information, the underlying nature of the disease indicates that other therapies may have been used either concomitantly or previously.

So to summarize this portion of the discussion, consistent with our product labeling, non-serious infections occurred somewhat more frequently in etanercept arms in clinical trials. However, serious infections were uncommon and did not increase in frequency over time. There were no cases of tuberculosis, demyelination, malignancy, or death in our clinical trials. And the distribution of post-marketing reports was similar in children and adults across indications.

I'd now like to update you on our ongoing evaluation of malignancy. Many, if not all of you, are aware of the early communication from the FDA on their ongoing review of childhood malignancies in patients who are taking TNF blockers, including

etanercept.

I'd like to begin by setting the stage. I'll talk about some of the basic reasons behind this investigation, summarize our adult data, and then update you on our ongoing review of our pediatric cases.

Obviously, immunosuppression has been associated with an increased risk of malignancy in other situations, including transplant populations, with the use of other immunosuppressive therapies, including some that are used to treat psoriasis, such as cyclosporine and methotrexate, and also in patients with congenital and acquired immunodeficiency syndromes. Because of this, potential links with malignancy have been studied in a number of settings with TNF blockers.

However, there are some challenges in evaluating the risks of malignancy associated with TNF blockers. First, elevated malignancy rates are associated with

some of the conditions that are treated with TNF blockers. This includes an association between lymphoma, with RA and psoriasis, and non-melanoma skin cancer with psoriasis. Additionally, some of the other drugs that are used to treat these conditions may also be in and of themselves associated with malignancy. That's true of methotrexate and cyclosporine, and it may be true of UVB with non-melanoma skin cancer.

Lastly, malignancies are rare events in clinical trials and in post-marketing databases, making their study challenging.

This next figure underscores the association between RA as a disease state, irrespective of therapy, and lymphoma. These studies looked at the rates of malignancy in RA patients treated with nonbiologic, traditional DMARDS, and compared them to the general population. As you can see, all studies showed some evidence of increased

risk, with the magnitude of effect generally being on the order of about twofold.

If we look at the risk of lymphoma in RA subjects and compare those receiving TNF blockers to those who were treated with traditional non-biologic DMARDS, we see a different picture, with the majority of studies showing no evidence of increased risk.

Bongartz and colleagues at the Mayo Clinic have performed two recent metanalyses looking at the risk of overall malignancy -- now including all tumor types -- in RA subjects receiving TNF blockers. The first of these was reported in JAMA in 2006, and the more recent -- the 2008 analysis was just presented a few days ago at EULAR, the European rheumatology meeting.

Both of these metanalyses suggested increased risks, having elevated point estimates for the odds ratio. The confidence intervals are wide, however, and are shown in

this diagram.

Other investigators have looked at this question and reached different conclusions, however.

Askling looked at a large Swedish registry and examined the risk of malignancy in patients receiving TNF blockers, and concluded that there was no increased risk relative to the general RA population.

In order to further investigate this, Amgen and Wyeth have conducted a pooled analysis of our own clinical trials. Here, we've looked at 45 clinical trials. Potential cases of malignancy were identified by an automated search, and cases were reviewed by three sponsor physicians.

If we first look at the relative risk for malignancy across all indications, we see no evidence of increased risk. And this pattern holds if we look at major indications that have been studied.

If we then ask whether the rates of

malignancy and etanercept subjects are more than would be expected in the general population, we see a very similar pattern. Again, for all indications, there's no evidence for increased risk.

I will now update you on our ongoing review of pediatric malignancies in our post-marketing experience. Here, we conducted two searches. The first is a pediatric search looking at etanercept exposure and diagnosis of malignancy at age less than 18. The second is an expanded search in which patients had exposure to etanercept in a pediatric age range less than age 18, but allowed for diagnosis of malignancy up to age 22.

This expanded search was performed because there is a possibility that there could be a latency period between exposure to an agent and development of malignancy.

This table summarizes the results, and I'll give you some more details in just a

second. Overall, we identified 9 cases in our pediatric search, and 6 cases in our expanded search, for a total of 15.

This next table gives you some more information on the nine patients who were identified in our pediatric search. Not surprisingly, given the age of these patients, the majority of malignancies were hematologic in nature. I'll call your attention to a few features, however. First, to be conservative, we've included a case of AML -- second from the top -- that was in fact recurrent. And we've also included a case of lymphoma, which is the third from the bottom, in which lymphoma appeared on the differential diagnosis, but in which the diagnosis was not confirmed.

There are also some additional caveats that are important to mention. We've included cases with unknown or very limited etanercept exposure, and this is particularly important because the presentation of

leukemia in children may often be confused with JRA in its initial diagnosis.

In addition, there were other medications administered to the majority of these patients, some of which are in and of themselves associated with malignancy. As you can see, methotrexate was the primary confounder here.

If we look at our expanded search, we identify six additional cases. Two are hematologic, two are melanoma, and two are thyroid cancer. Again, to be conservative, we've included a case of malignant melanoma that fell just outside of our search criteria, as etanercept was started three months after that subject's 18th birthday.

If we take these cases and ask whether the rates are greater than would be expected based on rates in the general population, we get a range of standardized incidence values. Here, I've split out U.S. and global experience because we have much

more precise exposure data by age within the U.S.

Here, you can see a range of estimates, which vary between 0.41 and 1.31.

So to summarize this section of the discussion across all indications, overall malignancy rates are similar to the general population. In multiple post hoc analyses of clinical trial data, an increased risk of malignancy can neither be confirmed nor excluded at this time. And our analysis of post-marketing data in children and young adults is ongoing. However, our ability to draw firm conclusions is limited by the rarity of the event, the potential for latency, imprecise exposure data, and multiple confounders, as I discussed during the presentation.

I would now like to discuss some special considerations for the use of etanercept in children. We did look at growth parameters within our clinical trial.

The data were presented in our briefing book. I haven't included them here in the interest of time. However, overall, we had no observed changes in age- or sex-adjusted parameters such as BMI, weight, or height percentile. There are a couple of caveats. These studies were not powered to detect a difference, and as noted in the discussion of the trial itself, many of our subjects were heavier than their age and sex-matched peers, and this may have limited our ability to see a difference.

We were also asked to comment on the impact of etanercept therapy on the developing immune system. There are very little clinical data that we can bring to bear on this question. However, if we look at the literature, we see that the majority of immune compartments, including T-cell compartments, T-independent, and T-dependent B-cell compartments, and the overall lymphoid architecture are well-developed by two years

of age -- two years before the lower end of the indication we are discussing today.

This figure, which is adapted from Rich -- Clinical Immunology: Principles and Practices -- makes that point. As a compartment matures, it is denoted by a solid blue bar on this chart. And as you can see, most of these compartments are intact very early, shortly after birth. And all are intact by two years of age.

Again, if we look at our JRA long-term experience, we see no increase in serious infections over time, and no unusual patterns of infection that would indicate a change in the nature of the immune response.

If we look at the use of immunizations in children taking etanercept, we again have little clinical data to bring to bear on the question. Our current labeling language for JRA indicates immunizations should be brought up-to-date before starting therapy with etanercept, that

inactive vaccines may be administered, but that live viral vaccines should be avoided. These would include vaccines such as MMR, varicella, and intranasal flu, and although not used frequently in this country, oral polio vaccine.

If we look at literature reports of response rates following the administration of inactive vaccines to subjects on etanercept, we generally see normal response rates but lower titers.

So for my overall summary and conclusions, a clear unmet need exists in patients with moderate/severe pediatric psoriasis. Substantial clinical benefit has been demonstrated in our pivotal controlled clinical trial. In multiple post hoc analyses, an increased risk of malignancy can neither be confirmed nor excluded at this time. Increased risks of non-serious infections are described in our current product labeling, and our post-marketing

reports of fatal infections include use in systemic illness, high-risk conditions, and use with significant concomitant immunosuppressive therapy.

I will now hand over the podium to Dr. Paul Eisenberg to discuss our risk management program.

DR. EISENBERG: Thank you. I'll conclude with a brief discussion of considerations around benefit-risk and how to assure safe use in this population. I think as summarized, the data clearly demonstrate the benefits of etanercept in the pediatric population with moderate/severe psoriasis. The question is, given the risks that we've discussed and the risks of other agents, how can we assure appropriate use?

First, we believe appropriate use of etanercept in a labeled indication is preferable to the current situation of having off-label use of multiple unapproved systemic agents. It's important to consider the

overall population. We've made some estimates here. I'd be happy to walk through them if you have questions about the estimated use. But we're estimating probably less than 1,000 new patients per year would be starting on etanercept. So that would be an incident rate. That's based on the number of patients with moderate to severe psoriasis in the age range we studied.

The use of systemic agents is less than 10 percent of those patients, and based on that, we've made an estimate of total use -- incident use per year. As well, it's important to recognize -- and I think this is critical in terms of how we look at risk communication and our target audience, that our data indicate that a very limited number of dermatologists prescribe biologic therapies to begin with. And in the pediatric population, that number of prescribers is even more limited.

The risks do need to be considered,

and have been highlighted within the context of the risks of other unapproved therapies.

So in terms of the risk management program, first we believe appropriate, conservative use, which is guided by labeling and how communication on this indication is provided to both providers and to patients and their caregivers, is critical. In addition, we believe it is important to collect long-term data. The benefit-risk here is different than JRA. We've highlighted and have successfully completed and continue to follow pediatric patients in the JRA indication, and propose to do the same for this indication.

We already have -- and it's highlighted in both our presentation and I know in the FDA presentations you'll be hearing later -- a boxed warning that highlights the risks of serious infections with the TNF blockers. We do not highlight, nor is it highlighted in the presentations

this morning, but we have been working and have in fact submitted a medication guide which is pending FDA approval -- for those of you not familiar with the medication guide tool, this is a communication that is provided in patient-friendly language, usable and understandable by patients and their caregivers.

Given the new FDA authorities, this is under their program -- the REMS authority. So they've indicated -- and with all the other medication guides that will be approved since this authority came into effect -- that we will have the opportunity to assess the effectiveness of understanding the information that's being provided to patients regarding risk.

We also have ongoing analyses. One is included in the FDA briefing book, which was proposed by the Division of Adverse Event Analysis, who are here today. And our own analyses, which we're in the context of

updated labeling. All sponsors, again, are required to update our labeling in what's referred to as the Physician Labeling Rule. And as a consequence, we've had an opportunity, in addition to our routine reviews, to review our labeling. And in particular, the risk of -- the potential risk for malignancy, even though as you've seen from the data for etanercept, it has not been demonstrated, but cannot be excluded -- we believe should be labeled.

In terms of the indication, we believe the indication should be limited to the patients we studied in the clinical trial. That is patients with chronic moderate to severe plaque psoriasis in the 4- to 17-year age group who are inadequately controlled with topical therapy or who have received systemic therapy or phototherapy.

Most of the systemic therapies as we note are off-label, so obviously the label indication would want to identify a limited

group but wouldn't refer to off-label product use.

In terms of our patient exposure, we think that there should be an effort to highlight means to limit patient exposure. As you saw in our clinical trial, not all patients respond to etanercept. Most do, the majority, but we should note and we would propose that if there is not a response within 12 weeks, which is when we would have gone into rescue therapy and we didn't see any response in our trial -- that that therapy should be discontinued.

Our study in terms of the pivotal trial demonstrated benefit-risk only within one year. We have long-term studies, but we believe labeling should highlight the fact that use beyond one year should be carefully considered with regards to the benefit-risk.

In terms of risk management measures as I highlighted, these are conservative. They're not extensive with

respect to how we would manage this.

It's important to recognize in this indication, etanercept has known benefits both for the adult psoriasis population -- so for patients that dermatologists would be treating who are adults, as well as for pediatric patients. So our efforts have to be directed specifically at this subgroup of patients, and we would do that with targeted education, again promoting conservative appropriate use. We have no intention of any consumer broadcast or print advertising for this indication.

We would use the medication guide as well, which is provided to patients with each dose that they receive of etanercept from a pharmacy or a provider -- that they would receive that medication guide. And we also are proposing a prescriber checklist that would be part of the safety registry enrollment -- to remind the prescriber of important considerations when using

etanercept.

Our risk assessment would include long-term studies. We discussed one of them. The second row is the study that Dr. Severino already highlighted, which is our three-year open-label extension. Should etanercept be approved for this indication, we believe that should be extended to five years. That's a relatively limited number of patients, so we would be adding on to that a prospective long-term safety registry with a minimum of five-year follow-up, potentially longer, and we can discuss that in a moment.

And we would also be looking at utilization studies to ensure and discuss with FDA on a regular basis that the use of etanercept is in appropriate patients and not extending beyond the proposed indication.

The registry is still -- the specifics are still under discussion. We included in the briefing book the concept that it takes about 300 patients followed for

five years -- that's about 1,500 patient-years -- to adequately assess serious infection rates.

That would be the most frequent type of event we would expect to see. Clearly, there is limited power in any of these studies to assess for rare events without long-term follow-up for malignancies.

However, it's important to note that these data do not stand alone. We have enormous experience already with etanercept. We have the JRA registry. About 900 patients. Other surveillance programs. Our pharmacovigilance programs, which will allow us in aggregate to have a long-term sense of what the overall risks are, and continue to follow the appropriate use.

So in closing, I think it's very clear there is an unmet medical need for an approved, well-characterized therapy in pediatric patients with moderate to severe psoriasis who require systemic therapy.

Etanercept has demonstrated durable efficacy in these patients, as we've shown you. There's substantial experience over the past decade in a variety of disease states, including JRA with etanercept.

In the current overall management of these patients, each of the agents that are being used -- immunologic therapy agents that are being used off-label -- have significant risks that are both identified and potential risks. We believe the appropriate management of these patients will be aided by approval and management within a risk management program and long-term safety registry of etanercept.

We hope you agree with this.

Thank you for your attention.

DR. BIGBY: Thank you. We'll open the floor for questions and clarifications. Dr. Katz.

DR. KATZ: Thank you. First, Dr. Eichenfield, I want to commend you first of

all on putting things in perspective. I would just like to reemphasize for the non-dermatologist members that the bulk of patients do respond to conventional therapy. We're talking about a very useful therapy for a very small subset. And you emphasized that, and I'd like to thank you for that.

Dr. Severino, in the chart on CDLQI where it says percent improvement from baseline at week 12, it continually is said to be the "majority" of patients improve. Now, this is percent improvement at week 12. Not to denigrate the importance of the drug, but there's a total of 35 percent improvement if you subtract the placebo.

It's not the majority.

DR. SEVERINO: So this is not the proportion of patients. This is the group change from baseline score. So the baseline in the group was reduced by 52.3 percent.

DR. KATZ: And 17 percent in the placebo group. So the effective is 35 percent.

DR. SEVERINO: The difference in the treatment effect is 35 percent at this time point.

DR. KATZ: Thirty-five percent. And if we go back to the charts of PASI 75 at 12 weeks, it's not the majority -- not being technical -- but it's 57 percent minus 11 percent placebo, which is 46 percent. That's not to minimize the usefulness in that group, but we shouldn't exaggerate to say that it's a majority.

The other point -- in multiple presenters, we're talking about moderate to severe psoriasis. So for the non-dermatologists on the panel to realize "moderate" is considered down to 10 percent body involvement for treating children with 10 percent body involvement with this drug. And when we're showing pictures here, we're showing pictures -- photos of 90 percent body involvement. Eighty percent body involvement. That's not moderate

involvement. So we need to keep that in mind -- in perspective. Thank you.

Dr. Eisenberg, I have one question. You mentioned the long-term studies that you've captured 900 patients with in the JRA study. Out of how many patients that were initially examined -- I know you have that here, but I can't see it. How many have been treated with JRA?

DR. EISENBERG: The overall treatment -- I don't know the overall treatment. The initial commitment for the study was for 500 patients over five years. And the total number captured in that particular study I believe is just short of -- there were 602, and then there have been some patients lost to follow-up, so the study was within the context of the commitment. In terms of overall patients treated from a marketing perspective -- you may know.

DR. SEVERINO: In a pediatric age range for all indications -- and since it's

post-marketing, we can't always track the indications -- it's estimated that there are 12,000 children treated with etanercept worldwide since its approval in 1999 and JRA.

DR. KATZ: So out of the 12,000, 900 are included in the long-term. The others, we don't know what happened with them.

DR. EISENBERG: 600 in the post-marketing commitment, which was a specific commitment. So that registry was designed to capture at least 500 actually over-enrolled.

DR. KATZ: Thank you.

DR. BIGBY: Not yet. I have a question for Dr. Severino. Can you put up your Slide 52?

DR. SEVERINO: Bring the slide up please. Thank you.

DR. BIGBY: This sort of reiterates what Dr. Katz was saying, and that is that the study population is skewed towards milder disease.

DR. SEVERINO: That's correct. The

distribution has shown -- and we had a median of 16 -- and a large number between 12 and 16 for baseline PASI.

DR. BIGBY: Then the other two slides are 63 and 64. I just wanted to point out to the Committee members that this is a kind of a deceptive graph, as is the one that follows, because the Y axis actually goes from 0.4 to 1.0 as opposed to 0. And on the next slide, it goes from 50 to 100.

So you can make very small differences look like they are significantly spreading by not -- you know, having a true Y axis.

DR. SEVERINO: Just to clarify, we note that point. We had reproduced the time event analysis from the FDA briefing materials and tried to present things on a similar scale. But we have also plotted this on a 0 to 100 scale. The difference between etanercept and placebo here in an absolute sense is not large, and we believe that that is due to the very

conservative retreatment rules and the fact that retreatment started as early as four weeks.

DR. BIGBY: But the graph is deceptive.

DR. SEVERINO: Point taken.

DR. BIGBY: Dr. Thiers?

DR. THIERS: I have two quick questions for Dr. Eisenberg and one for Dr. Eichenfield.

Dr. Eisenberg, you mentioned at least once the association of methotrexate with lymphoma. Do you have any data that quantifies this association, and can you state with any degree of confidence whether the association is greater for methotrexate than with etanercept?

DR. EISENBERG: We can look at post-marketing data that is publicly available, and we've done that -- that shows comparative rates for methotrexate, cyclosporine of rates of malignancies, lymphoma, and yes, they are greater. The problem is confounding by

indication.

DR. THIERS: I'm not talking about cyclosporine. I'm talking about methotrexate.

DR. EISENBERG: Methotrexate. Sure. If we could have the slide up. So this, for example, in the rheumatoid arthritis population, simply highlights -- and this is published data -- the relative rates of malignancy excess, Hodgkin's lymphoma, lung cancer, melanoma. With regards to non-Hodgkin's lymphoma from methotrexate, I believe we've looked at that as well.

Again, I think as was highlighted because of the background rates in the RA population, that doesn't distinguish as well. But we can show you that in a cohort of 458 patients -- slide up, please -- again, this looks at the overall rates, including non-Hodgkin's lymphoma. And the SIRs being the comparison. So that would be -- they'll give you standard incident ratios against the typical background population rates. And you

can see versus expected non-Hodgkin's lymphoma about a 5.1 SIR.

That's from methotrexate.

DR. THIERS: Thank you. The second question was, you mentioned in the proposed labeling a one-year treatment period. Now, I'm sure this is going to be promoted as the only approved treatment for moderate to severe pediatric psoriasis. So the clinician is going to be confused as to what happens after the first year. Do they keep the child on etanercept in contrast to the label's cautions, or do they switch to a non-approved drug? Could you comment on that?

DR. EISENBERG: It's a good question. It's not our intention to limit treatment absolutely to one year and -- you know, our dermatologists who advised us suggest that many patients -- in fact, we heard from one earlier -- will require treatment longer than one year. We do think it's important to highlight the safety and benefit-risks that

we've seen in the clinical trial really extend to one year, and would be supported, as in the JRA indication, over time by reporting out of a longer-term registry which would provide further -- hopefully further assurances to long-term safety.

DR. THIERS: I just hope it would be worded in such a way that the insurance companies don't use this as an out not to approve the drug after one year.

DR. EISENBERG: That's good advice.

Thank you.

DR. THIERS: One question for Dr. Eichenfield. My experience with etanercept is almost exclusively with adults. And I feel there is a really a direct correlation between dosing and weight. I think heavy patients have difficulty dropping from 100mg per week to 50mg per week. I'm wondering what your experience was with -- I noticed in the patient population, it looked like there were a couple of heavy pediatric kids -- heavy children in the study.

Did you find that they did not respond as well to the .8 mg per kg that you were giving them than the skinnier kids?

DR. EICHENFIELD: I'll take my general comment, then have Dr. Severino -- he can present the actual data. But it was actually intriguing, because from a pediatric standpoint, we hadn't really had a chance to study what the weight distribution would be in pediatric psoriasis. And it was interesting that there was an elevated BMI in the 4 to 11 year olds, as well as the 12 to 17 year olds.

So overall, it was a heavier population. And I actually hope to plumb that data in more detail to see if there is anything we can learn about what may be.

In terms of an impact on weight, there is actually an analysis that was performed.

I'll turn it over to Mike.

DR. SEVERINO: To address your specific question regarding the impact of

weight, the dosing regime was 0.8mg per kg up to a maximum of 50. So after 62.5kg, subjects received the 50mg dose. That was modeled after our 50mg dose in adults. And exposure levels were comparable.

If we look at response by that weight cutoff, which is also the change from mg per kg to fix-based dosing -- if you can bring the slide up -- we see generally similar patterns. There's fluctuation as we do the subset analysis, but you can see the data as shown.

I think the Committee was not done.

Can we bring that back up, please?

DR. HECKBERT: Can you walk us through that a little bit?

DR. SEVERINO: This shows PASI 75 response over time out to week 36. Subjects who were in the 62.5 -- below 62.5kg stratum are in the solid lines. Subjects who were above that weight cutoff are in the dash lines. We see here the double-blind portion of the trial. We

see generally similar response at most time points. There is some fluctuation. Heavier group below at 12, but above at week 16. On crossover, we see a response. The crossover group achieved a somewhat lower maximum response at the end of 36 weeks; however, the original etanercept group achieved a comparable response. So there's some variability in the subset analysis. Thank you.

DR. BIGBY: Dr. Crawford.

DR. CRAWFORD: Thank you. Actually, my questions are for Dr. Severino and Dr. Eisenberg, though one of them was exactly what Dr. Thiers just asked of the dosing regimen. So the other one, Dr. Severino, is a very quick one for you. With the Children's Dermatology Life Quality Index, who completed it for this subject population?

DR. SEVERINO: For younger children, it was completed by the parent using an age-appropriate form. For the older children, it was completed by the patient with assistance

from the parent. And that cutoff was in the 12-year age range in terms of patient versus parent completion.

DR. CRAWFORD: Thank you.

Dr. Eisenberg, the first line on the slide under the risk management programs had a bullet that said "appropriate and conservative use," which is quite appropriate in a conservative statement that's subject to interpretation. I must ask, and this is just in general -- knowing that there will always be questions about this -- at this point, can you elaborate more? I know you said it's in planning. But what are the thoughts that the sponsors have regarding to prospective long-term safety registry?

And especially, why so few -- 300 patients? Even when you put in the patient-years, especially if you're going to have physician checklists as part of it -- but I'd like to know a little bit more about development of that registry.

DR. EISENBERG: Sure. Our thinking is -- you know, the intent certainly would be to try to have every patient enrolled who receives etanercept for this indication, recognizing that we have to encourage physicians to do that and do it in a manner that facilitates enrollment rather than use of off-label products. And so I think there's a balance there.

The 300 was developed based on simply the estimates of rates of serious infection. I would say, again, we're not entirely certain -- since we really do believe this will be used quite conservatively -- that we will have an excess of 1,000 patients per year who might be treated. I would say the range, if I had to guess, we would probably want to target several thousand patients in a two- or three-year enrollment period, if possible.

That seems to be a reasonable number to follow long-term, but much depends on what the initial -- you know, what the

utilization would be. So that's the general thinking.

In terms of being able to estimate -- you know, if we think about it in terms of being estimated risk from something rare such as malignancy, we can't design a registry, nor would there be enough utilization to get to a registry that would provide precise estimates for malignancy.

So we would add this to the overall experience, recognizing that.

DR. CRAWFORD: Thank you. One follow-up. If your data show effective promotion that show 10,000 to 15,000 patients per year, would you want to look at a more extensive plan, perhaps that might be over-utilization?

DR. EISENBERG: I would be surprised. I think it is clearly the intent, and I would expect in our work with FDA to approve this that we would be reviewing the use -- if I could have this slide up, GE-87 -- thank you. This is what

we roughly estimate. It's probably worth just keeping in mind as the Committee deliberates. If we look -- this is how we get to the numbers. Currently, we believe there are about 17,500 children who might be considered candidates, but it is, as indicated, a very conservative use of a biologic by a dermatologist. And appropriately so.

So the prevalent population right now, we believe, is only about between 1,000 and 2,000 children. And we're guessing that it will be -- uptake will be slow. But I think those are important parameters to study in any risk management program with FDA. And if we had the sense that it was more -- that there was greater use, we certainly would want to evaluate whether we're getting -- you know, the appropriate follow-up in management.

DR. BIGBY: Dr. Ringel.

DR. RINGEL: I have what I hope will be quick questions, but they're on four slides.

Could you bring up 51?

This is just to clarify for me. Am I correct to assume that about 30 percent of patients received phototherapy before entering the study, based on this -- by subtracting -- you know, basically 31 from 69 and subtracting 28 from 55? Is that correct?

DR. SEVERINO: There could be subjects who received both. So the first line is -- the first line on the slide you see here is prior use of systemics. The second is the combination. I think we can pull up the number who have received any phototherapy, and that's about half of subjects in the trial received prior phototherapy.

So we can bring the next slide up. That breaks out those details. And the number you're looking for I believe is this one here. Prior use of phototherapy.

DR. RINGEL: Great. Thank you very much. Next slide is 70. If you -- I'm very concerned about the age group between 4 and 11.

After puberty, I think people sort of act like adults -- at least biologically, if not psychologically.

If one were to stratify these adverse events by age, would we be able to tell any difference between etanercept and placebo?

DR. SEVERINO: If we stratify by age?

DR. RINGEL: Age.

DR. SEVERINO: The patterns are very similar across all terms. One difference is in streptococcal pharyngitis, more of those occurred in the younger children, and that disease is somewhat more common in younger children in general.

DR. RINGEL: Slide 96. Is this all AERS data?

DR. SEVERINO: This is from our database, but it's reconciled against AERS. So that's correct.

DR. EISENBERG: We submit all our data to AERS.

DR. RINGEL: Okay. So this is not part of any controlled study or controlled follow-up? This is no special follow-up program? This is just what gets spontaneously reported; is that correct?

DR. SEVERINO: Between the pediatric and expanded search that I described, a small number -- four of the total were from European post-marketing registries -- so they're not formally spontaneous reports, but they're all from the post-marketing environment. So 4 of the 16 -- or 4 of the 15, rather, were from European registries.

DR. RINGEL: I understand. So it's a little bit of a mix. The problem, of course, with AERS, as everyone knows, is that not all cases get reported. So talking about incidence or comparing it with -- you know, baseline of anything is pretty much worthless, as everyone knows.

The other problem -- concern I had -- and I wonder if there's some

confounder here -- is that the age at initiation of therapy with etanercept for all these malignancies seems very young. I wonder if you could comment on that. Is there something that's driving this? Why is it that the people who are treated at a young age seem to develop more malignancies?

DR. SHWAYDER: The age onset is age 8.

DR. RINGEL: Etanercept -- initiation of onset -- I'm sorry. Let me try it again.

The age at initiation of onset of etanercept is young. They get the malignancies later on, but they seem to be first receiving this drug when they're younger. I wonder if there's something having to do with starting this drug younger that makes you prone to malignancy later, or is there some confounder?

DR. SEVERINO: Let's bring the slide up, please, that's shown here. This is the slide from our core presentation describing our pediatric search. The etanercept -- the column

labeled etanercept initiation to onset shows the time period in months or years indicated prior to the event that etanercept was started.

DR. RINGEL: I'm sorry. I apologize. That was my error. I misread it.

Last thing, 101. Before I came here, I just checked the development of the immune system in Nelson's Pediatric Textbook, for what it's worth, and it said that the thymus and peripheral lymphoid tissue didn't reach its maximal size until puberty.

And that seems to disagree with what's here. I was wondering if you had any comments on that.

DR. SEVERINO: Lymphoid tissue does not reach its maximum size until later in life. But the lymphoid architecture is in place, and function is in place in the age range shown here in Rich Clinical Immunology. So the size of the lymphoid tissue itself suggest the lymph nodes may change over time.

DR. RINGEL: It does seem clinically

that children have different immune responses from adults up until puberty, at least in my clinical experience. So I was just curious.

DR. SEVERINO: Dr. Modlin may want to comment on that.

DR. MODLIN: My name is John Modlin. I'm a pediatrician and chair of the Department of Pediatrics at Dartmouth Medical School, and an infections disease physician. I am here as a consultant -- a paid consultant to Amgen. I think in the interest of full disclosure, I need to also mention I'm a special government employee, and that I serve on the Vaccines and Related Biological Products Advisory Committee for the FDA as well. But of course, that's unrelated to the task at hand.

I was asked by Amgen originally to consult specifically around the issue of the effect of etanercept on immunization, both the safety and the efficacy of childhood immunization. But my overview has extended a bit to some of the infectious disease issues

that have been presented today.

In terms of the specific question about the relationship of the size of the thymus to development, I actually believe that the thymic size probably peaks at about seven or eight years of age compared to total body weight in terms of the actual proportion of the size of the thymus to total body weight.

Its function is well-intact well before two years of age, and the best we can tell from a functional standpoint, the thymus is fully functional and thymus function peaks, certainly, by two years of age.

I don't know if Bob has any different view of that.

In terms of -- I think this chart is -- from my understanding, it's pretty accurate with respect to the development of various limbs of the immune response. And I would guess that if there's anyone who actually wants to -- has a specific question

about this, I would be happy to try to address it. But I would view this as being a pretty accurate depiction of our understanding of the development of immunity in children.

DR. BIGBY: Thank you.

Dr. Stern.

DR. STERN: For Dr. Eisenberg, it's a two-part question because I'm afraid I know the answer to the first part. In your risk management measures, you say no consumer broadcast or print advertising for this indication. I'm assuming that means only pediatric psoriasis and not psoriasis.

If it's psoriasis, you don't have to answer the second part of my question. If it is only pediatric psoriasis, what evidence do you have, and what concept would there be, that advertising for psoriasis, as you've done it, and at one point been censored by the FDA for it to consumers, would not in fact impact on parents and children in

promoting this therapy?

DR. EISENBERG: I can't answer the question with regards to the specifics you've asked, because I don't know that we can determine -- and it's a fair question -- whether advertising that occurs for an adult condition would be assumed by a parent to apply to the pediatric condition. I think common sense would say that probably could be the case.

I do think, and we're committed here, given the difference in benefit-risk, to assure that we're not promoting in this specific indication.

DR. STERN: Again, the specific indication being pediatric.

DR. EISENBERG: Being pediatric; correct.

DR. STERN: So no changes in your widespread direct-to-consumer promotions?

DR. EISENBERG: I can't speak for the direct consumer promotions for the adult indication today.

DR. BIGBY: Dr. Daum?

DR. DAUM: So I have a relatively minor question, but along the same lines. Several people have alluded to problems with third-party payers and advertisements and stuff like that. So I'd be curious to know what the approximate retail cost would be for this therapy in, say, a 12-year-old child, recognizing that few people pay the retail cost, but some do. And I'd just like to get a sense from the company of what the cost would be -- charge would be.

DR. EISENBERG: I don't know. We'll see if we can give you that answer or we can come back to you with it. We don't have that answer. We don't actually have the market answer. It also would depend on the body weight and typical dose. But we could get that for you before the end --

DR. DAUM: Then I'll rephrase it. What's the approximate cost in an adult?

DR. SEVERINO: I don't have the exact

number for you, but I can get it. But it's approximately $15,000 for a year of therapy.

DR. DAUM: Fifteen or 50?

DR. SEVERINO: Fifteen.

DR. BIGBY: Dr. O'Neil.

DR. SEVERINO: In an adult.

DR. O'NEIL: Am I lit up?

My question is regarding the immunologic effects of etanercept, particularly in view of the fact that this population with chronic severe or moderately severe psoriasis probably does have a higher than general population risk of having common variable hypogammaglobulinanemia, or IgA deficiency, two of the more common immune deficiencies found in the general population, in reverse order.

My question is, do we have any data regarding whether the infectious complications -- well, I guess the first obvious question is do we have any data regarding the immunologic status of the

subjects at trial entry, even in the adult population?

Secondarily, if so, do we know if infectious complications are more common, and therefore perhaps you should label that caution should be especially taken regarding infectious complications in individuals who can be demonstrated to have immunodeficiency a priori? And also, if that has any relation to some of the malignancies that have been reported. Because especially with lymphoma, that's much more common in CVID and IgA deficiency.

DR. SEVERINO: Several parts to your question. Patients with no immunodeficiencies would not have been enrolled in the trial by the exclusion criteria. We don't have any data on undiagnosed CVID or isolated IgA deficiencies within this clinical trial. So I don't have direct clinical data to address your question at this point.

Again, patients with both the

immunodeficiency syndromes that you mentioned, or history of recurring infections, would have been excluded from these trials.

DR. O'NEIL: So that means you have not done any immunoglobulin quantitation on the serum that you have banked on these individuals?

DR. SEVERINO: We haven't done detailed quantitation, and we did not diagnose any cases of CVID or other immunodeficiencies during the course of the study.

DR. O'NEIL: It is -- particularly IgA deficiency is very common, and you should have at least four or five in this one small study.

DR. BIGBY: Dr. Shwayder.

DR. SHWAYDER: First question, Dr. Severino. Slide 46. What is a Grade 3 or 4 infection?

DR. SEVERINO: That is a CTC grading criteria that we had to use to standardize. So it is an infection that is rated severe by that CTC scale, meaning its impact on symptoms.

DR. SHWAYDER: I guess I still don't have a handle on it, but all right. Slide 82. If you could just walk me through this. You went over it a little too fast. So these are people who had died? They died while they were taking etanercept; correct?

DR. SEVERINO: That's correct.

DR. SHWAYDER: So 10 had JRA. Four of those 10 had bone marrow transplants.

DR. SEVERINO: So of the 16, 10 were in JRA.

DR. SHWAYDER: Okay.

DR. SEVERINO: Of those 10 in JRA, two had systemic onset disease, and eight had polyarticular disease.

DR. SHWAYDER: Then the next four?

DR. SEVERINO: So the 4 -- so the 10 are in JRA. They are four different patients.

DR. SHWAYDER: Okay.

DR. SEVERINO: In the setting of bone marrow transplantation.

DR. SHWAYDER: They were getting

etanercept for something other than psoriasis?

DR. SEVERINO: So they were getting etanercept for treatment of complications following bone marrow transplantation. In two cases, that complication was GVHD. And in two cases, it was idiopathic pneumonia syndrome.

DR. SHWAYDER: I'm sorry, they were using etanercept to treat GVHD or were they using etanercept and they got GVHD?

DR. SEVERINO: To the best of our understanding on medical review, they were to treat GVHD. There are lit data in the literature to indicate that TNF blockers have a role there.

DR. SHWAYDER: Then the next one had malignant histiocytosis. It was being used to treat it or they happened to have it?

DR. SEVERINO: There are limited data from that report. We can't answer from that one report.

DR. SHWAYDER: The next bullet point -- 12 out of 16 of the concomitant

immunosuppressive medication -- these again, they're using etanercept to treat what?

DR. SEVERINO: For various indications. The majority being -- yes, these are the same 16 patients. So the majority of the 16 were receiving other agents.

DR. SHWAYDER: This is the same 16. In the bottom one, the four with no -- it's the same 16?

DR. SEVERINO: Same 16. The top of the slide breaks out the disease state. The bottom of the slide breaks out the concomitant therapies. So 12 of 16 reported concomitant immunosuppressive therapy. Four did not have it reported in the spontaneous forms.

DR. SHWAYDER: The gentleman from Dartmouth, I wanted to ask why is it you can't give live vaccines? Just fill me in. It's been a while since I did pediatrics. I mean, obviously it has something to do with TNF.

DR. MODLIN: It's my understanding that live vaccines are a contraindication in the

label. The basis of that is, to my understanding, there have not been any known adverse events from live vaccines in patients taking any of these TNF alpha blockers.

So it's literally just a precaution. One of course has to take into account when you're considering vaccines of any kinds, a risk/benefit ratio. And of course, we're always concerned about the risk of vaccinating and the risk of not vaccinating. I think when I, as an infectious disease expert, am asked whether or not a child who is immunosuppressed for any reason should receive a vaccine, we always have to weigh both the risk and the benefit to the child in that respect.

In my view, the degree of immunosuppression that occurs with these agents, including etanercept, is relatively low compared to a lot of other immunosuppressive agents that we use.

And so I think -- we're not

strictly adhering to the label as a practitioner. I might often actually recommend this or that or the other vaccine be used in a certain situation, particularly if it's a child that has a high risk of being exposed to measles, or mumps, or rubella, or chicken pox, or whatever the disease may be.

DR. SHWAYDER: So it's really a belt and suspenders-type of thing without any data behind it?

DR. MODLIN: To the best of my knowledge, we don't have any data on live vaccines in children.

I don't know if Mike or the others want to address that more specifically.

DR. SEVERINO: It's a conservative recommendation made as a precaution. So there are very little data.

DR. SHWAYDER: I might put that in -- I have trouble enough just convincing the parents to get their kids vaccinated, which I think is extremely important. To have one more

excuse not to is -- I prefer not to have it if there is no data behind it.

And lastly, what is the pregnancy category? If someone gets pregnant while they're taking etanercept, what's the recommendation?

DR. SEVERINO: It's category B.

DR. SHWAYDER: I'll have to go look that up. Does that mean you tell them to get an abortion or not?

DR. SEVERINO: That means that the animal data do not indicate an increased risk, but there are no direct clinical data to make a recommendation.

DR. SHWAYDER: Okay, thank you.

DR. BIGBY: The FDA has requested the break to be 15 minutes. So we're going to go until 10:35. There are currently four people in the queue.

Dr. Drake.

DR. DRAKE: I'm not sure who to ask this question to, but I'm going to start with

Dr. Eichenfield. Most clinical studies are done either with biopsy-confirmed diagnosis or by clinicians who are expert in that area and can make a good clinical diagnosis.

Dr. Eichenfield, in your experience, or frankly, anybody who has seen a lot of these patients -- these kids -- how many kids have been sent in to you or have you seen carrying a diagnosis of psoriasis but may not actually have it?

They may have eczema or something else. And so you see where I'm going with this? What precautions should we consider as a Committee, or should the FDA consider, to make sure that only kids -- because this is a serious drug for a serious condition. What confirmation should -- perhaps, if any -- should be included in labeling or if this drug is approved in the process?

DR. EICHENFIELD: It probably relates to the expertise of the physicians who are taking care of the patients. In real life, it's

much more common for patients to have delayed diagnosis of psoriasis because they're carried as eczema patients. That's actually the more common thing that we see.

Of course -- you know, skilled dermatologists don't have a problem making that differential and diagnosis in the vast majority of patients. So I mean, in a clinical study it was very easy because there was a pretty expert panel of people involved in the study, and they had to have a minimal of six months duration for psoriasis. On average it was six to seven years, so it was easier in that context. But the generalization, I think it's a good point.

I wouldn't want it to be a biopsy diagnosis, because in the hands of the experts, we rarely have to biopsy for certainty.

DR. DRAKE: I guess I have a follow-up on that. I still have a concern -- because I'm not even a pediatric dermatologist, but I see

patients with some frequency that are referred in with diagnoses of psoriasis that in fact don't have psoriasis. I mean, that happens to dermatologists in almost every disease state. And I would hate for some child that had just a contact dermatitis or an eczema -- my concern is how do we deal with that? And there may be no way to deal with it, but I think it's an issue.

DR. EICHENFIELD: I think probably with many drugs, we label it according to diagnosis and then we leave it out there to the hands of physicians to figure out what a certain diagnosis is.

I do think in this case that because it's a systemic agent, therefore, in pediatrics, that means it's not easy. You know, we think of systemic agents as easy, and in pediatrics, kids generally don't like shots. They have to be really vested. So hopefully there would be a chronicity involved in the disease and a certainty before it's utilized.

DR. BIGBY: Dr. Walker.

DR. WALKER: I just had two clarifying questions -- you know, in turn.

DR. BIGBY: Dr. Heckbert.

DR. HECKBERT: Yes, I have a question for Dr. Eisenberg regarding both the JRA three-year prospective cohort study, and then the proposed pediatric psoriasis registry.

DR. EISENBERG: Yes.

DR. HECKBERT: Regarding the JRA three-year prospective cohort study, is Slide CC-79 a pretty good one to go by to look at how many patients we're talking about in that cohort study? So about 200 JRA patients received methotrexate, about 100 received etanercept only, and about 300 received both etanercept and methotrexate. Are those the 600 you're talking about?

DR. EISENBERG: No, no, no. If I could bring up the post-marketing commitment slide. It's a somewhat different population. I think that's in the risk management slides where

we have the post-marketing commitment. That was a specific long-term safety study. So it's a registry.

The next slide after that, I believe. Yes, if we can bring this slide up.

So there was a commitment to study -- 500 patients was the target with JRA. We don't actually have data from that study to provide to you at this point.

Obviously, in response to one of the questions earlier, if there are spontaneous events that are picked up in any of these studies, serious adverse events, those do get -- are tracked. But that study completed with 594 patients. The data are currently locked.

DR. HECKBERT: So I'm a little confused. This is a different study?

DR. EISENBERG: Yes.

DR. HECKBERT: From this JRA three-year prospective cohort study?

DR. EISENBERG: Yes.

DR. HECKBERT: And you don't have these data to show us today, is that --

DR. EISENBERG: These data? No.

DR. HECKBERT: In terms of safety?

DR. EISENBERG: This study has just locked, and that will be completed soon and reported.

DR. HECKBERT: Is this a voluntary follow-up?

DR. EISENBERG: Yes.

DR. HECKBERT: Can you tell us about how that study was conducted? Did you recruit physicians to participate in it? Could any physician -- pediatric dermatologist have participated? How did you conduct this study? Is this similar to what you're proposing for the psoriasis?

DR. EISENBERG: I think it is not similar to the psoriasis study in the sense that our intent with the psoriasis study would be to attempt to capture almost all patients who would be treated. If I can have the slide up. This

describes this study. I can't get into the details. I was not involved in it, but Dr. Severino could comment. It was an open-label study, non-randomized. It had an external advisory group and principal investigators involved with this. It's a prospective cohort, so the intent was to capture a specific number of patients. So by its nature, it's a voluntary study.

It's not an attempt to act as a registry for all patients who were treated.

In terms of how we're thinking about this particular indication, given the difference in benefit-risk, we think that in this study, we would want to be more aggressive, in an attempt to capture all patients treated. Again, we believe that should be possible. It's not going to be possible to capture every patient. We would propose it to be a voluntary study.

DR. HECKBERT: Okay, thank you.

DR. BIGBY: I have actually gotten

confused. I came here basically believing that TNF alpha inhibitors were causally associated with risk of infection, and also for the development of certain malignancies. And yet you've presented data trying to convince us that in pediatric use, it is not? So --

DR. EISENBERG: I think with regards to the risk of infection, the data overall do suggest that there are increased risk for infection. They're highlighted in the black box warning. In particular, tuberculosis. I think the evidence has suggested there is an increased risk -- for etanercept, the risk appears to actually be less than has been observed -- at least observed rates than have been observed for the antibody mechanism of action.

With regards to malignancy, we don't know. FDA may have some additional comments. That's one of the reasons this has been studied extensively. You've seen some of the data that Dr. Severino provided in terms of the overall experience. In fact,

for etanercept, we have not demonstrated increased risk relative to the SIR, which is epidemiologic data for background rates, and we've not demonstrated increased risk in clinical trials.

DR. BIGBY: Dr. Daum.

DR. DAUM: I have two questions related to the slide that was up about fatal infections in patients receiving the drug. And the first question is -- these both may have been answered and I just missed it, so apologies if that's true.

The first one is how were those data collected? How was the company made aware of those fatal infections?

And then the second one, granted that many of these patients were obviously very sick, getting other concomitant immunosuppressive therapies, getting bone marrow transplants, et cetera, but is there any pattern to -- I didn't see anything about the nature of the fatal infections. And is

there any pattern to them that would suggest an alarm or give a signal?

DR. SEVERINO: So to address the first part of your question, the cases are spontaneous reports. They can come in through any one of a number of mechanisms. And there's no particular pattern amongst the 16 in terms of how they were obtained.

DR. DAUM: Spontaneous reports to the company or to the FDA? I mean, how did you gather them?

DR. SEVERINO: So either. They could be spontaneous reports to the company or through the AERS system, and we would reconcile those databases.

DR. EISENBERG: Or European.

DR. SEVERINO: And we would do the same with --

DR. EISENBERG: We each have the same data.

DR. SEVERINO: And so as Dr. Eisenberg pointed out, if anyone didn't hear because he

wasn't miked, we would go through a similar reconciliation process with the European agencies to make sure that our databases were complete.

With respect to the pattern of infections, there was no consistent pattern of infections that pointed to any particular signal with respect to a type of organism. For example, many did not have causative organisms listed, did not have microbiologic diagnosis. It's somewhat limited in terms of the information that you can collect in a post-marketing experience. We often have incomplete records.

DR. BIGBY: Dr. Walker.

DR. WALKER: Slide 92. I just had a clarifying question about that.

DR. SEVERINO: We'll pull that up in just a second.

DR. WALKER: The question was -- this addresses malignancies, and did you break out the data for hematologic malignancies by any

chance?

DR. SEVERINO: In this particular analysis, we didn't. In the RA population, risk of lymphoma would be elevated. If we can bring this slide up.

In an RA population -- however, I did mention previously that there's an association between RA and lymphoma. And you also see the point estimate for psoriasis. We haven't broken it out specifically for leukemias.

DR. WALKER: What about in the pediatric population?

DR. SEVERINO: The pediatric population? There were no cases of malignancy in the pediatric population in clinical trials. In our post-marketing experience, I showed a table that listed the malignancies. In the younger children, the majority were hematologic.

I can bring up that slide if you'd like. I'll leave it up to the Chair, in the interest of time.

DR. WALKER: I think if you just had a rate in the pediatric population, that would just be of interest.

DR. SEVERINO: So you would like to see -- let's bring up the --

DR. WALKER: Do you have an SIR rate in the pediatric population for hematologic malignancies?

DR. SEVERINO: We didn't break it out for hematologic malignancies separately in terms of our SIR calculations. However, of all of the malignancies in the pediatric age range, seven of the nine were hematologic. So it would look very similar to the overall rate.

DR. WALKER: And slide 96 -- I think that's all cancers, but that excludes non-melanoma skin cancers; is that right?

DR. SEVERINO: This is all cancers. The SEER calculations excluded non-melanoma skin cancers, because those are not included in the SIR database for comparison.

DR. WALKER: So this does include

non-melanoma skin cancers?

DR. SEVERINO: This is all of the observed cancers that we had in our pediatric post-marketing database in this age range, and none of them were non-melanoma skin cancers.

DR. BIGBY: I think we're going to take the break now. We should be ready to go again at -- 15 minutes from now.

(Recess)

MS. WAPLES: Again, can you please take your seats? We are about to begin.

DR. BIGBY: So at this point in our proceedings, we'll hear the FDA presentation. So while they're waiting, Dr. Heckbert, do you want to just go back to your question, and we can clarify this issue?

DR. HECKBERT: Yes. My question was regarding the JRA three-year perspective cohort study, and I had asked whether the information on slide CC-79 represented basically the -- I was asking, was this a voluntary perspective cohort study, and I was asking about how it was

designed, how it was conducted.

And there was some confusion about whether this represented the post-marketing commitment that the company had agreed to with the FDA when the drug was approved for juvenile idiopathic arthritis.

DR. EISENBERG: Yes, if we bring up that slide, I was mistaken on CC-79. I'll actually ask Dr. Carol Wallace, one of the investigators of this, to comment. I don't know if we can bring it up, but you can comment. This is the slide that refers to the rates of serious infections with methotrexate versus etanercept, or on both.

DR. WALLACE: So this is indeed the post-marketing commitment study, and it had 594 patients total. This was voluntary, and the intent was to get as many patients as possible. At the time that this was developed, it was requested by the FDA to have a comparator arm; hence the methotrexate-only arm. Those patients were allowed, if they had insufficient response

to methotrexate, to roll over into the etanercept arm, and they could either be etanercept-only or etanercept and methotrexate.

But overall, there were 594 patients.

DR. HECKBERT: As a follow-up to that -- because that is what I thought this was but I wasn't sure -- do you have any estimate of the number of children who have likely received etanercept in the U.S. since it was approved in, I think, 1999? What proportion does 103 plus 294 represent? Is that a small proportion, or is that -- I'm just wondering what proportion of the total experience are we looking at here, of the U.S. experience?

DR. WALLACE: I'm going to have to let someone else answer that.

DR. SEVERINO: The number of children who have been treated with etanercept in a pediatric age range is estimated to be 9,400 in the U.S. I mentioned a 12,000 number -- that's the global estimate -- previously.

DR. HECKBERT: Thank you.

DR. BIGBY: We'll go on with the FDA presentation.

DR. KETTL: Good morning. My name is Dave Kettl. I'm a medical officer in the Division of Dermatology and Dental Products at FDA. I was the primary clinical reviewer for this application for etanercept in the treatment of pediatric plaque psoriasis. I'd like to acknowledge the efforts of many clinical and biostatistics colleagues who also reviewed this application.

I'll begin my presentation this morning with the discussion of background elements about pediatric psoriasis and etanercept relevant to this application, followed by several issues relating to efficacy and safety that became evident during the review of this BLA supplement.

As you've just heard, this study was conducted in response to a post-marketing commitment from 2004 from the approval action

for plaque psoriasis in adults. The indication proposed is for chronic, moderate to severe plaque psoriasis in patients who are inadequately controlled on topical therapy, or who have received systemic or phototherapy. 57 percent of subjects in the trial had previously received systemic therapy.

The literature estimates, as you've also heard this morning, are somewhat variable, and the prevalence in the pediatric age group ranges in the literature from 0.2 to 3 percent.

The National Center for Health Statistics of the Centers for Disease Control and Prevention estimated in a 1996 study that the prevalence of psoriasis was 0.32 percent in children less than 18 years of age. Most practitioners allude to the conclusion that most children do not have severe disease and are typically controlled by topical therapy.

The onset of psoriasis in childhood

does not always lead to persistence into adulthood, and is not correlated with severity of disease in adult life. No data to date demonstrate that aggressive treatment of pediatric psoriasis mitigates the course of disease into adult life.

As previously stated, most pediatric patients are adequately controlled with topical therapy. These treatments include emollients, which by themselves are often sufficient in mild disease.

The most common treatment is topical corticosteroids of varying potency, and some steroid preparations of higher potency are limited in labeling to 12 years of age and older. Other topical therapies, which are not approved in children include tars, anthralin, calcipotriene, topical retinoids such as tazarotene, and calcineurin inhibitors such as tacrolimus.

No systemic agents are Agency-approved for pediatric psoriasis, but

methotrexate, cyclosporin, oral retinoids, and phototherapy are sometimes used in children. With the advent of biologic products in 1998, there's been some off-label use of these products in children.

There are five biologic products approved for adult psoriasis, and they fall into two classes: TNF blockers and anti-T-cell surface protein products. The dates for Agency approval for adult psoriasis are included in parentheses. Etanercept was approved for adult plaque psoriasis in 2004. As stated by Dr. Eisenberg, there are no biologic products approved for pediatric plaque psoriasis.

This chart provides a frame of reference for pediatric indication approvals for biologic products. Adalimumab, approved for JIA from ages 4 to 17, initially was approved with a trial subject number of 171. Infliximab was also studied for JIA for a similar age group in a trial of 60 subjects

who received active treatment, but failed efficacy.

It's approved for Crohn's disease from ages 6 to 17, and the trial subject number was 112 in that initial study for approval. Etanercept was initially approved down to age 4 through age 17, and the number of trial subjects was 69. Alefacept, efalizumab have no pediatric indications. I've included certolizumab, which was just approved two months ago for adult Crohn's disease, but this also has no pediatric indications.

Focusing on etanercept, these are the indications that are approved and the date of initial agency approval. Each indication was licensed after a distinct evaluation of the benefits and risks for each distinct population. The Juvenile Idiopathic Arthritis indication is the only approved pediatric indication for etanercept, and it's currently licensed for use down to age two.

The benefit-risk analysis for plaque psoriasis in children may prove very different than the evaluation for JIA, which can be quite debilitating, with long-term joint damage and tissue loss.

The April 2004 approval for adult plaque psoriasis specified four post-marketing commitments. The first is the pediatric study which is the focus of this morning's discussion. The second was a two-year efficacy and safety assessment beyond 12 weeks, studied for initial approval. A study report with 144-week data has been submitted and is currently under agency review.

The third was a longer-term surveillance study to assess serious infections and malignancies in a population of 2,500 subjects over at least five years. According to the sponsor, enrollment is complete, but the five-year data is not expected until 2013.

The fourth is a pregnancy registry for patients treated for all approved indications. The projected study completion date is 2011. Other informational needs will be reviewed pending the recommendation of the Committee for this application.

At this point, I'll move on to a discussion of the single study submitted in support of the pediatric plaque psoriasis indication. The study was conducted over three periods: An initial 12-week randomized double-blind placebo-control period; the 24-week open-label treatment period; and a 12-week randomized double-blind period, where subjects were randomized to continued etanercept treatment or switched to placebo.

211 subjects, age 4 to 17 years of age, were included across 42 study sites in the United States and Canada. As noted, the primary endpoint was 75 percent or greater improvement from baseline in the Psoriasis Area and Severity Index, or a PASI 75

response at week 12. Secondary endpoints included the Physician's Global Assessment of zero or one on a zero-to-five-point scale, as well as other PASI assessments, quality of life measures, and safety assessments.

The Agency analysis and discussion will include both a discussion of PGA and PASI analyses.

The inclusion criteria for the study included a PGA greater than or equal to 3, at least a 10 percent body surface area, and a PASI greater than or equal to 12. The median PASI at baseline was 16. 57 percent had previous systemic or phototherapy.

The most severe forms of pediatric psoriasis, erythrodermic and pustular psoriasis, were excluded from the trial, as well as guttate psoriasis. Nine percent of subjects self-reported psoriatic arthritis. No baseline physical examination was performed to characterize the joint disease severity. These subjects were analyzed over

the trial with a visual analog scale that indicated the level of pain of the preceding seven days at various timepoint assessments through the trial and at the end of treatment.

During the Agency review of the study, several issues became evident that should be considered when evaluating the benefits of etanercept treatment for children with psoriasis, and to give some context to the efficacy results.

While the Agency analysis also shows that the primary efficacy of PASI 75 was demonstrated at the 12-week endpoint, several issues will be presented in the next few slides to consider whether additional informational needs are required prior to a definitive assessment of the benefit-risk decision for this application.

These include level of placebo response, the lack of clearance of skin disease for most subjects, maintenance of

efficacy over the 48-week trial, disease severity in the study population, variability of investigator assessments of disease, and whether the population studied is representative of the larger population for whom this treatment will be prescribed if this application is approved.

This chart illustrates the Agency's analysis of efficacy data at the 12-week primary endpoint. Slightly more than half the subjects demonstrated efficacy success at 12 weeks, with 50 percent measured by Physician's Global Assessment, and 57 percent by PASI 75 response.

The analysis shows statistical significance for both PGA and PASI 75 responses. The placebo response of 11 to 13 percent reminds us that pediatric psoriasis is somewhat unpredictable in its course. Psoriasis typically waxes and wanes unpredictably, and periods of remission are typical in the course of pediatric psoriasis.

Though not exactly comparable, the placebo response rate in the two etanercept adult psoriasis trials were 3 percent and 4 percent. While the primary endpoint was demonstrated, the overall treatment effect at 12 weeks is considered in this chart of various levels of PASI response at 12 weeks. It appears that less than 7 percent demonstrated a PASI 100, or clearance of the disease. This information should be considered when assessing the benefits of etanercept treatment compared with its risks, to be further outlined this morning.

These graphs depict the Agency analysis of proportion of successes over time for the initial 12-week randomized period, followed by the 24-week open-label period. Efficacy plateaus early in the open-label period, and few additional subjects obtain efficacy objectives after that timepoint.

Period C was designed to assess the effect of withdrawal of active treatment, and

138 subjects were re-randomized into two groups, etanercept and placebo. We again analyzed success by both PGA and PASI 75 analysis. The middle column, subjects randomized to etanercept therapy, demonstrates a waning response rate, even though these subjects continued active treatment from the open-label period through weeks 36 to 48.

This is evident in both PASI 75 response and PGA decrease over the last three months of the trial. The explanation for why this is seen is not yet clear. These data are illustrated in the following graph, which plots proportion of successes over time for Period C, 36 to 48 weeks.

The drop-off of efficacy of placebo-treated subjects, shown here in the red curve, is to be expected, since these subjects were treated with etanercept in the open-label middle period of the study, and then had active treatment withdrawn at 36

weeks. It's not clear why the etanercept subjects, shown here in blue, would show this waning of efficacy.

As we examine the reasons for the maintenance of efficacy, which would be important in prescribing treatment of a chronic condition such as psoriasis, we examine the population of subjects who are randomized to etanercept treatment in the initial 12-week Period A, then were randomized to active etanercept treatment in Period C, the withdrawal re-treatment period.

There were 31 subjects in this group, and they received etanercept for the entire 48 weeks of the trial. Several aspects of these graphs deserve comment, and the explanation of why they occurred is still unclear.

In both the PGA graph on the left and the PASI 75 graph on the right, efficacy appears to wane over the last 12 weeks, even though these subjects had continuous therapy

over the full 48 weeks, having been randomized to etanercept in both double-blind periods.

The slight spike in successes at 36 weeks, the time at which subjects were re-randomized for the final period of the trial, is also unexplained.

This is particularly evident in the PASI curve on the right.

The next few slides characterize the types of subjects that were studied in this trial to better inform the decision on the benefit-risk analysis, and whether the submitted information is adequate to decide what population, if any, is appropriate for etanercept treatment of pediatric psoriasis.

This slide depicts the distribution of PGA scores for subjects at baseline by treatment group. While the entry criteria specified a minimum PGA score of three, almost two-thirds of subjects fall into this category of PGA of 3, and only 3 percent of

subjects had the most severe PGA score of 5.

We compared the baseline PGA and PASI scores for subjects at baseline in order to look at the consistency of evaluation of disease severity between the two assays. This plot plots the baseline PASI score for each of the PGA score categories. I point your attention to the right of the slide, where subjects who are categorized at PGA 5 had a wide range of PASI baseline scores, from 13.2 to 51.6. Subjects with a PGA of 4 also had a wide range of PASI baseline scores, from 12 to 56.

Photographs of several subjects were included for review in this application. You've seen some of them already this morning. A comprehensive review was not possible, since photos were not submitted for all subjects, and complete sets of subject photos were not submitted for all timepoints for the subjects who had photos submitted.

Also, photographs are not intended

to replace the actual physical examination of study subjects. One subject of the six subjects with a PGA of five had photos submitted, and he is depicted in this slide. This subject had a wide distribution of psoriasis lesions, and the 12-week photo on the right appears to illustrate a good response to treatment, with PASI 75 success. His PGA at week 12 is 1.

40 of 66 subjects with a PGA of four had photos included for review. Roughly half of these were interpreted by my review as having mild disease. The next few slides illustrate two of these subjects, who were characterized at baseline with a PGA of 4 and a representative of this group.

Subject 1 has lesions on the abdomen, elbow, and leg, and PASI scoring demonstrated a large effect, from baseline at 22.8 to a week 12 PASI of 2.7. His PGA baseline was 5, and after the 12-week double-blind period, the PGA was 2. These

photos are the same subject's posterior view.

Subject 2 was scored with a PGA of 4, and the baseline PASI was 12.6, just over the baseline inclusion criteria. At week 12, the PASI was 0.3, and the PGA had improved from 4 to 1. This is the same subject in posterior view. His lesions are predominantly on the lower back and may not project well. But these photos illustrate the difficulty in categorizing disease severity, and may be informative if the Committee discussions include limitations on prescribing based on disease severity.

The baseline age distribution includes 135 subjects from ages 12 to 17, and 76 subjects from ages 4 to 11. 20 subjects under the age of eight were included in the study. Although the dosage of etanercept was weight-based up to the maximum 50mg dose, the population included in the study was heavier and larger than the general pediatric population.

The mean weight of the younger, age 4 to 11 cohort, 81 lb., is the average for an 11-1/2 year-old child. The mean weight for the adolescent cohort, 165 lb., exceeds the average weight of adults. The BMI numbers also show much larger than average children. For reference, the BMI for young adults is 22, and obesity is defined as a BMI of 30 or greater for adults. The mean weight of all subjects in the trial was 61kg, which was somewhat close to the hypothetical 70kg adult.

Moving on to a short discussion of safety issues, three levels of safety information deserve consideration for this application. The first is the adverse event seen in the trial itself; current warnings and precautions from what is known in existing product labeling, especially with respect to serious infection events, which prompted the addition of a box warning for etanercept in March of this year; and

finally, an evaluation of the post-marketing adverse events, including reports of malignancies in pediatric patients who use TNF blockers.

During the study, two subjects experienced three serious adverse infection events while on etanercept therapy. A 7-year-old presented with a fever of 105 degrees and vomiting, and her chest X-ray revealed a left basilar pneumonia with effusion. She was hospitalized, treated with intravenous antibiotics, and she was not bacteremic.

The nine-year-old presented with abdominal pain, vomiting, and diarrhea, and required hospitalization for IV rehydration.

In addition, two subjects with a prior history of chicken pox and documented immunity at baseline developed herpes zoster, or clinical shingles. One subject was treated and one was not. This incidence rate appears to be well above the baseline

background rate of zoster in children, as evidenced by the citation from the American Academy of Pediatrics Red Book on Infectious Disease.

This chart outlines common adverse events which occurred at greater than 3 percent from the two treatment arms in the placebo-control Period A. Of note are the incidence of infections from upper respiratory infections, influenza, and gastroenteritis.

An analysis of anti-infective use was conducted, and as might be expected from treatment with an immunosuppressant, antibiotic use is somewhat higher in the etanercept-treated subjects, both in the initial double-blind Period A and thereafter in the study.

A box warning was added to the labeling for etanercept in March, outlining concerns from cases of serious infections that led to hospitalization and death,

including sepsis and tuberculosis. The box warning supplements current label warnings and precautions, which include neurologic events, hematologic events, allergic reactions, heart failure, and autoimmunity. And as stated by the sponsor, approval of a medication guide is currently pending for etanercept.

An early communication about an Ongoing Safety Review was issued on June 4th of 2008. The Agency issues drug safety communications such as this to notify prescribers and share with the public information about an important emerging safety issue that has not been fully analyzed or confirmed.

Recently received adverse event reports are currently being reviewed regarding lymphoma and other malignancies with Enbrel and other TNF blockers in the treatment of JIA and other pediatric conditions. This data represents

approximately 30 cases of cancer in children and will be further discussed by the next two speakers, Dr. Siegel from DAARP, and Dr. Kwon on behalf of OSE.

In conclusion, there still may be informational needs regarding the safety and efficacy of etanercept to inform prescribers, patients, and their parents for this non-life-threatening pediatric condition.

The Committee is asked to comment on the adequacy of the safety and efficacy assessments for the pediatric age group, and how those informational needs should be addressed.

Thank you.

DR. SIEGEL: Morning. My name is Jeffrey Siegel. I'm a clinical team leader in the Division of Anesthesia, Analgesia, and Rheumatology Products.

In my presentation this morning, what I'll be doing is reviewing for you the safety of the approved TNF blocking agents,

with a focus particularly on concerns regarding malignancies.

Four TNF blockers are currently approved. The first ones approved were infliximab or Remicade, and etanercept. These were approved in 1998. Subsequently, adalimumab or Humira was approved in 1999, and most recently, certolizumab or Cimzia was approved for the indication of Crohn's disease this year.

TNF blockers are associated with clear benefits, but also clear risks. Infliximab, etanercept and adalimumab are approved for inflammatory arthritides, including rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, as well as for psoriasis. Infliximab, adalimumab, and certolizumab are also approved for Crohn's disease.

Studies of the three products that are approved for inflammatory arthritides have demonstrated high response rates in

patients not responsive to conventional disease-modifying drugs.

Each of these products, however, is associated with uncommon but serious adverse events. In general, our assessment has been that in the indicated patient population, the benefits of these products outweigh the potential risks.

Some of the TNF blockers are approved in children. Etanercept was approved in 1999 for use in children with Juvenile Idiopathic Arthritis, based on a study showing efficacy in patients refractory to conventional therapies. And etanercept is currently approved down to age two in Juvenile Idiopathic Arthritis.

Adalimumab was recently approved for children with JIA age four and older. Infliximab is approved for children with Crohn's disease ages six and older. And in general, the studies have indicated that the safety in children is similar to what's been

seen in adults.

I'm going to review for you briefly the clinical trials that were used for the pediatric approvals. In general, the important context to appreciate here is that extensive safety information was available in adults at the time of the pediatric approvals.

For etanercept for Juvenile Idiopathic Arthritis, the database consisted of 69 children treated in a randomized trial, ages 4 to 17. There was an initial three-month open-label lead-in, then a randomized withdrawal study for up to four months.

This was followed by an open-label extension study to collect additional safety information.

Infliximab was approved for pediatric Crohn's disease based on a clinical trial of 112 children ages 6 to 17. There was a one-year randomized open-label

comparison of two treatment regimens added to background immunosuppressive therapy.

For adalimumab for JIA, the clinical trial consisted of 117 children ages 4 to 17. There was an initial open-label lead-in period followed by a randomized withdrawal study, and subsequent open-label extension. Two-year data on these children were available at the time of approval.

A number of serious though uncommon adverse events are associated with the approved TNF blocking agents. These include serious infections, including tuberculosis, opportunistic infections such as histoplasmosis, listeriosis, coccidioidomycosis, and pneumocystis carinii pneumonia. In addition, more commonly than the opportunistic infections are the non-opportunistic infections. Other serious though uncommon adverse events with TNF blockers include demyelinating events, autoantibodies and autoimmune disease, and

malignancies.

And before I go on, let me just mention that the evidence for etanercept being associated with serious infections is not based on randomized trial evidence showing a higher rate, because in general, the rate has not been higher with drug than placebo in the context of clinical trials. The data supporting a risk of serious infection with etanercept has been based primarily on post-marketing adverse event data, suggesting something about the rate of these events.

So the mechanism underlying the serious adverse events differs depending on the different adverse event in question. Some of these serious adverse events are expected based on the mechanism of action; that is, the immunosuppressive properties. And this would include tuberculosis and serious infections. Others of the serious adverse events are unexpected. These would