V:SELIGMAN (discussion)

DR. SENIOR: My comment, just to pick up until people can get to the microphones, is that to do a rechallenge, a deliberate rechallenge, it has to be done very carefully. To do an inadequate rechallenge is unethical because it can give you a false sense of security.

I submit there are two reasons to do a rechallenge. One may be to determine whether or not the drug really caused the reaction or was it some other cause? The second reason is if the rechallenge, an adequate rechallenge in dose and duration, is negative, then one can then conclude it is safe to continue giving the drug, but the patient, if they initially had a reaction, has adapted, and it's safe to go ahead.

These are two reasons to do a rechallenge, but to do an inadequate rechallenge will give you a false sense to go ahead and that's a bad idea.

So are there any other questions? We heard a number of comments about reluctance to do rechallenge during clinical trials and maybe you want to amplify on that.

DR. SELIGMAN: Does anyone wish to amplify?

DR. AVIGAN: I think it is going to be problematic. One of the things we heard yesterday on post-marketing cases, on inadvertent rechallenge in the Glaxo group, was the fact that on the second exposure, there was a shorter time interval

typically until the reaction occurred. So if we assume that, then the rechallenge test has parameters that are convenient because you know how long to keep monitoring until you're home free.

The problem though is that we can't rely with certainty on that assumption, and we might have a problem. We know that with some idiosyncratic liver toxins the lag effect, or latency period from initiation of exposure until the event is very capricious and can be as long as six months or even longer. And these events occur out of the blue sometimes.

So the question, I'm just raising it rhetorically, is how long to look as you monitor carefully after the rechallenge.

DR. SELIGMAN: Historically rechallenge has been a useful pharmacovigilance tool because it's been at least a means for allowing us to assess the strength by which we can assess causality by looking at a spontaneous report. But it takes on a whole different set of issues and problems when you look at purposely rechallenging an individual in the context of a clinical trial. I think a lot of those issues were clearly raised and discussed yesterday. Yes, Dr.Regev.

DR. REGEV: Going back to Will Lee's comment from yesterday, those of us who saw liver patients long enough saw patients that died due to rechallenge. So it is an extremely dangerous thing –- first and foremost to the patient. In

addition, the comments in the Guidance will not necessarily protect an investigator that ends up doing a rechallenge and harming a patient.

I recommend that if those comments are left in the Guidance, we should qualify them very carefully and mention the fact that rechallenge is only for situations where the benefit of the drug is crucial or it may be life-saving for this patient. I would also qualify it by making sure that the patient has enough liver reserve to be able to survive rechallenge. And sometimes it may be necessary to consult a hepatologist for that or to make absolutely sure that this is not one of those patients that has already some type of underlying liver injury and this rechallenge might cause a critical decrease in his liver function. I would make sure that these qualifications are there, even though I'm not sure they promise 100 percent protection.

DR. BARTH: Jay Barth from Merck. I should like to ask a question not about rechallenge but about inclusion of patients with underlying liver disease, since you mentioned it briefly. Should a distinction be made in the Guidance between treatments of disease where there is a high incidence of a underlying liver disease (fatty liver, diabetes, hepatitis B or C, and HIV), as compared to conditions in which you don't expect an incidence higher than a general population and the numbers would be small. It would be important to study the

effects of the drug in the high-incidence patients and you would be able to get enough data to see the underlying liver disease. You would just not be able to get interpretable data in the low-incidence type, if those patients are included on those grounds.

DR. SENIOR: I think that belongs in the third discussion that John Pears is going to present.

DR. BARTH: Okay. Sorry.

DR. PEARS: I'm still here. I'm still here.

DR. SENIOR: Maybe we're through with rechallenge, I don't know.

DR. SELIGMAN: Any other comments? (No response.)

DR. SELIGMAN: I'll turn it over to you, John.