include demyelinating disease and exacerbation of severe congestive heart failure.

Now, ever since the approval of the first TNF blockers, there's been a concern about the potential for risk of malignancy, given the immunosuppressive properties, and the possibility for reduced immune surveillance leading to a greater malignancy risk. However, as I'll show you in the next few slides, the data on the risk of malignancies are conflicting.

So I'll start with the risk of lymphoma in adults. The risk of lymphoma was first noted for TNF blockers when an imbalance was seen for lymphomas in the pooled controlled clinical trials of the three TNF blockers. And this consisted of six lymphomas in the TNF blocker arm, compared to zero in the placebo control arms.

However, there are other potential explanations for this. For example, there

was an unequal randomization, three to one, to drug versus placebo. In the overall clinical trial experience, including randomized trials and the open-label extension studies, the relative risk of lymphoma was approximately three to fivefold with TNF blockers, compared to the risk expected in the general population. However, a similar relative risk has been noted in rheumatoid arthritis patients with highly active disease who are not treated with TNF blockers. And indeed, epidemiologic studies have suggested a similar rate of lymphoma in adult patients with rheumatoid arthritis receiving TNF blockers as compared to RA patients who are not receiving TNF blockers.

One particularly concerning risk of malignancy is the risk of hepatosplenic T-cell lymphoma in patients treated with infliximab for Crohn's disease. So rare cases of hepatosplenic T-cell lymphoma have been observed in adolescents and young adults

with Crohn's disease who received infliximab.

Hepatosplenic T-cell lymphoma is a rare, aggressive T-cell lymphoma that is usually fatal. And all of the cases of hepatosplenic T-cell lymphoma with infliximab were associated with concomitant immunosuppressives, azathioprine, or 6-mercaptopurine.

Turning now to the risk of solid malignancies in adults, the data for this are different, and they came initially from analysis of pooled randomized trials that the FDA looked at for each of the three approved TNF blockers at the time -- infliximab, adalimumab, and etanercept.

In these pooled randomized control trials, with infliximab, a higher rate of solid malignancies was seen compared to controls, a rate of 0.52 per hundred patient-years versus 0.11 in the controls, a severalfold increase. The same analysis with the adalimumab trials showed a rate of 0.6

events per hundred patient-years as compared to 0.4 per hundred patient-years with controls.

The solid tumors seen were a variety of solid tumors that are typical in the general population. The difficulty in interpreting these results comes from the fact that for infliximab and adalimumab, the malignancy rates were not higher than the expected rate in the general population.

The other complications in interpreting these data are the relatively short time of observation -- six months to two years -- and unequal randomization in the different study arms, making the interpretation somewhat uncertain. A similar analysis carried out with etanercept showed a rate of malignancy that was not higher with the etanercept arm than in the control arms.

Amgen recently submitted to the FDA a draft report on an independent meta-analysis of clinical trials to assess

cancer risks for approved TNF blockers, including etanercept. This draft report is currently under FDA review, and a final report is expected shortly.

So these data indicate that the randomized trial data are inconclusive for the risk of solid tumors. In long-term treatment studies of adalimumab and etanercept, there's no evidence for an increasing rate of malignancies with longer durations of exposure. And indeed, epidemiologic studies conducted in England and Sweden have shown no higher rate of malignancy in adults with RA receiving TNF blockers compared to patients not receiving TNF blockers.

A stronger signal for a risk of malignancy comes from two trials of TNF blockers in unapproved indications. Two of these controlled trials have shown a malignancy signal in the selected populations. First, in a randomized

controlled trial of etanercept in Wegener's granulomatosis, 5 of 89 patients in the etanercept arm developed solid malignancies, versus no malignancies in the control arm. All of these malignancies occurred in the subgroup of etanercept patients who were receiving concomitant cyclophosphamide.

A second study randomized patients with moderate to severe chronic obstructive pulmonary disease to infliximab or control. In this study, 9 of 57 infliximab-treated patients developed malignancies, compared to 1 of 77 control patients.

The rates of malignancies were 7.67 versus 1.63 events per hundred patient-years, a severalfold higher rate in the infliximab arm. Note here that this was a study of short duration, just six months.

The data here suggest that in certain populations at high risk of malignancy, the risk may be further increased by treatment with TNF blockers.

Turning now to malignancies in children receiving TNF blockers, recently the FDA has become aware of post-marketing reports of malignancies in children receiving the approved TNF blockers. Overall, as you've heard, approximately 30 cases have been reported, and this excludes the cases of hepatosplenic T-cell lymphoma seen in children receiving infliximab for inflammatory bowel disease.

Reports of malignancies in children have occurred in both the Juvenile Idiopathic Arthritis and in the Crohn's disease indications.

Approximately half of these 30 cases were cases of lymphoma, and half were other malignancies.

Lymphomas included Hodgkin's disease and non-Hodgkin's lymphomas. The non-lymphoma malignancies included leukemia, melanoma, and other solid organ cancers. And the rate of malignancy compared to the

background rate and its relationship to the use of TNF blockers is currently under investigation.

The sponsor earlier showed you data on their estimate of the standardized incidence ratio for malignancies compared to the expected rate. They also told you that seven of the nine malignancies in children were hematologic malignancies. So it'll be very important as part of this analysis to look at the expected rate of hematologic malignancies compared to the observed rate.

Turning now to the information we have from safety data in registries, in order to assess long-term safety of biologics in children, the FDA has made sure that observational registries was part of the post-approval safety assessment. And observational registries were established at the time of approval for pediatric use of all the TNF blockers.

These were established to fulfill

post-marketing commitments and post-marketing requirements. The etanercept registry was established for children with Juvenile Idiopathic Arthritis, and there was a registry established for infliximab for children with inflammatory bowel disease.

For the recent approval of adalimumab for Juvenile Idiopathic Arthritis, there is a registry called for children with Juvenile Idiopathic Arthritis.

For etanercept, the registry was designed to collect data on long-term use of etanercept in children with JIA using etanercept alone or in combination with methotrexate. And you've heard a little bit about this already. Enrollment was completed in January of 2005. Of the patients enrolled, 103 were on etanercept alone, 294 were on etanercept plus methotrexate, and 197 were on methotrexate alone. In this registry, no malignancies have been seen to date.

So in summary, TNF blockers as a class have proven highly efficacious in a variety of autoimmune conditions. Use of TNF blockers is associated with a variety of uncommon but serious adverse events. The risk-benefit relationship is considered favorable in the approved indications. In adults, there is evidence suggesting that TNF blockers may increase the risk in patients with an underlying elevated risk of malignancy.

And recent reports of malignancies in children receiving TNF blockers are of concern and are currently under investigation.

Thank you.

DR. KWON: Good morning. My name is KC Kwon, and I'm a safety evaluator in the Division of Adverse Event Analysis in the Office of Surveillance and Epidemiology. Today, I'll be presenting post-marketing adverse event data for etanercept in children aged 4 to 17 years

old.

The objective of my presentation is to inform the safety of etanercept as we consider its use in the pediatric plaque psoriasis population. For the purpose of our review and presentation, we considered children aged 4 to 17 years old as pediatrics, since this is the age group under consideration for pediatric psoriasis indication.

I will begin with some brief background, and provide drug usage data provided by the drug usage specialists in our office. Then I'll present an overview of all pediatric adverse events reported with etanercept, followed by discussion of specific post-marketing adverse events of interest, such as malignancies and infection. I will conclude with summary and conclusion.

As you have heard this morning, etanercept is a Tumor Necrosis Factor blocker, and is one of four approved TNF

blockers used for treatment of various inflammatory diseases. The safety profile of etanercept was obtained mainly from the use of this and other TNF blockers in adults and children with Juvenile Idiopathic Arthritis, which is the only approved pediatric indication for etanercept at this time.

And you have heard the safety concerns related to this class of biological product by Dr. Siegel in the previous presentation.

Before presenting our post-marketing adverse event data, I would like to provide a brief background of the AERS, or Adverse Event Reporting System, which is the FDA's post-marketing database that contains all adverse event reports.

Like any other system, this has strengths and limitations. The strengths include its usefulness in detecting events not seen in clinical trials, and it is especially good for events with rare

background rate or short latency, such as serious skin reactions.

The limitations include under-reporting, variable quality of reporting, reporting biases, and unknown denominator and numerator. It's also difficult to attribute events with high background rate, such as myocardial infarction, or long latency, such as malignancies.

This graph shows the projected number of patients who received etanercept in U.S. outpatient retail pharmacies, both total and subgroup of pediatric patients, since 2002. The red line shows the projected total number of patients of all ages, which increased from year 2002 to 2005, then declined slightly during 2007. The yellow line shows the projected number of pediatric patients who received etanercept, which accounted for about 3 percent of total patients during each year.

It's difficult to see the drug usage trends in the pediatric subgroup from this graph, but the number of patients who received etanercept in the pediatric subgroup increased from about 2,000 patients in year 2002 to 4,300 patients in year 2007.

Please bear in mind that this drug use data has some limitations as an accurate estimate of total usage. For one, retail pharmacies account for about 35 to 50 percent of yearly distribution, and the primary distribution channel in 2007 was mail order, which was not examined.

When we looked at prescribing physicians, not surprisingly, rheumatologists were the most common prescribers of etanercept. And the prescriptions associated with dermatologists showed the largest increase, from 3,000 prescriptions in year 2002 to 104,000 prescriptions in year 2007. Children were given etanercept for treatment of polyarthritis and psoriasis.

I've presented some brief background and drug usage information, and will now shift gear and begin discussion of post-marketing adverse event data.

This is an overview of all pediatric AERS reports for etanercept. The number of reports represent those in the AERS database since marketing in 1998 to April of this year. Please be reminded that this overview represents crude data, and therefore, duplicates haven not been reconciled.

There were over 54,000 reports associated with etanercept in the AERS database, and 949 were pediatric reports. More adverse events were reported in females, and the median age was 13 years. About 75 percent of reports came from the U.S.

I've listed the most commonly reported indications, and as expected, etanercept was most commonly used for treating JIA. A small proportion of

pediatric adverse event reports -- 61 reports -- occurred in children who received etanercept for psoriasis indication. Most of these were U.S. reports, and the most serious outcome reported was hospitalization, which occurred in five cases.

This shows all the outcomes reported in pediatric post-marketing reports with etanercept. Except for 14 cases with an outcome of death, the number of reports for other outcomes are again crude data. There were 200 hospitalizations; 6 were considered life-threatening; 3 required intervention for the reported event; and about 700 reports were others and non-serious reports.

Out of 14 pediatric post-marketing cases of etanercept with an outcome of death, eight occurred in patients who received etanercept for Juvenile Idiopathic Arthritis, three in Idiopathic Pulmonary Syndrome, two in Graft Versus Host Disease, and one was for an unknown indication.

Cases with indications other than Juvenile Idiopathic Arthritis, such as Idiopathic Pulmonary Syndrome and Graft Versus Host Disease, occurred in patients with severe comorbidity, and it was difficult to assess the role of etanercept in the outcome of death for these patients. For eight cases of JIA, the most commonly reported cause of death was infection-related, which occurred in four cases, and this included three cases of sepsis and one case of pneumococcal meningitis.

This slide describes a representative pediatric case who received etanercept and died due to infection-related complications. A 17-year-old girl received etanercept for treatment of JIA and died due to pneumococcal meningitis. Her concomitant medications included methotrexate, and after receiving etanercept for an unknown period, she presented to the emergency department

with a three-day history of fever and mental status changes.

The cerebrospinal fluid culture was positive for strep pneumoniae. She developed cerebral edema, increased intracranial pressure and brain death, and died.

In addition, we reviewed all domestic pediatric AERS reports reporting serious outcomes other than death, such as hospitalization and life-threatening events. And the most commonly reported adverse events were infections, which occurred in 31 unique cases. The types of serious infections are listed here, and included respiratory tract infection, skin and soft tissue infections such as abscesses and cellulitis, as well as urinary tract infections, sepsis, and osteomyelitis.

This table shows some characteristics of 31 cases reporting serious infections in pediatric patients after receiving etanercept. More females

experienced serious infections. The median age was 12 years, and the reported dose was within the recommended dose range. The time to onset of infection varied from one day to as late as four years after initiation of etanercept therapy.

22 of 31 cases reported concomitant use of other immunosuppressants such as methotrexate and/or corticosteroids.

These are representative pediatric cases who received etanercept and experience serious infection. An eight-year-old girl was hospitalized with staph aureus osteomyelitis after receiving etanercept for JIA therapy. Etanercept was discontinued and the infection was treated. The eventual outcome was not reported.

Another case was a 16-year-old girl who was hospitalized with systemic fungal infection that was thought to be histoplasmosis after receiving about 6-1/2 months of etanercept therapy for JIA. She

also received methotrexate, and the liver and lung biopsy revealed systemic fungal infection. She received amphotericin treatment and improved.

In addition, there were 10 cases of varicella reported in pediatric patients who received etanercept. Six of 10 cases resulted in hospitalizations, and based on the information provided, two cases appear to be primary infections, and two cases appear to be re-activations. Also, two cases of tuberculosis were reported in pediatric patients. One case reported tuberculosis in joint fluid, and the other was a pulmonary tuberculosis.

We also reviewed all pediatric malignancies reported with etanercept, and there were 12 post-marketing AERS cases. This morning, the sponsor presented 15 post-marketing cases of pediatric malignancies with etanercept, and the biggest reason for our difference in total number is

due to different case inclusion criteria.

For example, we excluded the recurrent leukemia case, and the case with possible lymphoma was determined to be not a lymphoma case based on our follow-up. It should be noted that 3 of 12 cases were patients who received etanercept when they were 17 years or younger and experienced malignancy as adults. As you can see here, 4 of 12 cases reported lymphomas, three were leukemias, and the remaining cases included one case each of myelodysplastic syndrome, papillary thyroid cancer, malignant melanoma, bladder cancer, and yolk sac tumor.

This table presents some characteristics of 12 malignancy cases. Female/male were equally represented, and the age range at the time of malignancy diagnosis was 10 to 19 years, with a median of 17 years. The majority of cases occurred in patients who received etanercept for JIA, and the time to onset varied from 29 days to

7 years, with a median of 3 years.

Eight of 12 cases reported concomitant use of other immunosuppressants such as methotrexate. Half of the 12 cases reported hospitalizations. The dose administered was within the recommended dose for children, and more than half of the cases were foreign cases.

This is a representative pediatric case of malignancy, where a 15-year-old girl developed Hodgkin's lymphoma after receiving 4-1/2 years of etanercept and 3-1/2 years of methotrexate therapy for polyarticular JIA. Both drugs were discontinued, and remission occurred after chemotherapy.

It's difficult to make a definitive conclusion about these post-marketing cases of malignancies that were reported in pediatric patients who received etanercept. And the malignancy cases that I presented today are part of the Agency's comprehensive review of all post-marketing pediatric

malignancies reported with all TNF blockers.

An Early Communication to alert the public was issued on June 3rd, and further findings from the Agency's ongoing review will be communicated to the public in the future.

Lastly, in addition to infections, other domestic serious events were reported. Similar to adults, neurologic events such as seizures, headaches, and multiple sclerosis were reported. Six serious hematologic events have been reported, which included aplastic anemia, pancytopenia, hemolytic anemia, and other blood disorders.

In summary, infections were the most commonly reported cause of death, and other serious outcomes such as hospitalizations and life-threatening. Although the overall evaluation is ongoing, malignancies observed in children who received etanercept pose potential long-term complication that is worrisome. And the

current etanercept usage in the pediatric population is low.

In conclusion, it is noteworthy that despite low etanercept usage in the pediatric population, we observed similar serious adverse events in children as those seen in adults, including serious infections with fatal outcome. Therefore, the use of etanercept therapy will likely place children with plaque psoriasis at a greater risk for developing serious adverse events that are not usually observed in this patient population.

I would like to acknowledge the assistance of my colleagues in the development of this presentation, and this concludes my presentation.

Thank you.

DR. SACHS: Hi. I'm Hari Sachs, and I'm one of the team leaders in the Pediatric and Maternal Health staff in the Office of New Drugs. And we want to thank you for your time.

The good news is, I'm the last formal presentation.

I'll try to review some of the (inaudible) and the theme we're having here about etanercept. Just briefly, from the pediatric perspective, according to the labeling, what is also known about the safety reviews that you've heard, the literature. And I'll briefly review the treatment benefits and risks that were seen in the trial, and present some additional pediatric considerations.

Now, as you all have heard, etanercept is a systemic therapy that is injected once or twice weekly for several types of arthritis in adults, and now Juvenile Idiopathic Arthritis, or what was Juvenile Rheumatoid Arthritis in children. And aside from the arthritis, we have the plaque psoriasis. And these are all pretty much conditions that have been associated with debilitating disease as well as

structural problems. And as you heard from the patients with psoriasis, certainly some interference with their lives.

The risk of etanercept therapy is well-known, and there's a box warning, as you've heard, regarding serious infections and tuberculosis, as well as the warnings enumerated for demyelinating diseases, hematologic diseases, neurological problems, and hepatitis B re-activation, some of which really can be linked to immunosuppression.

The precautions include the risk of anaphylaxis -- and I just wanted to remind you this would be an injection given at home -- worsening congestive heart failure, the immunosuppression, and for children, the precautions regarding vaccination. And although patients do mount effective B-cell responses, pneumococcal titers are lower.

Patients are advised not to receive live vaccines. It is recommended that all patients are brought up to date before

receiving etanercept therapy. And if the patient is exposed to chicken pox, cessation of therapy is advised, with possible treatment with immunoglobulin or VZIG.

Labeling also reflects the risk of serious adverse events in the pediatric populations, including the ones that you see on this slide. And what is particularly interesting is this two-thirds incidence of infections in patients with Juvenile Idiopathic Arthritis that was observed during the study. And as you've heard from the folks presenting -- during the trial we saw similar infections, including increased numbers of common infections: gastroenteritis and strep in particular -- and also the zoster during the open-label period.

And you've heard from Dr. Siegel and also Dr. Kwon about the Early Communication regarding malignancy, including lymphoma. And there was one case of malignant melanoma that was noted in an

18-year-old who was treated with etanercept for psoriasis, and her therapy was initiated at age 16.

Now, unfortunately, as you've heard, pediatric patients don't seem to be immune to all the serious adverse events, as the OSE reviewer reported. And the literature also supports this. As we see, a range of serious infections in the registries, including tuberculosis, and case reports ranging from mono and fungal infection to methicillin-resistant strep. And there is an additional report of a thyroid cancer as far as malignancy goes. And paralleling the neurologic events that you can see in adults, there have been some case reports of aseptic meningitis and optic neuritis.

Granted, these events are rare.

Now that you've heard a little bit about the risk, let's look back at the benefits. And during the 12-week trial, as

you've heard, there was statistically significant improvements in really all the outcome measures. But I just want to show you that patients did have residual disease. And if you look at the clear/almost clear sPGA, 48 percent had residual disease. 40 percent of patients had residual disease based on the PASI 75. More than 70 percent had it based on the PASI 90. And over 90 percent still had residual disease based on the PASI 100. And certainly there are statistically significant improvements compared with placebo.

You've seen this slide before, and this, as you know, is oriented toward the increased risk, increased loss of the PASI response during the withdrawal phase. And I won't belabor the point. You saw the same data here with the sPGA.

Now, since it appears, based on the fact that psoriasis is a chronic disease, and if you stop the treatment, the response does

disappear, it looks like treatment would be needed to be continued indefinitely. So responses to vaccine may be germane. As I mentioned, live vaccines are not actually contraindicated, but the recommendation is to avoid them. I guess I -- as a practicing pediatrician for 20-some years who still sees patients, would view this as a contraindication. And there is no data on the routine vaccines that are given during the vaccine platforms you see here.

And if you look at this, I just want to point out that most patients won't complete their series, their primary series, until they're older than 12, and many patients still receive significant boosters at 4 to 6 and 11 to 12.

The highlighted vaccines are the live ones, and you can see there are not a lot of live vaccines given.

Now, additional concerns that may be slightly less significant, but I think we

can still think about, are the effects on growth. And right now, we don't really know what etanercept does to young patients. The pediatric psoriasis patients, as you've heard, are really large, and so they probably did not grow too much during the trial. And the data on the patients with JIA is not clear.

I think the concern about the immune suppression in a growing child is what's of concern, as opposed to perhaps the developing immune system, but the effects really are unknown. And I think -- you know, we don't know 100 percent how vaccine response works for these kids.

So your task is to kind of weigh the risks and benefits that -- you've heard about the compelling need for therapy in these kids who have severe disease, as well as the fact that there are no approved systemic therapies. And you need to weigh this against the natural history of

psoriasis, which for many patients is sporadic and remitting, and the need for therapy that would be lifelong or at least continuous.

As we mentioned, psoriasis is not life-threatening, but there are some rare serious adverse events that are life-threatening that are associated with etanercept treatment, including sepsis, tuberculosis, and these long-term concerns about malignancy that we're still trying to sort out.

I just want to thank all the folks that helped contribute to these presentations, including my own, and you all for your deliberations today.

DR. BIGBY: Thank you. And I'm going to take the Chair's prerogative and eliminate the break. We'll have some clarifying questions. If you have to break before we start our panel discussion, you can do so at any time.

Is it possible for those of you who

haven't checked out -- I mean, we could have somebody sort of go down and check us out.

DR. THIERS: I have a question.

DR. BIGBY: Okay, great.

DR. THIERS: A couple comments and questions. First, Dr. Kettl's slide No. 24 or 23, could we get that back up? It was a clinical picture, either No. 24 or 23. Try 24.

Okay, I think you mentioned that these two pictures look the same, and the reason they look the same is because they are the same. If you notice, everything about the two pictures is the same, including the positioning of the Band-Aid on the antecubital fossa, the positioning of the legs, the positioning of the right palm, and the positioning of whatever it is on the wall. So for some reason, the same picture got placed in the two parts of the slide. So they look the same because they are the same.

DR. KETTL: I suspect that's my error. I apologize. The scores at the bottom are

indeed correct.

DR. THIERS: But was this the before or the after is what I want to know. It would be important to me to know whether this is before or after.

DR. KETTL: My sense is that they are the before pictures, but I'd have to verify that.

DR. THIERS: I don't know. I think they're afters, actually, but they're the same anyway, so that's why they look the same. Okay, one comment to Dr. Sachs and some others who mentioned residual disease in patients who reach PASI 75. Well, by definition, most patients who have PASI 75 do have some residual disease. And you mentioned PASI 90 and PASI 100. Well, to my knowledge, the bar that the FDA set for these new psoriasis drugs was PASI 75, so I don't think we have any data on any other drugs reaching PASI 90 or PASI 100 -- or any substantial data -- so I think to say that patients had residual disease does not take away

from the efficacy of the drug. That was just a comment.

A question for Dr. Siegel. In any of the data on cancer in patients treated with TNF alpha inhibitors, do you ever break out the data comparing the monoclonal antibodies and the diffusion proteins, or are they always looked at together?

DR. SIEGEL: We have looked at those data in general terms, and the malignancies seem to follow the use of the products. So the ones that are used more commonly seem to have more malignancies. We don't see a clear differentiation over and above the frequency of use of individual products.

DR. THIERS: But I'm thinking, is it the same for like adalimumab and infliximab as it is for etanercept?

DR. SIEGEL: Well, keep in mind that adalimumab was only just approved, so you'd expect very few cases, and indeed, that was what we saw. For infliximab, it's approved for

Crohn's disease, and that's where most of the cases were seen. And the relative amounts with infliximab and etanercept were in general consistent with the use of the two products.

DR. THIERS: The other question I had -- and I guess you can take this, or Dr. Kwon can take this -- it seems that most of the problems occur when etanercept is used with methotrexate. And I was just wondering, if we were sitting here talking about approving methotrexate, and etanercept was the drug that had been on the market for 30 years, whether we'd be having this debate -- being more critical of methotrexate.

In other words, what I'm trying to say is, can you tell from the data that's been presented, is etanercept the real protagonist and methotrexate the facilitator, or is methotrexate the protagonist and etanercept the facilitator?

I'm just wondering if we're being -- you know, we're looking at this in a

certain way because we have one drug that's been around for a long time and another drug that's looking for a new indication.

DR. SIEGEL: I'll give my answer, and maybe Dr. Kwon will also want to comment. I think you're raising an important point, which is the relative contribution of the concomitant medication methotrexate and the TNF blocker, and we don't have data to definitively answer that.

One of the difficulties is that patients with inflammatory arthritis who get a TNF blocker usually don't have the disease reduced to very low levels. It's typical to use a TNF blocker with methotrexate to get disease down to an acceptable level. This is particularly true in adults, where monotherapy is uncommon. And based on the enrolment in the prospective trial with etanercept in children with JIA, it looks like it may be true in children, too. So it's impossible to sort the relative contribution of the products out, from my

point of view, from the data so far.

DR. KWON: Similarly, it's difficult to sort that issue out in terms of looking at post-marketing cases, because a lot of times, they are using etanercept concomitantly with methotrexate in JIA patients in post-marketing cases that I've observed. So whether the use of both is the issue, or etanercept is the sole responsible agent, it would be difficult to tease out in the post-marketing setting.

DR. BIGBY: Dr. Levin this morning had a question for the sponsors.

DR. LEVIN: Going back to this safety registry, you indicated you hoped every patient would enroll, but we know there's sort of a distance between what we hope for in enrollment and what we get. So why wouldn't it be possible to mandate enrollment, to say no registry, no drug?

DR. EISENBERG: It's a fair question. We've thought about it. I think the reality is, when you have a product such as etanercept

approved for other indications and approved in terms of the target prescriber for different indications, and the drug is distributed through a pharmacy, it would be extremely difficult, if not impossible, without regulating the drug completely, to target one specific group.

That said, we believe, given the conservative nature of the prescribers in this population, that they will be interested in participating, and we can monitor how well we do, and work with FDA to ensure that that happens as robustly as possible.

DR. BIGBY: Dr. Katz had a question about administration of drug?

DR. KATZ: Initially, when we treat adults with Enbrel, we use it twice weekly, and then as the patient does well, may decrease to once weekly. Why is this initiated once-weekly injection rather than twice weekly? Is there a particular reason for that?

DR. SEVERINO: As pointed out, in adults we often start with a 100mg total weekly

dose, and then reduce to 50mg after some period of therapy, typically three months. The pediatric regimen modeled the lower 50mg dose to be conservative. The 0.8mg/kg/week regimen was modeled after that 50mg adult dose and gives comparable concentrations. So it was a conservative bias, given this was our first study in children with the disease.

DR. BIGBY: With regard to the severity distribution of your patients, did you analyze the response to therapy in terms of the initial PASI score, and if so, what was the result?

DR. SEVERINO: We did do that analysis. We looked at subjects who were above or below the median at baseline, and the efficacy results were quite comparable. We can bring the slide up. This shows those results for the primary endpoint, with subjects who were below the median in the solid bars, above the median in the cross-hatched bars.

And this is PASI 75.

DR. BIGBY: Thank you.

Dr. Shwayder?

DR. SHWAYDER: I was thankful to Dr. Kettl for bringing up the point that the amount of psoriasis on these kids to be negligible to what I see on a weekly basis in my office, which I guess reflects how difficult it is to enroll people in studies like this. So I have to ask the sponsors, on these Enbrel studies, was one of the enrollment criteria that they had, for example, UVB before they went to Enbrel?

DR. SEVERINO: Subjects in this trial were required to have either failed topicals or received systemic therapy or UV. So they may have, but they were not required to receive UV.

DR. SHWAYDER: I'm just trying to decide, for something that has potential death as an outcome, whether it would be probably not such a bad idea to have some sort of requirement of something that does not have death as an outcome as the first treatment, such as topical

steroids or UVB, or both, before they get it.

DR. SEVERINO: If I could just clarify: Topical steroids, topical agents, were required prior to entry. It's different to require systemic agents since none are approved.

DR. SHWAYDER: Right. I understand the difficulty enrolling people like that. But it also shows again yesterday what Dr. Kimball was saying, that 10 percent is life-threatening to some people.

Ten percent is -- elbows, knees, and the scalp would be 10 percent -- if I remember my body surface areas -- which would not seem significant to the normal dermatologist.

One other question: Is there any data using Enbrel in pustular psoriasis?

DR. SEVERINO: The studies with Enbrel have been in plaque psoriasis exclusively, so we don't have --

DR. SHWAYDER: Any anecdotal reports? Anything in the literature, Larry?

DR. EICHENFIELD: Nothing.

DR. SHWAYDER: Thanks. That's all I have.

DR. BIGBY: Dr. Daum?

DR. DAUM: I have three questions for Dr. Kwon, all of which relate to the infectious complications she described. And I could maybe ask them one by one, or all three at once. I think one by one might be better.

DR. KWON: Sure.

DR. DAUM: On the handout that I have, on page 8, slide No. 16, you talked about 10 cases of varicella, and 6 of them required hospitalization. And I recognize these are AERS data, and all the caveats about AERS are understood, but do you think that's a reporting bias, that patients with varicella that get hospitalized are more likely to get reported? That's a very high rate of hospitalization.

DR. KWON: Yes.

DR. DAUM: If it's a rate.

DR. KWON: Right. Yeah, it is a high

rate. Well, that is part of the issues with the AERS database. Maybe I could answer that indirectly. All the cases in the AERS database are serious unlabeled or serious labeled, and the non-serious reports are only included during the first three years. So in a sense, the cases we have in the AERS database are going to be shifted more toward the cases with serious outcome. Does that answer your question in a way?

DR. DAUM: It makes me thirsty for more information, but I guess with respect to what we have, it probably answers my question. You sort of wonder if there might be a much higher rate of varicella that's occurring --

DR. KWON: Exactly.

DR. DAUM: That you're not getting AERS reports about.

DR. KWON: And under-reporting is a huge limitation associated with --

DR. DAUM: So in the same vein, on the same slide, which is up there, so that's

great -- TB, two cases. Do we know anything about -- I mean, TB in children has such a broad clinical spectrum, and the question would be, is there anything in these reports about a PPD in advance? I mean, is this an exacerbation of a known infection? Does anyone recommend or practice routine PPDs before starting a drug like this, which I certainly would recommend?

DR. KWON: I think that is generally recommended, that you do PPD testing to make sure that you don't have --

DR. DAUM: But in these two reports, is there any information about that?

DR. KWON: They did not have information in regard to the previous PPD --

DR. DAUM: And was this miliary or disseminated or a --

DR. KWON: No, one was TB in joint fluid, and the other was pulmonary tuberculosis. So they were not the usual -- the disseminated TB that you've heard before in association with TNFs.

DR. DAUM: And were they U.S. or foreign?

DR. KWON: They were both foreign, actually.

DR. AVIGAN: Can I just add to that, because we do have some --

DR. DAUM: Yes, but I have one more question when you're done.

DR. AVIGAN: Sure. On the TB question, because this has been -- to what we have been extensively reviewed in the past, and most of our information around TB and its clinical phenotype with regard to TNF alpha blockers -- and etanercept is one of them -- is from adult experience. And the general gestalt of it is that we do see patients who -- we see, actually a phenotype of miliary TB and extrapulmonary TB as commonly reported with each of the three TNF alphas that have been marketed over the last few years, including etanercept.

And one of the themes is that patients in some cases have risk factors

which are demographically driven, and occasionally even have negative skin tests in this screen.

DR. DAUM: Negative tests while on the drug or before the drug?

DR. AVIGAN: Before the drug is started, because that would typically be done.

DR. DAUM: Thank you. That's actually helpful. My last question is in a similar vein, but excuse me, it's sort of what I do for a living. You talked about reported causes of death in JIA cases.

I think it's slide No. 11 on my handout on page 6. And there's a line there that says infections, four, and I think you said three cases of sepsis.

DR. KWON: Right.

DR. DAUM: Such a squishy term. Can you tell us a little bit more about what sepsis means in this context?

DR. KWON: The sepsis is -- a lot of times -- you know, going back to some of the

limitations with the AERS reports, is that it doesn't provide a lot of information. And the reported information in these cases was sepsis. I didn't determine it to be sepsis, but it was reported as a case of sepsis by the reporting health care practitioner. So if you're asking me how I determined it to be a sepsis case, I didn't make the diagnosis. I simply used the diagnosis I was provided by the reporter.

Does that answer your question?

DR. DAUM: I guess it does. It leaves me a little, again, starving for some more information. The reason I say that is because things that look like they are sepsis aren't always, and if they are sepsis, that's kind of worrisome. And I'd just like to know more about what they are.

DR. KWON: They didn't really provide autopsy information, from my recollection, or any --

DR. BIGBY: I'd just add that this is a big problem we have with all of the AERS

reports when you review drugs. Even if you had the whole report and you went through it, you would still have the same questions, because the reporting is often incomplete, inadequate.

DR. DAUM: No, I understand that. I was just hoping that there might be some more information in the reports.

DR. BIGBY: Dr. O'Neil?

DR. O'NEIL: When the warning or alert came out from the FDA at the beginning of this month regarding childhood malignancies, that set up quite a stir, as you can imagine, in the pediatric rheumatology community. There was a lot of concern and debate on our pediatric rheumatology listserv, and so I have to give credit where credit is due: one of my colleagues actually looked up and tried to calculate the risk of pediatric malignancies in the general pediatric population. And I think this is pertinent, although it's still somewhat comparing apples and oranges, because we have squishy numerators because they're

self-reported, and we also have squishy denominators. But it helps give us a little bit of a perspective, and I wanted to share that with the panel.

A paper published -- and I'm sorry; I don't have the reference with me -- gave an incidence rate in the United States in children under the age of 18 as 1 in 7,252. The American Cancer Society in 2007 projected a pediatric cancer rate in children under 15 as 10,400. And if you extrapolate that and correct for the census for children under 18 being 73 million, that gives us 1 in about 7,082 children under the age of 18.

So we're talking about a rate of cancer in children per year of 1 in about 7,000 to 8,000. If we look at the five cases reported over 10 years, use of etanercept in the U.S. -- because that's the only rate that we have, and we can actually extrapolate the numbers, too, there -- that gives us five cases, one of whom is in a child who had only

been exposed to etanercept for 29 days, raising the question of link or causality, although we have to continue to look at that.

So what I did was I took the data that was given us in our preliminary packet from the FDA showing the number of individuals exposed to the drug over time. Now, we just had the last six years, and I took the liberty of extrapolating down, and that gave us about 27,000 patient-years in the pediatric population of exposure to etanercept, going back to its inception and approval for children's use.

And that gave us a rate of about 8.3 anticipated cases, and there were actually five actual cases. And if the one that had only 29 days' exposure to the drug is not drug-related, then actually you're right on at 4 and 3.8.

DR. STERN: A comment about that. The one issue there is, even the most optimistic person thinks that about 10 percent of serious

events are reported to AERS, and for things that are -- as was pointed out -- that are not closely and temporally related, the chances of the person making the association and making the report are even less. So even if you use the very conservative multiplier of 10, you're suggesting that our data has a tenfold increase in cancer risk among those exposed. That would be an extremely conservative look at those data.

DR. O'NEIL: But I also don't think that pediatric oncologists under-report the rate of cancer. I also don't think that -- I think that because of the heightened surveillance, at least in the rheumatology community, we've been extremely worried about this and have been watching it very closely, so I think it's not going to be 100 percent. I agree.

So I think it probably is inflated, and there probably is some real risk, but we don't know what it is. But it's not as huge as it sounded when we first heard 30 cases.

DR. BIGBY: I think we should go and

start trying to address the questions, if people don't object. If you have questions, either for the FDA or the sponsor, I would encourage them to just be of a clarifying nature, and not of an argumentative nature.

So the first series of questions have to do with efficacy. For the sake of efficiency, please discuss the adequacy of the assessment of efficacy for the pediatric population. For efficiency, my suggestion is that we just vote on number one and have the discussion without a lot of pre-discussion.

Is that okay with the panel?

So, has the applicant provided sufficient information to demonstrate efficacy of etanercept in the pediatric population? Those voting yes, please raise your hand. Those voting no, please raise your hand. And those abstaining, please raise your hand.

There are two absent. So there were seven affirmatives, one abstention, and

three absent. When the absents come back, I will poll them on this, and I will let them make their statement.

DR. DAUM: I haven't voted yet, and it's because I have a question. Can I pose the question?

DR. BIGBY: Of course.

DR. DAUM: So when we consider this question -- I maybe just need some advice from the Chair -- are we to consider any efficacy or complete efficacy or partial efficacy? What does the word mean in this context? My opinion is that some efficacy was demonstrated.

DR. BIGBY: I would say the answer to that would be clinically meaningful efficacy. And I'd welcome any comment from any of the other dermatologists on the -- I mean, a clinically meaningful therapeutic response is what I would say is the answer to your question.

DR. DAUM: In some patients, or in most patients? How do you want us to interpret that part?

DR. BIGBY: Some patients.

DR. KATZ: I would say significant efficacy, albeit even in a small portion of patients, over placebo.

DR. DAUM: I guess the question is, is that what the Agency thought when they posed the question?

DR. BIGBY: Susan?

DR. WALKER: I think if you just think of it in terms of were the clinical trials successful to demonstrate clinically meaningful efficacy. Does it work?

DR. DAUM: In my opinion, it really isn't a simple question, and I will vote yes, they did, but I would like to qualify my response by saying that it was way less than complete efficacy, and it was only demonstrated in a proportion of the patients.

DR. BIGBY: For Lynn and Bruce, we have voted -- let's just redo the vote. Okay. Well, you can add your vote at the end, and then I'll re-summarize it.

Dr. Shwayder, you want to start?

And remember, you have to give your name. The reason for this is that the proceedings are transcripted, so in order to have your comments attributed to you as opposed to someone else or no one, you have to state your name, and that's the reason.

DR. SHWAYDER: Tor Shwayder. I voted yes. I agree with the statement just made, that the efficacy was there, but not startling.

DR. HECKBERT: I abstained. I did recognize that there is efficacy demonstrated, but my concern was that a large proportion of the patients studied may not have been the severity of pediatric psoriasis that we might have been interested in seeing in these trials. So it's a mixed answer, which is why I abstained.

DR. BIGBY: Lynn, you have to identify yourself, add your vote, and make your comments. This is question one.

DR. DRAKE: Lynn Drake. I'm going to

vote yes. I think efficacy has been demonstrated, but I must admit that a couple of the enrollment pictures were a little bit concerning. I'm not sure they met the enrollment criteria, is how I would grade them.

But having said that, I'm going to vote yes, because I think there's enough efficacy to support that.

DR. CRAWFORD: Stephanie Crawford. Yes, just also noting the inherent subjectivity in assessing disease severity.

DR. DAUM: Oh, I'm sorry. I'm Robert Daum, and I voted yes, with the comments that I made before as qualifiers.

DR. LEVIN: Arthur Levin. Yes, with all the concerns that have been expressed.

DR. THIERS: Bruce Thiers. Ditto yes. I agree it's effective.

DR. BIGBY: Michael Bigby. Yes.

DR. MAJUMDER: Mary Majumder. Yes.

DR. O'NEIL: Kathleen O'Neil. Yes.

DR. STERN: Rob Stern. Yes.

DR. KATZ: Robert Katz. Yes.

DR. BIGBY: Eileen, we need to back to you. We sort of -- without pre-discussion, we sort of voted on the first question about efficacy, and we need for you to add your vote. The question being, has the applicant provided sufficient information to demonstrate efficacy of etanercept in the pediatric population?

DR. RINGEL: Eileen Ringel. Yes.

DR. BIGBY: So the summary was 12 yes, 0 noes, and 1 abstention. So we move on to the second part of this question: Has the applicant provided sufficient information concerning the maintenance of treatment effect with this therapy?

I'll open the floor for discussion.

DR. CRAWFORD: Thanks. Again, I'm asking for a point of clarification. The way the question is asked, I can answer it yes in two totally different interpretations. I could answer yes, meaning there was sufficient information to show a maintenance effect, or I

could answer yes, sufficient evidence was shown, although it was not for a sustained period of time. So I'm just asking, can we clarify how the yes answer is going to be interpreted?

DR. WALKER: Do you want me to clarify there? Okay. It would be helpful to have discussion from the Committee about the amount of information the sponsor has provided concerning the maintenance treatment with their product, assuming that this product won't be used for a short period of time; it could potentially be used for a long period of time. How long, potentially -- what implications are there for labeling, what implications are there for approval. That's the intent of this question.

DR. SHWAYDER: I was a little disturbed by the graph that showed the drop of efficacy at the end of the study, which I believe is 40 or 48 weeks. So I need to ask, have there been any studies that go into the second year, and what happened to efficacy? I

don't think those were presented this morning.

DR. BIGBY: Rob?

DR. STERN: To me, two and three are related in that I was also concerned about the rapid drop-off of effect, the relatively small difference between those withdrawn and those continued. And as I think we talked about both yesterday, and even more in pediatrics, as was pointed out today, that the paradigm for treating psoriasis, which is a disease that varies substantially in effect over time and for whom some patients, when you clear them, can be managed on very much less therapy of whatever cleared them -- the idea of long-term maintenance in this pediatric group with relatively little observed benefit in these limited studies really concerns me.

And I wonder whether we want to think about really having this agent for this indication have some encouragement to try tapering, since -- and also to warn people about loss of effect, which at least I've

observed in my adults as well -- that people essentially become hardened to this over time and either need higher doses or an alternative therapy.

DR. BIGBY: Tor, do you want to make some comment about when you manage pediatric patients on etanercept, do you stop it when they're clear or almost clear? How long do you wait before you restart it? Do you continue people, taper the dose? I mean --

DR. SHWAYDER: My gestalt is, anything I use for psoriasis is good for a year or two, and then it stops working. So I just find myself going from lights to topicals to day hospital to biologics to methotrexate, kind of skipping through the years, trying to keep the toxicities to a minimum.

DR. BIGBY: Would the sponsor like to respond to this issue?

DR. SEVERINO: Part of the discussion was, are there additional studies? The only additional study is the open-label extension

that I referred to, where patients who completed this trial will receive up to an additional three years of therapy.

There will be efficacy data reported from that study, but we've not reached the analysis point at this time.

DR. BIGBY: Thank you. Dr. Daum?

DR. DAUM: So the question goes to sufficient information concerning the maintenance of treatment, and I guess the first point I'd like to make with that is that there is a substantial population, based on what I saw this morning, that didn't respond at all. So I guess that's an important part of how I'm thinking about this in terms of -- it seems senseless to flog those non-responders with the drug, and a stopping point should be considered early on.

And also, the percent of responders went up for a while and then sort of plateaued, as I recall the data that I saw this morning. And I think that should be

noted as well, that it doesn't continue to increase. And then I think the waning with continuous use is concerning, and I don't understand it, although it sounds like we're in good company here with the adult colleagues who see the same kind of thing.

And finally, I don't think we saw anything about effect, one way or the other, after a year. So I think we're really limited in terms of what we can conclude about long-term use. I mean, we heard a wonderful -- Kelsey's story before we started, and obviously, she's benefited greatly from this, and I'm delighted for her that that's true. But we don't know anything about more than one year in the scientific trials.

DR. BIGBY: Bruce?

DR. THIERS: I agree. The only data we have was the data presented, and that's limited.

That's, I guess, 48 weeks, so I

would have to answer no to number two.

DR. BIGBY: Dr. O'Neil?

DR. O'NEIL: Dr. Severino, you answered the question by giving just pediatric data, which is very understandable that you have not yet analyzed the second-year data in these follow-up studies. Do you have any adult follow-up studies speaking to the durability of response?

DR. SEVERINO: There are adult studies that are ongoing open-label extensions. I don't have the data to show you today beyond 48 weeks, but we do have a proportion that maintain efficacy in those open-label studies in adults. And as I mentioned, we have an open-label extension in pediatrics, which we'll also report.

We agree that today, in pediatric subjects, we don't have data beyond 48 weeks. And we have tried to address that in our proposed labeling.

DR. BIGBY: Before I put this to a

sort of official vote, would the sponsor like to respond to the issue about the high placebo response in your pediatric trial, in the double-blind portion of the pediatric trial?

DR. SEVERINO: As noted during the course of the discussion, the placebo rate observed in the pediatric trial is higher than that which has typically been observed in our adult trials. However, as also pointed out, the differences between the treated group and placebo were significant. I'll actually ask Dr. Eichenfield if he wants to comment on placebo response in pediatric psoriasis.

DR. EICHENFELD: Thank you. Really, the way I look at the data, it really depends on if you're looking at the PASI score or the clear or almost clear. I really think with pediatric psoriasis, there's a population effect in terms of both severity, natural history, and response. So the almost clear at 12 weeks was 13 percent. I assume that that's natural remission in that subset of the population. And that contributed

a lot to low PASI scores in the placebo arm. But a significant percent of the population, obviously in placebo group, did not do well, and that's a population that had more significant disease, or just did not have that natural remission during that period of time.

DR. BIGBY: Thank you. Dr. O'Neil?

DR. O'NEIL: Very quickly. As a pediatric rheumatologist, we have a number of multicenter placebo-controlled trials, and in the pediatric population, with relapsing, remitting chronic inflammatory disease, the placebo effect is usually somewhere between 15, and as high as 40 percent. It was 40 percent in the original methotrexate trial.

DR. BIGBY: Dr. Katz? This will be the last comment before we actually vote.

DR. KATZ: We are spoiled, because yesterday's drug, which is not up for discussion now, had a very low placebo response. I forget -- 2 or 4 percent. But as I remember, in the studies that the panel did three or four

years ago on alefacept and all that, they had placebo responses of 15 percent, 17 percent, which would go along with Dr. O'Neil.

I mean, there were PASI 75s of 27 percent versus 14 percent placebo, which was an effective rate of about 13 percent.

So I don't think that's unusual.

DR. BIGBY: It's time to vote on two. Has the applicant provided sufficient information concerning the maintenance treatment effect with this therapy? Those voting yes, please raise your hand. Those voting no, please raise your hand. Abstentions?

We'll start this one with Dr. Katz.

DR. KATZ: Robert Katz, and I voted no because we just don't have the data. It doesn't go out far enough.

DR. STERN: I voted yes -- Robert Stern. I voted yes because I think these are about as good of data we're going to get in such a specialized population. And the data do say that it is not a terrific maintenance agent in

this population that, as has just been pointed out, has frequent remissions. And therefore, these data tell me something about strategy that is important. And I'm not sure longer-term data is highly likely to change my mind about that.

DR. BIGBY: I just have to interrupt a second to say that the tally was 10 noes and 3 yeses.

DR. O'NEIL: This is Kathleen O'Neil. I voted no because the data are not there. And I think it would have been nice to see what is known about the second year of adult treatment, and I suspect those data are more available.

DR. MAJUMDER: Mary Majumder. I voted no.

DR. BIGBY: Michael Bigby. I voted no for many reasons that were expressed. And the problem I have that in practice, most of the time, you get a patient nearly clear and stop therapy, or they stop therapy, or you stop seeing them, and they return in a state that's much worse than the re-treatment portion of the

trial. And I don't think that you'll ever get adequate information about maintenance of therapy from a controlled trial done the way that they are.

DR. THIERS: Bruce Thiers. I voted no because, again, we didn't have the data. I would really be interested in seeing what happens in the second year. Does the treatment response fall off a cliff? Does it plateau? Does the patient have a severe post-treatment flare, as Dr. Bigby mentioned?

I think there's a lot of information we'd like to have about that second year. That hopefully will be forthcoming.

DR. LEVIN: Arthur Levin. No.

DR. DAUM: I voted no, but I interpreted the word "sufficient" to mean what I would really want if I were out in the community taking care of patients. I think there is sufficient information in the first 48 weeks to understand this question. But I think that

given the chronicity of the disease, and some of the difficulties we sense from comments and data about stopping therapy in flares, we've got to know more than that. So I think overall, it's insufficient, although what was presented for the 48 weeks was okay.

DR. CRAWFORD: Stephanie Crawford. No.

DR. DRAKE: Lynn Drake. I voted yes for many of the reasons that Dr. Stern outlined. I think the word -- the hang-up on this question has to do with "sufficient." You know, I don't know that we ever have sufficient evidence for anything. But having sat on this panel many times before, we've approved many drugs with this amount of evidence, or thereabouts. I think if we approve the drug based on one of the factors, such as safety or whatever, disapprove, that's a different issue. But if we were just looking at efficacy -- and as a clinician, could I make a decision on how to treat my patient with this? To me, this is consistent with

almost any drug that comes out of the door, because it's only through real-world use do you answer some of the questions about maintenance, and duration, and the ebb and flow of the disease.

DR. HECKBERT: Susan Heckbert. I voted no because I don't believe we have sufficient information about the long-term efficacy beyond 48 to 52 weeks.

DR. RINGEL: Eileen Ringel. I voted yes, largely for the reasons that Lynn has stated of the word "sufficient." Is it sufficient to approve the drug? I think it is. I think the drug effect does wane, and my response to that is, what else is new? I have drugs that I use all the time, the response wanes, and I go on to something else. That doesn't bother me.

The other thing -- very quickly, about placebo is I think you have to be very careful with psoriasis to look at when you ran those studies, was it summer or winter?

Or were you doing it in the North or doing it in the South? And that's going to affect your placebo rate in addition to any natural variation in children. So placebo rate doesn't bother me that much, either.

DR. SHWAYDER: Tor Shwayder. I voted no.

DR. BIGBY: I'm going to go ahead and ask for a vote on question 3. The question is, has the applicant provided sufficient information regarding stopping withdrawal of treatment with this line of therapy?

Those voting yes, please raise your hand. Those voting no, please raise your hand.

Abstentions? You're an abstention? So the tally is seven yes, three no, one abstention.

You want to start a discussion?

DR. MAJUMDER: I'm Mary Majumder. I abstained because I just didn't feel that I'd formed an opinion on this question. And without

further discussion, if a layperson knew the Committee, I didn't want to vote where I had no opinion.

DR. BIGBY: I'll go next. I'm Michael Bigby. I voted no because I don't think there is a sufficient length of time of stopping the medicine, or very early re-treatment in the after-treatment group, to really know very much of anything about this question.

DR. THIERS: Bruce Thiers. I echo what Dr. Bigby says. I think we have some information on temporary withholding therapy, but not on stopping or withdrawal of therapy.

I'll also add, in contrast -- in follow up to what Dr. Drake said, I personally don't feel a vote no on 2 or 3 really means the drug should not be approved. I'm just saying we don't have that data. It doesn't mean the drug should not be approved.

DR. LEVIN: I wasn't here for the vote. So --

DR. BIGBY: So do you know the

question?

DR. LEVIN: Number 3?

DR. BIGBY: Yes.

DR. LEVIN: I would vote no.

DR. BIGBY: And your reasoning?

DR. LEVIN: I don't think we have the data. We didn't have the data presented.

DR. BIGBY: The new tally is eight yeses, three noes -- no, oh -- seven yeses, five noes, one abstention.

Can we just do the vote over again, because there's some discrepancy about the numbers.

Those that voted yes, raise your hand.

DR. STERN: We have to vote the same?

DR. BIGBY: Absolutely not. Absolutely. Absolutely.

You have to keep your same vote, I'm told.

DR. STERN: Even if we (inaudible) verbally recorded (inaudible).

DR. BIGBY: Yes. Those voting -- you got your count?

MS. WAPLES: Yes.

DR. BIGBY: Those voting no? You were right. And abstentions?

So the total is seven yes, five no, one abstention. My apologies.

DR. DAUM: So I thought I saw enough data to realize that stopping the drug in people that responded was associated with problems. And so the data was sufficient, but not encouraging. The non-responders -- I presume stopping the therapy didn't make anything happen, but we didn't really see data about that. The responders, it looked like, stopping or giving it were both associated with exacerbation.

So I thought I saw enough data to conclude that stopping it is bad, and that focuses, again, on the one year, 48-week follow-up issue, which makes me really feel the need for those data.

DR. CRAWFORD: Stephanie Crawford. I voted yes, kind of echoing what Dr. Daum and others who voted yes have said. While we would ideally of course like a longer trial period, I think the research design attempted to provide an answer for this question.

DR. DRAKE: I voted yes for many of the same reasons I outlined on my yes vote on No. 2.

This is Lynn Drake, I'm sorry. I think there was -- the sponsor provided introductory information. And once again, so many of these questions are never answered until you use it over a period of time in the real world. It's sufficient for me, if approved, to know how to start using this drug in treating my patients.

DR. HECKBERT: Susan Heckbert. I voted no, and for the same reasons Dr. Bigby gave.

DR. RINGEL: This is Eileen Ringel. I voted no because the criteria for restarting the

placebo group was loss of PASI 75, that means they could have gone from PASI 76 to PASI 74, and then restarted the next day. I don't call that taking them off the drug.

DR. SHWAYDER: Tor Shwayder. I voted yes. Two reasons: One, Kelsey told us she missed one shot in Paris and she got worse; then two, from the crossover study, when they're on the placebo arm and they got worse, they got restarted. So it tells me when you stop the medicine, you get worse fairly promptly.

DR. KATZ: Robert Katz. I voted yes because I think they clearly showed when they stopped the drug, it decreased. And like we discussed yesterday, we're going to have to find out how long to use it, when to reintroduce it, with practice and -- during practice, which is what we do with every drug, including the use of tetracycline in acne. I would not want to argue with Bruce, but he said he voted no because they showed what happened when they withheld the drug, but not when they stopped the drug.

What's the difference, Bruce?

DR. THIERS: No. I said, when they temporarily -- because they withheld it for a short period of time and then they restarted on a certain schedule. I would be interested in seeing what if somebody had an adverse event, came off it, and stayed off it, for example.

DR. KATZ: Okay.

DR. STERN: I had voted yes, but in fact, once more, the Chairman persuaded me that I was incorrect for the very reasons he stated, in terms of really the amount of information there was -- essentially beyond four or six weeks, given the way their rescue strategy was.

DR. O'NEIL: Kathleen O'Neil. I voted yes, based on the fact that they did demonstrate the effect and the loss of effect with withdrawal. And I agree that withdrawal was for a short period, but I think in the bounds of ethical conduct of research, that was the best that can be done.

DR. BIGBY: We'll move on to

question 4. Are there additional informational needs? If so, what are they?

We can discuss this one.

DR. LEVIN: Doesn't the Agency think that -- we've sort of suggested what they are?

DR. WALKER: I mean, we've heard from you about an early stopping point, issues about continuous use -- need the one-year data. I mean, I think if you can just delineate what some of the informational needs are, that would be helpful.

DR. BIGBY: I would say the one that is very clinically relevant is having the drug stopped for a longer period of time, which in practice often happens, and the patient -- I'm not -- I'm actually not advocating or suggesting that there is a -- you know, rebound phenomena, but when you stop the drugs, people tend to get worse if they have chronic psoriasis that hasn't gone into remission. And so what happens when you re-treat them after they've gotten substantially worse than a drop in their PASI

score of one.

DR. O'NEIL: Kathleen O'Neil. I would also like to see what happens if people flare and then are re-treated. Do they have the same magnitude of effect that they had with the original treatment.

And that's something that could be delineated with the post-marketing survey that you recommend.

DR. WALKER: That's helpful, because this is a chance to delineate clinical outcomes or trial outcomes, or post-marketing outcomes that you'd like to see explored.

DR. BIGBY: Do you actually want a yes/no vote on the first part of question 4? Because I basically think in people's comments, they've really answered this.

DR. WALKER: No, I think the comments are adequate.

DR. BIGBY: Okay.

DR. WALKER: Thanks.

DR. STERN: Michael.

DR. BIGBY: Now we go to the easy part.

DR. STERN: Michael.

DR. BIGBY: Oh, sorry.

DR. STERN: If we're talking about informing clinical practice, I mean, we really have in dermatology and psoriasis some drugs that lead to remission and some drugs that generally require continued and sometimes increasing doses to maintain remission. And I think to inform people about that, since clearly, the risks of this drug are likely to be proportional to duration of use -- I think what would be the most information to me as a clinician would be a randomized -- I know it wouldn't be blinded -- study between this drug and narrowband UVB for plaque-type psoriasis in children, looking at not only clearing rates, but also looking at time of remission and need for what -- how quickly and badly people reoccur. I think that's what would inform me, as a clinician, more than anything else in this

age group.

DR. SHWAYDER: I might just comment that getting kids into a box less than age 10 is very difficult.

DR. STERN: Two-thirds were over 11.

DR. BIGBY: I'd like to open the discussion to the issue of safety, starting first with infection. So question 5 is has the applicant provided sufficient information regarding the risk of infection in the target pediatric population?

So if there are no comments, we can proceed to a vote.

All those who think the information is sufficient, would -- how many would vote yes? How many no? And abstentions?

So there were 12 yeses and one no. Dr. Katz, you want to get us started this time?

DR. KATZ: Robert Katz. I don't think there's anything to add here, except what we're going to deal with with the long-term follow-up.

Obviously, we're going to need much more information, which would not have been obtained in this brief period of time. So I think we have to deal with that, with post-marketing surveillance, however we decide on that.

DR. STERN: Yes, and I think for labeling purposes, there's sufficient information. And to me, the small amount of pediatric data relative to adult data is a little bit like it was for Lamictal and the risks of Stevens-Johnson in TEN, that there's enough information to give extra strong warnings in the black box for infection for children.

DR. O'NEIL: Kathleen O'Neil. I voted yes. And the on-going data collection will of course be important.

DR. MAJUMDER: Mary Majumder. I voted yes, and I second the comments from the prior voters.

DR. BIGBY: Michael Bigby, and I voted yes. I think the thing to remember here is that there is a signal for increased risk of

infection, and they can be severe. I think the fact that there were two serious infections in the pediatric study is telling, and I'm not so sure we need more data.

DR. THIERS: Bruce Thiers, yes.

DR. LEVIN: Arthur Levin, yes. But understanding that we'd always like more information to better inform both prescribers and patients about what the risks are.

DR. DAUM: And I said no, and it turns on this use of the word "sufficient" again. Sufficient to do what? I didn't hear an alarming signal that the infection rate is off the wall and not limiting to use this. I think my issue for voting no was I wouldn't know exactly what to tell a patient that I was putting on it with regard to the risk of infection. Okay, there's an increased risk, but is it high? Is it low? What do you expect. When do you call me? I'm not sure I know enough to know that, so I voted no for that reason.

DR. CRAWFORD: Stephanie Crawford,

yes. In terms -- from the applicant, there was quite a bit of information regarding non-serious infections, and there were more questions about what happens with serious infections. I also considered the FDA's interpretation. So although I voted yes, there seems to be the need for more study, especially with the serious infections and the possible influence of the comorbid conditions.

DR. DRAKE: Lynn Drake, and I voted yes for the same reasons that have been given for yes and no answers at the table. You know, it seems to me that this whole thing's a little bit confounding, because the number -- some of the data that is entering my mind when I think about it is data that comes from the Juvenile Arthritis, and they're on other drugs -- many times there are cofactors -- you know, impacting the case, as well as the underlying disease may have a confounding impact.

So it seems to me that the post-marketing surveillance is going to give

us a lot of information, because it will be -- if you decide to approve it -- it'll be in a group that's probably more pristine in terms of just pure pediatric psoriasis, and you may find more, you may find less, you may find the same, so -- it certainly needs post-marketing surveillance, if that's the way we go.

DR. HECKBERT: Susan Heckbert. I voted yes. There is certainly adequate information to understand that there's an increased risk of infection. But I think that additional information is definitely needed to further refine that understanding.

DR. RINGEL: Eileen Ringel. I voted yes. Everyone has pretty much said what I was going to say, so I'll leave it at that.

DR. SHWAYDER: Tor Shwayder. I voted yes. Ongoing data collection, and we will need to know which bugs to look out for, whether it'll be bacterial, viral, fungal, or acid fascia, so that we can better address the needs

of our patient.

DR. BIGBY: Has the applicant provided sufficient information regarding the risk of malignancy in the target pediatric population?

That's open for discussion.

DR. CRAWFORD: Thank you. The Chairman kindly invited us to ask questions, as long as they were not argumentative, from earlier. So Dr. Kwon, I just have a quick -- a couple of quick questions, either for you or any member of the panel.

When you were presenting the data for etanercept for the pediatric AERS reports, a striking observation that girls, female patients, had 2.6 times the reporting rates of male patients; 71 percent for girls experienced a serious adverse effect, compared to 27 percent of boys.

My first question, and there's a quick follow-up -- do you believe this is just an artifact of who reports more, or do you suspect there's a need for more study to

see if there's a gender difference?

DR. KWON: I think --

DR. CRAWFORD: In general.

DR. KWON: My sense is it's -- in general, it's probably artifact. I don't believe there's a true different --

DR. CRAWFORD: Given the specific question about malignancies, from that same AERS reporting, even though there was 2.6 times the reporting by females, it was an even number of cases: Five and five, and two unknown gender, between cases of malignancy. So to me, those aren't quite matching. So do you have any opinion about why that might be?

DR. KWON: It's -- again, it's difficult to say why that occurs, just because -- you know, it's a voluntary reporting system and -- you know, all I can say is that's what's reported and I can't really attribute gender difference to what we observed in terms of -- you know, how many females -- the proportion of females getting malignancies.

DR. LEVIN: Just a question for FDA. How does your June 3rd warning sort of play into the labeling? I don't remember whether warnings have -- you know, an entree point into the labeling warning or not.

DR. SIEGEL: In general terms, the review of these pediatric malignancy cases is ongoing. At the conclusion of the review, any labeling changes that are warranted would be part of the action.

DR. LEVIN: And that review is --

MR. BIGBY:: Lynn, Lynn. Everybody can hear your phone.

DR. DRAKE: I apologize --

DR. LEVIN: And the contemplated date of completion of the review?

DR. SIEGEL: I think the Early Communication said six months.

DR. BIGBY: Eileen.

DR. RINGEL: When I think about malignancy, I need to think about it for this indication in this population. And the reason

we're here is because this is in children, and I'd like to bring up the discussion of how treating children differs from treating adults. In my mind, at least in the matters of malignancy in particular, I think of three things.

First of all, children have a longer time to develop complications than do adults. Is that important here? I'm not sure, actually. I don't think it really is. Malignancy takes a long time to develop. We're already treating 18 years olds, does it matter if we treat 16 year olds? I don't know. I'm not that impressed by that argument.

There's another one. Are children a different species from grown-ups? And I'm not being totally facetious. I mean, there are good reasons to think that children do react to things immunologically differently from adults -- despite the fact that we were told that the immune system is mature at two

years old, we all know from our clinical practice that juvenile dermatomyositis is different from adult dermatomyositis. Langerhans' cell histiocytosis, atopic eczema, molluscum contagiosum, kids' immune systems are different from adults'. I don't know how -- I don't know how to test it, they just are.

At any rate, so I don't know if that increased incidence of malignancy in children is going to be -- you know, in hematopoietic malignancy in children is going to be real or not, I have no idea. But that's something I could be concerned with.

And the last thing is children cannot give their own consents. Even if as much as their parents care about them, it's very different to have your mom give your consent for you for something that can kill you, from you giving yourself consent. One thing that really struck me was Kelsey, because it sounded so familiar from my

practice. She is a remarkably eloquent and mature child to be coming up in front of all these people and giving that kind of a talk with pictures. I'm so impressed you can't begin to know. However, what you said was, when you were discussing risks -- I wasn't concerned with them. I just wanted it to work.

I understand. If I were 16 years old in high school, I wouldn't be concerned with risks. I'd just want it to work. And if I were your mom, I would feel the same way. God Bless -- I'm so glad God gave you a mother, because she will look after you. But it must be so hard for your mother to look at you in that much pain and say you can't have this drug.

Even when asked what if it gave you a 50 percent chance of malignancy? That stopped me in my tracks. It really did.

So I guess what I'm saying, after my long speech, is that I am okay with this

risk of malignancy for severe psoriasis. I am not sure I'm okay for moderate psoriasis. And that's my long speech. There we go.

DR. STERN: I do think in the younger ages of the look for approval, there is one other factor of special concern. That is, if you look at at least immunosuppressed individuals on transplant, one of the biggest risk factors is EBV conversion, which typically occurs up to age five, six, or seven, as I understand it. But one of the ID doctors can better inform me. So I don't think everyone is converted by age four. But perhaps they are.

DR. MAJUMDER: This is Mary Majumder. I just wanted to in some way second but maybe disagree a little bit with Dr. Ringel. In reading through the materials in advance, the question that was in my mind is, I can clearly imagine cases where I think this would be justified. And so it doesn't bother me that severe might be a little subjective.

But I felt comfortable if it was

severe, and very comfortable if it was not, with approving this.

I do think that the interaction between Kelsey and her mom was informative in the sense that it was the kind of relationship and consideration that I would hope for as the ideal, where it's not solely left up to the adolescent or the -- you know, that feeling. But at the same time, the psychosocial aspects, as well as the itching and the pain, do factor into the parents' consideration of whether these risks are justified.

So I don't know if you'd see that universally, but it did seem to me that that's sort of a model of how this would be handled.

DR. LEVIN: Arthur Levin. The severe/moderate thing is disturbing, and it's a little disturbing, increasingly disturbing, because we've got some data in a couple months, or six months, or -- I'm still not clear when

the FDA is going to report out on that data.

For my part, I would be more comfortable with severe and sort of hooking, perhaps extending the indication, perhaps, depending on what the analysis of the data says. I mean, it's just troubling to know that somebody's looking at data and it's going to have some more information for us in the near future. I wouldn't suggest holding up -- you know, approval, but the issue of the indication, perhaps, to severe -- limiting it to severe, at least until we know more, has some appeal.

On the consent issue, in pediatric research, at least when I was on an IRB, there is such a thing as assent for children of a certain age, where you actually get the parent to consent, then you can get a child to assent. And I never hear it talked about in these settings. It's out there. It's reasonable to expect that children of a certain age are of a certain maturity to

participate fully in the discussion of risks and benefits, and indicate whether they assent or don't assent to the treatment. And I think it should be, really, something that we integrate into our thinking around the table.

DR. BIGBY: We're having a little bit of a question creep, here. So let's take a vote on No. 6: Has the applicant provided sufficient information regarding the risk of malignancy in the target pediatric population?

Those voting yes, raise your hand? Those voting no, raise your hand? Abstentions?

We'll start with Dr. Daum.

DR. DAUM: Yikes. So again, it's the word "sufficient," and I'm -- it doesn't mean that they haven't done -- the study they presented was fine in terms of assessing what's going on in 48 weeks. But it's not sufficient to make me comfortable in thinking of a role of counseling a parent, with or without pediatric

assent. And so I voted no. It's not sufficient, but it doesn't mean someone's done something wrong in their presentation to the Committee.

DR. BIGBY: I need to give the summary of the count. There was four yeses, seven noes, and two abstentions.

We'll keep coming in this direction. So Dr. Levin.

DR. LEVIN: Arthur Levin, no. I guess I would be echoing my colleague's comments.

DR. THIERS: Bruce Theirs. I voted yes, because I thought we had a great deal of information from pediatric patients who were treated with other indications, like JIA. So I was comfortable extrapolating that data to the pediatric psoriasis population. What I would really like to see, and I know the data was there among all the hundreds of other slides we saw, is a really cleaned-up few slides and -- please not now -- a few cleaned-up slides indicating how many children got malignancies

who were on etanercept monotherapy. Because it seems that almost every patient that we were given information about had some other confounding factor.

I'd like to know how many kids who are otherwise healthy except for psoriasis or arthritis, no other immunosuppressive drugs, got a malignancy. I know the data's there, but I'd just kind of like to have presented in a concise manner.

But I was satisfied with the data we had from other indications to vote yes for this question.

DR. BIGBY: So this is a perfect example of blind men examining an elephant, because based on the very same argument that Bruce made, I voted no, because I don't think that the data from patients with Juvenile Arthritis or Crohn's disease is actually informative for this situation, because those patients are much sicker. They have diseases that may or may not be associated with

malignancy to a greater degree than patients with psoriasis. The concomitant medication use, I think is much much higher than we'd do in -- certainly in pediatric psoriasis. In terms of the data presented in patients with psoriasis that were treated, the number of people exposed, and the length of follow-up, I don't think anyone would argue is adequate.

DR. MAJUMDER: Mary Majumder. I voted no, and I second Dr. Bigby's comments.

DR. O'NEIL: Kathleen O'Neil. I voted yes, although I do agree with Dr. Bigby's comments.

DR. STERN: Rob Stern. I voted no, for Dr. Bigby's reasons, but I think if you look at the power considerations and the prevalence of the disease, that we'll never have a robust answer for this. It is what it is, and I'm not sure we can do anything but warn about the possibility of it.

DR. KATZ: I voted yes. The only way you're going to get sufficient information is

with long-term follow-up. There's no way, in a brief study, it's going to be sufficient. So we'll have to take care of that with the reporting.

DR. SHWAYDER: Tor Shwayder. I voted no. It's very difficult to enroll children in studies because you can't give money. The money would go to the parent and it'd be considered coercion, then, for the parent to enroll the child -- that they are paid to do something that's against the child's wishes. I don't how big a risk would make this uncomfortable.

As I was talking with Mrs. Larson, you know, what number will make her not do it. Losing a patient is heartbreaking to the physician as well as to the family, for a non-lethal condition. And I think we need data for psoriasis only that's not muddied by the confounding variables of JRA.

DR. RINGEL: Eileen Ringel. I abstained. It all hinges, for me, on the matter of moderate to severe. I've gone over that