is known to occur in premature infants, infants of diabetic mothers, and several of these therapies, as well as potentially with alendronate.

So, in conclusion, only a handful of adverse events were noted. Most did have confounders or insufficient information to ascribe

causality. We did look at a preliminary analysis of the adult hepatic events, and that does not seem to raise any concerns. And this will complete the mandated reporting for alendronate from BPCA, but we will continue its routine monitoring.

Are there any questions?

DR. CHESNEY: Dr. Maldonado, and then Dr. Nelson.

DR. MALDONADO: I observed that in the ofloxacin you had only one adverse event, and it was a different drug product, it was not the same drug product in the United States?

DR. SACHS: Right. Well, it's the ointment form as opposed to we just have drops.

DR. MALDONADO: So it's a different drug product.

DR. SACHS: Correct.

DR. MALDONADO: And in Fosamax, also the four reports were ex-U.S.

DR. SACHS: That's correct. They were foreign reports.

DR. MALDONADO: Do you know if it's the

same drug product, or is there a possibility that it is a different drug product?

DR. SACHS: I believe that it's the same drug product.

DR. MALDONADO: And the reason I ask, for those who are not familiar, you see internationally the same names, and sometimes they are different products actually, because the FDA approves drug products, not drugs or--and sometimes there are different components in the drug product. So when you include them, actually that's good that you highlighted that, because that may be relevant to the adverse events.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: Just a question about labeling, but not in the safety and efficacy component. I don't understand, if, in fact, there's been a pharmacokinetic study, why we would say that the pharmacokinetics have not been investigated in patients less than 18 years of age. I mean, that's what the label says. Wouldn't we normally include some pharmacokinetic data even if

we don't think safety and efficacy has been established?

DR. MURPHY: No.

DR. NELSON: Why?

DR. MURPHY: Because you're giving it an implied approval. You're giving the dosing. Now, if the--not always.

DR. NELSON: Well, we can--

DR. MURPHY: Let me--you know, that's a whole big discussion, and you heard we have this tension between trying to inform and not providing a marketing freebie at the same time. So if that pharmacokinetic study was done and found that there was, you know, something very different going on or some concern, then we could say on a dosing--I'm talking about past. I'm talking about prior practice, okay? So whether that's all going to change--you know, it's good to provide you feedback on this. I just wanted to say that in the past one of the concerns that has been expressed has been any information you put in the label about pediatrics--I'm just starting from the big global

concern--depending on what it is, if it's not a safety, you know, warning, in essence provides a de facto approval and/or an ability of the company to market it.

As an example, they could go out and say, well, look, FDA put this information in the label about how to use it in kids. So there is that balance of trying to make sure that it's clear if we put information in, in what context that information is put in the label.

Now, I mean, please proceed to say you think we should have put it in the label; we're interested in hearing that sort of stuff. But I'm just trying to provide why we routinely wouldn't put information that we obtain into the label.

DR. NELSON: Just a quick response. I was heartened to hear from Bob Temple yesterday that that position was being readdressed. I previously, until your comment, wouldn't have applied it to just basically the pharmacokinetic information. But I'll also point out that most people, myself included, get my information from personal device-

based systems, which do include dosing data. And, in fact, one of those two systems I have on my Palm actually included depression as an indication for an unlabeled use.

So I appreciate the concern about encouraging it, but I actually think adding more information might, in fact, discourage it if there was an emphasis of making sure that information was, in fact, accurate and then transmitted accurately to clinicians. I know that's a whole broader discussion, but--

DR. MURPHY: I think we need to hear that. I mean, that's what this committee is here for. You're looking at the pediatric perspective on this, and there has always been this tension. And I think I've told this committee before, there are those of us who think we are mandated in some ways to put some of this information in the label. There have been others in the agency who have been very concerned about doing that.

I think what you heard yesterday was a very different approach that's being considered.

So we do want to hear these comments.

DR. CHESNEY: Dr. Maldonado, then Dr. Fant.

DR. MALDONADO: I'm just going to give you a perspective, and Dr. Murphy is right, people may misuse the information. I'm not saying that that wouldn't happen. But, for example, the drugs that are being used off-label--and we know--and I'll just give you the perspective of one that I'm working--it's a company, and we rarely have the PK data. And we now found out, although we believe that the dose being used off-label was the correct dose, and that's the dose that we use in the PK, we found out that that's incorrect, that children are being underdosed. This is an antimicrobial.

The clinical studies are ongoing, and they may be ready in five years, by the way, because of the long-term follow-up that we need to do. In the meantime, people are using off-label this drug incorrectly. And you're in the bind that you cannot communicate that because it may be perceived as, you know, promotion. But you want to

communicate it. It's difficult. I know exactly the concern that the FDA has because it can be misused. But at the same time, not conveying it, it allows people to continue using the drug incorrectly.

DR. NELSON: Can't your solution be--I assume there's some academic investigators potentially involved at study sites, letting them release at least the PK data in a publication? Or does that also violate--I mean, here it sounds like you might even have a moral obligation to put out that data.

DR. NELSON: Yes, the data has actually been published in a poster format so people who are more sophisticated in the area of infectious diseases already know that that's incorrect. And that's as far as we've gone.

DR. MURPHY: But I think that this is a perfect example of the quandary, because as all of you know--and you heard yesterday--we have a history of putting things in the label that nobody ever finds anything about the information. I mean,

that's just the way life is. And with our health care system the way it is right now, it's actually getting worse, one could say, I think, as far as physicians having time to access some of this information in a timely manner.

But I would say, you know, if I were in the Anti-Infectives Division and the company came to me and said, oh, we've got this information, we want you to put it in the label, but we're not ready to submit our application yet to show you whether it's safe or efficacious, you can see what the problem is.

DR. CHESNEY: Dr. Fant?

DR. FANT: One small point for completeness related to the case of neonatal hypocalcemia. You highlighted with an asterisk the drugs known to be associated with hypocalcemia, but it may be worth also putting an asterisk and highlighting the condition of diabetes itself in addition to the prematurity.

DR. SACHS: Yes, I mentioned that.

DR. FANT: Oh, okay.

DR. SACHS: I just put the medications, but yes, oh, yes.

Behind these presentations, actually, are a group of folks at ODS and in the divisions that contributed to the report, and I just want to kind of publicly acknowledge them as well: Jennie Change, Renan Bonnel, Mark Avigan, Wiley Chambers, Gianna Rigoni, Judy Shaffer, and Michael Evans. So there's actually a lot of people that go into these presentations that you don't see.

I would now like to introduce Dr. Susan McCune, who is a neonatologist, whose previous experience has included academic neonatal practice at Johns Hopkins and Children's National Medical Center. She recently received her master's degree in education and has worked on computer-based educational models for pediatrics. She will be presenting the adverse events for fludarabine.

On a personal note, it's a pleasure for me to be working with her again because she was, I think, my chief resident when I was a resident at Children's. Things go full circle.

DR. McCUNE: Thank you, Hari.

It was an honor to work with Hari as a resident, and it's an honor and a privilege 20 years later to work with her again at the FDA.

As Dr. Sachs said, I'm going to discuss the one-year post-exclusivity report for the adverse events for fludarabine.

In terms of background information, fludarabine, or trade name Fludara, is a synthetic adenine nucleoside analog that primarily acts through inhibition of DNA synthesis. It is produced by Berlex Laboratories. Its indication in adults is for the treatment of adult patients with unresponsive B-cell chronic lymphocytic leukemia. Of note, there are no pediatric indications that are approved for this drug. The original marketing approval date was April 18, 1991, and pediatric exclusivity was granted on April 3, 2003.

I want to stop for a moment and talk to you a little bit about the background of oncology and pediatric drugs at the FDA, and I think this gets a little bit to some of the questions that

you've been asking about because oncology drugs are a little bit different from some of the other drugs.

There has been a special initiative at the FDA to increase pediatric drug labeling for oncology drugs and to prioritize the availability of new oncologic agents to pediatric patients. To achieve this goal, three items that I'd like to point out for your attention:

The first is the draft guidance for industry that's entitled "Pediatric Oncology Studies in Response to a Written Request" that was published in June of 2000. The guidance is part of this initiative to generate new knowledge to assist practitioners and to provide early access to emerging new drugs.

In addition, the Best Pharmaceuticals for Children Act that was signed into law on January 4, 2002, established the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee and prioritized new and emerging therapeutic alternatives that could be available to treat pediatric patients with

cancer.

Another report entitled "Patient Access to New Therapeutic Agents for Pediatric Cancer," which was published in December 2003 and was a report to Congress, was a report that identified areas in pediatric drug development that could be improved to facilitate access to new agents.

Now I'm going to focus a little bit on the trials that were done for exclusivity for fludarabine.

Exclusivity was based on data that was submitted from two previously published COG trials: CCG-097 and CCG-0895. CCG-097 was a Phase I dose-finding and PK study of a loading bolus followed by a continuous infusion of fludarabine in patients with acute non-lymphocytic leukemia, acute lymphocytic leukemia, and solid tumors. CCG-0895 was a Phase I/II dose-finding, PK, and pharmacodynamic study of a loading bolus followed by continuous infusion of fludarabine, then followed by a loading bolus and continuous infusion of Ara-C in children with previously treated acute

leukemias.

I'm going to talk a little bit in detail about the first trial, which was CCG-097. There were two groups of patients, first those with solid tumors and those with the acute leukemias. The patients with the solid tumors reached a maximum tolerated dose because of dose-limiting toxicities that were hematologic--in other words, myelosuppression. The patients with the acute leukemia, the goal was marrow ablation, so their maximum tolerate dose was not reached based on this toxicity--toxicity associated with the solid tumors, but their dose was limited by the concern for potential CNS toxicity that had been seen with adults. Of note in this trial, there was one complete and three partial remissions in 26 evaluable children with ALL.

The pediatric adverse events that were noted in this trial and are included in the label are marrow suppression, especially of platelets, fever, chills, asthenia, rash, nausea, vomiting, diarrhea, and infection. No peripheral neuropathy

or pulmonary hypersensitivity was seen in these trials.

The second trial, CCG-0895, which I had previously told you was a sequential administration of fludarabine followed by Ara-C, was undertaken in 31 patients either with ALL or AML. Of note, in the patients with ALL there was a 33-percent complete or partial response, and in those patients with AML, there was a 50-percent complete or partial response. This study was not able to provide data on the efficacy of fludarabine alone, but did provide efficacy and safety data for the combination.

I'd like to just point out--let me see if I can do it here--that this information from the first trial, CCG-097, has been included in the label as of October 2003. There are two parts of the label that have been changed. The first is the clinical pharmacology in special populations pediatric patients, which highlights that steady-state conditions were reached early. And then in the precautions section, pediatric use, this is a

description of that trial that I just told you about, followed by the treatment toxicity that I also pointed out to you.

In terms of drug use trends in the outpatient setting or sales of fludarabine, this is considerably different from what Dr. Sachs presented to you with her millions of prescriptions. Approximately 280,000 vials only of fludarabine were sold in the U.S. annually from May 2001 through April 2004, with no significant increase seen after exclusivity. And as Dr. Iyasu pointed out to you, this particular database is one that does not divide it up in terms of pediatric and adult use. Just as you would expect, fludarabine was primarily sold to clinics and non-federal hospitals during the 12-month post-exclusivity period.

In terms of drug use trends in the inpatient setting, where we do have some pediatric data, Premier data showed us that pediatric use accounted for 3 percent of discharges between 2002 and 2003 in which fludarabine was billed. And CHCA

data demonstrated that from October 2002 through September 2003, there were 95 discharges associated with fludarabine, which were essentially unchanged from the previous year.

Now I'm going to switch gears and talk to you about the adverse event reports for fludarabine in the one-year post-exclusivity period from April 2003 to May 2004.

The total number of reports for all ages were 300, with approximately a third of them occurring in the United States. As expected, almost all of them were serious, and over a third of them involved deaths.

In terms of the pediatric reports, all of them were serious. There were ten unduplicated pediatric reports, only one of which was in the United States, and the outcomes for three were death, and seven were hospitalized, one which suffered continuing sequelae.

Of those ten pediatric patients, the recorded use was for six preconditioning for bone marrow or stem cell transplant; for three, AML

relapse; and for one, JMML with splenectomy prior to bone marrow transplant. The age for these reports was predominantly in the 2 to 5 age range with six reports, one each in the one month to less than 2 years, and the 6 to 11 year age ranges, and two in the adolescent population.

Dr. Maldonado, this may get to your question earlier. These are all the adverse event reports for fludarabine in the one-year post-exclusivity period, both adults and pediatric patients. As you can see, there are a significant number of adverse events. Those that are underlined are actually unlabeled events, including increased bilirubin, abdominal pain, and then three related to either drug ineffective or disease recurrence. In the pediatric population, the only unlabeled event was abdominal pain.

I'm now going to give you a brief discussion of each of the ten pediatric patients followed by a summary of their categories and a comparison with the adult information in the label.

There were three deaths. The first was a

four-year-old with ALL who received fludarabine for preconditioning for stem cell transplant. The day after transplant, she developed fever, shock, and multi-organ failure. This was one of the cases that also reported abdominal pain.

An eight-year-old with ALL who received irradiation, fludarabine, and cyclosporine followed by stem cell transplant, who six days after transplant became febrile with a rash, generalized edema, tachycardia, abdominal pain, and cardiac arrest.

Of note, one of the later cases is a cardiac tamponade patient. We don't have additional information, but the tachycardia to over 200 along with the edema could be possibly concerning for that as well. But there is no additional information.

And the third and final death is a 13-year-old with bone sarcoma of the rib who received fludarabine as preconditioning for stem cell transplant and then developed carcinomatous pleurisy and died of disease progression.

In terms of the seven hospitalizations, there was an 18-month-old with hepatic veno-occlusive disease after bone marrow transplant for beta-thalassemia. There was a two-year-old with relapsed AML who developed photophobia on the FLAG study, which is fludarabine, cytarabine, and granulocyte colony stimulating factor. There was no photophobia noted on rechallenge.

And then I want to highlight an additional visual disturbance in a three-year-old with relapsed AML also on the FLAG study that developed bilateral blindness, which resolved leaving some degree of blindness, and that's the sequelae that I spoke of.

There was a four-year-old with AML relapse who developed encephalopathy and recovered.

The only United States case is a four-year-old with JMML with splenectomy in preparation for bone marrow transplant, who developed fever and pneumonia.

There was a five-year-old with AML after bone marrow transplant who developed aphasia,

vigilance disturbance, and non-specific encephalopathy. This is a foreign report. It's not clear whether vigilance disturbance is a disturbance of state associated with encephalopathy or could potentially also be visual disturbance, although most likely just a disturbance associated with the encephalopathy.

And then, as I previously mentioned, a 13-year-old with bone marrow transplant for aplastic anemia who developed cardiac tamponade and cardiac failure four days after transplant, who recovered with diuretics and pressors.

So, in summary, there were ten clinically significant pediatric adverse events, and if you break them down into four categories, there was cardiac failure in two, cardiac tamponade in one, and cardiac arrest in two. This is labeled for adults for edema and pericardial effusion. The abdominal pain that I pointed out to you before that was not labeled in adults, it is labeled for nausea, vomiting, anorexia, diarrhea, stomatitis, and GI bleeding in adults. And as I pointed out,

the two patients that had abdominal pain in the pediatric age range were those with multi-organ failure and death.

There were two pediatric patients with blindness and optic nerve disorder, and this label, as I will show you in a moment, is labeled for visual disturbance and blindness in adults. And encephalopathy is also labeled in adults.

Just to give you an idea in terms of whether this is a different signal from what's seen in adults, I showed you the most common adverse events in terms of those that were more than 20. In this same period of time, all of these events were reported in adults in the range of three to five adult reports.

And I just wanted to show you, this is the boxed warning for Fludara, and this gets at a couple of issues that were discussed actually yesterday. This drug should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. In addition, it is labeled in the boxed warning

that it is associated with severe neurologic effects, including blindness, coma, and death. Also labeled here are fatal autoimmune hemolytic anemia, and down here a warning about the combination of use with pentostatin and fatal pulmonary toxicity.

So, in summary, there are labeled and unlabeled adverse events for fludarabine that have been reported. There are a number of pediatric adverse events that were reported in the post-exclusivity period that were not recognized in the clinical trials that were done for exclusivity. These adverse events, however, have been labeled for adults. These serious adverse events include encephalopathy, blindness and other visual disturbances, and cardiac tamponade and failure. These patients tend to be on very complicated, pre-transplant regimens that involve multiple medications and immunosuppression. I just want to note that this completes the one-year post-exclusive adverse event monitoring as mandated by BPCA. But the FDA will continue its routine

monitoring of these adverse events for this drug.

Any questions?

DR. CHESNEY: Thank you very much.

Comments, questions? We need Dr. Santana, who is in Oslo.

Any other comments? Dr. Murphy, are there any--

DR. MURPHY: I think, you know, this is just one of the things we'll be looking at in the future when we review these and we don't think we see anything going on. How much information do you want? Do you want us to present it? Do you want us to send it to you beforehand? When we say we are going to no longer do--when we say this completes the exclusivity reporting, it means that this process will no longer occur, and that we are basically telling you that we think that that appears to be an appropriate outcome, unless you tell us something differently than that. We'll now go back to the usual process of just the Office of Drug Safety doing their reviews and we won't be reporting this to you.

So I did want to make that clear to the new committee members. That's what that means when we say that. We don't have any specific questions for this product.

DR. CHESNEY: Dr. Fant?

DR. FANT: Yes, just a question. Out of curiosity, how did the signals that emerged from the use of this drug, given the complex nature of the disease and the drug regimens that these kids are on, compare with the signals that emerged in previous reports for some of the other drugs?

DR. McCUNE: For the other oncologic agents or other drugs in general?

DR. FANT: Well, the other oncologic agents in these types of patients. Any way to sort of get a sense of whether there's something unique about these signals versus the others?

DR. McCUNE: I actually reviewed two oncologic drugs the last time we presented for this committee, and I think the process that we're really looking for is what you all have pointed out: Are there substantial differences from the

adult population? Are there substantial differences from what's in the label that should be potentially added to the label? Although that's very difficult given all the confound--the small numbers of patients and the confounding. And I think that it becomes very difficult because most of these drugs are not used except in patients who have recurrent disease, so they have disease progression. They're also on multiple other drugs and multiple other regimens.

So it can be difficult to pull out a signal. That's why we very carefully look at each one of these adverse event reports to try to see if maybe there's something more there or if there's a relationship that does not show up in the label for the adults. And so far, with the three drugs that we've reviewed in the last year, I haven't seen a substantial difference. They're very low numbers of usage for the drugs in general in the population, 200,000 versus millions of prescriptions. And then the pediatric use in that is very low. Because of that low number, that's

why there's been this initiative to try to get drug labeling for oncologic drugs because, otherwise, we wouldn't have the data to be able to do labeling or to be able to get these drugs to the population quickly.

DR. CHESNEY: Dr. Ebert, and then Dr. Nelson.

DR. EBERT: When you identify adverse events that have not been seen previously in pediatrics but have been seen in adults and are in the labeling, is the implication that the labeling does not need to be modified or that it does need to be modified?

DR. McCUNE: In general, when it's been stated in the label for adults, that's considered labeling. If there were something where there was a substantial signal without the confounding variables, that would be something that could be discussed. But, in general, unless there's a very strong signal that is different from what's seen in the adults, the label is considered to be adequate.

DR. CHESNEY: Thank you. I had that same

question, so thank you.

Dr. Nelson?

DR. NELSON: Just a comment before leading up to a question. I noticed the significant amount of pharmacological information in the label, as you pointed out, in terms of pharmacokinetics, and I speculate I know part of my comfort level with the use of these drugs is the fact that in the United States 90 percent of the children are treated on protocol, and the chances of this being used off-label are exceedingly low. Is that different in Europe? Is this either labeled or do they have--I mean, I'm just wondering why this seems to be used more frequently. Maybe, you know, in that case, I assume it's not labeled for a pediatric indication in Europe, but they must not have as much of a control over what happens to where someone's obviously using it for bone marrow transplant protocols.

DR. McCUNE: I don't know the answer about labeling in Europe.

DR. MURPHY: That's one place we haven't

looked. But I do think that you're making a good point. There has been a concerted effort within the FDA, working with both NCI and the American Academy of Pediatrics, to address the issue that was being brought up here. But the fact is that you won't have these products in Phase III trials for children. I mean, that just is not the process that happens for oncology drugs, though they're almost all--most of the children are in trials. It has to do with the paucity of, you know, the population and the ability to actually conduct Phase III trials.

I know this seems schizophrenic, so I just--so dealing with that issue, the quandary was we would never have products labeled for kids who have cancer which--yet we would have a tremendous amount of information. So there was an entire process and a number of meetings to look at how can we make the information available that is developed for this population. That's why there's a guidance on how to do that and how you can--and encourage the development of these products and research into

these products for children. And that's why the statement was that you don't actually have to have the product approved for children for certain indications to get this information into the label. But it is, you know, a product, a disease-specific process, and it's appropriate that information will go into the label for the oncology drugs.

DR. NELSON: But I guess if the comfort level in doing that is because there won't be the opportunity given the professional organization for extensive off-label use, then I guess as a group at some point in the future we should tackle about how one could discourage off-label use while at the same time providing information.

DR. McCUNE: That's one of the reasons why I wanted to point out in the boxed warning that it does state that a qualified physician using anti-neoplastic therapy be the one to administer the drug.

DR. CHESNEY: Dr. O'Fallon?

DR. O'FALLON: Well, you know, this is a real quandary because you're absolutely right that

the vast majority of children are on these studies, which is wonderful because they are being monitored very carefully. The ones that don't make it on to the protocols are usually, in my opinion, ones with comorbidities or some--or there's such an advanced disease. So they're starting to treat them with these things.

I'm wondering if given the fact that a year doesn't--given the fact that there isn't a huge population of off-label use out there, a year's data doesn't give us very much of a chance to see off-label problems. Do you see what I mean? If they're treating--a million kids were treated with something in that year, then you've got a pretty good idea--a pretty good chance to pick up anything that was somehow missed in the clinical trial. But if it's a very small number of kids that were treated in that year, then we really don't have very much of a chance of picking up anything either.

DR. McCUNE: The division continues to follow reports associated with the use of this

drug, so it's not like we don't have any follow-up. But we just wouldn't come back to present it necessarily to you unless there was something that would be--

DR. O'FALLON: You don't diminish your surveillance. You just diminish your reporting to us. Is that what we're talking about?

DR. McCUNE: That's correct.

DR. MURPHY: Well, we diminish going back and reporting to you. We don't go back and look at the, you know, trials that you've already seen. I mean, since that process has occurred. If additional studies had come in, you know, there might be an opportunity. But I think the only thing I would say is that if there's something that concerns you in the report and it was combined with the issue of either a small population or, as some of you know from the prior committee, the exclusivity is granted before the approval sometimes. That's changing because of the timing on the approvals, but there may not actually be much postmarketing in some certain situations. If

those situations--if you are concerned about something and either of those two situations exists, you could recommend that we come back and report to you relevant to whatever, you wanted more time to see what was happening. I mean, that is an option I think this committee has actually utilized earlier on when we had a very short postmarketing period.

But, again, I think just having a short postmarketing period wouldn't be the only reason to do it. It would be because there was a question or some concern that you would like us to come back and report to you about.

DR. O'FALLON: Isn't the purpose of postmarketing to pick up something that probably--that could have slipped through the cracks on the studies? That's all. If we don't give ourselves a very good chance at doing that, we're not going to have a chance to pick it up as much. That's all.

DR. MURPHY: Yes, I mean, and for the things you mentioned, I mean, the studies often--of course, the cancer studies--but, still,

particularly in other studies, they're much more exclusionary, and when it gets out there, it's used in the broader population. And as has been pointed out before, AERS is good over time picking up the rare, serious events that occur. So if those are concerns that you have, then you could recommend that we continue to report to you.

DR. CHESNEY: Thank you very much. Could I suggest that maybe we take a ten-minute break before the next speaker? I did want to ask if there was anybody here for the open public hearing. Nobody has registered yet, but we just wanted to check.

[No response.]

DR. CHESNEY: No. So I think if we could come back in ten minutes at 10 after 11:00, and we'll continue on with all the subsequent presentations. Thank you.

[Recess.]

DR. CHESNEY: I think we're ready to get started. It looked like we should be able to finish pretty close to our allotted time for those

with appointments with planes, trains and automobiles at the end of the meeting. So we'll move on to the next presentation.

DR. McCUNE: Thank you. It gives me great pleasure to introduce Dr. Jane Filie. Dr. Filie is a general pediatrician and pediatric rheumatologist. After years of doing basic research on connective tissue disorders and genetics at the NIH, Dr. Filie was a pediatrician in private practice prior to joining the FDA.

Today Dr. Filie is going to talk to you about desloratadine.

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DR. FILIE: Thank you, Dr. McCune.

Good morning, everyone. I would like to present the adverse event review for desloratadine during the one year post exclusivity.

Desloratadine is an antihistamine by Schering Corporation. It was originally approved in December 2001, and pediatric exclusivity was granted in February 2003. It is indicated for the treatment of seasonal allergic rhinitis in patients 2 years and older, and for the treatment or

perennial allergic rhinitis and chronic idiopathic urticaria in patients six months and older. The recommended doses are listed on the slide.

I would point some facts regarding loratadine, which is the predecessor of desloratadine. Loratadine is approved for children 2 years and older, whereas desloratadine is approved for children 6 months and older. Desloratadine is the major metabolite of loratadine and possesses similar pharmacodynamic activity. It also has less extensive first-pass metabolism and a longer half life than loratadine.

Now, the drug use trends for desloratadine. It accounted for 15 percent of the prescription non-sedating antihistamine market from March 2003 to February 2004. The total number of prescriptions increased slightly from 9.8 million to 10.2 million during the same period. Pediatric prescriptions accounted for 1.3 million prescriptions.

For pediatric exclusivity 246 children, 6 months to 11 years of age were exposed to

desloratadine in three two-week, double-blind, placebo-controlled safety studies. The efficacy of the drug was extrapolated from the adult efficacy data. The safety studies identified a subset of pediatric patients who are slow metabolizers of desloratadine, approximately 6 percent of all pediatric and adult patients, and 17 percent of the African-American patients. There was no difference in the prevalence of poor metabolizers across age groups, and there was no significant difference in adverse events, laboratory tests or vital signs between the pediatric poor metabolizers and normal metabolizers who received desloratadine or placebo.

The adverse events that occurred more than 2 percent during the clinical trials, which included adults and children over 12 years of age are listed on this slide.

In the pediatric clinical trials there were no adverse events reported that occurred more than 2 percent of patients in the age group of 6 to 11 years of age. The adverse events that occurred more than 2 percent in frequency greater than

placebo are listed on the slide according to different age groups as well.

During the one-year post exclusivity, there were 185 reports for all ages. Among the 185 reports there were 20 pediatric reports, 6 of them in the United States. Among the 20 pediatric reports, there were five serious pediatric event reports and there were no deaths.

The pediatric adverse events reported are listed on this slide. Even though there were 20 reports, these events do not add to 20 because some reports contained more than one event. The underlying events are unlabeled events.

I now proceed with a synopsis of the serious adverse event reports. 12 year old on desloratadine and nasal beclomethasone for unspecified allergy had bronchospasm and shortness of breath, hospitalized for an unknown period of time.

An 11-year-old on 5 milligram desloratadine, unknown indication, developed two asthma attacks within one month requiring

hospitalization. The patient had five doses of the drug between the asthma attacks without difficulty.

And a 6-year-old on desloratadine, 2-1/2 milligrams daily for urticaria, presented with Kawasaki disease three months after the initiation of treatment.

A 5-year-old on 1.25 milligrams desloratadine daily for cough and nasal secretion experienced somnolence, bradycardia, diplopia, dizziness and motor uncoordination, and this patient was hospitalized for 12 hours.

Last: a 2-year-old with a history of bronchiolitis and wheezing on desloratadine, 1.25 milligrams, for coughing and rhinitis, who experienced status asthmatic as requiring hospitalization on two successive days.

Notice that these were all non-U.S. cases.

Although not reported as serious adverse events, there are a few adverse event reports that were clinically significant. For example, a 5-year-old on desloratadine, 125 milligrams daily for rhinitis, experienced two days later somnolence,

disorientation, and an unspecified extrapyramidal disorder, one week later became unconscious, and recovered one day after the drug was discontinued.

Another relevant case was a 4-year-old girl on 2-1/2 milligrams of desloratadine daily, had been on the drug for a week from mosquito bites and no other medications, experienced spasms of the upper body which resolved weeks later after discontinuation of the drug.

Lastly, a 3-year-old on desloratadine for 8 days of a known dose and specified medication, no concomitant medications, experienced torticollis, and no other data was available.

Also notice that these are all cases that occurred abroad.

In summary, there were a few pediatric adverse event reports during the pediatric exclusivity period. There are no new safety concerns regarding the use of desloratadine in the pediatric population. This completes the one-year post exclusivity adverse event monitoring, as mandated by BPCA, and the FDA will continue its

routine monitoring of adverse events for this drug.

DR. CHESNEY: Any questions? Yes, Dr. Newman.

DR. NEWMAN: I have two questions. You listed a whole of kind of common pediatric things that were listed as more commonly occurring with medication than placebo. Were any of those statistically significant?

DR. FILIE: Which--

DR. NEWMAN: This was in the exclusivity trial, the fever, diarrhea, upper respiratory tract infections, coughing, all of those things. It's your ninth slide. Greater than 2 percent in frequency, greater than placebo.

DR. FILIE: No. These were really not so much different, and the range, the incidence of these side effects, adverse events, was around not more than 4 percent each, and they were not really clinically significant.

DR. NEWMAN: But all of these were more frequent with drug than with placebo?

DR. FILIE: Exactly. Which slide are you

talking about?

DR. NEWMAN: It's Slide 9.

DR. FILIE: Yes. These did occur more than 2 percent, and more frequently than placebo.

DR. NEWMAN: And were there some sort of equal number of adverse effects that happened less often with medication than placebo? I mean, I don't know how--if you look at 100 different things, and your standard is just more rather than statistically significant more, you'll find a bunch.

DR. FILIE: You're asking if there were some adverse events that occurred more frequently in placebo than with the drug?

DR. NEWMAN: Right.

DR. FILIE: Probably so, but I do not have the numbers. I cannot tell you that, but this is what is expressed in the label. Usually what they will have on the label is what occurs more frequently on the drug.

DR. NEWMAN: Unless you can tell how often it occurred with both and whether any of them are

significant, this kind of labeling just doesn't really help at all. It's not informative.

DR. FILIE: Yeah. Would anyone like to add? I would like to invite the Review Division if they would like to chime in and give any additional information. But as far as I can tell without looking at the reviews, the clinical reviews right now, I don't have the numbers.

DR. MURPHY: I think what you're getting at is how we do adverse event reporting in our labels. Is that the issue?

DR. NEWMAN: I'm just saying, you know, if you look for 100 different things and your only standard for reporting it is that it occurred more often with--I mean they're not going to occur at exactly the same rate with drug and placebo. They're not going to occur at exactly the same rate, so the fact that it occurs a little more with drug than placebo doesn't really indicate anything, you know. The question is does it occur either any one outcome statistically significantly more, or a lot more, or if you add them all together and say,

okay, any adverse event, was any adverse event, if you pool all these together, are one or more adverse events more likely with drug than placebo?

As a clinician who sees a lot of kids who get antihistamines and sees all of these things on the list every day, I mean a lot, I suspect that this is not a real association, but then why put it on the label? It just doesn't help me at all.

DR. MURPHY: What is done is if there are statistically significant differences in the trials, clearly that is put into the label, okay? But what is also then done--and one could argue the usefulness of that--but because trials are very, you know, as we've discussed, limited in number, limited in duration, limited in the population, what is also provided is additional information about adverse events that occurred more frequently in the treatment group than in the placebo group. I mean you're right from a mathematical point of view, but it is felt that because we know we're only looking at a limited amount of data that it is appropriate to define that which we think is

clearly statistically significantly different and that which we think is just reported that was seen in the clinical trials.

And actually there's been discussion of should we even be including those things that are 1 percent--what percentage should we have a cutoff and how useful it is? But that is some of the thinking behind why doing it, is that you don't really know what the entire context--I mean the entire spectrum might be, and this is the controlled clinical trial against placebo, and you know that in a population you're going to have background noise, so at least you can report against placebo what was seen.

Is Badrul here? Would you like to comment on how your division reports, particularly I think for the antihistamines. But it gets to the bigger labeling issues.

DR. CHOWDHURY: I'm Dr. Badrul Chowdhury, the Division Director in Pulmonary and Allergy Drugs.

What you're asking is a pretty broad

question I think, is not necessarily applicable to this drug as a single entity that applies across how an adverse event is reported in the product label following clinical trials.

The general practice is--I mean knowing it's a very limited database for a clinical trial, it's usually a few hundred to thousands, and you cannot really capture everything that has happened or could happen. The practice generally is to look at the numbers that happened with the drug, look at the numbers that happened with placebo, and make some reasonable cutoff of event that is more commonly happening with drug than with placebo, and put the numbers then.

Statistical influential statistics on adverse events is completely useless because you cannot really put a p-value against an adverse event and conclude it is significant or not. It really isn't worth an observation. And it is really during clinical practice that more and more is known, and adverse events, as it is reported, gets modified. It is not uncommon for a drug to

have an adverse event that you did not think of as being a drug-associated adverse event, but later on there's cases it bears out to be the case.

DR. NEWMAN: I would disagree with that, that there's no way that in practice anyone would pick up any of these adverse events as being drug related in the absence of a randomized trial because the background noise for all of these things is a lot.

DR. CHOWDHURY: Nobody's saying that is drug-related or drug-causes adverse events. It is just that these were observed. And add that to the interpretation of ultimate use because if you see something which is happening more commonly with the drug and not happening with placebo, I mean, it's not possible to go after each and every adverse event and try to make a cause and association if it is caused by the drug or not. I mean, just cannot happen in development in the limited time period. We're just reporting what was seen.

DR. NEWMAN: Okay. My guess is this is not the time to try to--

DR. CHOWDHURY: Oh, it probably is not, and this is really I think a more broader issue of adverse event reporting in the product label that comes out of clinical trials across drugs and across drug classes done specifically for desloratadine.

DR. NEWMAN: So maybe we could discuss it more at another time, but just as a consumer of this information, I find it pretty useless.

DR. CHOWDHURY: I mean I would really not discount it to that of an extent because I mean there are also adverse events that are here which actually may even turn out to be meaningful. I mean if I just pick an example for here, appetite increase. Somebody can say it's completely useless. But if you really go back and look at all antihistamines, it is not uncommon for some older antihistamines actually to cause persons to gain weight. This was the case with older antihistamines. Nobody would really link that association, but it is known that some older antihistamine which is not marketed in the U.S. any

more, actually caused increased weight.

And when you see in this report this appetite increase, I mean you can discount it being useless, but who knows? It actually may in the future might turn out to be useful.

So it's just a pure reporting of the number that were seen, not necessarily making a conclusion if that is associated with the drug or not.

DR. MURPHY: Again, it gets back to what do you think you're trying to achieve? I think the thought here is that, again, this is the controlled trial against placebo. You're going to have problems once it's out with all the confounders of background noise, and that it's appropriate to let people know in a controlled trial, this occurred more frequently than placebo, not making attribution. But over time you may, as Badrul pointed out, we will come back and revisit that which has been labeled from controlled trials and see if it's becoming relevant or more relevant. I guess better more relevant.

DR. CHESNEY: Thank you. I think this could be something that was readdressed, and Dr. Ebert and Dr. Nelson have questions. I also.

I've wondered, what stands out to me here is the movement disorders. What do you make of that, and is that a common finding in other antihistamines. I'm not used to using it to prevent them.

DR. FILIE: Usually it is not common to occur with antihistamines, but these are newer generations of antihistamines. It was not described in the clinical trials either adults or children. This was never described. So this is why we brought it up as important, and again, we need to report the information as it is and the numbers as they are, but, yeah, it had not been described in the clinical trials for adults of children. The earlier generations, like super heptadine, which was an older antihistamine, was known to cause some purposeless movements in rats in preclinical studies. So again, this is something that I think we need to watch.

We're looking at an ocean and these little signals pop here and there, and probably only with time and more numbers, we'll be able to make a better interpretation of this.

DR. CHESNEY: Thank you. Dr. Ebert and then Dr. Nelson.

DR. EBERT: Could you provide a little more detail about the two cases of congenital abnormalities?

DR. FILIE: Certainly. Let me see if she can pull this. It's a back-up slide. Can you find it? It's called maternal exposures.

These were two cases, and again, these reports have very little information. They are very vague, and it's very difficult to make any attribution of congenital malformation and link this to the exposure to the drug. As you can see, one baby was born with cryptorchidism and hernia and was exposed to desloratadine for five days, unknown gestational age, and the mother had concomitant use of amitriptyline. And the other case was a baby born with a cleft lip and palate,

and was exposed to multiple medications for an unknown length of time and unknown period of the pregnancy.

So it's really very vague and difficult to make any assumption given even the background rate of the occurrence of these malformations.

DR. CHESNEY: Dr. Nelson and then Dr. Fant.

DR. NELSON: I think you correctly observed that these are isolated events in an ocean, but I'd like to comment on the size of the ocean. What strikes me is that these are non-USA reports that you're reporting, and that if we want to try to get some estimate of frequency that what we really need--and I guess I would be making Dr. Iyasu's job more difficult--the European Union, if that's where they're from, is a smaller market than United States, and in fact it may then reflect a higher frequency than we might think if we look at our 10 million prescriptions here. We don't know then how many prescriptions were actually written for the population that's reporting these events.

DR. FILIE: That is correct.

DR. NELSON: And it also raises an interesting question whether their ascertainment system's better or whether their physicians are just more socialized into--I don't use that term politically--into reporting, etc. But the data that is not comparable, we have isolated events out of a market that we don't have the denominator, and we have a denominator out of a market we have no isolated events. So either we're much safer here, or what? So comment.

DR. FILIE: Exactly, and I think you're correct.

DR. IYASU: Could I make a comment here? I wouldn't presume to sort of evaluate how different our systems are. I won't make a comment about that.

But in terms of foreign reports, what we get is probably a very small percentage of the actual volume because the requirements are there for serious events to be preferentially reported from those serious sources. There's no requirement

to. So there is also, you know, many--there's more focus on the serious events. But in terms of exposure, I don't know of any database that we have access to at FDA that will sort of estimate what the exposure that was in Europe, although they do have their own databases as well. And IMS has different streams that also is only probably making estimates in drug exposures in Europe.

So I don't think we have the right databases to try to tease out what the differences are, but I think we need to be careful, wherever the reports come from, that if there is an opportunity to explore them further, that would be an important activity which you say you would make my job more difficult. But I think this is something that we can entertain.

DR. CHESNEY: So you can add a European database to your American database in your spare time.

[Laughter.]

DR. CHESNEY: Dr. Fant?

DR. FANT: Just one comment that stems

from one of your case reports, and I think it just underscores the importance of these narratives, at least from what I can glean.

In the 5-year-old, who basically over the course--two days after starting the medication, over the course of a week, developed somnolence, disorientation, unspecified extrapyramidal disorder, which seemed to progress over a week to a state of unconsciousness, and then recovered one day after the drug was discontinued. What you told us was that one of the features of this drug was its relatively long half life. So it's just kind of perplexing, just from a pharmacokinetic standpoint how such severe symptoms--now they may be connected; this may be a connection, but it's kind of a strange one from the way I interpret this, and it's worth noting because it may be real or it may be something that emerges as some bizarre quality related to this particular drug in terms of the idiosyncratic reactions it may elicit in people. But I just don't understand how such severe symptoms can resolve in one day after being

on a drug with a long half life for a week.

DR. FILIE: Yes. I agree with you. And again, these reports are very vague, so it doesn't give us much information. And you're right, how could he just recover in one day how disoriented and somnolent this child was. Could be that this child would have been in that category if this all metabolized and really had a more significant presentation of the side effects. We just don't know and can't tell just from the report.

DR. CHESNEY: Thank you very much.

I think we'll move on to the next topic of adverse events for budesonide and fluticasone.

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DR. CHOWDHURY: Moving on with the next section of the presentations. In this section you're going to hear information regarding adverse events that have been reported to the air system for budesonide and fluticasone containing products. These adverse events may have been reported by patients, physicians, health professionals or the companies themselves, and specifically they're reporting of these adverse events to you, the

Pediatric Advisory Committee, as I mentioned before, is monitored by the BPCA. It's only for one year, so you'll hear a lot of information from a series of presenters. So we'll have questions for clarification and also discussions of the question that has been posed to the Committee at the end of the series of presentations.

So you will hear from four speakers this morning. The first speaker is Dr. Peter Starke. Dr. Peter Starke is a pediatrician and a medical team leader in the Division of Pulmonary and Allergy Drug Products. He has been with the Agency since 2000. Dr. Starke will be summarizing the regulatory history and the labeling changes and will provide a perspective on the safety of these drug products which include the orally inhaled and intranasal budesonide and fluticasone propionate drug products. So this will give you I think a good background in context for the next set of presentations that will focus on the summaries of clinical trials as well as the adverse event reports.

Dr. Peter Starke.

x DR. STARKE: Good morning. I'm Dr. Peter Starke. As you've heard, I'm a pediatrician and a medical team leader in the Division of Pulmonary and Allergy Drug Products. This morning I will attempt to place the written request studies and the adverse event information, particularly the adverse event information that you're about to hear, into some perspective.

Although you will hear about adverse events with all the budesonide and fluticasone drug products, we're specifically going to deal with just the orally-inhaled and intranasal drug products, and not the cutaneous drug products, at least my talk.

I want to assure you that we've reviewed this information carefully and are comfortable with the adverse events that you'll hear discussed, that they're appropriately represented in the label for both of these drug products. In addition, many of these types of adverse events occur with other orally-inhaled and intranasal corticosteroids and

those two, as appropriate, appear in the labels for those drug products.

This is an outline of my talk. I'll set the stage for the discussion with some background on the burden or allergic rhinitis and asthma in the United States. I'll then focus on asthma and review what is considered appropriate and necessary treatment for persistent asthma as defined by the National Asthma Education and Prevention Program in cooperation with the National Heart, Lung and Blood Institute.

These guidelines for the diagnosis and management of asthma were first published in the early '90s and then again in 1997, and again in 2002. You see the URL for the website listed at the bottom of the slides.

Then I'll go into some of the regulatory history and labeling chronology. The labeling for these drug products has changed dramatically over the last 10 years and I'll show you a lot of what has happened in that time period. We'll go over the specific results of growth suppression studies

with both budesonide and fluticasone, covering the orally inhaled and then later the intranasal drug products, and then I'll touch on the status of the current labeling for safety findings for these products.

This slide shows you a little bit of the burden of allergic and non-allergic rhinitis in the United States today. Allergic rhinitis is a very common disease and it represents significant morbidity as you see shown. The figures you see come from the 1998 Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology, and I'll touch later on their recommendations for us of corticosteroids in the treatment of allergic rhinitis. I'm not going to talk at all about non-allergic rhinitis.

However, we'll focus a little bit more on the burden of asthma. This information and the information on the next several slides comes from the National Information Survey which is conducted annually by the National Center for Health Statistics at the CDC, and this information can be

found on both the NHLBI and the CDC websites.

Asthma is a significant public health concern in the United States. It's associated with significant morbidity and mortality. In the United States it's estimated that over 20 million persons are affected including over 6 million children. You see on the slide the associated emergency department, hospitalization and deaths during 1999.

This slide represents the burden of asthma in terms of the prevalence per thousand population in the United States today. Again this comes from the National Health Interview Survey, and you can see that the questions on the survey changed after a period of time, and these questions represent slightly different questions after--I can't see the date from here, but something like 1999. Now, what you see is a rise in prevalence in asthma over time, starting in 1980 at about 31 per thousand, increasing by 1996 to 54 per thousand, an increase of about 74 percent.

Here you see the mortality rates for asthma in the United States over approximately the

same time period. This again comes from the same database. You can see that the ICD codes changed slightly around the year 1999 so they represent slightly different coding, but again give you a good sense of the mortality rates and what you see as an increase from 14.4 in 1980--this is per million--to a peak of 21.9 million, and then a decrease to about 16 million by the year 2000. So the peak prevalence was in 1995.

What I've shown you is that in the United States this represents, asthma represents a huge burden to individuals as well as to the health care system, and while the prevalence of asthma has increased and increased quite a bit since 1980, the overall increase in mortality has not reflected the same rate of rise as the increase in prevalence. The mortality peaked in 1995 and is now declining, and most practitioners feel that this is due to a combination of advances and care that are monitoring, patient education and the use of controller medications including the use of corticosteroids for persistent disease.

This slide represents a brief summary of the medications used in clinical practice for the treatment of asthma, and you see quick relief and long-term controller medications listed. I've highlighted corticosteroids and want to place their role into some--as a controller therapy into some perspective here. Originally the NAEPP guidelines recommended the use of controller medications for moderate and severe persistent asthma, but the latest recommendations now state that corticosteroids should be used for all forms of persistent disease.

Now I'm going to switch topics a little bit and start to give you a sense of what's changed in the labels over the last 10 years. All of these drugs were approved during the 1980s and 1990s including budesonide and fluticasone. There are a number of years during which some significant events occurred. The first was 1994. In that year the Pediatric Labeling Rule took effect, and that labeling rule did a number of things, but among the things that it did was that it required sponsors of

approved products to examine the existing data in the product label to determine whether the pediatric use subsection should be updated, and this prompted a number of pediatric efficacy supplements and many of these products were approved to lower age ranges down to about 4 to 6, and subsequently some lower.

In that same year the FDA began to review the labels for all orally-inhaled and intranasal corticosteroids and made a number of changes over time. They started doing it then, but over time have made a number of changes with the additions to the labels of adverse events as reported to the companies and to MedWatch.

Now, in 1997 several important events occurred. First the NAEPP expert panel issued their second report and I've discussed the results of their recommendations already, and you see them up here. Second major event was that a growth suppression study was submitted to the Agency, and this study was a one-year study with intranasal budesonide. The dose that was used was the highest

approved dose of 336 micrograms a day, and it showed a statistically significant growth suppression effect, but no significant effect on hypothalamic-pituitary-adrenal or HPA access function.

In addition, other growth studies were submitted and are published, but particularly they were submitted, and for both orally-inhaled and intranasal drug products, but particularly for the orally inhaled, and with this information several things occurred.

I'm going to skip over what happened and just talk briefly first of 1998, come back to the allergic rhinitis, and the Joint Task Force for Practice Parameters, in conjunction with the American Academy of Allergy, Asthma and Immunology recognized intranasal corticosteroids as the most effective medication for the treatment of severe allergic rhinitis.

Going back to asthma, because of the growth studies that came in a Joint Advisory Committee meeting was held. This was a Joint

Pulmonary Allergy and Metabolic and Endocrine Disease Advisory Committee meeting, at which time the results of the growth studies that had come into the Agency were discussed. They did recommend a number of labeling changes, and I'll show them to you in the next several slides. That included putting results of growth studies in the label, and adding class labeling for risks for adverse events to all labels for orally inhaled and intranasal corticosteroid drug products.

In November of that year, in November of 1998, the FDA implemented these recommendations, sent letters to each of the sponsors requesting supplements with additional labeling. Now, this is the labeling in two of three locations that was added to the labels, and as I just started to say, there are three locations on the label where labeling was added. You see the first two, the Precautions, general and the Adverse Reactions sections, and under Precautions, pediatric use section, a long paragraph was added.

I haven't shown you the whole paragraph.

I have it if you want to see it, but this is a synopsis of what was said, which is that: Orally inhaled or intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. The growth effect may occur in the absence of laboratory evidence of HPA axis suppression. The potential for "catch up" growth following discontinuation of treatment was not addressed. Growth should be monitored routinely in patients. To minimize the systemic effects, each patient should be titrated to his or her lowest effective dose.

Now, through our evaluations of growth studies, we've come to understand a number of important points about these studies. First, we feel that growth suppression reflects systemic exposure to the corticosteroid. This is likely to be due to a direct bone effect on osteoclastic-osteoblastic activity. That's a presumption that I'm saying. We believe it's a very sensitive indicator of systemic effects, and therefore, the potential to cause systemic toxicity. And that

effect may be generalized to adults as well as children. In other words, the growth suppressive effect, being an indicator of the potential for toxicity is not specific to just the growth population that's looked at in the studies.

I'm showing you where a growth defect study may be positive where an HPA axis study was negative. Because of the way we want the information, we request that these studies look at, as accurately as possible, and characterize the difference in growth rate in patients treated with active and with control. Now, they're quite technically difficult to perform, and I do want to congratulate both drug companies for having growth studies with the intranasal and the orally inhaled drug products, and I'm going to show the results shortly.

I'm not going to go into the details of the technical difficulties with doing them and/or assessing them, but keep in mind that these require at least a year on treatment, height measurements with stadiometry, and they must be performed during

the relatively level or flat growth phase, generally between 3 and 9 or 10 years of age, after the infant growth spurt and before the pubertal growth spurt.

There are a number of limitations to interpretation of these studies. They are not designed to demonstrate reversibility with continued use after a year or after stopping a medication. They're not designed to evaluate the effects on final adult height, and you cannot take the growth effect and relate it at all to the individual patient. For these reasons, they are very difficult to interpret out of context of the study itself.

All the studies were designed prior to when we published a growth guidance in 2001, and no two studies had the same design. Therefore, it's quite difficult to do any kind of cross-study comparison, and I won't attempt to do so.

So here's the growth study for inhaled budesonide. This is the design of the growth study. It used Pulmicort Respules. This is, by

the way, not in the label. What's in the label is the growth results for the 12-week study that gave the indication. This information, however, was discussed at the 1998 Advisory Committee meeting, and therefore I'm showing it to you now.

This was a 12-month open label extension of a 12-week double-blind study. The arms you see with inhaled budesonide and nonsteroidal. There were several analyses done for different age groups, 9 months through 3 years and 4 through 8 years. Before I show you the results, I just want to caution you about interpreting results for the 9 month to 3 year age range, where growth is not linear and where one generally has to measure length rather than statutory height, and this introduces a large variable into these kinds of studies.

So here are the results for the orally inhaled budesonide. You see at the top the 4- to 8-year-olds, and below it the 9 through 3-year-olds. You see also the budesonide and then the nonsteroidal groups below it, and the height

changes over the year--I'm sorry, the growth rate over a year. The delta is what I would point out to you. That's the difference between the active and control groups. A negative number implies a growth rate effect, a positive growth rate effect. So you see for the age range of 4 to 8 a growth suppressive effect of half centimeter, and for the lower age range, 1.8 centimeters. So there clearly is some difference between the two, but again, it's hard to interpret what that difference actually is.

This is the growth study using inhaled fluticasone propionate, and I believe this is in the labeling. This used the Flovent Rotadisk. It was randomized, placebo-controlled one-year study in prepubertal children. You see that two doses of fluticasone propionate were used in this study, 50 and 100 micrograms twice daily.

There are the results. There was some indication of a dose response in this study, and if you look at the first two lines of the delta you see the results compared to placebo for the 50 and 100 micrograms twice daily.

So just to continue and update from 1998 to 2004, the Advisory Committee recommendations were implemented, as I've shown you. I mentioned already that we published a draft growth guidance in 2001. Guidances represent the best thinking of the Agency, but they do not require sponsors to follow that thinking if they can show us some alternative methodology.

The labels have been reviewed and updated with new labeling supplements as they come in, with post-marketing adverse events as reported. You'll hear the pediatric exclusivity studies next. They're updated with pediatric exclusivity studies results as appropriate and with the results of Phase IV growth studies as they come in.

Here are the results for the intranasal budesonide and fluticasone growth studies, and you see the moiety on the left, the dose, the N, the growth rate over a year, the difference between active and placebo and the 95 percent confidence intervals when we have them. For convenience I put on the slide the results of the beclomethasone

study that started this all off in 1997, and you see only a very small effect for each of these two drug products. But I just want to point out the budesonide used the lowest approved dose; fluticasone used the highest. We do recommend at this point that sponsors use the highest approved dose in these studies.

So the labeling status as of 2004. All labels clearly describe the potential risks for adverse events; HPA axis studies. We've included the class labeling. There are some minor differences between various drug products in the wording, but that's probably fine. Growth studies, as they come in; and all the labels are being reviewed and updated as new labeling supplements are submitted.

Specific labeling for budesonide and fluticasone is shown in this slide. Both the orally inhaled and intranasal drug products for both of these drugs have HPA axis growth and post-marketing adverse events labeled. In addition--and this relatively new information, so I've included

it separately--budesonide--and you saw the results of the growth study. That study is now in the label as of the last month or two. In addition, as of the end of August, budesonide was relabeled as Pregnancy Category B, and this is as the results of information from three Swedish birth registries. You see a representative of what Category B, one of the requirements for Category B. It was changed from Category C to Category B.

So in summary, asthma is a chronic inflammatory disease of the airways. It represents a huge burden to the health care system. While the prevalence of asthma has increased since 1980, the mortality rates increased, and then have declined, although the overall mortality rate is higher now than it was in 1980. Corticosteroids are recommended as a primary controller therapy for persistent asthma, all forms, and as the most effective therapy for severe allergic rhinitis.

The types of adverse events that may be expected with this class of compounds, namely corticosteroids, have been well documented over the

years, and the FDA is continually reviewing and updating the labeling as we get more and more information about the individual drug products.

I've shown you how the labels have changed dramatically over the last 10 years with class labeling. We really haven't gone into HPA axis information, but you'll hear more about that in the written request studies. I've shown you about the growth studies. You'll hear about the adverse event data. At this point we believe that the current labeling for these drugs is concurrent with the latest safety data for these products.

I leave you with this quote from the NAEPP guidelines, from the 2000 guidelines, which state that: "Inhaled corticosteroids improve health outcomes for children with mild or moderate persistent asthma," and obviously with severe, "and the potential but small risk of delayed growth is well balanced by their effectiveness."

Thank you.

Now I'm going to introduce to you Dr. ShaAvhree Buckman. She is a pediatrician with the

Division of Pediatrics. She has Ph.D. training in molecular cell biology and pharmacology. She's been a medical officer in the Division of Pediatrics for the last two years. She will be presenting on the clinical studies for budesonide and fluticasone.

x DR. BUCKMAN: I can now say good afternoon.

[Laughter.]

DR. BUCKMAN: I will be presenting a summary of clinical trial data for fluticasone and budesonide. As an overview this table describes the various fluticasone dosage forms, the original dates of approval and current pediatric approval information. This table includes topical, intranasal and orally inhaled products.

The most recent approval, as of May of 2004, was for Flovent HFA Meter Dose Inhaler. HFA stands for hydrofluoroalkane, and this inhaler is designed with a CFC-free propellant that is more environmentally friendly.

This table describes the various

budesonide dosage forms which include orally inhaled, intranasal and oral products. Because the names of some of these products can become confusing, the slide just shows some examples of some of these products. The Advair Diskus, Flovent Rotadisk and Pulmicort Turbuhaler are inhaled powders. Pulmicort Respules are a solution for inhalation used in conjunction with compressed air-driven jet nebulizers. Also shown here is a typical Flovent Metered Dose Inhaler which delivers aerosolized drug, and Entocort, which is shown in the corner, is indicated for oral use only in adult patients who have Crohn's disease. We will not be discussing this product during today's presentation, but it is a budesonide containing product. Also shown here are two nasal preparations, Flonase as well as Rhinocort Aqua.

Seven dermatology and pulmonary studies were requested for pediatric exclusivity for the fluticasone moiety. Four studies were requested for Cutivate, which is the dermatologic product. One study was requested for Flonase, two studies

for Flovent, and there was also requested an in vitro study report as well as a population PK report for Flovent.

First we will discuss the studies for Cutivate. As background, Cutivate cream has been approved for use in children 3 months of age and older since June 17th of 1999. A written request was issued for other fluticasone containing formulations on June 25th of 1999. This written request included three studies for Cutivate lotion and one study for Cutivate ointment. Also as background, an Advisory Committee was held in October of 2003, which many of you may have attended, that discussed the clinical risk management of HPA axis suppression in children with atopic dermatitis who are treated with topical corticosteroids. Presently, only Cutivate cream is indicated for pediatric use, not the ointment.

The current labeling for Cutivate cream includes studies which were not requested for pediatric exclusivity. 43 pediatric patients were treated with Cutivate .05 percent cream for atopic

dermatitis covering at least 35 percent of their body surface area for four weeks. 2 out of the 43 patients had HPA axis suppression, and follow-up testing was available for one of those two patients, which demonstrated a normally responsive HPA axis on follow up.

This study using Cutivate ointment was requested for exclusivity. 35 pediatric patients were treated with Cutivate ointment for atopic dermatitis covering at least 35 percent of their body surface area for three to four weeks. Subnormal adrenal function was observed with cosyntropin stimulation testing in 4 of the 35 patients. The recovery of adrenal function in these patients was unknown and follow-up testing was not performed. This information was incorporated into the Pediatric Use subsection of the labeling as shown here. It is important to note that Cutivate ointment is not indicated for pediatric use.

Now we will discuss the clinical studies for Flonase, the intranasal product. This study

was described to you briefly by Dr. Starke in the previous presentation, and it was not requested for pediatric exclusivity. This was a one-year multi-center placebo-controlled trial looking at longitudinal growth of 150 children, ages 3 to 9 years with perennial allergic rhinitis.

The mean reduction in growth velocity after one year of treatment with Flonase at 200 micrograms per day was estimated at .137 centimeters per year. HPA axis evaluation in these patients showed no interpretable effects on urinary free cortisol. And this study supported safety in children at the maximum approved dose and twice the daily dose typically used in patients at this age group.

The recommendation was made for the results of this one-year growth study to be incorporated into labeling, and you can see where this was incorporated.

This study for Flonase was requested for pediatric exclusivity. It was a six-week, multicenter, placebo controlled HPA axis study in

65 patients between the ages of 2 and 4 years with allergic rhinitis. 12-hour urinary free cortisol was used to evaluate the HPA axis. The results of this study were deemed indeterminate due to limitations in urine collection and wide variations in baseline urinary free cortisol levels between treatments groups. Therefore, no labeling change resulted.

Now we will discuss clinical studies for Flovent. We have discussed studies for Cutivate and Flonase, and now we'll briefly touch on an in vitro study report that was done for Flovent for exclusivity.

Prior to starting the clinical program with Flovent, the sponsor performed a comparison of the particle size distribution by cascade impaction for Flovent CFC Metered Dose Inhaler with and without the use of various spacers as shown here.

The results appear to indicate that the in vitro respirable particle content was similar whether the metered dose inhaler was studied alone or in combination with either of three different

spacers. However, the study was unable to evaluate factors that would have been important to the in vivo clinical setting, and this would include variations such as variations in flow rates, delay between actuation of a dose and actual inflow, how long a mask was held over the nose and mouth of a child, and therefore, result of this study were not incorporated into labeling.

These studies for Flovent were requested for pediatric exclusivity as well. Two 12-week placebo controlled efficacy and safety studies were performed in children with symptomatic asthma, who were between 6 and 47 months of age. Detectible plasma levels of fluticasone were seen in 13 of the placebo treated patients. Therefore, it was impossible to evaluate the actual extent of patient exposure and made the interpretation of the PK/PD relationship difficult to assess. The interpretation of this study was that it was impossible to determine whether the studies derived an accurate estimate of either safety or efficacy, and therefore, no labeling change resulted from

these studies.

Now we will discuss the clinical studies for budesonide. Two studies were requested for exclusivity. One was a safety study of budesonide nebulizing solution for the treatment of asthma in children 6 months to 1 year of age, and the second was an HPA axis safety study of the budesonide nasal spray in children between 2 and 6 years of age.

First we will discuss the studies for Rhinocort Aqua, the nasal spray. This was a 6-week multicenter placebo controlled study to evaluate the effect of Rhinocort Aqua on HPA axis in patients with allergic rhinitis. 78 children were studied between the ages of 2 and less than 6 years of age. The HPA axis function was evaluated by low-dose cosyntropin stimulated plasma cortisol measurements at baseline and following six weeks of treatment. The results of this study were deemed indeterminate because of difficulties in determining patient compliance, and no labeling change resulted.

Now we will discuss a clinical study for exclusivity using Pulmicort Respules. This was a 12-week randomized placebo-controlled study to evaluate the safety of Pulmicort Respules at .5 and 1 milligram daily in pediatric patients with mild to moderate asthma or recurrent persistent wheezing. 141 patients were studied between the ages of 6 and 12 months. The main safety concerns that were evaluated were concern for HPA axis suppression and suppression of linear growth.

Of the 141 patients that were randomized, 76 patients had an ACTH stimulation test at the beginning and the end of the study. The mean values of the three treatment groups did not indicate any difference in adrenal responsiveness. However, six patients with Pulmicort Respules and one patient in the placebo group had post-ACTH plasma cortisol levels that were below normal.

There was also noted in the bottom study a dose-dependant decrease in growth velocity between the placebo and budesonide treated groups. Also of note, pneumonia was observed more frequently in

patients treated with Pulmicort Respules than placebo. Three patients were noted in the budesonide treated group who developed pneumonia during this study.

These findings were incorporated into the clinical pharmacology and precautions subsections of the label show here. In summary, the studies for pediatric exclusivity have resulted in labeling changes for fluticasone and budesonide containing products. Pediatric trials for fluticasone and budesonide have identified important safety concerns which have been incorporated into labeling.

This concludes my presentation, and I thank you for your attention.

The next presentation will be given by Dr. Joyce Weaver, who is a Safety Evaluator in the Division of Drug Risk Evaluation in the Office of Drug Safety at the FDA. She will be presenting the adverse events for budesonide and fluticasone.

x DR. WEAVER: Good afternoon. I'm going to be presenting both use data and information about

adverse events reported to the FDA's Adverse Event Reporting System for budesonide and fluticasone.

First I'll talk about budesonide. The total number of prescriptions dispensed for all budesonide products increase from approximately 6 million in 2001 to 7.8 million in 2003 with pediatric patients accounting for about 29 percent of the total prescriptions. Rhinocort, the nasal product, is the most commonly used budesonide product, accounting for over half of the budesonide prescriptions, and of those, 17 percent were for pediatric patients.

The inhalation product, Pulmicort Respules, represents most of the rest of the prescriptions for budesonide. Over half of the Pulmicort prescriptions are for pediatric patients. Entocort represents a very small portion of budesonide dispensed.

The FDA's Adverse Event Reporting System, or AERS, contains about 2,800 adverse event reports for all ages covering the lifetime of the budesonide products. For the one-year period