gotten lots of signals from around the table that a bathroom break is in order, instead of waiting until 11:15.

But, right before we do that, those of you on the committee who have worked with me before know that I distinguish between points of clarification and discussion. What I would like to do now is just take a few minutes to see if there are any specific points of clarification that you would like to ask any presenters from the sponsor before we move on to the FDA presentation afterwards.

Then the discussion will begin after we finish everything. So, are there points of clarification that you would like to ask any presenter from the sponsor right now? You also will have another chance, but I just thought there might be something burning.

Yes, Lloyd? Or, Dr. King, I guess I should say. He helped train me so it is very easy for me to bounce back into the familiar role there.

DR. KING: Thank you. My point of clarification is, in reading the background, it seemed to be that the response to the fixed dose did not matter about the weight of the patient;

that is, you gave it and the response to the T-cells and all that was the same. Seeing the complications were in diabetics, and being diabetic, I wonder if the sponsor had looked at the role of diabetes, weight and response that they saw.

DR. VAISHNAW: We have not specifically addressed the issue of diabetes, weight and outcome. If you were interested in understanding the issue of diabetes and the potential issue of infections, we have some data to speak to that. Was that the--

DR. KING: One of the clinical observations is that diabetics are more predisposed to serious infections and other things. I just wondered if that was not something you could tease out because it may have something to do with diabetes and infections.

DR. VAISHNAW: In the database of over 1500 individuals exposed, the number of serious infections that would see were low. In the placebo-controlled studies, it was under 1 percent both in the alefacept and the placebo group.

So, whilst that is an important topic, there really weren't sufficient number of

infections to study within the diabetic subgroup to definitively determine a relationship or not.

DR. DRAKE: Other points?

Because we are little bit over, although I must say that Dr. Lebwohl did a great job in catching us up, what I would like to do is call for a ten-minute recess. We will reconvene in ten minutes. I hope we can make that goal. We will aim for it; all right? Thank you.

[Break.]

DR. DRAKE: I would like to invite the FDA to begin their presentations. I would really like the audience--would the audience please be seated or step outside the room.

I believe the first presentation by the FDA is Dr. Marzella. You are the gentleman leading off. Please proceed.

FDA Presentation

DR. MARZELLA: Madame Chairman, distinguished members of the advisory committee, ladies and gentlemen, good morning. In the next hour, we will consider the FDA perspective on the efficacy and safety of alefacept.

[Slide.]

The FDA presentation has two main

objectives. The first objective is to confirm the analysis and the interpretations of the key clinical data that you have already heard this morning from the sponsor. The second objective is to point out, and hopefully explain, areas where there are different points of view about the interpretation of the data.

These areas are primarily in things such as safety where the clinical data are too few or inconclusive to provide definitive answers. We will be asking the committee to discuss these issues and provide guidance.

[Slide.]

Biogen is seeking to market alefacept for the treatment of adults with chronic plaque psoriasis. As you have heard, the clinical trials evaluated patients with moderate to severe disease which was defined as involvement of greater than 10 percent body-surface area. Patients had previously received or were judged to be candidates for systemic therapy or phototherapy.

[Slide.]

You have heard this morning already about the significant impact that this disease has on a lot of Americans. It is seen in about 2 percent of

the U.S. population. There is a genetic component in the disease. Caucasians are affected primarily, other ethnic groups less commonly. There are two peaks of onset, one which is at around twenty years of age and one which is in later years, around sixty.

[Slide.]

Psoriasis in children tends to have a more severe disease expression. There is also a family history associated. Biogen has requested and received from the agency a deferral of the requirement to conduct pediatric studies. The agency will ask the committee to provide advice on the need and timing of pediatric studies of alefacept in children.

[Slide.]

As you have heard again this morning, psoriasis is a hyperproliferative disease. It is associated with significant morbidity particularly in the 30 percent or more patients who have moderate to severe disease. We have heard about the impact that this disease has on quality of life and it is well known that it is associated with an increased risk of suicide.

[Slide.]

Let's move on to the analysis of the clinical trials. In my presentation, we will go trial by trial to sort of highlight the key points. The clinical study of alefacept began with single-dose dose-escalation studies of IV and IM dosing in 110 healthy subjects and continued with multiple-dose dose-escalation studies in patients with psoriasis.

[Slide.]

The healthy volunteer study showed rapid maximal reduction in CD4 cells and CD8, primarily. They decreased up to 40 and 70 percent of baseline respectively. Time to recovery was generally hours to days but occasionally lasted several weeks. There was a suggestion of dose relationship of the effect on lymphocytes.

The effects of alefacept on lymphocytes will be discussed in more detail when we talk about the Phase 2 and Phase 3 studies. Let me mention another finding of the early studies which was a rise in neutrophil counts which rose to about sometimes as high as four times normal. This rise usually peaked at around 4 hours and it was not associated with changes in body temperature.

No other hematologic abnormalities were

seen. Consistent with this protein configuration, alefacept has a long elimination half-life, about 250 hours. The initial study showed that the IM route of administration was approximately 50 percent less bioavailable than the IV route.

[Slide.]

Let's move on to the main Phase 1 multiple-dose dose-escalation study which was done in patients with psoriasis. As you can see from the slide, the doses bracketed ranged from 0.005 to 0.075 milligrams per kilogram IV, and a regimen of intramuscular dosing was also tested. The treatment schedule consisted of once weekly administration for eight weeks.

The main safety observation from this Phase 1 study was the relationship between dose and reduction in lymphocyte counts. The number of subjects with low lymphocyte counts and the duration of low counts increased with dose. At the highest dose level, some subjects experienced prolonged decrease in CD4 and CD8 counts, up to 53 days and 117 days, respectively. Again, we will have more to say about these drops when we talk about the Phase 2 and Phase 3 data.

This was the first study to give

information on the time course of drops in lymphocyte counts. Various patterns of change were observed. An important general observation was that lymphocyte counts following an initial drop did not continue to decline as dosing continued.

The study also examined delayed type hypersensitivity to intradermal challenge with various antigens. Antigens were applied before the treatment and after the end of the treatment intradermally to non-lesional skin. A number of patients tested positive at baseline and negative post-treatment to specific antigens. In the example shown here, which is the most dramatic, for example for tetanus, there were eight shifts from positive to negative out of a total of nine patients who were positive at baseline and no patients shifted in the opposite direction.

[Slide.]

Let's discuss next the Phase 2 and Phase 3 studies.

[Slide.]

Let's consider first the general design issues. The studies were randomized, double-blinded and placebo-controlled. An important provision for maintaining the study blind was

Biogen's use of a laboratory physician who evaluated the laboratory data. The physician ordered placebo substitutions if T-cell counts were below specified thresholds for age and laboratory range.

Now, in brief, let me characterize what the three main Phase 2 and Phase 3 studies were. Study 708 was a Phase 2 dose-ranging study that used weigh-based IV dosing. 711 was a fixed-dose IV administration study that evaluated two courses of treatment. Finally, 712 was a dose-comparison study that used fixed-dose intramuscular administration.

For all these courses, the drug was administered once weekly for a total of twelve weeks.

[Slide.]

Let's discuss the primary efficacy outcomes. The primary outcome in Study 708 was a static PGA of mild or better. In Study 711 and 712, the main efficacy outcome was a 75 percent reduction in PASI score from baseline.

Now, the handling of patients who used disallowed therapies during study was as follows. In Study 708, any topical antipsoriatic drug was

allowed on specific areas of the body such as groin, scalp, palms and soles. Low potency topical corticosteroids were allowed on any skin lesion other than target lesion.

Systemic therapy and phototherapy, however, were not allowed. However, in the primary efficacy analysis, patients who used disallowed treatments were not considered treatment failures. On the other hand, in the Phase 3 studies, namely 711 and 712, patients who received systemic therapy or phototherapy were considered treatment failures for the primary efficacy analysis and for most secondary analysis.

It is important to note that the prespecified time to assess treatment outcome was two weeks after the end of treatment.

[Slide.]

There is a suggestion in a number of studies that patients continued to respond to the study treatment beyond the prespecified time point. This is a plausible suggestion given, as you have heard, the long half-life of the drug and also the long duration of its pharmacodynamic effect.

However, as we will discuss in detail, there are some caveats to take into consideration

in interpreting treatment responses in the follow-up period. For this reason, we think that this hypothesis about response needs further corroboration.

[Slide.]

Let's go, then, to recap, in the next slide, what 708 was, again a dose-ranging study. The dose groups were placebo, 0.025, 0.075 and 0.15 milligrams per kilogram IV. Certain concomitant antipsoriatic medications were allowed and dose--and this is an important provision of all of the trials from now on--was withheld if CD4 count was less than 300 in this particular study.

[Slide.]

The next slide indicates, as a sponsor has already shown, that 708 provided evidence of treatment effect. Based on the primary efficacy outcome, there was a 20 percent absolute increase in the proportion of responders.

The primary outcome did not provide sufficient information about the relative clinical activity of alefacept doses. However, secondary efficacy analysis such as PASI and pharmacodynamic analysis did allow further delineation of a dose response and, ultimately, this was the dose that

was selected for the Phase 3 study, intravenous study.

[Slide.]

Evidence of treatment effect can be seen starting at about 60 days after the beginning of treatment. This is the placebo plot. These plots are for the alefacept groups. This line indicates the time for assessment of endpoint which was two weeks after the end of the treatment period. So, again, there is a suggestion that both in the placebo group and in the alefacept arms, patients continued to respond. The issue is going to be to see--for instance, if one looks at the alefacept group, what is the contribution of placebo in addition to other issues that we will talk about in a moment.

[Slide.]

This figure is taken--a very elegant figure--from the sponsor's study report. What this shows is the response of lymphocyte counts in Study 708 to dosing. The bar here shows the duration of the dosing period. These are the various groups. As you can see, there is a nice dose response in terms of decrease in lymphocyte counts.

The pattern of drop is also informative.

It tends to be greatest within four weeks and, after that, it sort of stabilizes. Following the end of the treatment period, you will notice that, for the groups, there is a tendency for the counts to recover. However, by the last observation in the study, the counts have not returned to baseline.

[Slide.]

As Biogen indicated, obviously, these are mean data. To look at specific clinically meaningful effects in patients, we have to go to another type of analysis which essentially looks at the proportion of patients that fall under specific thresholds at any time during the treatment course.

In this particular case, we are looking at CD4 T-cell counts but the same phenomena can be seen with other T-lymphocyte subsets. Namely, what is occurring is that there is a definite dose response in the proportion of patients who, at any time, have decrease in CD4 cell counts below normal.

The other interesting thing is that the magnitude of the drop is also dose dependent. You will notice that, as we go from low dose to high dose, the proportion of patients falling below a

clinically significant threshold, potentially clinically significant threshold, of 200 also increases.

[Slide.]

The next slide also shows the correlation of this finding, namely that the laboratory assessing physician ordered substitution of blinded study drug with placebo whenever he observed abnormal CD4 counts. So what this slide shows also is a dose relationship in the proportion of patients who had to receive placebo substitutions because of a drop in CD4 counts. Again, the percentage is dose related and I will remind you, this is the dose that was tested further in the Phase 3 study.

A caveat here is that, for this analysis, only patients who completed treatment and received all twelve injections were used.

[Slide.]

There was some suggestion, in the previous study, that there might have been some shift in TDH testing. Again, to remind you, this was done using a commercial test kit and the antigens, about a dozen of them, were applied intradermally before treatment and then after the end of treatment.

Again, there is noise in this data but there is a suggestion that the alefacept groups had, perhaps, a higher number of shifts than placebo. This is not consistent for all antigens.

[Slide.]

If we go to the next group, we can see that, perhaps, there is a trend with Proteus but not with Trichophyton. So we think that this is suggestive data and one should be mindful of it particularly because it has a lot of plausibility due to the mechanism of action of the drug. We will be asking the committee to provide advice on this issue.

[Slide.]

So, in conclusion, then, 708 provided evidence of treatment effect. The sponsor used pharmacodynamic and secondary efficacy outcomes to identify a dose that appeared to have a suitable risk-benefit profile and, in particular, the high dose was not chosen because, as you saw, about 50 percent of patients had to have reductions for lymphocyte counts.

The onset of response tended to occur towards the latter part of the dosing period--it began after 60 days in this study and the median

time in response plus treatment, I didn't actually show the data but it was estimated to be around 70 days. I will show that in more detail in further studies and I also indicate how that was analyzed because you have heard different estimates and I want to try to reconcile them and explain how they were arrived at.

[Slide.]

The study also confirmed that alefacept induces dose-dependent reduction in total lymphocyte counts and lymphocyte subsets primarily CD4 and CD8. Lymphocyte counts did not return to pretreatment baseline by the time of the last hematology assessment which was twelve weeks post-treatment in all subjects.

There were also safety observations related to infections and malignancy but we will discuss those as the sponsor has done in the integrated safety analysis.

[Slide.]

Let's move on to Study 711 which was the Phase 3 intravenous dosing study.

[Slide.]

This study compared alefacept given IV as a 7.5 milligram fixed dose to placebo. The study

was also designed to evaluate two treatment courses of alefacept. A minimum interval of twelve weeks was specified between treatment courses to allow for recovery of lymphocyte counts before a second treatment course.

Note that in the first treatment course, Cohort 1 and Cohort 2 received alefacept so, for a lot of the analysis, these two cohorts are pooled and are referred to as the combined alefacept arm. The comparator group for that analysis will be Cohort 3 which received placebo in the first treatment course.

[Slide.]

The primary efficacy outcome was the proportion of patients again who experienced PASI 75 percent improvement. As you can see, after placebo adjustment, the proportion of responders is 10 percent. These are the confidence intervals of the difference. As you can see, they exclude zero. Using a criterion of PASI 50 percent improvement from baseline, the placebo-adjusted rate is 28 percent. These are the confidence intervals around that difference.

Using a criterion of PGA almost clear or clear, the absolute difference, after adjustment

for placebo, is 7 percent. So we are in basic agreement with the finding of the sponsors that there is evidence of a treatment effect--it is 10 percent--that the evidence of efficacy is corroborated by secondary efficacy outcomes. And we agree with the sponsor that all of these outcomes, and there are several others, in general, track very well with each other, perhaps not surprisingly because they essentially assess the very same manifestations of disease.

[Slide.]

Let's spend a little bit of time looking in detail at this slide which tries to examine the changes in median PASI score over time over two treatment courses. Let me, again, explain that there are two treatment courses here and that the sponsor defines a treatment course as an initial dosing interval which, as you see here, is twelve weeks followed by a follow-up period, which is another two weeks, followed by an interval which can be more than twelve weeks to allow for patients who were clear before--and, of course, did not qualify for redosing, as well as to allow for patients who had variable intervals of times during which their CD4 counts were too low for

retreatment.

The reason that this plot is truncated here is that that interval is nonlinear and it is variable.

Let's look at the various groups again. This is the placebo group, the brown line. This is the alefacept-placebo group and this is the alefacept-alefacept group. It is important to note that the median scores for all three groups were similar at the beginning of the first treatment course.

So, when one compares the combined alefacept group at the end of the treatment period at endpoint to the placebo group, one sees that the median score in the alefacept arm is lower than the placebo group. This is, of course, consistent with the primary efficacy outcome using a responder analysis.

It is informative to ask what happens after the second treatment course. First of all, one notices that, in the follow-up period, there is a tendency for the median PASI scores to rise in the treatment group. Following a second treatment course, you can see that there is a further decline in median PASI score.

There are two ways to look at the magnitude of the second treatment response. One can use as baseline the first treatment course, as the sponsor has done, and that results in a greater estimate of proportion of responders. If one looks as baseline the first treatment course, the magnitude of the second treatment course is lower.

In any case, I think it is reasonable to conclude that this plot shows that that two treatments are active, the two courses of treatment are active. A little bit inconsistent with this observation, however, is the fact that in the placebo arm, you can see that an initial placebo response following a course of alefacept, this group ultimately ends up where the other group ends up who received two courses of treatment.

Now, of course, for the purpose of this comparison, we are doing a landmark analysis and we are purposefully disregarding the area under the curve which shows that this group did, in fact, benefit. But I am pointing this fact to sort of point to some of the potential complications in comparing these effects.

Another comparison that is informative is to look at the alefacept-placebo group. One can

see that, over the course of about nine months, essentially all of the treatment response is lost and one goes back, then, to the placebo-placebo level. So, again, if you are now thinking back on what the sponsor talked about in terms of median responses of nine months, you sort of have to wonder about that interpretation.

The final point that I wanted to make is that, interestingly, there is a maintenance of response following the end of the treatment. The maintenance of response occurs in both the active and the placebo group. So the comparison of these two is not straightforward.

I have throw a lot of sort of analysis at you and, of course, I want to sort of make it clear that these are all post hoc analyses, but I think that it is informative to carefully look at these values and try to interpret the various effects of this treatment regimen.

[Slide.]

Let me go next quickly to the observed mean changes in patient-reported outcomes. I think that the FDA and the sponsor are in complete agreement on what the data show. Actually, as you saw in the meeting package, we--meaning I--misinterpreted

some of the values and we corrected that in the agenda. But there is no disagreement on the figures.

The only thing that I want to point out, as the sponsor did, I guess, is that there is some response in the placebo group and that if one looks at the absolute difference, it is in favor of alefacept. But the question is how meaningful this is.

[Slide.]

This is for the DLQI which was considered the primary score. Looking at another scale, the DQOLS, there is also, again, a response in placebo. Again, negative scores mean improvement. If you compare the difference between arms, there is a difference in favor of alefacept. But, again, the question is how clinically significant that magnitude is.

[Slide.]

Moving on to the next slide, we want to look at an estimate of the duration of a 75 percent reduction from baseline in PASI in those patients who achieved a response at the end of the treatment.

As you can see from this Kaplan-Meier

plot, a rough estimate of the median duration of treatment response is, perhaps, about 100 days or so in the alefacept arm and it is about--I think it is about 30 days in the placebo arm. Again, this is looking at--it is, admittedly, a somewhat conservative analysis looking at patients who achieve and maintain a 75 percent response.

[Slide.]

There was a question earlier about effects of weight on treatment response. This post hoc analysis did suggest that if you look at treatment responses in placebo and alefacept and you divide them weight quartiles that, if you look at the patients in the heavier weight quartiles, that the proportion of responders corrected for placebo is very low. We have a 4 percent, 5 percent and this contrasts with about 18 percent treatment effect adjusted for placebo in patients with lower body weight.

Then, if you look overall to try to increase the power, if you make a cut point which is roughly close to the median, and we used for this greater than 85 and less than 85, again, you can see that there is about a four-fold difference in response in favor of patients with lower body

weight.

Now, of course, it is not clear what this association is due to. There are multiple factors but it certainly raises the question of whether patients with greater body weight are being appropriately dosed.

[Slide.]

The next slide shows the relationship between efficacy and CD4. The sponsor also showed this correlation. I think that the main point that we would like to make here is that is, indeed, a correlation but that the correlation is very weak. This is taking total CD4 counts. The sponsor showed data focusing only on memory cells.

There are two ways of looking at these data. You can look at the--this data, let me explain what this shows. This is categorizing patients in terms of magnitude of response. Here we have patients that respond 75 percent or more, 50 to 75, less than 50 percent. The question that we ask, then, within each of these groups, what proportions of patients have low CD4 counts.

There are two ways of looking at the data. If you look this way, we just calculated the numbers. I don't happen to have them in front of

me, but another way, perhaps, intuitively to look at the data is to look at the proportion of patients who had 75 percent improvement who were below 300. There is 33 percent of these as opposed to 11 percent who were below 50.

So you have to look at these two numbers, 11 percent less than 300, 68 percent greater than 400. So there seems to be a correlation. If you look at nonresponders, more tend to be over on this side whereas if you look at patients who responded more, more tend to be on the opposite side.

However, if you look at--oh; thank you. My office director actually calculated these numbers so I have to give him credit. The percentages are 53 percent for 75 percent improvement, 36 percent and 31 percent. So there is a general correlation.

However, if one tries to estimate what proportion of the drop in CD4 accounts for the response, you can see that the correlation is very weak. So, by this estimate, and I have to acknowledge Dr. Chao's analysis for this, only 4 percent of the treatment effect can be accounted for by dropping CD4s. So it is a modest correlation at best.

[Slide.]

The next slide also is a busy slide but I think it is very informative. So I will try to spend a few minutes to try to go over that. This is essentially a correlate of the slide that you showed before except that, now, this one asks what happens to median CD4 counts over time in patients who receive two treatment courses.

There is a lot of, I think, informative points to be made here. One is that if one looks at the alefacept-alefacept that, following an initial alefacept treatment, there is a tendency for the counts to recover. But, by the time that you get a second treatment, you still haven't recovered to baseline and, in fact, these data suggest that you get a cumulative drop in counts.

You go from basically a median of 600 to 400. I want to emphasize that these are essentially median counts. These are not in the individual patients.

The other point to make is that--actually, this is a very important point to make. This particular study has the best controlled data on long-term safety of a single alefacept treatment because, as you will remember, this group got

alefacept only during this three-month treatment interval. Then they had a three-month follow up and then they went into a placebo phase where they got three months of placebo followed by another three months of placebo follow up.

So, the interesting point here to note is that nine months after the end of the treatment, the median CD4 counts are still low so there is substantial duration of time that it takes for CD4 counts to recover.

Of course the clinical significance of this is unknown but we would argue that, in view of the suggestion that these effects may be cumulative, that they are long-lasting, that caution and conservatism is called for interpreting the data.

[Slide.]

Let's look at the same analysis that we talked about earlier. This one now looks at drops below normal in individual patients. These are the proportions of patients that fall below specific thresholds. As you can see, at any time, there is a proportion of patients that drop below threshold.

[Slide.]

In comparing Course 1 and Course 2 as well

as comparing multiple treatment courses, the problem is that there is a potential enrichment in patients who are resistant to the potential toxic effects of the product. So these analyses are essentially potential underestimates of what the potential for cumulative toxicity would be for this product.

If you carefully noted the numbers in the treatment cycles that the sponsor showed, I think that there was a substantial drop, at least 50 percent or more, with each treatment cycle. So the conclusion that there is no cumulative safety risk of adverse events with cumulative cycles has to be tempered by the realization that there is a substantial drop in the number of patients with subsequent cycles.

[Slide.]

We agree with the sponsor's interpretation that most of the effects are seen in CD4 and CD8 counts, particularly in memory cells. However, we would like to point out, and I am not showing the data here, that if you look at individual patients, there are patients who also experience drops in naive cells. NK cells also do show a drop. It is not that dramatic. If you look at mean percent

changes at nadir, there are drops both in placebo and in the alefacept groups so there is a small differential, but it is reproducible and the counts return to normal.

So the point we are making here is that potentially there is a range of CD2-positive cells that can be affected by the drug. Again, the clinical consequences of that may be benign but are certainly unknown at this point.

[Slide.]

The next slide, again, shows the same issue which is important for clinical use of this product which is the proportion of patients that require placebo substitutions because of CD4 counts. Of course, the proportion is--the total numbers of patients is as you see here.

This is in the first course, second course, and this is in the drug course of this particular group.

[Slide.]

So, in conclusions for 711, the trial demonstrated convincingly that alefacept was superior to placebo. The placebo-adjusted response rate was 11 percent absolute. Alefacept was also active for a second treatment course and, depending

on where one pegs the baseline, the response was either 15 percent or 6 percent.

There was a suggestion that body weight was associated with a differential effect on response. There is insufficient data in subjects weighing less than 50 kilos. In the clinical trial, these patients were dosed at about one-third less but there is no enough experience to indicate whether there is sufficient rationale for making that recommendation for these patients. The patient-reported outcomes also showed trends in favor of alefacept.

[Slide.]

In terms of immunologic parameters, it is clear that alefacept lowers lymphocyte counts. CD4s and CD8s are affected most, NK cells to a lesser degree. Consideration should be given to the potential that lymphocyte reductions may be cumulative and the decrease in CD4 counts are only weakly associated with treatment response.

[Slide.]

Now, lymphocyte counts may not return to baseline for up to nine months treatment, certainly on average, and certainly they were identical in specific patients, individual patients. The

pharmacologic effect was potentially greater without appropriate monitoring because one rule that was strictly adhered to in the clinical trial is that weekly monitoring and that the dose was held if counts were less than 250.

[Slide.]

Let's move on to the intramuscular dosing study. This was this design.

[Slide.]

This was a study that compared two intramuscular doses of alefacept, 10 and 15 milligrams, weekly for twelve weeks to placebo. The stratification was by the two variables of PASI score and prior systemic therapy.

[Slide.]

These are the efficacy outcomes for the study. We agree completely with the sponsor's interpretation. The placebo-adjusted difference for the 15 milligram dose group is about 17 percent. The confidence intervals around that difference between the two groups excludes zero. Interestingly, as the sponsor indicated, the 10 milligram dose is also active. In fact, there is a suggestion--I shouldn't say there is a suggestion of a dose-dependent effect, but let me leave it

that it is intermediate.

The p-value that was calculated was about, I think, 0.04. The reason that it did not make it into significance was because of the multiplicity of comparisons, the prespecified p-value was 0.025. So there is a definite suggestion that this is also active. Again, if you use secondary outcomes, let's say 50 percent improvement or a PGA of almost clear to clear, that this is supported by the secondary efficacy outcomes.

[Slide.]

As in 711, there was a suggestion, at least in the 10 milligram dose group, that retreatment response was associated with weight. As you can see here, these are the proportion of responders in patients in the highest quartiles. This is the next highest above the mean and these are the two lowest. There is certainly a suggestion that patients, again, with higher body weights do not respond as well as patients with lower body weights.

This effect was not seen, however, in the 15 milligram dose which is what the sponsor is seeking for a label.

[Slide.]

This slide, again, shows the relationship between efficacy and CD4 counts. If anything, in this particular slide, the correlation is a little bit even weaker than in the previous study. I think roughly 2 percent of the response can be accounted for by CD4 counts. I don't think I will go into the details there.

[Slide.]

The time to treatment response is shown in this slide. Consistent with what was seen in earlier studies, the onset of response is fairly late in the treatment period. This was the time to endpoint. This is the period of dosing. As you can see, time to response, this is the placebo arm. These are the two active arms.

There is a difference between the two but, as you can see, separation occurs fairly late, around after Week 9 or so of the treatment period. Again, there is this suggestion that there are additional responders in the post-treatment period.

[Slide.]

The sponsor--I should have given Biogen credit for the previous plot as well as this plot--this shows the median duration of treatment response. As you can see, this is the placebo

curve--I cannot read this number from here. It is probably 43--right; it is 43. Actually, let me make sure that I don't misrepresent that. Anyway, it is roughly maybe around 30 or so. It is very hard to see the slides from here. For the active arms, it is around 60. I will stand corrected if I don't read this. Is that reasonable? Okay.

[Slide.]

Again, we entirely agree with the sponsor, with their analysis of the mean changes in patient reported outcomes. Again, the placebo group tended to respond as well as the active arm but the mean difference between groups favored alefacept. Again, the question that we would like to ask the committee is does this provide additional clinically meaningful information for the label, for a potential label.

[Slide.]

This analysis looks at the proportion of patients who have abnormal CD4 counts at any time during the treatment period. As you can see, the proportion of patients with abnormal counts and the thresholds that they reach are certainly higher in the active arms confirming previous results.

[Slide.]

The subjects with abnormal cell counts at the last visit is shown here. There is about 8 percent of patients at the last visit whenever that happened to occur have abnormal CD4 counts.

[Slide.]

So the efficacy conclusion for this study is that, compared to placebo, the 15 milligram group is superior and the placebo-adjusted response is 15 percent. The 10 milligram group has intermediate activity. Response for body weight is different in the 10 milligram dose group depending on which cohort you are in and the association between efficacy and reduction in CD4 counts is weak.

[Slide.]

For patients who responded at any time, the median time to response is certainly near the end of the 84-day dosing period, approximately 90 days for both alefacept and placebo groups. The median duration of response in this particular study was 40 days for placebo and 64 days for alefacept. Again, this is a 75 percent criterion.

[Slide.]

Alefacept, then, induced decreases in CD4 and CD8 cell counts. They persist until the end of

the study in some patients. I didn't show the data but there was a proportion of patients who developed alefacept antibodies, 4 percent, as the sponsor indicated.

Let's look at the summary of safety. Here we have, I think it is fair to say, some differences in interpretation with the sponsor. Before going into the integrated safety, I want to comment on the toxicology data. As my colleague, David Green, who made this slide, would like to point out, that similar toxicities were observed at the 1 and 20 milligrams per kilogram dose.

So, given the fact that no nontoxic doses were identified, we are not sure what the linearity is between the toxicity of 1 and 20. Potentially, there might be some saturation effect. So we have a word of caution about that.

Perhaps another fair caution is that if you look at the animal that, as Dr. Seigel pointed out, developed a lymphoma, the pharmacodynamic correlate of that was some drop in CD4 counts which was that dramatically different, if I remember. I shouldn't, perhaps, be so glib, but it was dramatically different from what one sees in humans.

[Slide.]

So I think the concept to emphasize here is that if one looks at pharmacodynamic effects in addition to dose toxicity, one, perhaps, would adjust downward the safety factor that one is dealing with in the toxicology data and apply that to the human.

Let's look at the issue of serious adverse events. The sponsor indicated that the incidence of serious adverse events was the same, 5 percent in both placebo and alefacept arms. But what the sponsor also pointed out was that there was a disproportionate amount of patients in the placebo arm who had serious adverse events which were called psoriasis.

We didn't have a chance to go back and analyze those closely, but it is a reasonable assumption to make that these are essentially--the disproportion is because this is essentially a manifestation of efficacy.

So another way, then, to consider the safety experience is, perhaps, to exclude patients that have serious adverse events due to psoriasis because one would expect a disproportion in the placebo patients. If one recalculates the data

this way, then the proportion is 3 percent in placebo and 5 percent in the alefacept arms.

The other point to make is that the sponsor indicated that the incidence--these are, admittedly, very low numbers but it is the best controlled experience that we have. It is in Course 1. So the intervals of exposures are comparable. We have a controlled experience.

I think that it is not reasonable to sort of discount both of these as being less than 1 percent. Again, the numbers are low but another way to look at this is that there is a signal, that the relative proportions are higher in the alefacept arm.

This is further supported when one goes and looks clinically at the description of the serious adverse events. The numbers are a little bit different. We excluded one patient from the placebo group because that patient had pancreatitis due to alcohol intoxication and he was classified as an infectious event. So, excluding that event, we have one patient who was a patient with chronic COPD who developed decreased O2 saturation, was admitted, was treated with oral antimicrobials and improved.

One would contrast that with patients who had peritonsillar abscess, serious cellulitis. For instance, the diabetes mellitus patients, we confirmed the sponsor's observation that this was in a patient with a preexisting risk factor, but this maybe makes it more likely that, perhaps, a signal might be seen in this population.

So the fact that the patient had several episodes of external otitis and that, in this particular instance, developed necrotizing facial cellulitis requiring debridement and intravenous antimicrobials is certainly, we would argue, a complicated situation.

There are examples, also, from the noncontrolled data. For instance, we would argue that the patient who developed cellulitis is not atypical in patients with psoriasis. But this particular patient developed septic shock and developed renal failure, respiratory failure. With good medical care, he did survive. But, again, we would argue that that is a complicated event.

There was another patient, again this one with diabetes mellitus, who had a very complicated course following repair of a rotator cuff. He had multiple abscesses, had to have multiple operating-room

debridement and wound up, finally, with having to be reoperated and having some residual loss of range of motion.

So, again, the numbers are few but we would argue that caution is called for in the interpretation of these numbers.

[Slide.]

Let's look at malignancies. Again, the sponsor sort of chose to interpret this as less than 1 percent. But, again, there is potentially--the numbers are few but there is a suggestion of a signal, we would argue, potentially. The interesting fact is that the skin cancer seen in the placebo group was a basal-cell carcinoma.

There were two basal cells in the alefacept arm and four squamous-cell carcinomas, and the percentages you have to have those. So, again, we would argue that clearly the observation period is short. There are questions about whether we are dealing with development of cancer, promotion of cancer, a clinical diagnosis of cancer, but we think that this cannot be ignored.

[Slide.]

Let's look at the incidence during treatment of anti-alefacept antibodies. We agree

with the sponsor's analysis. In the IV group, the incidence was less than 1 percent. The highest titer was 1 to 160. The proportion of patients, not surprisingly, who developed antibodies was 4 percent which is notable. The highest titer was 1 to 40 and there was no evidence--we agree with the sponsor that these titers resulted in adverse events or loss of efficacy.

[Slide.]

Let's look, then at the overall conclusions.

[Slide.]

Alefacept efficacy; the responders compared to placebo, by a criterion of PASI 75--75 percent in PASI from baseline, the placebo-adjusted response is 10 to 15 percent higher--it is 10 to 15 percent in the alefacept-treated groups. Using PASI 50, the response is 25 percent.

Now the median time to response is approximately 90 day both by the IV and IM route. Again, this may seem plausible given the lag time following the pharmacodynamic effects. Then the median duration of response is approximately 105 days or 64 days. As we have cautioned, the interpretation of this response is fraught with

dangers and it is something that needs to be confirmed with additional studies.

[Slide.]

With regard to reduced lymphocyte numbers, it is clear, as the sponsor has indicated, that phenotypes with higher levels of CD2 counts, with CD2 expression, are affected most. This means T-cells with memory phenotypes. But, again, we would point out that in individual patient-data listings, there were examples of patients who had also naive cells affected. This did not show in the mean counts.

NK cells were also affected to a minor extent. There is a suggestion that needs to be considered that the reduction may be cumulative with additional therapy cycles. Again, the comment that we would make, looking at cumulative cycles, is that, given the considerable dropoffs in numbers with subsequent cycles, it is very difficult to interpret that data.

Recovery to normal levels or to baseline is slow and/or incomplete in some patients. That data, again, beyond the second cycle is incomplete.

[Slide.]

We would like to focus the key issue of

what is the significance of the reduction in CD4 and CD8 cells in terms of clinical events. I think that the sheer magnitude of the drop, as I have shown in different studies in as much as 50 percent, suggests that the impact is likely, very likely, to go beyond psoriasis or immunity or any specific--recall to any specific antigen and it is likely to impact on immune defenses in general.

Again, this is an interpretation of the magnitude of the drops. We would argue, also, that there are some signals. There is some suggestion of decreased DTH responses. This is something that was also observed in the animal data. There is a high plausibility for this effect being seen, so the fact that we would, perhaps, admit to overinterpreting this. But it seems to us to be a signal.

There are trends in increased incidence of infections and malignancies that also cannot be disregarded. We acknowledge that the database is small to assess risk but, perhaps, this is the best-controlled way to certainly look at the incidence of infections.

[Slide.]

W also would like to caution that

reduction in CD4 counts may be potentially greater without strict monitoring. The sponsor should be complimented for their strict monitor and adherence to safety in the studies. The drug was withheld if CD4 counts were less than 250 and we would think that this would be the regimen that ought to be continued until this additional data that longer periods of observation are just as safe.

The other question is the issue of we don't know what happens to noncirculating T-cell pools. We are looking at, basically, a pool that is in the circulation. We know from animal data that lymphoid tissues are all affected. But, obviously, this is not easy to evaluate in humans.

[Slide.]

So we conclude with this slide indicating that there would appear to be need for long-term monitoring of immune function using clinical and laboratory assessment. More data are needed. Large-scale long-term studies are needed to assess the risk of infections in neoplasms and we are encouraged to see that the sponsor is giving strong consideration to how to design these studies.

We have a question for the committee about what is the appropriate timing of the safety and

efficacy studies in children.

DR. DRAKE: Thank you very much. Gosh; you know, this is just a ton of material and I want to compliment both the sponsor and the FDA for concise, thorough presentations. It is a tremendous amount of information to cover, as those of us who spent hours on our briefing books know.

I want to do just a second of housekeeping because the notion of this being a holiday weekend and people have already come up to me, would you believe this early in the morning, being concerned about missing flights because the flights are all booked full because of the holiday weekend.

So I want to make sure we get our work done on time. That is one reason I have been kind of tight with the time this morning, not to be punitive but to make sure I keep my committee intact until we get to the vote. So I think that is real important.

What I would like to do is we have a little bit of time before lunch, so, at this moment, I would like to allow some Q&A to occur. I would like some questions to be directed toward the FDA or the sponsor. Dr. Swerlick, I know you are a nonvoting member but you are here because of your

expertise, and so I want to absolutely encourage you to participate in the question and in the discussions. You just can't raise your hand when I get to that point. I am not sure why. That just has to do with the process of the FDA.

Questions from the Committee

DR. DRAKE: Questions for anyone from the committee? Seth? By the way, for those of you don't know, if you will just raise your hand and signal me, I make a little note of who has got their hands raised and I will call on you in the order that I spot you.

I have now seen Elizabeth and Seth.

DR. STEVENS: The question is for Dr. Marzella and it relates to your observations about possible differential benefit based on patient weight. Did you do analysis on risk for adverse events based on weight and did you see any difference between the heavier and the lighter patients in that regard?

DR. MARZELLA: We did look at that and we did not see a correlation. We looked, for instance, at effect of weight on CD4 counts and the correlation was not that strong. I wonder if the sponsor has any comments on that?

DR. VAISHNAW: I can clarify with just a few brief comments. We, in fact, did divide the Phase 3 patients both from the IV and IM into weight quartiles and examined the adverse-event rate by weight quartile and we saw no trend that was at variance between the various weight quartiles.

DR. STEVENS: Thank you.

DR. DRAKE: Elizabeth, and then Dr. Katz.

DR. ABEL: This was also in regard to the weight, Dr. Vaishnaw. If there is a dose-response curve in terms of effect on lymphocyte counts and the patients of low body weight would be more affected, do we have any data on decreased lymphocyte counts in the patients with low weight compared to high weight and why was this milligram per kilogram dosage schedule abandoned?

DR. VAISHNAW: Let me take the issue of lymphocyte changes in the lower weight segments. If I could have Slide 1051, please.

[Slide.]

This slide illustrates the CD4 memory cells which are the key targets which we defined in our presentation of the drug and the extent of change in the CD4 memory T-cells by the four weight

quartiles indicated. You can see that there are no significant changes between the four weight quartiles. I already made a comment as to the safety which parallels with this.

The second part of your question is important to us in terms of why did we transition from milligram per kilogram to fixed-dose regimens. Essentially, that relates to several factors. One is, in order to insure that in Phase 3 and beyond we could have an accurate calculation of dosing and so that people didn't have to kind of fiddle around with vials and calculate the dose that was required, it is a safety issue and we thought it would be preferable to have a fixed dose. It is more convenient and more accurate. That is the reason why we transition.

We had pharmacokinetic data in Phase 2 that demonstrated that body mass between lean individuals and heavier individuals was not a significant influence on the major pharmacokinetic parameters. So we took the 0.075 milligram per kilogram dose which was optimum risk-benefit in Phase 2 and converted that to the fixed-dose equivalents in Phase 3.

DR. DRAKE: Dr. Katz?

DR. KATZ: Dr. Vaishnaw, I just want to have two points of clarification. In the cohort that got the two--the drug-drug cohort, you said there was evidence then that they got further improvement. But in the second part of that drug-drug cohort, there was no continual placebo control; is that not correct? In other words, it was placebo-drug. There is no placebo-placebo so there is no control over that continued improvement with placebo. Is that correct?

DR. VAISHNAW: I need to, indeed, clarify that point. So, to do that, let me have the Phase 3 IV study design slide, just to begin with that to refresh myself.

[Slide.]

What you see here is, as you say, we were analyzing the response rates in Cohort 1 during Course 1 and comparing them to Course 2 coming to the conclusion that there was evidence of incremental efficacy. You are inquiring as to whether a formal placebo control comparison was conducted.

One of the things I want to point out whilst we are on this diagram is Cohort 2, who became placebo in the second course, had that

prolonged duration of benefit that was the carryover. So this tends to confound the comparisons versus placebo in the second course.

If we go to Slide 123, now--

[Slide.]

On the left, you see the outcomes for Cohorts 1 and 2 in terms of PASI response rates over time. These are data we have already discussed. At the bottom, you see the placebo group. In the second course, Cohorts 1 and 2 which represent the yellow line here were broken out into those that received alefacept again, and that is the yellow line there, and those that received placebo.

You can see that there is a substantial carryover effect because the proportions of patients who are responding at PASI 75 are clearly significant. So the placebo-controlled comparisons were carried out and I will go on to discuss them now. But there is significant underestimate because of this carryover effect and the persistent benefit in the population group.

Finally, if I could have Display 414 from the briefing document which is where these data were summarized for you.

[Slide.]

This is a complicated table but let's just focus on the second part here. So this is Study 711. It is IV study, Course 2 outcomes. Here is placebo response rate and here is the alefacept response rate. Two weeks after last dose, the response rate in the placebo group was 7 percent. Note that it is higher than the response rate in the first course of the placebo group. This is the late carryover effect.

When we compare the 7 percent response rate here in the placebo group for Cohort 2, in the second course, versus Cohort 1 who received drug, it is 23 percent in the alefacept group and the difference was highly statistically significant.

DR. KATZ: But that group that got drug-placebo weren't really--they were decreasing because they came off the drug in the first--so we are really not getting a true placebo response in the second course. So it is not a true comparison.

DR. VAISHNAW: It is not a true comparison and it tends to weight against alefacept so to speak because of this carryover effect of the alefacept effect from the first course into the second placebo course. It was a formal

prespecified placebo-controlled comparison, but the response rate in the second course, in the placebo group, is still influenced by the alefacept they were exposed to in the first course.

DR. DRAKE: Dr. Seigel, I think, has a comment on that question.

DR. SEIGEL: There is no question, I think as was pointed out, that the data indicate that patients who get the second course do better, which is to say compared to where they start the second course and, at the end of the second course, they are somewhat better.

If the question is whether there is a cumulative effect, they reach a better status on the second course then they did on the first course, aside from the carryover issues, there is another complicating factor here which is that there is some amount of dropout in between the two course. I think, in the controlled study, it may only have been 20 percent of patients, or something.

In larger and uncontrolled studies, the dropouts are for any of a variety of reasons. Some or nonresponses. Some are toxicities. Probably some are that they are still in response and not

interested in getting it again, whatever they are.

So you are not necessarily comparing the same patients when you look at the percent response. You are looking at percent responses of a somewhat smaller denominator on the second course. So we have had, for that reason as well, trouble making any definitive determination as to whether there is any evidence of cumulative benefit.

DR. KATZ: Thank you. One more question. May I?

DR. DRAKE: Yes; please.

DR. KATZ: On the diagram that you have on primary efficacy endpoint in Phase 3 based on prior therapy, the point also should be made that only 9 percent in the people who improved on previous treatment, which you are taking 100 percent of people who improved on previous treatment because that is in that group, in this study, only 9 percent over placebo improved with the drug.

So, in human terms, taking 100 percent of people who respond, the drug is only having 9 percent--unless I am missing something--9 percent improvement in those people. In people who had no change with previous systemic treatment, there is a

17 percent response over placebo. Is that correct?

DR. VAISHNAW: Right. We illustrated these data terms as one point but the treatment effect is consistent over placebo irrespective of the high response status to the other therapies. I think you have paraphrased the data with respect to this group that reported improving to previous agents.

The other data set that I would like to point out here is the differential between placebo response rates for those that reported no change or worsening on the previous therapies and the 20.2. So that is an approximate 17 percent differential to those that responded to alefacept.

So this is just a spectrum of analysis to see whether patients are likely to respond to alefacept based on their previous response status.

DR. KATZ: Thank you.

DR. DRAKE: You may have commented on this, but I have a quick question on that last slide. The previous therapies, were those all systemic or were those both topical and systemic.

DR. VAISHNAW: No; those were all the major systemic and--

DR. DRAKE: That's what I thought it was.

Okay; thank you.

DR. LEBWOHL: May I also comment that that is PASI 75 and it is at the primary endpoint two weeks after. So anyone who would have achieved PASI 75 six weeks after or twelve weeks after would not be counted there and also anyone who would have achieved PASI 50 wouldn't have been counted there.

DR. DRAKE: Dr. Morison.

DR. MORISON: I had a couple of questions. The first one, I guess I am getting back to this weight business because one of the things that strikes you with that data no matter which way you look at it is that the actual response rate in comparison to some other systemic therapies is really very low. You come away with the idea, what is the chance that people who are not responding, not reaching 75 or not reaching 50, are actually being underdosed.

Is that an issue you have thought about addressing?

DR. VAISHNAW: As Dr. Marzella summarized, in the Phase 3 IV study, there was a trend towards lower response rates as you went significantly above 100 kilograms. In the Phase 3 IM study, we didn't see the same type of variation. and those

are the data summarized here for the PASI 75 response rate two weeks after last day. So, again, this is the kind of primary efficacy-endpoint analysis.

You can see, in the upper weight segments, you don't see the tail-off in the response. So certainly IM is an option for patients who are in the higher weight category.

The other point that you made that I would like to address is the issue of efficacy. If we go to Slide 1059.

[Slide.]

On the left you see the stringent two weeks after last dose landmark analysis of the right, the overall response rate. What these overall response rates are informing is of, perhaps, very significant clinical efficacy with the majority of patients responding at the level of PASI 50. We provided several lines of evidence demonstrating the kind of quality-of-life benefit patients are attaining with PASI 50.

Certainly, in a population like this with this burden of disease with the types of other factors at play in terms of baseline severity, potentially previous response, poor response to

previous agents. We think these kinds of profiles are very significant and helpful.

Mark, do you want to comment on the clinical relevance of the--

DR. LEBWOHL: I hope that some of the photos that I showed you express the importance of PASI 50. The PASI score is one that is a high hurdle to climb if you ask for 75 percent improvement because if someone starts out with severe disease over a large body-surface area and has a dramatic reduction in the severity of disease, say from a 3 to 1 in all parameters but has the same area involved, you won't necessarily achieve a PASI 75 in that patient even though the quality-of-life benefit is dramatic.

DR. DRAKE: I would like to comment just quickly from a historical perspective. This committee has had, in March of 1988 and October of 1988, there were meetings that were just to discuss how to evaluate patients with psoriasis, and what was the utility of the PASI score and what was the physician's global assessment and how did those all weigh together.

I can just tell you that we had experts around the table who couldn't come to closure on

it. We decided the PASI score was certainly far from perfect. We decided the physician's global assessment was probably better. But we also acknowledged that it is almost impossible to put all patients with psoriasis into one bucket because they have different types of psoriasis, different locations, different everywhere.

So I would encourage the committee to think more globally and not get hung up on a specific number but more what your gestalt is because everyone around this table understands psoriasis. I don't know how to tell you how to think about it except that I wouldn't get too hung up on a number because the PASI number is not a great number. We just don't have a great substitute for it.

If anybody comes up with one, I am certain the FDA and all of us would be very interested in that. So, if that is of any help on this scoring business.

DR. VAISHNAW: Could I just also, just interject there, Dr. Drake.

DR. DRAKE: Yes.

DR. VAISHNAW: Dr. Krueger has also been studying the issue of what is efficacy and he has a

different approach, and perhaps, Dr. Krueger, do you want to discuss some of your findings with respect to efficacy at a more kind of skin--

DR. DRAKE: If it is efficacy related to this, Dr. Krueger, but not a whole new scheme for efficacy. When I was asking for additional comments on PASI, I don't mean to develop a new scheme right now.

DR. VAISHNAW: No, no, no. It is not with respect to--

DR. DRAKE: Okay; good. My Executive Officer will kill me if I get us off schedule that much.

DR. KRUEGER: I have generated some alternate analysis of patients treated with alefacept in a small study that I conducted.

DR. DRAKE: Excuse me. Dr. Krueger, would you mind identifying yourself and where you are from.

DR. KRUEGER: I am Dr. Jim Krueger. I am from the Rockefeller University. I am a dermatologist.

DR. DRAKE: I knew that. I was just checking. Actually, we need it for the record.

DR. KRUEGER: I want to say that I have,

under an investigator IND, conducted an independent study of the effects of alefacept and have used what I view as hard endpoints in a histological assessment of plaques to look at both the response and to look at T-cell effects of skin because T-cell are clearly differentiated home to different compartments and this gives us some direct idea of the disease-relevant T-cell population.

DR. DRAKE: Dr. Marzella, have you had a chance to review this information he is about to share with us?

DR. KRUEGER: He has not because my data are independent of the Biogen submission under an investigator IND.

DR. DRAKE: I would like an opinion. I don't know if we can discuss it at this time. I would like an opinion from the FDA because we really kind of have to have it on schedule.

DR. SEIGEL: An opinion as to procedure regarding the data?

DR. DRAKE: Yes; procedure.

DR. SEIGEL: We don't ban the presentation of new data. We would caution that no data look quite the same after we have analyzed them as they do when they first come to us. I don't mean to

cast aspersions. So that is something you want to bear in mind but it is certainly up to the chair to see whatever data you choose.

DR. DRAKE: Jim, because of time constraints, not that we would disregard your data, but please go ahead. Can you keep it brief.

DR. KRUEGER: I will actually limit it to this one slide.

DR. DRAKE: Oh; that is really brief.

[Slide.]

DR. KRUEGER: This is an assessment of what happens to epidermal hyperplasia in patients that either fail to respond or respond to alefacept based upon an endpoint where keratin 16 is either eliminated from lesions or continues to be expressed.

So, in the nonresponding patients here, we have very little change happening on the average in this epidermal hyperplasia. This is a group of eight responders out of thirteen in a study that I set up. They are unselected in that these are all sequential enrollees. What we have here is, over the thirteen weeks of treatment, sequential measures of thickness showing a progressive reduction.

What you can see here at the end is an endpoint that is not so terribly different from the thickness of normal skin. In each of these instances, keratin 16 is turned off. You can see, associated with this in the responding patients, are really dramatic reductions and progressive reductions in the number of T-cells that are infiltrating the epidermis whereas, in the nonresponding patients, the corollary data are that there are not progressive and much lower magnitude changes in T-cell in tissue.

So I think, based upon this objective endpoint, it says that this drug is capable of turning off hyperplasia. I have gene expression measures that say all inflammation that is associated and driven by T-cells is also turned off in skin lesions.

The problem with the PASI, I believe, is that it is a stochastic measure. I just need to say this, that a 75 percent improvement in the PASI doesn't translate to a 75 percent improvement in disease. In fact, it may be a 95 percent improvement in disease reflected by the PASI of 75.

DR. DRAKE: Thank you, Jim.

DR. SEIGEL: Just one additional

perspective. I think we certainly agree with the sponsor that PASI 75 is a relatively high bar. I would also agree that there is not a linear relationship between PASI and amount of clinical benefit. Also, any cut point is an insensitive measure of benefit. Some people probably had a 20 percent and would have, on placebo, had a 0 percent or something like that and there is potentially some benefit there.

Two things to speak to just to understand and counterbalance against that is that, by any standard, there is a "response rate" in the placebo arm. We wouldn't call that necessarily a placebo response in the sense that it may not have been induced by placebo. It may simply be regression to the mean. People tend to enroll in studies and see their doctors when they are doing poorly because of the cyclic nature--not cyclic nature, but variable nature over time of the disease, when people enroll in studies at times when they are doing poorly, they are often likely to get better on the placebo arm.

Some of that was observed here. So when one looks at the placebo rates, as we did, when one looks at the different cutoffs, one needs to also

look at the placebo rates. So, when you look at the PASI 50, I guess as was pointed out, the response rates go up on both placebo and nonplacebo. They go up differentially. So, instead of seeing a 10 or 15 percent difference, you see I think it was a 23 and 28 percent difference between groups, something larger but still, again, in the 25 percent range.

The other thing I would note is another way of looking at this, because of the problem with cut point, are the data on the median score of patients or mean or other aggregate data which Dr. Marzella presented, and just to summarize briefly in one or two sentences, the placebo patients on the first cycle of the study went from a median score of 15 to 12 at their primary endpoint and went from 15 to 8 on treatment.

So their status was 8. The treated patients were at 8 whereas the nontreated patients on median was at 12. Again, there is not necessarily a linearity in terms of what the implications of disease are. So one-third lower PASI may or may not mean being one-third or two-thirds as ill. Those comparisons are judgmental and hard to come by.

DR. VAISNAW: We do have some data that addresses that if there is inflation in the placebo rate and the alefacept rate, how can we differentiate between the extent of benefit in alefacept versus placebo. When we examine the number of times patients hit the endpoint in the placebo group, they hit it many fewer times than those in the placebo groups

Although the rates of proportion responding are as we have discussed, the responses you see with the alefacept group tend to be more sustained and so, therefore, of clinical relevance.

DR. DRAKE: Dr. Morison, you had a quick follow up?

DR. MORISON: Just a quick question for clarification, really. You gave huge doses to the nonhuman primates.

DR. VAISHNAW: Yes.

DR. MORISON: I presume that the conclusion you would draw is that these animals are much much much less sensitive than humans because, otherwise, they would be dead, wouldn't they?

DR. VAISHNAW: Did you say more or less sensitive.

DR. MORISON: Much less sensitive. In

other words, have you got any information on if you give the same sort of dose as you have given in humans, 10 to 15 milligrams, does that produce any change in the primate?

DR. VAISHNAW: The object of the nonhuman primate studies, as always, was to really push the test system, as they say in the jargon, that is to give as high a dose as possible for as long as possible to induce changes, to look at the potential range of events that can occur.

Under those circumstances, I think, as you are intimating, we would also urge some caution because you start seeing changes which may not be necessarily representative. So, for example, in the 20 milligram per kilogram dose group in the nonhuman primate, we saw over 80 percent reductions in lymphocytes which are far in excess of what we see in man at the therapeutic regimens requested.

The other point to note there is that, at those levels of reductions in the nonhuman primate, you lose that selectivity which we spoke about during that main presentation where, with the therapeutic regimen, you see an effect on memory not on naive. In these nonhuman primates with these reductions in excess of 80 percent, you are

hitting everything.

So you start getting into a setting where the toxicologic findings that may or may not occur always are relevant but you can't be sure that they are the result of the kind of mechanism that is operative in man.

We have got studies at lower doses. Those more closely resembling the clinical regimen are associated with T-cell reductions of a lower degree. In those settings, we did not see any significant changes of clinical note.

DR. DRAKE: I am going to ask Dr. Weiss--

DR. WEISS: I just was going to ask if Dr. Green who is at the FDA, who is a toxicologist who reviewed the animal data, if he would just make a comment regarding the data.

DR. GREEN (FDA): Thank you. I think that our interpretation of the an toxicology data is at variance with the sponsor and that although a very high dose of 20 milligram per kilogram was used in many of their studies, pharmacodynamically, in terms of immunological endpoints, there was, oftentimes no difference between 20 and 1 milligram per kilogram as Dr. Marzella pointed out.

I think that we would find that, for very

many of the important characteristics such as CD4 depressions, we would find a great similarity between the response of the cynomolgus monkeys and other studies including baboons and that which was seen clinically. So I think that some of the factors that have been suggesting that there is a very high difference in terms of safety factors will not translate out.

As was pointed out, there is no no-effect dose or no nontoxic dose that we know of. I would say there is probably a grade equivalence between the nonhuman-primate studies and the clinical situation.

DR. DRAKE: So the agency is at variance with the sponsor on this issue of dosing. And you are concerned--clarify just a bit more for me.

DR. GREEN (FDA): I think we are at variance in terms of the safety factors that were reported. Although there is a difference in the time that the animals were exposed, they gave a factor of, as I recall, about 600. In other documents, they have said there is about a 200 safety factor. But that is based on a dose, 20 milligram per kilogram, which is functionally equivalent to a much lower dose, and the 1

milligram per kilogram is approximately, even by the sponsor's statements, about thirteen-fold different than the clinic which puts it exactly in the ball park.

DR. DRAKE: Right. Good. Thank you very much.

I have a whole list of questions. You guys are getting into this. This is great. Dr. Abel is next, then Dr. Tan and Dr. Swerlick, Dr. Taylor, Dr. Morison, Stevens, Epps and Katz. That is the order in which I seen your hands.

DR. ABEL: I have two questions. One is this drug seems to have--it does have a selective action on the memory T-cells. Point of information; do we know what the proportion is of memory T-cells to naive T-cells and could this somehow have to do with responders versus nonresponders, those people who have a lot of memory T-cells and the drug selectively inhibiting them? What are the ranges in normal subjects?

DR. VAISHNAW: There is a very wide range of CD4 and CD8 memory T-cell counts in normals. We have generated the largest pharmacodynamic database of this type of lymphocytes in humans to our knowledge.

[Slide.]

For example, here, you can see, at the top, for CD4 memory T-cells, the point I am making about this very wide range.

With response to the specific point that did baseline counts for these memory cells predict outcome. The answer to that is no. The most important predictor of outcome, looking at the memory cells that are targeted, was the extent of reduction seen on a percentage basis.

That goes back to that slide I showed in the core presentation where, for those that had the greatest reductions in the so-called fourth quartile, 40 percent of them achieved PASI 75.

DR. ABEL: Thank you. My second question has to do with therapies that were disallowed. In some of the Phase 1 I believe dose-ranging studies--or that they allowed. There were exceptions to the rule. They allowed them to use treatments, antipsoriatic treatments on the scalp, topicals, palms and soles.

Was this the same in the Phase 3 studies that they were allowed to use topical steroids or other antipsoriatic treatments to the palms, soles, groin area, scalp?

DR. VAISHNAW: I am happy to address that. The Phase 3 setup is described on this slide.

[Slide.]

These are the therapies that disqualified patients and classified them as treatment failures. So, if you took any of this range of agents from the top down, and they include the phototherapies and the major systemic agents. At the bottom, you see if patients indiscriminantly used moderate-potency topical corticosteroids, D analogues, et cetera, as in beyond the palms and soles and the scalps, then they were treatment failures from that point on.

So if we look at the data by taking into account all of these, then the primary efficacy data which we report and the agency reported are what you get. So you are looking at the effect of alefacept as a monotherapy.

So the entire efficacy dataset you see today is devoid of the use of these agents respective to all the endpoints.

DR. ABEL: But certain sites, they were allowed to use these topical agents in certain sites, and that does have an impact on the PASI. I think if I recall the scalp and the face are 6

percent of the total body-surface area, and each palm and sole is another 1, 2, 3, 4 percent if you are counting palms and soles. So was that taken into account and subtracted from the PASI response?

DR. VAISHNAW: Right. So let's deal with that with Slide 1211.

[Slide.]

In order to address the issue of how robust are the conclusion from the primary efficacy endpoints, we did what is termed a sensitivity analysis in the jargon. What you see here are the response rates under three sets of conditions; first PASI 75 responders irrespective of the disqualifying medications. We went through that list just now.

The response rates you see here are 4 versus 15 for placebo versus 7.5 and 7 versus 22 for the IM study. In the middle, you see what is termed the prespecified primary efficacy endpoint and those are the data we discussed in the main presentation and the data exactly as we spoke before, and the agency also commented on those.

Finally, at the bottom, we looked at the range of medications of the type you are suggesting. I think the agency was also interested

to explore this further. In their briefing document, they had two tables, Table 29 and Table 53, that brought up the issue of these medications that have been used.

Then, when we disqualified those patients from the analysis, again we found that the response rates were stable and very comparable to the primary efficacy analysis. So, by these analyses, we have concluded that the data are devoid of the use of the effect of the list of disqualifying medications that we had and also the medications pointed out by the--

DR. ABEL: I wasn't talking about patients who were disqualified because they were indiscriminantly using. I was talking about patients who were using in the allowed sites and how that affected the PASI.

DR. VAISHNAW: The last analysis just takes them out of the analysis. I can't specifically comment for those patients that were using it on the scale, to what extent it had any effect on their PASI.

DR. DRAKE: I think that is the answer. By the way, for the folks from the FDA, when the questions are asked the sponsor is answering, but

if you guys have an answer or a counter answer, please speak up.

DR. VAISHNAW: I think Dr. Lebwohl is indicating to me that he just wanted to make a point.

DR. DRAKE: But, before that, Dr. Bonvini had his hand up.

DR. BONVINI: I had a comment on your previous question pertaining to the selectivity of action. Again, we have no contention on the evidence that memory cells are substantially more affected than the T-cells in this context. That may be due because these are selectively targeted or perhaps because memory cells tend to die much more rapidly, more quickly, be more susceptible to an action by alefacept or some other agent who might target them.

There is evidence that memory cells may be prone to apoptosis. The fact is that we don't know what the exact mechanism of action is. This may be semantic to some extent, but it may not necessarily be in the terms of the selectivity of targeting in one case versus targeting of the whole population. As a matter of fact with higher doses in the animal studies, more than just memory cells were affected.

DR. DRAKE: Dr. Lebwohl.

DR. LEBWOHL: Just to address Dr. Abel's comment. It was first double-blind placebo-controlled so that the impact on PASI score would be seen both in the active treatment group and in the placebo group. At the investigator's meeting, many investigators were unhappy with the prospect that patients would be treated with twelve weeks of placebo and twelve weeks off therapy, almost six months, with no therapy at all on visible areas, scalp and hands.

So they bore down on the sponsor to add that possibility with weak topical steroids in those areas.

DR. DRAKE: I have just a quick request. I have to ask everybody in the room who has a cell phone to please turn it off. I am embarrassed to ask that because the very first cell phone that rang was mine. So I have now turned mine off. If I have to turn mine off, so do all you guys. I appreciate your cooperation on that issue.

Dr. Tan.

DR. TAN: The incidence of adverse events in the alefacept group is consistently higher. The incidence in the alefacept group is consistently

higher than those in the placebo group. I wonder if this trend is statistically significant where it is stabilized. Is there any statistical analysis about this adverse event--

DR. VAISHNAW: Right. So the issue did we power the studies or do we have a statistical insight into the rates of adverse events that we have seen. So, in keeping with the usual approach, the studies were powered for efficacy rather than safety.

DR. TAN: No; I understand that.

DR. VAISHNAW: To take the question of have we had a statistical approach to some of the rarer events, for I think my colleague, Dr. Vigliani, addressed that with just one of our sites. We have others of that type. But, for example, if you take the total malignancy rate, the rate expected is within the rate expected for this type of moderate to severe psoriasis population when you look at the rates reported in the literature. The means and confidence intervals are almost overlapping.

We have similar data for other types of rare adverse events. The other point, of course, is that in the alefacept group, there were far

greater numbers of patients. So the period observation of patient years observed is greater for alefacept in the placebo-controlled studies and so you are more likely to pick up rare events

DR. TAN: But in terms of it, you look at infection, you look at neoplasm, but they are all like relative instances, like at least doubled, more of these.

DR. DRAKE: Dr. Seigel?

DR. SEIGEL: Certainly, I think in the areas that we highlighted concern about, which were serious infections, and this is corrected; these are in the controlled trials and patients in both groups were followed approximately six months in the course, 0.9 versus 0.2 percent. For a malignancy, 1.1 versus 0.5 for the subset of skin malignancies, I think it also around 0.9 versus 0.2. None of those comparisons are statistically significant. We are talking about a handful of cases.

I think, as Dr. Marzella correctly said, they have raised concerns. They hardly stand as definitive evidence of treatment-associated adverse effect. But, if there are adverse effects at the levels suggested, at a half percent per half year

increase, or about a 1 percent year increase, if those do exist, then these trials--the controlled part of the data here are well under-powered to look at that.

DR. VAISHNAW: The other way we have addressed the issue given the low incidences of numbers in both the placebo and the alefacept group is to ask ourselves the questions are the rates increased over time with multiple course of exposure because one might expect to see a rise in the rates of serious infections if that is one of the points of debate.

We have consistently failed to see a lack of rise in the infection rate with multiple course of exposure. Under the issue of low numbers, these are other ways to look at it. The last point I would make on the topic is that naturally we, like the agency, are very diligently addressing the issue of what is the risk of infection in this population and does the agent predispose to that.

The central question there to ask has been that, given that this is an agent that targets T-cells, is there a pattern of events in terms of infections or malignancies that are representative of T-cell immunodeficiency. Most of us are very

familiar with the pattern of infections you would expect to see in T-cell immunodeficiency and we have failed to consistently see that and both we and the agency included in our briefing documents that we have not seen a relationship between alefacept treatment and the occurrence of opportunistic infections or atypical infections.

DR. TAN: Of the 2 million patients with psoriasis, how many of them would be as severe a psoriasis as you defined?

DR. VAISHNAW: Of the 2 million patients, how many would be classified as moderate to severe

DR. TAN: Yes.

DR. VAISHNAW: I am not an expert on this. Dr. Lebwohl will correct me, but I believe of the 2 million or so in the U.S., probably 20 percent are moderate to severe.

DR. LEBWOHL: The number from the survey of the Psoriasis Foundation was 7 million psoriasis patients and someone had a number of 30 percent. Certainly, there are a minimum of half a million and probably about a million severe psoriasis patients.

DR. DRAKE: Dr. Swerlick, finally.

DR. SWERLICK: Thank you. A comment about

some confusion in definitions. It is easy to get confused as returning to baseline as opposed to returning to normal.

DR. VAISHNAW: Yes.

DR. SWERLICK: In terms of looking at T-cell counts, I think we should try to be really explicit about sort of defining that. The reason I raise that has to do with the next series of questions I have. Do we really know if there is any difference between normal CD4 counts and normal memory-cell counts in psoriatics versus normal individuals or individuals with other inflammatory skin diseases?

DR. VAISHNAW: Shall I take that question?

DR. SWERLICK: Yes. Anybody.

DR. VAISHNAW: We are privileged to have the largest database on this topic so I guess I have to answer this. What we have found is that if we look at the entire cohort of alefacept-treated chronic plaque psoriasis patients at our disposal for analysis, there is a minor elevation in the CD4 and CD8 memory counts versus the healthy volunteer database that we have.

There are lots of caveats to that kind of comparison, clearly. It is not an order of

magnitude. It is maybe a 5 to 10 percent elevation. It reaches statistical significance but we do detect that. The issue hasn't been addressed in the literature as yet.

Dr. Krueger?

DR. KRUEGER: I would like to comment also because I think you raise a very important point, that return to normal and return to baseline may be different kinds of considerations. From study of psoriasis patients outside of this study, there have been two kinds of expansions of T-cells that have been found in the peripheral blood of psoriasis patients.

One is that there is a higher proportion of CD25-positive T-cells. Those are proliferative T-cells. One might conclude, therefore, that if those were reduced, there was some reduction, they are about 10 percent elevated over normal, that you could say that a 10 percent reduction might, in fact, bring these people back down to normal.

The second thing is there is an expansion of Type 1 T-cells, so psoriasis is a disease of immune deviation. Again, there is about a twofold elevation of Type 1 T-cells in psoriasis patients compared to normals.

So, in my view, if you take both of these sets out, you might, in fact, derive sort of a normal set for these patients that might have a reduced number from their baseline.

DR. VAISHNAW: Thank you, Dr. Krueger.

DR. BONVINI: Can I ask a question to Dr. Krueger?

DR. DRAKE: We are not done with you

DR. BONVINI: Sorry, Dr. Krueger. Your CD25-positive T-cells were affected to CD25 negative by alefacept? In other words, binding appears to be identical as far as I understood. I was wondering if actually the susceptibility to the two subsets is identical.

DR. KRUEGER: CD25-positive T-cells tend to be CD2 high. Therefore, they are affected selectively by this drug, if that answers the question

DR. BONVINI: Can you repeat that?

DR. KRUEGER: I said CD25-positive T-cells, the activated T-cell group which tends to be memory T-cells, have high levels of expression of CD2 and therefore they are selectively reduced by alefacept

DR. BONVINI: Comparing CD25, the high

level of expression of CD25 and the low level of expression in memory cells.

DR. KRUEGER: Yes. In fact, in peripheral blood, there are about 20 percent of circulating T-cells that are CD25-positive. The other 80 percent of CD25-negative.

DR. VAISHNAW: Just to finish that point, I think neither Dr. Marzella nor myself included these data. This was addressed in one of the earlier Biogen studies, the issue of CD25-positive cells. Indeed, the findings that Dr. Krueger is reporting from his study were corroborated by the findings in ours that, as expected, CD25 are preferentially targeted.

DR. DRAKE: Dr. Swerlick?

DR. SWERLICK: Is there any data looking at conventional therapies such as methotrexate or even systemic corticosteroids and their effect on lymphocyte CD4 counts? Are they equivalent to what is seen? Are they larger? Are they smaller? Is it known?

DR. VAISHNAW: I am not familiar with the investigations of methotrexate and its effects on CD4 T-cells in psoriasis. Again, I appeal to someone from one of our consultants because they

are dermatologists. They might be familiar. As I think Dr. Krueger mentioned, there was an investigation of methotrexate and its effect on memory T-cells, I believe.

DR. KRUEGER: I have to say, for the most part, these are not points that were taken up in the prior studies of older drugs simply because, at that time, we weren't thinking about T-cells in this disease. Subsequent studies haven't really looked at that.

DR. SWERLICK: One last question, and that is getting back to the studies with DTH, again, we are studying patients undergoing this therapy. Do we know what we are comparing it to? For example, if you put a series of DTH reactions on normals, what is the reproducibility? How many of those individuals change from negative to positive or positive to negative?

DR. VAISHNAW: To address that, I would like to bring Slide 1110 up, please.

[Slide.]

These are, I think, the data that Dr. Marzella was drawing your attention to during part of his presentation. So this is the DTH response converting from positive to negative in the Phase 2

IV study.

At the bottom, I point out an important caveat and this begins to address the issue you have raised. Less than 30 percent of patients were reactive at baseline. So this is one of the caveats when you are interpreting the data. The next point is the issue of how many people just convert from positive to negative without the influence of alefacept. Do we have any insight?

The response to that is yes. If we look at the placebo group here, you can see significant conversion rates to negativity. These are patients, of course, that didn't receive placebo. So I would argue that yes, you are raising some important caveats. The performance of these tests is difficult. Their clinical implications are not well understood.

Whilst, as Dr. Marzella said, and we acknowledge there are some trends for one or two of these, the fact that so many patients are not reactive at baseline, the fact that many normals convert to negative and the fact that for many of these antigens that are on this table, the antibody response is much more dominant than the T-cell response for protection.

We would have our own set of caveats for interpretation of these data but these are precisely the data that Dr. Marzella showed.

Slide 1111, if we could go to that.

[Slide.]

This is the same type of analysis. This is a less-conservative analysis that we also did just to see how things spun out because, for the last analysis, if you converted from positive to positive and then negative, because there were two time points at which they were reevaluated, if you were positive on one and negative on the other one, you were counted as a negative.

Here, this is an analysis of the data where, if you were positive at baseline and you were positive in one of the two post-treatment visits, you were counted as positive and you start seeing loss of the trend.

So we acknowledge what Dr. Marzella is saying, but we have had interpretation difficulties with this assay.

DR. DRAKE: Dr. Morison had a comment on this.

DR. MORISON: I would comment, anybody who has used this particular system, there is so much

noise in the system, I don't think the results mean anything. I am amazed you actually picked that as a means of looking. Looking at DNCB sensitization would have been much more attractive an approach than this.

DR. VAISHNAW: To that point, that is why I drew your attention, also, in fair balance, to the phi-X-174 study which is pioneered by Hans Ochs who is a leader in the investigation of immunodeficiency. Both Ochs' literature and many others have demonstrated that failure of response to phi-X-174 is clearly correlated with immunodeficiency.

DR. SEIGEL: I had a question about that, though. It looked like, from your slide, that the primary immunization to phi-X-174 was given at the time of the onset of treatment, not at the time when the patient had become lymphopenic but prior to where the lymphopenic effects of the drug had kicked in.

DR. VAISHNAW: I would be happy to address that, Dr. Seigel. Can we have the slide from the main presentation because this does require a clarification for Dr. Seigel.

[Slide.]

This slide was corrected within the last 48 hours just to try and make it simpler. This is in error so you are quite right to point that out. Let's go and clarify for the audience the actual data.

If would could have the CD4 and CD8 changes and their relative timing to the point of immunization, please.

[Slide.]

Here we have the conversion. So you can see, in orange, is the reduction in CD4 memory T-cell count. In blue, you see the naive T-cells which are relatively constant. You can see here is the primary challenge. It is back in the middle of the period of exposure to the drug. And here is the rechallange.

So this study which was designed in conjunction with the agency, was a kind of maximal test of the hypothesis that if you push the T-cell experience, will these patients mount antibody responses. Our conclusions were yes.

DR. DRAKE: Dr. Swerlick, are you done?

DR. SWERLICK: Yes.

DR. DRAKE: Dr. Taylor

DR. TAYLOR: I had two points I wanted to

make. One of them has already been taken care of and that has to do with the PASI score. I think it has been adequately pointed out that PASI 75 is a very, very high bar to reach and probably doesn't reflect how much clearing that occurs in patients with a PASI 75 response.

The other point had to do with dosing by weight. It seems to me that the company seems to be resistant to dose by weight but yet there has been some evidence here that dosing by weight may have been better in some respects. For example, some of the heavier people were underdosed and some of the lighter people had to have their dose withheld because their CD4 counts dropped too low.

So is it too late to dose by weight?

DR. VAISHNAW: Just to go to that issue. We found an evidence, just as Dr. Marzella pointed out, of diminishing response at the higher weight ranges in the IV study but not in the IM. So the IM route provides an option for patients across all weight ranges.

Now, in the 10 milligram group in the IM study, yes; there was also a slight loss of response at the higher weight brackets, but the 50 milligram--you know, our conclusion of the data has

been that we don't conclusively show that kind of trend.

So there is a validated dose option and route for the full spectrum of patients. With respect to the IV, we acknowledge the point that has been brought up by the agency and we look forward to working with them whether we need to do further studies to determine the optimum approach in the heavier patients via the IV route.

DR. SEIGEL: I would just like to comment that the lack of a dose response observed in the 15 milligram IM population was based on the heaviest quartile--well, not exactly quartile, but the heaviest subpopulation you saw there had a 22 percent response. That was six responders out of 27 patients. A confidence interval around that range could include that that true response range was well under 10 percent, not 22 percent.

So we do not know that there isn't a dose response on the 15, or a weight-related response on the 15. It may well be we simply don't know.

I would also add that in terms of is it too late, I am not sure that the agency would be comfortable recommending a higher dose than tested in heavier people because there are suggestions

that it may work better, but not all toxicities or efficacies vary with weight. But what certainly wouldn't be too late to do would be to look at whether the tested dose versus a somewhat higher dose, for example, in heavier people--whether a higher dose had a better efficacy-safety profile if we were interested in that. So, further study could be done.

DR. DRAKE: I think, Lloyd, you had a comment on this?

DR. KING: Just a follow up. Body weight can reflect large people who are not obese if you are thinking football players, et cetera. It also can reflect adult-onset diabetes. That is often used as the marker. Since people with diabetes are less likely to respond well to treatments for psoriasis and are likely to have increased susceptibility to infections, it seems to me that there is a surrogate marker that you may want to look at rather than just say big people.

To distinguish this body weight over 100 kilograms predisposes to IV decreased responsiveness, I suggest that the sponsor consider using serum hemoglobin A1C as a surrogate marker for decreased responsiveness to treatment and

predisposition potential to infections.

DR. DRAKE: Thank you, Lloyd.

DR. VAISHNAW: Thank you for your comment.

DR. KING: Then I have a second comment.

DR. DRAKE: I have already taken you out of order. Go ahead and finish it up.

DR. KING: According to where you are, similar observations that all politics are local, a general assumption is that immune reaction and psoriasis are ultimately localized to the affected skin. In essence, the alefacept is targeting the entire population T-cells to deplete the terrorist T-cells that are going to target the psoriatic skin. Surrogate markers, other than just measuring just cell population, being the ultimate product would be quite helpful.

It seems to me that, since the sponsor has already done a preliminary study, studying psoriatic arthritis using serum C-reactive protein as a marker for inflammation, it would seem appropriate to use that signature for psoriasis not affecting the joints.

So C-reactive protein would be a great marker for that since it is also a marker for things like atherosclerosis and inflammation in

general.

DR. DRAKE: I am going to move to Dr. Epps in just a minute but I saw Dr. Wilkins in here earlier. This PASI thing keeps coming up. Is he still in here? There he is. John, do you have anything to add? Dr. Wilkins was kind of the FDA honcho on those October meetings on the PASI. I thought you might have something to add to what has been said.

DR. WILKINS: No. This is a CBER meeting.

DR. DRAKE: I know it is a CBER meeting. I read all these transcripts last night. I thought I had it in my head but I thought, well, I will just double-check with you, Dr. Wilkins to see if we have missed anything. All right.

Now that we have digressed. Dr. Epps. I am going to ask you because you haven't had a question yet and then I want to go to the people who have second rounds of questions.

DR. EPPS: I just have a couple of quick questions, hopefully. The drug we are referring to right now is the human fusion protein. Without revealing secrets, what does that mean?

DR. VAISHNAW: No secrets. The extracellular domain of LF3--

DR. EPPS: No; I mean is it pooled products? Is it recombinant?

DR. VAISHNAW: Oh; it is recombinant. It is a recombinant fusion protein produced by a mammalian cell line.

DR. EPPS: Okay; great. Is there any idea what the etiology to the transient neutrophilia might be?

DR. VAISHNAW: Dr. Marzella pointed out some findings from some of those smaller, earlier studies. In the Phase 3 studies and Phase 2 studies where we have very large analyses of over 1300 individuals, we failed to confirm any evidence for alefacept changing neutrophil levels. So we don't know how to consider the significance of that.

DR. SEIGEL: So you had measured, like, 4 hour and 24 hour--I mean, that when it was seen in the first study. You measured that in the 1300 patients?

DR. VAISHNAW: Oh, right. No; that is a point of clarification. We didn't. Those were measured at weekly intervals. But if there had been a sustained effect on neutrophils, then I would say we would probably have detected it given

the approach to the studies and we failed to see that.

DR. EPPS: In regards to the delayed type hypersensitivity and tetanus and diphtheria, have any of those patients been retested or would they respond to a booster?

DR. VAISHNAW: The best way to answer that is to go back to that graph that was in error, but it would make the point for us to answer your question.

If we could have the phi-X.

[Slide.]

What we have here is that, at the index point here, when patients are in the middle of dosing, they had had challenge with phi-X-174. Then, six weeks later, they are being rechallenged. So it is the surrogate for a booster that we would do with a conventional immunization. You can see that there is a brisk rise which parallels the changes in the control group.

The other thing to point out is that the IgG content in both groups is identical which is reassuring regarding the integrity of the memory cells to help the B-cells despite the action of alefacept

What you are looking at here on the left is the percentage of patients that had IgG greater than 30 percent in their phi-X-174 response. You can see control and alefacept are identical. Then these patients went on to have further challenges in the follow-up period and that is the third and fourth. We didn't do that in the control group. When they had the third and fourth challenges, they did boost their responses further and the responses were in a logarithmic scale on the last.

The ultimate responses at the fourth challenge were exactly what is reported in the literature for this antigen for which there is a lot of existing information.

With respect to the booster with tetanus, we also identified that tetanus immunization in this same study was associated with a twofold rise in both control and alefacept groups as predefined in the study.

DR. EPPS: Lastly, according to your protocol, you had a four-week washout period for systemic immunosuppressants. Do you think that that may be too brief and, perhaps, the prolonged depression in the CD4 counts may be due to a confounding factor or some kind of a synergy there?

DR. VAISHNAW: That is an issue we analyzed by looking at patients that had or had not had systemic agents or UV prior to the onset of the immunotherapy with alefacept. You don't find any significant changes in the pharmacodynamic profile in those that are coming off those agents and then going on to alefacept versus those that are not coming off those agents.

For the same reasons that I think you are intimating, we also looked at the safety profile by that type of analysis and we found no difference if patients had previously been exposed to immunotherapies versus if they had.

DR. EPPS: So there may be suppression regardless of whether or not they had been on it.

DR. VAISHNAW: In other words, the changes that we are witnessing and discussing today are the effects of alefacept rather than a combination of effects from previous agents and alefacept.

DR. DRAKE: Dr. Marzella, you had a comment?

DR. MARZELLA: I wanted to follow up on the question of neutrophilia because potentially it is a signal that alefacept may be inducing some activation of inflammatory or chemotactic factors.

One reason that I think that it was striking how elevated it was in the Phase 1 studies.

The other point that is relevant, as has been pointed out, a lot of the patients in the studies have a great deal of cardiovascular risk factors. So there is a high proportion of cardiovascular events--well, I shouldn't say a high proportion, but I was struck looking at the listing, by how many patients had cardiovascular events.

So I think it is reasonable to ask whether there is some potential relationship and to look further into this issue of what is the potential significance of the neutrophilia.

I know that it is not associated with--I didn't notice any drops in platelet counts. There was no fever. But I think it is potentially something that might be followed up.

DR. VAISHNAW: I take your comments--

DR. DRAKE: Dr. Stevens.

DR. STEVENS: I have a number of questions. Just a follow-up to that last one. Do neutrophils express the appropriate FC receptor to bind this molecule?

DR. VAISHNAW: You know, I am not an

expert on that. The answer is yes. I am getting a nod from my scientific colleague here. I don't know about the expression levels and whether they can support the kind of mechanism that we are describing.

DR. SEIGEL: I was just going to interject. That also speaks to part of our concern about safety. I think we agree with the company that, in this experience, we haven't seen any signal of the types of opportunistic infections you would find with T-cell depletion. But the immune system is complex. CD2 exists on CD8 cells, CD4 cells. It exists on some B-cell precursors and some other cells in the immune system.

LFA exists on some of those cells. FC receptors exist on a broad variety of cells. All of those cells interact with each other and the cytokines that the CD4 cells make interact and activate all of those cells.

So there exists at least as theoretical possibilities that any aspect of immune--or inflammation can be influence. If the finding of a neutrophilia, somewhat transient, but highlights that, I think, as an issue.

DR. STEVENS: That brings me to another

one of my questions which is can you educate me on the role of CD2 in T-cell ontogeny. We are going to be asked to consider the use of this in children, perhaps young people. Can you tell us whether CD2 is important in the development of T-cell responses during young childhood and childhood, role in thymic development, et cetera?

DR. VAISHNAW: Now you really have me at a weakness. Either Dr. Krueger or--Jim, do you want to come up?

DR. STEVENS: I won't ask you to do math.

DR. KRUEGER: There aren't good human data on that but there have been knockout mice made with the CD2 deficiency. Those mice develop T-cells normally. The immune abnormality that exists, if you will, in these animals is that they appear to be about tenfold less susceptible to a given concentration of antigen, and that is we think CD2 dials up, or dials down, the threshold at which T-cells become antigen-activated.

So I think, from that, and I will admit that that is not completely reassuring data for humans since there may be some differences in development. But, to the first step, it says that there should be a developmental problem. What