DR. BIGBY: The reason behind that, though, is sort of stability and availability of the product. I mean, if they're only going to make it in the single dose -- you know, like a single injection 45 and 90, you're either going -- you're going to throw some away.

Hold on one second. Can you clarify sort of how it is packaged and presented and what's the stability?

DR. GUZZO: So the drug will be delivered in liquid in vial in -- 45mg liquid in vial or 90mg liquid in vial. Once the vial is open, the stability is only five hours, so there's no preservative in it so it would have to be used.

DR. RINGEL: I still don't necessarily see that as a problem. Metholicimab (?) people use portions of vials and throw them away if they need to. If a patient is seen by a physician, he okays the administration, writes that prescription, the patient gives himself the

dose, I don't see a problem.

DR. THIERS: But I think, again, sticking with the tempo, the tone of the discussion today, I think the only choices that we're really being asked to choose from are 45 or 90mg. I don't think there's any discussion of mg/kg dosing. Am I correct? I think what you're asking us to choose from is the two, either 45 or 45 and 90, but the mg/kg was not discussed.

DR. WALKER: No, there were two dosing regimens. One was the sponsor's original two-step dosing, but the third was the one that you heard from the FDA presenter who had three potential doses by weight.

DR. THIERS: Right, but we never talked about mg/kg based on the patient's exact weight. That's not on the table.

DR. WALKER: No, no, not continuous. We talk about two cut points, one cut point or two cut points, so two available doses or three. And patients would fit into one of those groups.

DR. DRAKE: How does this question allow us to answer which one of the three? It's sort of a --

DR. WALKER: It allows you to answer that you would either support having two available doses or three available doses based upon patient weight. It's what you do with that extra 6 or 7 percent, potentially, of --

DR. BIGBY: Dr. Levin?

DR. LEVIN: No.

DR. BIGBY: You've got to turn your microphone off.

So let me ask the sponsor, do you have a big objection to having an intermediate dose? And if so, why?

DR. GUZZO: The sponsor would support a two-dose regimen for the reasons that I outlined. First of all, we feel that the high-weight patients will benefit greatly from the 90mg dose. We would not support a three-dose regimen. We have not studied the 67.5mg dose. And in addition, the data that the

FDA showed even suggest -- and when we look in our data, even looking at a 90mg dose in that mid-weight population, we see no benefit. And even the data that the FDA suggested at week 28, where they said there was some benefit in our clinical trial -- I want to remind you, that's with the 90mg dose in the mid-weight patients. So we have not studied a 67.5mg dose.

We don't see the benefit of exposing that mid-weight group of patients to additional drug, and even when you look at the FDA modeling, the benefit in a model is only 5 to 6 percent, and it's not realized in the clinical population.

DR. CRAWFORD: Can I ask a follow-up to that? Thank you. Dr. Guzzo, I don't remember the speaker, but one of the sponsors, when it was discussed would there be an intermediate or mid-range dose had actually stated the sponsor didn't see the need for the complexity, and I didn't understand that response. Can you elaborate on that?

DR. GUZZO: Well, I think our main objection is giving the patient additional drug without additional benefit that we can see. Or, even in the model, not substantial benefit. Will it add additional complexity? Yes, it will, because now you have a third dose. And so people make mistakes if they have three doses to choose from.

Additionally, I think it will -- if longer down the road, we have, as Dr. Bigby pointed out, an auto-delivery device which is fixed dose, it adds additional complexity there. Finally, there are issues -- since that drug delivery at 67.5 is not available right now, we will have to use 90mg and waste a significant amount of drug.

DR. BIGBY: Hold on one second. If you want to speak, turn your light on. Everybody can talk, it's just -- so I don't know which order you came out at.

DR. STERN: So I guess I -- to me, going from two to three is not complex. And if

you believe there's a relationship between weight and needed dose, the idea that somehow something happens to you if I were to put on 20 pounds that isn't happening to me now relative to whether I weighed -- when I weighed 60kg in high school -- just doesn't make scientific sense.

So it's true that given how the product's going to be administered, kilogram per kilogram or some sliding scale makes no sense, but I don't see how you can argue that there should be a cut point, and somehow it only makes sense at 100kg.

You know, your studies that you say don't support the intermediate dose are so woefully underpowered that we can't say anything about them, but either weight matters or weight doesn't matter. And if it matters, it may not be linear, it may be some complex function. But the idea that that function for your drug will happen to have the critical period between 70 and 100kgs

strikes me as extraordinarily unlikely.

DR. KATZ: You're concerned about overdosing people. On the other hand, despite the small numbers, we haven't talked about somebody who is 50kg who's 100 percent of them are responding. So clearly in clinical practice, if you have 100 percent response with any of these drugs, you give less drug. Now, you're starting them off with more drug. You're treating a person who's 110 pounds with the same dose that you'd give somebody 190 pounds -- 110 pounds, 190 pounds. Clearly you've shown that the people over 100 kilos don't respond as well to the lower dose, so maybe for all we know, 50kg would get half the dose.

So even though it's questionable on that 70 to 100 kilo -- and I would agree with you on that, of the 6 percent, for all we know, there's a 20 percent difference down here.

DR. GUZZO: Yes. I'm sure there is a range of dosing, but I think the clinical

data -- with the clinical data that we have, I think we've demonstrated that between 90 and 45, we don't see a narrow therapeutic index. Fixed dose biologics are well-recognized. You would see the same range of dosing with the three biologics that are on the market and are fixed dose. But again, I do think that for this mid-weight, even in the model that the FDA proposes, we don't think that the benefit is significant enough to necessitate having a third dose for them.

DR. BIGBY: Tor?

DR. SHWAYDER: Several comments. With due respect to the gentleman who was talking about self-administration while playing soccer, I have plenty of patients who say if a little works, twice as much works twice as well, and you know if they have self-administration in the home, your psoriasis flares before you go on a date, you're going to give yourself two shots. That's just going to happen.

Now, I saw your data on monkeys

with IV, and I think -- I can't remember the other dosing, 45mg/kg, I think it was. Is there any data in human -- if you give two doses instead of one for someone who doesn't need it, was there any toxicity from it?

DR. GUZZO: So in the Phase 3 studies, we gave -- in the first Phase 2 study, we gave four doses of 90 and the safety profile was similar. In our MS studies, we administered significantly more drugs, so that the concentration was approximately -- the exposure was approximately 30 times what it was in our psoriasis studies. And the AE profile was similar across the placebo groups and the active treatment groups, and we saw no dose response. So we do have significant multiples of data.

DR. SHWAYDER: Did you present that this morning? Was I asleep or something?

DR. GUZZO: No, I did not present the MS data. But again, I can show you that.

DR. SHWAYDER: The other comment I have is, when it comes out, us pediatric

dermatologists are going to use it, and we'll just figure out ourselves what the mg/kg dose is by hook and by crook, and it will probably be done outside the area where there are too many lawyers, like -- you know, in Europe or South Africa or something, but we're going to need to know that data. I was hoping it would come from Centocor and not by hook and by crook.

DR. BIGBY: This part of the program is to hear the discussion from the panel, and I think we should use the FDA and the sponsor to answer sort of the factual questions and not engage them in a discussion of pros and cons.

DR. CALLEGARI: Mr. Chairman, I just need to address the dose issue, because it was raised -- excuse me. Again, I'm Peter Callegari. It was raised that a patient might overdose themselves or dose themselves equivalently.

The proposed distribution for this product is direct delivery to the patient

with a single dose that's required, so the patient will not be able to overdose or change the interval, because that's the distribution model that exists.

DR. STRAHLMAN: With regard to this question, I wanted to go back to the slide that -- forgive me, I'll pronounce your name incorrectly probably, but Dr. Jadhav had mentioned earlier. I think the FDA has asked us for two choices -- the two doses or the three doses. I first just want to make just a slight comment to say that the FDA model is an outstanding piece of work, and validate what looks like a very linear direct relationship between weight and the dose, just speaking from the science.

In many medications, for adults, the window is very large. Many, many drugs are given at the same dose for someone who weighs 120 pounds and 180 pounds, so I think the question, in choosing between two doses and three doses, the slide that you showed,

shows the model and the elegance of three doses, and then on the left-hand side was the actual data itself, what was observed, understanding the limitations of size in the study, but in that midrange, you didn't see the difference that you saw in the top dose.

So I just put these thoughts before the committee in making that choice, because we have the practical issue of what was actually observed and we have a model that elegantly -- you know, if anything, validates the observation. And also, like I said, it's just really thrilling to see that piece of work.

So I guess I wanted to just say for purposes of the discussion of the committee, it almost feels like possibly a practical decision. We have two doses, they have been studied, we have some observational data. We have a model that shows that a third dose might be an approach. The question is, which one do we choose, and is there anything else

we might want to recommend either now or later to look into that, and not only for the intermediate dose, but to the questions that were posed earlier about very low-weight patients. And I think we can separate the issue of the choice that we have before us right now and what we may consider afterwards.

I hope that's helpful.

DR. BIGBY: I'd like to make a comment. I think that if you look at all of the data provided, I think we can all come to an agreement that there is a gradation in dose response such that if you had an infinite number -- not an infinite number -- but if you had more increments of being able to deliver the drug, you could match the dose more precisely to the patient's weight.

However, we have to live in the real world. You can't expect that the sponsor is going to make 10 different doses

so that we can do this. And I think the data that they did present, you don't mis-serve very many people in the middle by having just two doses, and it's not so clear to me that you make the lives of those people between 70 and 100 kilograms so much better by providing that middle dose that it is worth the increment in work and expense to product this third dose.

That's just my opinion about it.

Lynn?

DR. DRAKE: Very eloquently stated, Michael. I apologize, Mr. Chairman, I have to kind of jump to a question that's later because I think it's related. And that has to do with the sponsor's statement they'd like to just distribute directly to the patient. We haven't decided yet -- made recommendations with respect to self-administration. This is a first-in-class drug. I'm apprehensive, very apprehensive about just turning this loose with patients. I have the utmost respect for

patients. I think they're smart and they do a better job than we possibly can credit them for. But I would still like the physician involved in the dosing.

Now, if the physician is still involved in the dosing, then I think we can more accurately define who needs what dose. So to me, they're related. I don't know how you separate them, because direct distribution to a patient at home without a physician interval means I vote one way; on the other hand, it means if the doctor is making the decision based upon everything else they should be observing on this first-in-class drug, that's a different scenario. And I don't know how to answer that.

Maybe you could help me, Michael.

DR. BIGBY: So what way would you vote if the drug was going to the doctor, and what way would you vote if the drug were being directly sent to the patient?

DR. DRAKE: I knew you'd come back with that question.

I think in a real word, we have to be practical. On the other hand, I think Bob Katz has raised some very legitimate points. So I would like -- as with many things, I guess on a first-in-class drug, I would be way in favor of better dosing range available to the physician, and let the physician be making that decision until we have more data. This is a very small cohort. It's a very small amount of patients. It's a first-in-class drug.

I think it should not be self-administered with just two well-defined doses. I still think the physician has to be involved in the decision-making process. So I don't know if that answered your question.

If I had to vote, I'd say let's do the three-step and let's leave it in the hands of the physician until we have more data.

That's always an ominous sign when nobody responds.

DR. BIGBY: So this is an interesting thing to have to call into question. I think what they want is some consensus from the panel about which dosing paradigm people favor.

Go ahead.

DR. RINGEL: I'd like to ask the company -- if the panel votes for the three-tiered dosing, what is the manufacturer going to do with the packaging? Are you going to keep it the same and have people try to adjust it on their own, or are you going to come out with a third dose?

DR. GUZZO: I just want to clarify that the physician will decide on the dose, whether it's administered at home or whether it's administered in the physician's office. And as Dr. Callegari said, our plan with a two-dose regimen was to only deliver the drug to the patient, the exact amount of dose, so there

would be no decision on how the dose is given.

However, we only have a 90mg vial and a 45mg vial, so in order to develop a 67.5mg vial, it takes a long time to develop stability data on that.

So we would not have that available.

DR. DRAKE: Cynthia, as a follow-up question to that -- Mr. Chairman, may I ask her a follow-up question? You know, right now, as a physician, when I write things, I frequently rely upon the pharmacist to also make sure the dosing is correct. I mean, pharmacists are very good at their job.

If we're going to directly distribute this to the patient, again I go back to the issue this is a first-in-class. What if there's a mistake made? Because mistakes do happen. There's no checks and balances in this system. Even if the physician writes the prescription one way, if it's mailed directly to the patient, there's

no protective barrier there, or additional input to make sure it's the correct dose. So how would you address that issue? And I see Stephanie may have a comment on that.

DR. GUZZO: I'm going to have Dr. Callegari explain the distribution.

DR. CRAWFORD: The proposed distribution? But may I make a quick statement? I am a pharmacist, or at least the great state of North Carolina seems to still think so, but as you're talking about this, please tell us more about the sponsor's proposed distribution model. I'm not clear, Dr. Callegari, what you mean by direct delivery to the patient. That could be via a retail pharmacy, via mail order pharmacies, coming from some other source, or it could be office-based. It would all be direct to the patient, so please clarify what is proposed.

DR. KIMBALL: I'm just going to make a quick comment, as someone who uses drugs like this all the time, how I think in reality this

will pan out.

In general, those of us who use drugs like this do see patients every three months for lots of different reasons -- we want to make sure they're okay, that they're maintaining, that there's no safety issues. The issue about administering in the office is, I can't buy the drug ahead of time and give it to them at that visit, because I then potentially waste the drug if I make a change.

So what I think practically is optimal for the patients, they come in and see me -- I say this is great, let's continue your therapy. I'm writing the prescription -- I'll let Dr. Callegari go over how that actually then gets to the patient -- the patient then receives it at home and injects at home. It saves them an additional trip to the office, which is where I think the big gain is for the patient.

I don't think any of us are likely

to prescribe this without having a close relationship with our patients to make sure they're doing okay. I think we all do that on a regular basis, and so that's where I think the benefit for the patients really is.

DR. CALLEGARI: There is no intent to have this delivered to the physician's office and have the physician pay for it. This is a patient-based payment. There will be an SVP-like distribution, with the direct delivery to the patient based on the prescription written by the physician, the prescribing physician. Through the SVP Pharmacy, there will be -- there are checks and balances to make sure the appropriate dose is delivered to the patient, since there are really only two dose choices that are present.

DR. BIGBY: Does it come at room temperature?

DR. CALLEGARI: You know, I actually don't know the answer to that question, and I will defer to one of my colleagues to deliver

it.

DR. KIMBALL: Many of the drugs we use this way that get shipped to the patients do require refrigeration, and I will say the pharmacies are expert at getting it to them in an adequate kind of way. And I would say again, if a patient couldn't do the injections at home, you would then say, bring your drug in and we'll do it for you, or arrange a different alternative. So I think a lot of these patients -- initially especially -- will be very experienced in self-injection because many of them will have been on biologic therapy before.

I think having the option is important.

DR. BIGBY: Currently, is the drug shipped at room temperature or --

DR. CALLEGARI: It's shipped at room temperature. It's like etanercept and Humira and that sense.

DR. CRAWFORD: Please clarify -- it's still unclear. I'm a patient. I get a

prescription from Dr. Drake. What happens next? Please go through all the steps, please. Don't say direct delivery. Presuming it was approved.

DR. CALLEGARI: The patient would then need to contact a specialty pharmacy provider, and then the specialty pharmacy provider would verify the prescription is correct, verify with the physician, and then would be allowed to ship directly to the patient.

DR. BIGBY: Does it come in the preloaded syringe?

DR. CALLEGARI: This is liquid in a vial. It will come liquid in a vial. Forgive me, I misspoke, it is not room temperature, it is 2 to 8 degrees.

DR. BIGBY: And it comes in a breakable (inaudible) vial? Puncture?

DR. CALLEGARI: It's a puncture vial.

DR. JONES: It's a glass vial.

DR. BIGBY: Rubber stop?

DR. CALLEGARI: Yes, rubber stop.

DR. SHWAYDER: I have a question. How

easy is it for a layperson to tell whether the medicine is ready for injection as opposed to being cloudy? I mean, are you going to have little pictures in the inserts saying yes, no, maybe? And then what happens? They send it back and five weeks go by before they get another vial?

DR. CALLEGARI: There will be videos provided to the patient. There will be a potential for direct instruction into the patient's home via a nurse to help assist in the initial injection process. This is a model that's been used -- liquid in vial is a model that has been used with other biologics as well prior to auto-injectors, so it's not a reconstitution phenomenon, it's a liquid in vial, so it requires drawing it up into a syringe. So the earlier sub-cu injectable anti-TNF agents, that's the way they are delivered.

DR. JONES: Right. It's supplied as a sterile solution in a single-use Type-I glass

vial with a coated stopper. It does not contain preservatives. It's stored between 2 to 8 degrees Centigrade.

DR. BIGBY: Just a comment about the video. I have given out, when they had them, many, many isotrentinoin videos. I don't know a single patient that ever looked at the videos.

Other comments? I don't know -- I almost don't know how to proceed with this one. I think what we could do -- I mean, if the two choices are two doses or three doses, we can sort of get a sense of the panel on that one, and then we can go around and people can make their final comments with their name attached, no more anonymous comments.

So if the two choices are limited to two or three doses, how many would vote for two doses? And how many would vote for three doses? And abstentions?

DR. KATZ: Abstain. Should I give the

reason, or do you want that afterwards?

DR. BIGBY: No, go right ahead, but also give your name. Give your name.

DR. KATZ: This is Robert Katz. We're still ignoring chart 72, where patients 110 pounds, which is not that unusual, are being dosed with a drug that's been shown to be dose-relevant as the same dose as somebody who's 200 pounds, less than 100 kilos. So we're dosing somebody -- group of patients, 100 percent of which out of 13 patients have responded with a PASI 75, and for all we know, they responded with a PASI of 90, which is fabulous because the drug looks fabulous, but we may well be overdosing them. Then you have to tell the patient when they get the medication that 45 grams -- only give two-thirds of that. It's complicated enough without doing that.

So I don't know -- I can't vote on that.

DR. STERN: So Rob Stern. I voted for three. Once I heard about the dose delivery

system, the arguments about another vial went out the window. It seems to me it's fairly easy if people are given the intermediate dose to send them the 90mg and have clear instructions in the syringe that you have a mark when you're getting it for the intermediate dose and another mark for the full dose, and instructions, and that there will be some left in the vial. So I don't see the arguments about delay. And to me when you have something that's reasonably linear with weight in terms of its effectiveness, why not use it as optimally as you can?

I had almost been persuaded when I thought there were self-injectors, and that gets to be much more complicated in terms of development, but if you're doing it the old-fashioned way, we can use old-fashioned principles.

DR. MAJUMDER: I'm Mary Majumder. I voted for the two-step, even though I found it very difficult to make a decision, because I thought the argument was compelling. It just

seemed to me that practically, it would be simpler, and if a physician is deciding to take control of the process, then there's the opportunity for more gradations.

So then you're -- why just stop at three? But in terms of just practicality, two seem to have something to be said for it.

DR. BIGBY: I'm Michael Bigby. I voted for just two doses, for the very reason that I think even though you could optimize a group in between, it would be more sort of work to the sponsor than it's worth, and that I think what will happen in practice is that the dose adjustments will be made in consultation between the patient and the doctor.

DR. THIERS: Bruce Thiers. I voted for two, not with a lot of enthusiasm. I would certainly like to see a 67.5mg vial. I'm not sure -- if there was a comment that it would be an ordeal to do stability studies on, I'm not sure how long that would take, but given that

this is going to be a -- I'm sure a popular and high-priced drug, I think that the sponsor should show some initiative and do those studies. And similarly, as Bob Katz mentioned, for the skinny people on this planet, I think there should be some studies with less than 45mg dosing.

DR. LEVIN: Arthur Levin. I voted for two, and I second everything that Bruce said.

DR. CRAWFORD: Stephanie Crawford. I would recommend three, because I found the analysis of the FDA to be more compelling. In addition, if there were to be self-administration by the patient, I believe a mid-range dose would result in fewer errors in terms of self-administration dosing.

DR. DRAKE: Lynn Drake. I voted for three because I'd like to ditto -- it's interesting to me. I think Rob and Bruce said the same thing in many respects, except they voted differently. But I agree with both of them. One reason I would like the three -- as a

matter of fact, I'd probably like 23 -- the reason being is I think that side effects and drug reactions and what not are so dose-dependent. And if we have a 50kg person, if we have a skinny person, and we can give them less drug and get the same effect, I think we ought to go that way, because the higher dose, the more the side effects, the more the immunosuppression. And I'm falling back on, above all else, do no harm. I'd like to see this -- you know, I think the drug's very efficacious, but I really would like to see more control of the dosing.

I don't think we need to give any patient more drug than they need. It just increases all the bad side effects.

DR. HECKBERT: Susan Heckbert. I voted for the two doses. I voted that way because that's what's been studied, although I suspect that what the analysis the FDA has done is correct. But I'd like to see it studied before I would recommend it. And I also agree

with Dr. Katz and others who have indicated that the people with very low or on the low end of body weights should also be studied separately.

So I think more study is needed for the low-weight individuals as well as whether that intermediate dose is appropriate.

DR. RINGEL: Eileen Ringel. I voted for the two-tier system simply because that's what the drug company has studied and that's what they're willing to do. I don't think Rob's system will work, although I would love it if it did because of the evil insurance companies. They are not going to allow you to dispense the 90mg dose to people who weigh less than 100kg. They simply aren't. So I'm going to vote for the two-tiered system, but strongly encourage the drug company to look at the middle range.

DR. SHWAYDER: Tor Shwayder. I encourage the drug company to look at both the lower and the upper range, and ideally work out a mg/kg dosing for the less than 100 pounders. I always dose methotrexate so that I can still

see one or two plaques because then I know I'm not giving too much, because once they're clear, you could be giving 100 or 200 times the dose you're giving.

I also want to make sure that it's listed as suggested and not mandatory for many reasons, but the least of which is what Dr. Ringel just said, is that the insurance companies won't give you the 90mg because somebody wrote in a monograph someplace that you have to be over 100 kilos.

DR. BIGBY: There was a statement made during this discussion about side effects being related to the dose given, and I just want to give the sponsor a chance to respond to that.

DR. YEILDING: Thank you very much.

I think I had reviewed in my overview of safety that we have not observed any safety -- any dose-related safety issues either in our Phase 3 trials, in our Phase 2 trial, where we studied both lower and higher

doses or in our Phase 1 study where we studied IV administration as well as subcutaneous administration. So we have not observed any dose effects in terms of safety.

As Dr. Jones points out to me as well, we actually have studied -- in other indications, we've studied much higher doses, as high as 180mg weekly for four consecutive weeks, and then every four weeks for up to approximately six months -- 19 weeks, in our multiple sclerosis trial, where we observed no dose-related safety events.

DR. DRAKE: Since I'm the one that made that statement, I think that that answer was helpful, actually. I would have liked to have seen that data presented today because it would have given us a little bit of background, but as a general rule, you always want to -- in my mind, you want to treat with as minimal a dose as you can treat and get the efficacy you want.

Because remember, the duration is

steady, which is the next question, or one of the other questions. We only have 18 months really of knowledgeable data. I mean, I'm not anti this drug. It's very interesting. I find myself in a conundrum here. But I feel like I don't have enough information. We're being asked very hard questions with maybe too little information. And that's the point I was trying to make, Michael, is that I think we need a little more information.

DR. BIGBY: I think we'll move on to question four. Has the applicant provided sufficient information to inform patients, physicians, regarding when and how to stop treatment with ustekinumab?

DR. THIERS: Nobody knows how to pronounce it. Including me.

DR. BIGBY: Open for discussion.

DR. STRAHLMAN: I just had a clarification question, because FDA has of course asked the committee to give some suggestions on this. But just to be clear, has

the company done what FDA has asked with regard to safety, and the requirements that you outlined? Because that is a different question. So I didn't want to leave the impression that something was left undone that hadn't at least been asked about.

DR. WALKER: I think that's actually a very interesting question, and I'll answer it this way. These therapies have been developed over a long period of time through various meetings with FDA, through various protocols, and what we're looking for is as we evolve and look at these biologic products, I think we all have to understand what would be the very best way to label these for patients and physicians.

So based upon the question we've asked, what we're interested in is hearing from the committee as to whether they would feel that the information exists to inform patients and physicians about this question. And that's really the basis for our question today.

DR. KATZ: Are we discussing question four?

DR. BIGBY: Absolutely, we are.

DR. KATZ: This is, as we alluded to before, basically how and when to stop treatment and lower dosages -- as you mentioned and I mentioned before that, it's implicit in everything we do with every drug we do, whether you prescribe a drug for acne or for topical treatment for psoriasis or methotrexate or Enbrel or whatever.

So you can't give instructions ahead of time as to inform patients when and how to stop treatment -- stop treatment when you're 80 percent better or 60 percent better. The doctor is going to see the patient; they're going to get sufficiently better. They're going to have only one or two patches left, which you like to know you're not overdosing, so you're not getting them 100 percent better. They're 100 percent better, you're going to lower the dose and

you're going to increase the interval.

So I don't think this can be stated. I think that's not going to be the company's responsibility. It will be the physician's responsibility.

DR. STERN: I think that the design of these studies were such that -- I know I'm a very simple person, but even interpreting what was best to do up to week 40 with the number of different crossovers and the size of the groups is very difficult to judge in a quantitative sense. So on the one hand, I echo Dr. Katz's position that it will take clinical practice.

For the company, I would say that this is about the information we have for the comparative agents, and to me, the real issue about when to stop treatment or how much to use is not so much an efficacy, because that's an individual experience issue -- and they have reasonably addressed the issue of do you get rapid flares with withdrawal -- but it comes down to when will

we have information about how long we can continue the drug in the individual patient for whom it continues to be effective?

So I guess I would say they've given us all we can expect on the efficacy side before approval. We'll learn from clinical experience with respect to continuing efficacy, but they haven't told us how long it's safe to use this drug by any stretch of my imagination.

DR. BIGBY: Other comments?

DR. CRAWFORD: Hi. Crawford. I'll make it quick. Just looking at how the question is asked, the sponsor presented data on some patient subjects who were discontinued from the trials for various reasons. Long-term data are not yet available. So the strict answer is, have they provided some information? Yes. Is it sufficient?

We don't know. So it's hard to answer this one.

DR. BIGBY: Let's put this to the

vote. Those who would vote yes in answer to this question, raise your hand. So there was one yes. Those who would vote no to this question, raise your hand. That's 10. And abstentions. That's none.

Tor, do you want to start us off with another recitation of names?

DR. SHWAYDER: Tor Shwayder. I voted no. I don't think the question was addressed really by the data.

DR. RINGEL: I voted no because --

DR. BIGBY: Name.

DR. RINGEL: I'm sorry. Ringel. I voted no because I don't think it was addressed, but I don't think it's possible to have been addressed. I'm sort of in a quandary, but I guess not. I'm not blaming anyone for it.

DR. HECKBERT: Susan Heckbert. I voted no, that they've not provided sufficient information, but I think we've heard from the dermatologists that they can operate without that information in the early going, although

they'll be happy to have more information as time goes on.

DR. DRAKE: Lynn Drake. I voted no. I think the reason that -- as the question was asked, the information has not been provided. On the other hand, how long to continue treatment usually comes out in the wash. You should begin treating it and using the drug.

DR. CRAWFORD: Stephanie Crawford. I voted no, for reasons previously stated.

DR. LEVIN: Arthur Levin. No.

DR. THIERS: Bruce Thiers. I voted no because I don't think we have this information for any drug that comes on the market. And as Bob Katz said, it's just by clinical experience that we learn how to do it.

DR. BIGBY: Michael Bigby. I voted no. So the issue for me here is when you stop the drug and the psoriasis gradually comes back, I think we have no data to know whether or not in those patients in whom it stopped and psoriasis got real bad, what

their response to therapy again would be.

So therefore, if it's not good and the drug is safe, should you stop it at all? So I think the answer is definitely no, and I'm not so sure that we're going to find that out by studies that the company does.

DR. MAJUMDER: Mary Majumder. No, for reasons previously stated.

DR. STERN: Rob Stern. No, for reasons I stated, and also for Michael's reasons.

DR. KATZ: Robert Katz. Yes, the company has provided as much information as they can. The rest will have to be determined clinically. And they also provided information as to what happens when you stop. There's a very, very gradual response, and so they've given us what we have to know and then the rest will -- as Lynn said, come out in the wash.

DR. BIGBY: We're going to move on to question five.

Discuss the critical safety

concerns with ustekinumab and the sufficiency of the database to characterize them. Have a sufficient number of subjects been studied?

DR. STERN: Cancer, infection, and with respect to sufficient number of patients at interval, are you kidding me?

DR. BIGBY: Other comments?

DR. KATZ: I think it's a little deceptive to talk about patient years. So it's not the sufficient number of patients, it's the length of time. So you could have lots of patients for one year, you're not going to be reassured about the long time, long-term occurrence of immunosuppression and so forth, lymphoma.

So it's length of time which is important, which will -- and so the number of patients, I would say it's okay -- the more the better, but sufficient length of time, we'll get with time. The drug is very effective, and we'll get into the registration issues afterwards, I assume,

following questions.

DR. BIGBY: I thank you. I left out that last line. Have subjects been followed for a sufficient length of time? So those are all part of this question five.

DR. SHWAYDER: This is the most worrisome question for me. Just in five minutes, and when I cross-reference on pubmed, IL-12 and angiogenesis, I came up with eight articles just in 2007. Use of IL-12 to treat cancer, IL-12 positive tumors, patients survive longer than IL-12 negative. IL-12 deficient promotes photo carcinogenicity in mice. IL-12 acts as a tumor suppressor in human B-cell malignancy. IL-12 was cytostatic when given as an antitumor. IL-12 and 23 promote inflammatory spots as the tumors. IL-12 at the angiogenic cytokines helpful in tumors.

So I don't know if we're opening a Pandora's box by blocking IL-12, and that's really the elephant in the room with this. They've had a couple dozen patients. They

have a little bit of data -- I was just looking at slides 117 through 120 and I just don't know that the N (?) is big enough to answer that question. And that's what I said we have 20 years when we have 20 years, but that's the question we need to answer for patient safety.

DR. THIERS: I think that's the whole -- the crux of the matter. I think it's going to turn out we're all convinced about the efficacy of the drug. Are we comfortable enough about the drug to let it go on the market and wait for X years to see what happens? Because we don't know how long you have to wait to see if this is a safe drug in terms of carcinogenicity. That's the issue. And I'm not sure there's a right or wrong or a yes or no answer to it, but that's what we have to come to grips with.

DR. DRAKE: I'd like a point of clarification from the FDA. I brought up the issue of promises made, results not

delivered -- through nobody's fault. I'm not blaming anybody -- if in fact the -- what I think -- the kindase grappling (?) I think -- we know the efficacy pretty good. And we have concerns about some other variables, even if this -- and Centocor, I apologize to the sponsor right now because you're being painted with a broad brush, which is totally unfair to you because you haven't been at this table -- particularly with this issue, I don't think. Why yes, they have. Excuse me. Beg your pardon. Yes. Can I take back my apology?

My question is, how can the FDA make sure that some of these questions that the advisory committee has posed that we feel we really need answers to, what's your enforcement authority? There's some new regulations out there where I think you can request absolutely that these studies be done. What are your remedies, so to speak, if the studies are not done? Can you give us an update on that?

DR. BEITZ: Let me just address that briefly. We do have under the FDA Amendments Act the ability to require studies post-approval. We're still evaluating the complexities of this new authority, so it's very hard for me to say today what we might do down the road. But the law does give us the ability to invoke civil penalties in the event that we find that a particular requirement was not fulfilled in the way that we had all thought, but I can't really give you any specifics today.

DR. STERN: Michael? And to Lynn's point, we should remember that at least as proposed by the sponsor, in contrast to the drug that the sponsor has a track record with, which is an infusion that takes three hours -- and we've heard from someone who's an investigator about how little progress they've been able to make in terms of an optional safety study -- we would have here a drug that you basically get through the mail and that is not under the same degree of supervision in a medical facility.

So one has to wonder about, if that's how well you do when you have the patients captive for three hours, how are you going to do when you have them captive for three minutes when they come in for their appointment?

DR. BIGBY: Hold on. Dr. Heckbert, you had a comment? No. Eileen?

DR. RINGEL: I'm going to use this opportunity to just discuss three things that have to do with safety that have been niggling at me and I want to just get them on the record.

The important issue is clearly malignancy, number one, and infection, number two, and that's fairly obvious to everyone. Let me just say three things.

When I looked at the data when it came from the company, there seemed to be a little blip in the incidence of influenza. You've got a lot of older people here that are on immunosuppressive agents. We have no idea if the influenza vaccine is going to

work. I noticed that they tested the pneumococcal vaccine. I'd really like to know if they tested the influenza vaccine, and people die of influenza.

That's number one.

Number two is they kept on talking about MI and stroke, but they didn't talk about acute coronary events and TIAs, and that's terribly important. I mean, people may not be listed as MI because they had treatment. They had thrombolytic therapy or whatever, and they never had the MI, but they still had an acute coronary event and they would have had they not been treated. That needs to be included.

And the third thing has to do with asthma. I believe there were three asthmatics in this study. That's not enough. We need to look at that. And I know those are small points, I just wanted to get them on the record, and there they are.

DR. KATZ: To bring up the point that

Dr. Heckbert brought up, what recourse and follow-up, wouldn't that involve a discussion of question number eight at the bottom of the page?

DR. BIGBY: Right.

DR. KATZ: So I would assume, Doctor, that the FDA does have some recourse on really getting the follow-up. We'd have to deal with that with question eight.

DR. BIGBY: I also had just one comment about the safety issue. I agree with what's been said about infection, malignancy. I mean, it is both theoretically, and based on animal and some human data unlikely that certainly infection won't be a problem.

In terms of cardiovascular risk, the sponsor slide number 124 doesn't actually exclude a risk difference of 1 percent for cardiovascular events, which means that you'd have one extra event for every 100 patients treated so that the existing data doesn't exclude a risk of 1 percent.

You were asking for an opportunity

to respond to -- yeah?

DR. KRUEGER: So without a slide, I just want to make the comment that the committee is concerned about the consequences about blocking IL-12 in humans. This particular antibody is very selective in that it blocks the p40 subunit, and therefore blocks IL-12 and 23. But I want the committee members to understand that all of the other drugs that are biologics and some of the non-biologics, including cyclosporine, are strong inhibitors of the p40 cytokines, and they effectively block the production of the p40 cytokines as well as having immune effects outside of this axis.

And therefore, the safety data that exists with cyclosporine and with the other biologics are actually relevant to your concerns about what happens in humans when IL-12 is blocked, because it has been blocked in thousands of patients who have been treated with not only biologics, but also cyclosporine.

DR. CALLEGARI: I really need to address clearly some misinformation in terms of our ability to fulfill regulatory commitments. I certainly cannot speak for other sponsors, but I want this committee to realize that we have met our post-marketing regulatory commitments.

This is a slide of post-marketing regulatory commitments. The first is TREAT. It is a 5,000 patient Crohn's disease registry, enrolled on time in the United States as part of a post-regulatory commitment that we had to the Agency. The second, the PSOLAR registry -- and I'll be glad to talk a bit more about that, but the PSOLAR registry, we also had first patient in on time. It is ongoing, and I can correct some misperceptions about that.

In addition, in agreement with the Agency, we've gone ahead and initiated a Pediatric Crohn's Disease Registry which we are currently enrolling. Just recently initiated, it's a 20-year registry.

So aside from that, we have also supported a number of other projects including CORRONA, the rheumatic disease registry form Fred Wolfe, as well as we've fulfilled a lymphoma-pooled analysis that the Agency had requested from us.

In addition, we are currently conducting a pregnancy research initiative, which again, we agreed to with the Agency and we are conducting it. So in terms of our ability to fulfill regulatory requirements, please don't paint industry with as broad a brush. Centocor has fulfilled their regulatory requirements as requested.

Next slide, please. The second thing I want to address is PSOLAR. A lot has been discussed about PSOLAR, and I need to remind you that PSOLAR represents only one aspect of the comprehensive risk management plan that we've proposed today.

The second thing I want to clarify is some of the dates around PSOLAR.

Infliximab was indeed approved in September 2006. However, the post-marketing commitment to launch PSOLAR started on July 1, 2007, with agreement with OSC -- the FDA and OSC. There are three phases of release in this registry. This was agreed upon by the steering committee.

The first phase, the initial phase, was -- as I had said earlier, the initial phase was for user acceptance testing of the CRFs, the Clinical Research Forms. The second phase is an expanded phase and the third phase will ultimately be full (?).

The first phase took about six months of user acceptance testing in 30 sites, and currently, there are 485 patients enrolled as of June 16th. What has happened is we are currently expanding the number of sites, and we are currently enrolling 40 patients a week from these sites. So the proposal is ultimately to expand the number of sites -- the limitations on expansion came

from clarifying the CRFs, and now, we fully intend to expand the sites.

In addition, for ustekinumab, we no longer have to go through any of the initiation start-up because we've already done that. We spent time developing and validating and testing the electronic data capture forms. Thank you.

DR. STERN: Michael, I would like to ask two questions. The first is, could you please tell me, in the history of epidemiology, any 450-center study that has been successful in robustly evaluating any endpoint? I'm not aware of that. Where I come from, we call 450 site studies seeding studies, not research studies.

And the second is, am I correct that you had within one year an 8 percent loss to follow-up in your Crohn's disease study already in the first year?

DR. CALLEGARI: That is true. No, no, not in the first year. Per year. But we've continued to enroll that study. We enrolled

over 6,000 patients in that study.

DR. STERN: Right. So where I come from, if you're losing 8 percent per year, your ability to detect substantial increases in the risk of important endpoints goes out the window after a couple of years. PSOLAR is only my experience.

DR. CALLEGARI: PSOLAR is not a seeding study. It is a clinical trial. No one is compensated for putting Remicade patients in the trial any more than they are compensated for putting non-Remicade patients in the trial. And it has -- it follows good clinical practice guidelines, there are design endpoints, there is an independent steering committee that exists within the trial proper. So that is not a correct characterization of that trial.

DR. STERN: So could you tell me about these epidemiologic studies that have had 450 centers that have contributed substantially to our understanding of the safety of a therapy and long-term use?

DR. CALLEGARI: Before I turn it over to my colleague, Dr. Berlin, I can tell you that our other registry commitments, as Dr. Siegel from the FDA had mentioned earlier, have indeed contributed to the Agency's ability to interpret signal that they've detected in their AERS dataset.

In addition, they have provided a number of new insights into the disease proper -- Crohn's disease, even rheumatoid arthritis, through various publications and presentations at national meetings.

I'm going to defer to my colleague, Dr. Berlin, to address your 450-site question.

DR. BERLIN: Thanks. I'm Jesse Berlin. I head the epidemiology group within Johnson & Johnson Pharmaceutical Research and Development. I'm not going to have those numbers off the tip of my nose, head, but there are some well-known very large epidemiologic studies. In fact, it's a Zodiac study that was

just completed in the CNS area. It's a Pfizer study comparing ziprasidone with olanzapine. And I think it's on the order of 400 or more centers. That was actually initial randomization, but became essentially an observational study after that.

With respect to your -- so I think if we looked, we could find examples of studies. There are some I know in the oral contraceptive literature as well where -- in the oral contraceptive literature, there are some very large studies that have looked at broad population-based enrollment on that same order of very, very large numbers of studies.

With respect to the loss of follow-up, no one's going to argue that 8 percent loss per year is not something that would concern us. I think there are two points in response to that. One is there may be 8 percent per year, but I'm assuming that there will be a core of people, and granted

with a loss of sample size, who will be retained throughout for long-term follow-up. So the 8 percent a year alone doesn't preclude the possibility of at least a core of patients being followed for longer-term.

The other point I'll say in response is that at least if you look in the anti-TNF data, somebody mentioned this morning that randomized trials, the controlled portions of the randomized trials have been able to demonstrate -- maybe I'm not supposed to be saying this -- we've seen a fairly clear increase in lymphoma risk, for example, over the 12- to 16-week follow-up period from the anti-TNF drugs. So I'm not completely convinced myself that multiple years of follow-up, although valuable, are going to be necessary to detect all signals.

DR. JONES: Dr. Bigby, can we address Dr. Ringel's question?

DR. BIGBY: Sure.

DR. YEILDING: Thank you very much.

In terms of asthma, I just wanted to point out that 8 percent of subjects in the clinical trial had asthma, so a total of approximately 160 subjects in the clinical trials had asthma. I just wanted to correct that. I think I had provided that information on my medical history slide, and we looked at adverse events of asthma. Adverse events of asthma are very low. No serious adverse events of asthma in the ustekinumab treated group.

The only serious adverse event that we observed was in a placebo-treated subject. No treatment discontinuations due to asthma, and patients responded appropriately to therapy. There was nothing unusual about their course, and we actually looked at that fairly carefully.

In terms of influenza, and you are correct, we pointed out in our briefing document that when -- if you could bring the slide up -- we pointed out in our briefing document that when we look at data through

the BLA cutoff, so that includes the controlled and the uncontrolled portions of the trials, we do see a different rate of influenza -- 2.7 compared to 7.

Now, if you look at the placebo control period only, we don't see a difference in rate of influenza, and we believe that the reason for the difference in the BLA cutoff is that very little of the trials after the placebo control period was conducted during flu season.

Only 13 percent of placebo follow-up occurred during flu season. So that -- in the T08 study, that's on average 4.1 weeks per patient; in the T09, that's 2.6 weeks on average. And that compares to the active treatment groups where we had 41 percent of follow-up.

Now, what we did -- you can go to the next slide -- what we did was to look at other viruses, because we wondered whether this could possibly represent a signal in

terms of viral infections. And if you look at other viral infections, looking at placebo in ustekinumab groups, controlled for follow-up, you can see that if we look at a variety of different viral infections, in general, we're not seeing a difference rates of viral infections.

DR. RINGEL: I'm just curious. Did you look at the response to influenza vaccine?

DR. YEILDING: We did not look at the response to influenza vaccine. We do know that we had a number of investigators that inquired about the use of influenza vaccine. We've encouraged investigators not to use the live attenuated version of the vaccine, but we know that a number of patients used the non-live injection, the flu vaccine. Obviously, we don't have data on its efficacy.

DR. BIGBY: Other comments?

DR. KATZ: Relative to the concern about long-term suppression by IL-12 that Dr. Shwayder brought up, Dr. Krueger, you're

hardly reassuring saying that the same thing occurs with cyclosporine. Who's using that long term? And this drug is so effective, it certainly is going to be used long-term and so it's not an analogous situation.

DR. BIGBY: So if no one objects, we can put this to a vote. So I won't read the opening sentence, but have a sufficient number of subjects been studied? Those who would like to vote yes to this, raise your hand. Zero. Those who would vote, no, raise your hand. I think that's everybody.

Are there any abstentions? One abstention. So since you are unique among us, you can start the discussion.

DR. CRAWFORD: Thank you, Mr. Chairman. The reason I abstained -- Crawford -- the reason I abstained is because I would have had to make a split vote, which is not a possibility in answering the question have a sufficient number of subjects been studied. The numbers that were

presented in the trials are well above the minimum guidelines that were referred to. On that side, yes. My split, however, is in terms of were all the trials adequately powered to date to find some safety events, and the answer is clearly no.

DR. BIGBY: Lynn? We'll go that way to the end.

DR. DRAKE: Lynn Drake. I voted no.

DR. HECKBERT: Susan Heckbert. I voted no. Certainly for malignancy, there's no way that this is a sufficient number.

DR. RINGEL: I voted no.

DR. SHWAYDER: Tor Shwayder. I voted no.

DR. BIGBY: Bob?

DR. KATZ: Robert Katz. No.

DR. STERN: Rob Stern. No.

DR. MAJUMDER: Mary Majumder. No.

DR. BIGBY: Michael Bigby. No.

DR. THIERS: Bruce Thiers. No, simply because I don't think there were enough patients

to identify rare side effects.

DR. LEVIN: Arthur Levin. No.

DR. BIGBY: We'll vote on the second part of this question. Have subjects been followed for a sufficient length of time? Those voting yes, please raise your hand. Those voting no, please raise your hand. And abstainers?

We'll start with you this time, Robert.

DR. KATZ: I feel ambivalent voting no on this because the drug is so effective that I could be convinced to vote yes on both these points temporarily if we considered question eight with a mandatory registry where we would get guaranteed long-term follow-up. So without that, since we haven't approached that yet, I'd have to vote no. But that could be changed if other things came to the fore.

DR. STERN: No. Rob Stern.

DR. MAJUMDER: Mary Majumder. No, because on this question what I'm hearing is a

consensus that for things like malignancy, you would need to follow patients for a longer period of time -- and with the understanding that question eight, which relates directly to approval and further studies, is a different question.

DR. BIGBY: I was admonished that I'm supposed to announce that the vote on this one was yes, 0, no, 11, abstentions, 0. I'm Michael Bigby, and I voted no simply because the number of years in the patient years are insufficient for things, especially like malignancy.

DR. THIERS: Bruce Thiers. I voted no because the answer is no, but it does not mean that the issue cannot be addressed by the sponsor, but the answer to the question as written is no.

DR. LEVIN: Arthur Levin. No.

DR. CRAWFORD: Stephanie Crawford. No.

DR. DRAKE: Lynn Drake. No. As a

caveat, the sponsor's slide that showed that the studies, the post-marketing surveillance have been enrolled, was very helpful. It would have been helpful if that had been in the main presentation along with any preliminary data they might have. And so they may have something to present in addition.

DR. HECKBERT: Susan Heckbert. No.

DR. RINGEL: Eileen Ringel. No. I'm just going to throw in a little caveat here. No in particular because the regulatory environment and public opinion have changed a lot since previous systemic and biologic agents were approved.

DR. SHWAYDER: Tor Shwayder. No. And I just want to comment. I wonder if the people who presented their personal stories were given that Faustian choice -- we can get rid of your psoriasis, but you have a fill in the blank percent of getting lymphoma five or ten years from now, which would you choose? And the answer, I'm sure for most of them, was get rid

of my psoriasis, I'll deal with the other one later, but that's when I get sued.

DR. BIGBY: We're going to take a break in a minute, but don't go yet. It was a little bit of confusion about the answer to question two, because some people changed their mind in between voting. This was about the alternative weight-based dosing paradigms. So we just need to get an accurate count about where we stand on this.

And the choices were two doses and three doses, and a few of you changed your minds in the middle.

Question three, right. So if the choice is two doses, how many would favor two doses? Just a show of hands. And how many favor three doses? And abstentions?

Okay, so are we all set?

We'll take a 15-minute break and reconvene at 3:45.

(Recess)

MS. WAPLES: Everybody please be

seated. We are about to begin.

DR. BIGBY: Would all the committee members return to the table? We're going to move on to question six.

Discuss the potential for malignancy demonstrated by this class of compounds, including the findings from animal studies that indicated an increased carcinogenetic risk with inhibitors of IL-12, IL-23. And the questions are, is it important to communicate these findings to prescribers? Are additional animal studies needed?

Comments from the committee?

DR. SHWAYDER: Let's see if I phrase myself correctly here. I think it's always better to put out all the data there is and let the prescriber have it in their hand. I think the problems in the past have been when the companies had data which they didn't publish and then it inevitably snuck out. I don't know if Vioxx is a good example, but something along

those lines, where the data was hidden. In that way, I could make those Faustian bargains with my patients, saying this is the data, we'll decide together whether we want to use it.

But to answer the question, yes. I think there's a carcinogenic risk, and the magnitude of it has to be determined in the future.

DR. KATZ: Yes, it's of great concern. The animal studies are various one-sided -- are very concerning, especially with a drug that's going to be used long-term. That doesn't mean it shouldn't be used. Is it important to communicate these findings to prescribers? Absolutely. Not only to prescribers, to patients, because we share a risk and it's an important-enough drug so you would have to tell the patient outright the risk.

DR. LEVIN: Thank you, Bob. I think anything you tell prescribers, you need to tell patients. There's no difference in that relationship. I mean, both sides need to know

all the facts.

DR. HECKBERT: I agree completely with these comments about informing patients and physicians of what we know about the risks. Regarding the question are additional animal studies needed, I think we've had several animal studies that suggest there is a risk. I'm not sure that doing more animal studies will add. What we need is more information in humans.

DR. BIGBY: Other comments? So I think --

DR. STERN: It's a three-part question. So maybe we can vote on it in three parts. Are we concerned about malignancy? If so, is it important to communicate these findings to prescribers? And the third, are additional animal studies needed? So I think it's sort of a three-part question.

DR. BIGBY: I agree.

DR. STERN: That's twice in 26 years.

DR. BIGBY: Even the first statement is not written as a question. I

can make it into a yes or no question. And that is, are the members of the committee concerned about the potential for the development of malignancy in patients treated with IL-12, IL-23? And those who are would vote yes. Please raise your hand. No? Abstentions? I'm going to get this one right. So in summary, there were 11 yes votes, 0 no votes, and 0 abstentions.

Tor, do you want to start?

DR. SHWAYDER: Tor Shwayder. I agree. There's a risk for a malignancy.

DR. RINGEL: I agree. The in vitro animal studies show there's a risk for malignancy. Ringel.

DR. HECKBERT: Susan Heckbert. Yes, there's a significant concern about malignancy.

DR. DRAKE: Yes, there's a concern for malignancy, but I'd like to caveat that. There's been a risk with many of these biologics with that issue, and in fact, it's going to take many years to figure out if it's a real risk or

if it's a hypothetical risk. What happens in mice does not necessarily happen in humans.

So I would be remiss if I didn't say, yes, there's a risk. If all things being equal, this alone would probably not hold up my opinion of the efficacy -- in making this available to patients, as long as everybody is fully informed and as long as there's ongoing studies to monitor --

DR. CRAWFORD: Yes, there's a concern for the malignancy based on our available data from the animal studies.

DR. LEVIN: Arthur Levin. Yes.

DR. THIERS: Bruce Thiers. Yes.

DR. BIGBY: I think that sort of based on known -- Michael Bigby, and I voted yes. I think based on known mechanism of action and the action of IL-12, there is sort of theoretical basis for concern. There is some data from animals. I think the current lack of a signal in the data they collected is not necessarily reassuring.

DR. MAJUMDER: Mary Majumder. I forgot -- ah, yes.

DR. STERN: Rob Stern. Yes.

DR. KATZ: Robert Katz. Yes.

DR. BIGBY: Second part, is it important to communicate these findings to prescribers -- and I would add patients -- although I'm not supposed to add that? Those that would respond to this yes, raise your hand. No? Abstentions? So again, it was a unanimous yes vote.

Robert?

DR. KATZ: We're just voting?

Robert Katz. Yes.

DR. STERN: Robert Stern. Yes.

DR. MAJUMDER: Mary Majumder. Yes, and I think we may get into this, but I think it's important that as more data is available, that that also be communicated. So this isn't just about past studies, but an obligation to communicate as things develop.

DR. BIGBY: Michael Bigby. Yes.

DR. THIERS: Bruce Thiers. Yes.

DR. LEVIN: Arthur Levin. Yes.

DR. CRAWFORD: Stephanie Crawford. Yes. I think it should be communicated through product labeling at a minimum.

DR. DRAKE: Lynn Drake. Yes.

DR. HECKBERT: Susan Heckbert. Yes.

DR. RINGEL: Eileen Ringel. Yes.

DR. SHWAYDER: Tor Shwayder. Yes.

DR. BIGBY: Third part of this question is, are additional animal studies needed? All of those voting yes, please raise your hand. Noes? Abstentions? So the summary is there was one yes, nine noes, one abstention.

Tor?

DR. SHWAYDER: Tor Shwayder. Yes. More studies will be needed.

DR. BIGBY: Do you want to say a little more?

DR. SHWAYDER: I always think more data points are better, and it's a lot easier to

do it on mice and monkeys than it is in humans. And those data would be reassuring to me.

DR. RINGEL: This is Eileen Ringel. I voted no. I don't think more mice studies will convince anyone.

DR. HECKBERT: Susan Heckbert. I voted no, for the reasons I've already stated.

DR. DRAKE: Lynn Drake. No.

DR. CRAWFORD: Stephanie Crawford. No, I agree with Dr. Heckbert's assessment. We need more people studies.

DR. LEVIN: Arthur Levin. I abstained because I really didn't know the answer.

DR. THIERS: Bruce Thiers. I can't imagine what additional data any animal studies would bring us that would make it not -- would reassure us that the drug was totally safe, so I think what we need is human data.

DR. BIGBY: Michael Bigby. I voted no, and I think at this point in the development of this agent, what is really needed is clinical results in real humans.

And I think that they should be aware that there is a potential risk even if there hasn't been a signal.

DR. MAJUMDER: Mary Majumder. No.

DR. STERN: Rob Stern. No.

DR. KATZ: Robert Katz. No. We know enough from the studies already done.

DR. BIGBY: So this one is underlined and bold. Please discuss the relative benefits and risks of the use of ustekinumab in patients with moderate to severe plaque psoriasis. And the question is, do the benefits of therapy in adult patients with moderate to severe psoriasis outweigh the risks?

The floor is open for discussion.

DR. THIERS: I would move that we vote on the issue, as we've discussed this for the last seven hours.

DR. BIGBY: I'm very much in favor of that if no one objects.

DR. KATZ: I won't make a long

comment, but when you talk about risk-benefit, we can answer that, but for each patient it's different, because different patients are different risk-averse, so many of our patients we tell them about the animal studies and potential risk, they have 75 percent body involvement, they take it in a snap of a finger. Somebody else has 10 percent body involvement, they're more risk-averse, they're not going to do it. So we're just answering this in general terms. Is that correct?

DR. MAJUMDER: I would just second that. Question eight about approval is just a question about whether to make it available so that physicians and patients can then engage in that discussion that's tailored to individualized circumstances, but the weighing of risks and benefits is going to be a part of that individualized assessment.

I could still answer this question.

DR. LEVIN: I'm sort of confused about seven and eight, only because you can't answer

the first part of eight -- I mean, it's the same question. You don't approve a drug unless you believe the benefits outweigh the risk, so why ask it twice?

DR. BIGBY: So let's answer seven and then we can maybe skip eight, okay?

DR. LEVIN: I would vote the other way around. Let's move to eight.

DR. WALKER: I have a comment on the questions. The purpose of question seven really was to hear from the committee on their summary of the benefits and risks. The purpose of question eight is to ask you about a recommendation for approval.

I think they're slightly different.

DR. BIGBY: Eileen?

DR. RINGEL: I really apologize for taking up extra time, but here I go again. I would vote differently for moderate psoriasis from severe psoriasis. The package labeling indicates it's for patients who would be considered for phototherapy and systemic

therapy. I have different feelings about phototherapy, narrow band UVB in particular, versus systemic therapy. So for me, I would have to tease this apart, and it makes it very difficult.

DR. BIGBY: Tor?

DR. SHWAYDER: I was just going to say, the data presented, it looks very good and there's no doubt in my mind that something you use every 12 weeks certainly outweighs something I'd give every day or even once a week, so you know, it's an exciting concept to have such an infrequent administration for such a wonderful benefit.

And the risks are the elephant in the room. And to comment on what Eileen said, we already heard the person with 10 percent psoriasis thing of committing suicide from the data that Alexa was giving, so that's always a difficult one, how you weigh the risk for the perception of how severe it is in any given patient.

DR. DRAKE: Mr. Chairman?

DR. BIGBY: Lynn?

DR. DRAKE: I'd like to just maybe ask you as the chairman and maybe even poll the committee, I don't know, I think Bob Katz said something earlier, that the vote on all these last few questions might be directly related to the registry and the reporting requirements, because some of these side effects are so long-term, like malignancies.

We've approved previous biologics with these same questions. I think, at least for some of us, the elephant in the room is the fact that we haven't heard back on any of this stuff, and so now, at least on a personal level, I'm a little gun shy.

And I don't know, what do you think, Mr. Chairman? Would it help to know if it's going to be mandatory reporting? Would it change the vote any? Would it influence anybody's opinions? I mean, Bob had suggested that. So it's a question, sir.

DR. BIGBY: I would say to help the Agency get to answers and advice from the committee that they need, I think that this question is a fairly straightforward question, and that is, given the data that you have in hand, do you think the benefit outweighs the risk? And I don't think that you really need to make it provisional on -- I mean, you can answer this question and then you can also advise the Agency that you think they ought to strengthen post-marketing surveillance, but I don't think that needs to be a prerequisite for being able to answer this question yes or no.

And actually, that was one of the reasons I asked earlier on do you ever give provisional approval, and the answer to that one is no.

DR. LEVIN: I'm sorry. Bob?

DR. STERN: So my answer to this is for up to 40 weeks of therapy, the perceived benefits outweigh -- the documented benefits

outweigh the risks, but that for anything beyond 40 weeks, we have a complete black box, and therefore, if approval -- as opposed to the usual thing that says experience is limited to 40 or 52 weeks, which is the usual kind of -- or 16 weeks, whatever it happens to be -- right now, I would vote for approval for 40 weeks and 40 weeks only until and unless there are some other things that will give us information beyond 40 weeks that are in place that will give us reasonable information in the time I hope to be alive.

DR. LEVIN: So I guess I would think of this question is, do the benefits as we know them today outweigh the risk as we know them today? And that, sort of, at least for me, helps clarify what my answer will be. And then we move on in eight to sort of dealing with the unknowns.

DR. BIGBY: I think that -- I mean, I think that that's a fair understanding. That's an understanding of that risk-benefit

question in general.

DR. THIERS: Rob, what you were addressing, I think, is 8(b)(1), describe the recommended dosing regimen and length of treatment.

But I think if we vote no on seven, eight becomes moot, so I think we've got to do seven first, then move on.

DR. BIGBY: You have a comment or no?

So I will put this to the vote. Do the benefits of therapy in adult patients with moderate to severe psoriasis outweigh the risks? Those voting yes, raise your hand. Those voting no, raise your hand. And those abstaining? So there were nine yes votes, one no vote, and one abstention.

We'll start with Tor.

DR. SHWAYDER: The data as presented today, the answer is yes.

DR. RINGEL: I think this drug is -- the benefits outweigh the risks for severe

psoriasis. I don't think they outweigh the risks for moderate psoriasis, and it's important to know how I'm defining that. It's not by percentage of body involvement, it's not by a PASI score, it's by a physician discussing it with their patient. So if they're suicidal, that's severe. If they have 90 percent body involvement and they don't care, then that's moderate.

But it's -- the other issue is the way the indications are written right now, it's who are candidates for phototherapy -- I'm sorry, phototherapy is a benign modality. It is inconvenient, but I want to make sure that those people who are going to go on this drug have either failed phototherapy or considered it and rejected it for whatever reason. I think that's terribly important.

I don't like this idea of saying phototherapy, number one, lumping it in with systemic -- and number two, lumping it

together with PUVA. They are very different things. So no.

DR. BIGBY: And the risk concerns that make you not want to use it in moderate psoriasis?

DR. RINGEL: It's that I think that the animal studies are very worrisome for malignancy compared with the other biologics that I've heard about today, and people -- I'm sorry, let me start again. The risk for malignancy is considerable, and the risk for infection is considerable. And I think we're too cavalier with biologicals in general.

DR. HECKBERT: This is Susan Heckbert. I voted yes, and in voting yes, really, it's a more complex question than that, but in a different way for me than for Eileen. I'd say that overall, we don't know whether the benefits of treatment with this agent outweigh the risks for the short-term based on what was presented up to 40 to 52 weeks. The benefits do appear to outweigh the risks. So that's the basis of my

vote yes. But for the long-term, we don't have information. And overall, I would say therefore, we don't have information.

DR. BIGBY: You get skipped for a second, Lynn.

DR. DRAKE: Good.

DR. CRAWFORD: Stephanie Crawford. Yes, based on the data that we were provided.

DR. LEVIN: Arthur Levin. Yes. Always difficult to weigh the unknown. It always makes me extremely uncomfortable, and most of the time I vote the opposite way as a result. I think the remarkable efficacy I think is a very convincing factor, and the hope that we can find a way in the post-market period to really find more information.

The animal studies are worrisome, but we didn't have lots of other signals saying, whoa, let's not go ahead with this.

DR. THIERS: Bruce Thiers. Dr. Levin stated perfectly what I was going to say, so I'll move on to Dr. Bigby.

DR. BIGBY: Michael Bigby. I voted yes, and I think the thing to remember is if you look at the risk-benefit ratios of the other available modalities, I think this one turns out to look pretty good, and that -- long-term, we have a hypothetical and I think that we should remember that in terms of surveillance and in terms of communicating potential risk. But I think if you concentrate on risk-benefit compared to almost everything else we have available, the drug looks pretty good.

DR. MAJUMDER: Mary Majumder. Yes, given current information.

DR. STERN: Rob Stern. Yes, up to 40 weeks.

DR. KATZ: Robert Katz. Yes, but for each individual, this risk-benefit ratio will be different depending on how risk-averse the individual patient is.

DR. BIGBY: Lynn, you do have to make a comment.

DR. DRAKE: Lynn Drake. I abstained because I just had to put myself in the position -- if I was talking to a patient about this tomorrow, if they asked me what was the risk-benefit ratio, in all honesty, I would have to say I honestly don't know. That's a totally different comment than if my patient asked me what do you recommend I do. So for me, I would have to answer my patient, I simply don't know.

That's why I abstained.

DR. BIGBY: The next question turns out to be ten questions. But I mean, I think we could do eight as a separate question and then go on. Do you recommend approval of ustekinumab for the treatment of adult patients with moderate to severe plaque psoriasis? And I'll open the floor for comments before we vote.

DR. STERN: At least for me, so much of it depends on, quite frankly, the answers to the subparts, because if this is going to be another drug with -- yes, we promise to get back

to you by -- well, now it would be 2015 -- with some data, with -- if we're hopeful, 8 percent follow-up loss a year, which would mean less than half the patients would still be around and we'd know nothing, I'd vote no, quite frankly.

If we can cement in some real studies with very much verifiable endpoints in terms of performance, and some penalty if the performance isn't reached, then I think it's an approvable drug, and the data will drive for how long its use is safe for, and clinical experience will drive how long it's effective for and whether it's effective -- I guess the one thing that Michael brought up, I would like to see a clinical study in people -- responders who have been withdrawn who had a substantial return of psoriasis and whether or not they're more like TNF-alpha inhibitors or more like infliximab in terms of their response.

But I really think we need the subparts under yes before I'd vote yes.

DR. BIGBY: I hate to put him on the spot, but Mr. Levin, you had some query about being able -- wanting to answer this question before seven. Now that seven was voted on, would you like to make a comment?

DR. LEVIN: I've been at a lot of these meetings where there's sort of a desire to approve, but also a desire to impose a lot of conditions on approval, because there's often a lot of uncertainty, so people are trying to address that issue. I mean, for example, you could argue the concern about length of time of treatment could be part of the labeling.

You could argue that the moderate versus severe could be dealt with in the labeling in one way or another. So I mean, I don't know how comfortable the FDA is, but there are a lot of concerns that were expressed around the table that at least you could make an attempt to deal with the labeling.

And we know that that puts pen to

paper but doesn't necessarily change clinical practice. At least it's something. It expresses some parameters for how this drug gets used based on what we know and what we don't know.

The question is whether FDA -- you didn't ask those questions in this part. A lot of times, they will be part of this last question about what does the label look like, what are the restrictions, if any, and so forth.

So are you comfortable with us discussing it that way?

DR. BEITZ: I just wanted to comment that there are obviously a lot of ways to do this. There is labeling which would provide recommendations to prescribers on what we would recommend to be the duration or recommend the dose, but I've also heard folks say that they wanted to cement things in, and that's more than what a label generally does. To cement things in, you are talking about some of the more

restricted types of tools that one might consider. So just bear that in mind.

DR. LEVIN: Those also aren't discussed in this question. I mean, things like restrictive distribution, something like the Accutane program --

DR. KATZ: (inaudible)

DR. SHWAYDER: I just want to make a comment. Dr. Stern keeps talking about 40 weeks, but the T08 study went off the 56 weeks. I was wondering why you were glomming on to 40?

DR. STERN: I think the oldest person on the panel, and my recollection that most of the studies had about 40 weeks of exposure, and the amount of exposure much beyond 40 weeks was really quite small in terms of total exposure, but I could be wrong. Am I wrong on that? I'm often wrong about almost everything, but --

DR. YEILDING: I think that Dr. Guzzo had shown the efficacy after week 56, and we had shown the safety out to week 76, so remember that there were 1,285 subjects that were exposed

for at least a year -- and there were -- I think it was 373 subjects that were exposed for at least 18 months, so a year and a half.

DR. KIMBALL: (inaudible)

DR. YEILDING: These are ongoing studies, approximately 2,000 patients -- but again, I'm sorry, I read this a few days ago, but it was my recollection that among the originally placebo-treated group, there was 12 weeks they were on placebo in the one-year studies and 40 weeks exposed to drug, so about a quarter of the population had 40 weeks' exposure; plus, there were a fair number of dropouts. So when I looked at what was the large number of people who had 40 weeks of drug, it seemed to me that there was a more substantial number who had at least 40 weeks of drug exposure as opposed to elapsed time than any other group.

DR. STERN: I'm sorry.

DR. YEILDING: We did adjust for the placebo group, so we frame-shifted that group so

they were only counted in exposures when they were actually receiving drug.

DR. BIGBY: So put another way, though, how many patients have you had that have been exposed to drug for more than 40 weeks?

DR. YEILDING: Can you bring that up, please? For more than 40 weeks, I cannot answer that question. Can you bring the slide up, please? I can't answer 40 weeks, but I can answer 52 weeks -- so you can see down there at the bottom, there are 1,285 patients that have been exposed for at least 52 weeks, and 373 for at least 18 months.

DR. STERN: On drug?

DR. YEILDING: Correct. That's adjusted for the placebo -- the placebo follow-up is not counted towards exposure.

DR. BIGBY: Just say that again.

DR. YEILDING: So there are 1,285 patients that have received drug for at least one year, and there are 373 patients that have

received drug for at least 18 months.

DR. STERN: You're saying if -- again, this design was very complicated with crossovers, but what I did in thinking about the one-year data was to net out the 12 weeks of at least the initial placebo -- and then there are other people who will go off drug on placebo, and I sort of said that reduces it. You're telling me let's make it simple. You're telling me someone who did 12 weeks on placebo and then happened to end up on an exposed arm for the rest of the study -- for them to count as one year, they were followed for 64 weeks. It wasn't until the 64th week that they would have counted as a year.

DR. YEILDING: That is correct.

DR. STERN: So I guess my comments would then apply to 52 weeks rather than 40. I'm sorry.

DR. KIMBALL: So in that slide, the fact that you have people up to 18 months means that cohort just hasn't moved all the way there.

That's not the remaining people in the study; correct? You have people in the 12- to 18-month window who are still moving through, so that's not a dropout rate?

DR. GUZZO: Ongoing five-year study.

DR. STERN: But the difference where I got confused was, when I usually see a year, I think of elapsed time from either randomization or first dose to follow-up, and you're telling me that it's not that, that for any period an individual is on placebo, that time doesn't count in those data. That's my confusion.

DR. YEILDING: That's correct.

DR. THIERS: Rob, what I've heard from a lot of people here is that we're concerned about long-term safety data. If we're going to recommend approval for only 52 weeks, how are we ever going to get this long-term data?

DR. STERN: I think what I was hoping to have said, but probably didn't, was that I think if an approval is coupled with studies where there are enforceable milestones and some

real penalty if enrollment, percentage of follow-up, et cetera, et cetera, are not met, something bad happens other than a letter that says you've been a very bad company, that really has some effect, then I think it's approvable.

I mean, it's a moving target. One would hope in three years, we'd have four years' data on a substantial -- or we'd have two years' data on a large population, three years' data on a medium sized population, and a small amount of data from those people who remain on these trials on a small population.

So I didn't say -- you know, approve it and then stop it. What I said is, you approve it, but then at some reasonable intervals, agreed upon, oh, yes, you promised to do the study with this number of patients with this rate of follow-up with these milestones. If you fall below this, we've got to talk about this and maybe restrict --

DR. THIERS: I understand what you're saying, but I thought you were only suggesting

that patients only be -- that it only be recommended that patients could stay on it for 52 weeks, because if that was true, then we wouldn't get the long-term data that we need.

DR. STERN: I think I was being my pedantic self and saying the data I was aware of showed that the benefits outweighed the risks for up to 52 weeks, and that we were --

DR. THIERS: (inaudible)

DR. RINGEL: I'm going to say a bunch of completely contradictory things, so you'll have to put up with me.

First of all, I would -- were if someone to say do you recommend approval of ustekinumab for the treatment of adult patients with moderate to severe plaque type psoriasis, I'd say yes, even though I said no to the preceding question, simply because this is saying do I want to keep this drug off the market or not, and I do not want to keep it off the market. So given that all the other biologicals have been approved for

moderate to severe psoriasis, I suppose I would say, well, I shouldn't really discriminate against this one. It doesn't make me happy, but I would not discriminate.

So I do not think the risk-benefit ratio is okay, but no, I wouldn't keep it off the market. That's number one.

Number two is that I think people really need to take very seriously those in vitro, and particularly the animal studies. There's a lot of data that said this is going to be carcinogenic. It reminds me of HRT. You know, it was around for years, and everybody knew that estrogen was thrombogenic and all the in vivo animal studies and the in vitro studies said it should be thrombogenic, but I didn't do the right studies and didn't do the right studies, and by gosh, when the NIH got it in there and they did the right studies, well my goodness, it made people have strokes and heart attacks.

The risk here isn't LFT elevations,

it's not a little drop in platelets. This is people dying of cancer. I think that we have a drug where there is good indication that it may be a significant risk for cancer.

We've run studies where it really isn't going to show up. We know it can't show up in this period of time. It's not powered for that. I think we have to be careful. This is potentially -- we don't know, but it could be a life-threatening drug, and people are going to be really angry if, five years from now, people are getting lymphoma. I think that we need to be very circumspect about this medication.

I would be very happy to approve it for multiple sclerosis or Crohn's disease or severe psoriasis, but moderate psoriasis? I don't know. That makes me nervous. So I guess I don't want to keep it off the market, but it's not making me happy.

DR. HECKBERT: I had just a comment about our ability to find out whether there is a