DISCUSSION IIA

DR. SELIGMAN: We have an additional half an hour, excuse me, an additional 25 minutes for discussion. We're open for questions. I guess the first thing I'd like to do is key up for our panelists. I'd like to challenge either our panelists or our audience, so we've provided this Guidance document related to the premarketing clinical evaluation. We have a section in there on rechallenge in the context of clinical trials and I understood from hearing from those in the audience what the potential implications of that section are, and whether there's a potential for rethinking about rechallenges, in the context of clinical trials as a way to gather more information and better information about causality.

DR. PEARS: John Pears from AstraZeneca. We have a similar policy to GSK, which is that we don't recommend rechallenge, deliberate rechallenge, in a clinical trial setting. I haven't heard anything today that makes me want to change that, and I suggest that perhaps the wording needs to come out or perhaps be softened in the FDA Guidance document because people could use that to overrule that policy without necessarily thinking and understanding all the background information that's going on in here. .

DR. SELIGMAN: Any additional comments?

DR. BONKOVSKY: Just a couple of comments. The first one is that this problem of positive rechallenge is

not limited only to ethical agents. We have seen at least one very well documented case of severe recurrent injury from a concoction of green tea extract in one of our patients that patient is in the DILIN network. So this also occurs for complementary alternative medications.

With respect to the question about could we desensitize people, I'm not aware of any good data specifically with respect to liver injury but I think there is an extensive literature about being able to do that, like with penicillin, with skin allergy and things like that. So, yes, I think it could be done but I would think it would be a very rare instance where for some reason this is the only drug and it really is absolutely essential that the patient take that drug and not some other drug. And I would share your great reluctance to undertake any of these rechallenges, and I can't imagine doing this in a clinical trial for a drug that hasn't been approved.

DR. REGEV: Just to reiterate, but before I do that, can I ask you a question? I'm not sure you can provide me with this data. How many of those patients had ALT more than two times the upper limit of normal and less than three times the upper limit of normal? Between the 2 and 3 limit, in this group of 88 patients?

DR. PAPAY: Well, that's a great question. I don't know the answer off the top of my head. I mean an overwhelming proportion of the 88 cases had really high elevations in ALTs. So we had the data set that I showed

you that had ALTs less than five times the upper limit of normal. That was sixteen cases.

DR. REGEV: Sixteen.

DR. PAPAY: Sixteen. And three cases actually had a similar or worse experience. And so those cases, two of them described jaundice and what we're suggesting is that perhaps what might augment the draft FDA Guidance is including an ALT less than five but also no jaundice if you're going to consider rechallenge. But I'd have to say just from recollection, the number of cases with ALT between two and less than three is probably a very small subset in this data set.

DR. REGEV: Well, regardless of what it is, I think the fact that you chose such a broad margin and you did have patients that had ALT just two times the upper limit of normal, that improves the safety of rechallenge because some of those were probably just a blip in the ALT level that we wouldn't even consider real drug-induced damage. So I just would like to support things that people said previously. I think despite the fact that it would look here a little safer than it is, rechallenge is extremely dangerous, and I would take those patients that were the higher levels and the more dangerous ones as an example and not the entire group as an example of the outcome.

DR. FRESTON: Freston, University of Connecticut. Thank you for that splendid presentation. Let me ask you

for some details about those two deaths, and then I'd like to make a suggestion. They both had CHF. Do you have any information on whether or not they were in worse shape with regard to their CHF when they were rechallenged than they were with the initial presentation? What I'm getting at, of course, is the contribution of comorbidity here. Do you have any information on that?

DR. PAPAY: Chris (Hunt), my recollection is that those were stable patients with respect to their congestive heart failure and that's why the suspect drugs were implicated as being the offender that contributed to the drug-induced liver injury. Chris is nodding yes.

DR. FRESTON: So they were stable with respect to their CHF. Well, I'd just say as a clinician, try to find a rationale for rechallenging. We all agree there is some wiggle room in the Guidance document. I'd just suggest, that based on your two cases, that in the risk benefit analysis, comorbidity should be taken into account.

In DILIN we've had deaths that weren't directly due to a liver disease, but it was the straw that broke the camel's back.

DR. PAPAY: I think that's a great point. Thanks, Jim. We do consider comorbidity that might be tipping the balance, if you will, regarding drug-induced liver injury, and I think that one point that we shared with John Senior on a teleconference was the paroxetine death that occurred in an 83-year-old gentleman. He was

actually hospitalized for his first event, was transferred to a nursing care facility and was inadvertently readmininstered paroxetine. So I think there's a public health message there as well, to let people know that the healthcare system needs to communicate across the spectrum to make sure that these patients aren't reexposed to a suspect drug that's caused drug-induced liver injury.

DR. SENIOR: I think Jim Freston has raised a very, very important point, and it has to do with what I was saying earlier, about the ability to recover from an injury. If a drug causes an injury, the outcome, the final outcome may not depend so much on the drug and the injury but on the patient's ability to withstand it, to recover from the injury, and that is undoubtedly impaired in people with congestive heart failure, which all by itself can cause quite severe injury. In fact, the so-called ischemic hepatitis is more often associated with right heart failure than with shock. And that was shown in studies done I think in San Francisco.

So I think this whole issue of comorbidity and the ability of the patient to recover from injury is critical and I would be very reluctant to take elderly, you said they were old people with congestive failure, and reexpose them to a drug that had injured them.

DR. PAPAY: We aren't doing them any favors, are we?

DR. LEE: Yes, Will Lee, Dallas. I have two

personal instances of rechallenge that were fatal that I can recall right off the top of my head, and they were both related to sulfa.

One was a young man who had inflammatory bowel disease and had a reaction to azulfidine. Several years later, a different physician put him on azulfidine again and he had a fatal outcome. So it gets to the point that you made, Julie, about the bracelet and the education of the patient. The patient had no idea what he had taken and that he had had this reaction. He happened to be readmitted to the same hospital but not to have been treated by the same physician.

And the second case was an HIV patient who was given a sulfa drug a second time and had a fatal reaction.

We've got to recognize also that you have the GSK database only. So certain drugs would be out of your purview totally, and certain ones would be coming to the fore, but wasn't Septra one of the --

DR. PAPAY: Yes, cotrimoxazole.

DR. LEE: Yes. So -- that's right. You had one case.

DR. PAPAY: Right.

DR. LEE: But you didn't have a lot of cases. I'm a little surprised at that because sulfa drugs are so common.

DR. PAPAY: Correct. Actually there were two cases in the data set and they both occurred in children.

One was 10 and one was 11, suspiciously similar but not quite similar enough to call them the same case. Both of them were published, available in the published literature, and they recovered from the liver injury thank goodness. But I think you raise a good point, particularly with antibiotics because I know when I don't feel well, I don't tend to remember that, oh, by the way, tetracycline makes my stomach upset. I just know that I have sinusitis and feeling crummy. I've got a medication bottle sitting in the medicine chest, didn't take all of it last time, so I'll take it again. And that's what actually happened with some antibiotic cases that are documented in the literature. There's a great case of a younger woman who self re-took amoxicillin-clavulanic acid for acute sinusitis. You know, you've got it lying in your medicine chest. They think it's an opportunity there to save the patient who had a serious adverse reaction to this drug, if there's anything, if there's any unused portion, you need to dispose of it or get it back to me and I would dispose of it so you don't have those inadvertent challenges occurring.

DR. PIERCE: Ross Pierce, FDA. In analyzing efficacy, we talk about number of patients needed to be treated in order to get one positive outcome like, you know, not having a heart attack or something like that, and if we think that these data may be representative of rechallenge in general with drugs and hepatotoxicity, then we see that for every one case of a positive rechallenge we

might expect about eight cases where the rechallenge would be negative.

We already know that the negative rechallenge cases are not particularly instructive because they well may have had a drug-induced phenomenon even if they had a negative rechallenge. So if you combine the yield, if you will, to be about one out of nine patients having a positive rechallenge, together with the fact that not everybody that we propose a rechallenge to is going to accept and give informed consent for that. Not every clinician is going to propose rechallenging, investigators that is, in a trial to their patients. I can understand why we've heard that two major pharmaceutical companies have a policy not to rechallenge.

DR. PAPAY: That's a great point. We did not do a numbers needed to treat analysis but I think the data set that is available is compelling enough to suggest that rechallenge should only be undertaken when there's no other clear therapeutic benefit available and the patient fully understands the risk.

DR. MAYNE: Jim Mayne, from Pfizer. I have heard from three major pharmaceutical companies (laughter) and I haven't heard anything here today either to tell us that we should reconsider that.

DR. STONE: Hi. Marc Stone, FDA. I'm afraid I didn't understand Ross' point because I'm looking up at the graphic there and depending what level you go at, that you

identified 1200 or 1100 rechallenge cases, and about 60 percent of them were positive rechallenge.

DR. PAPAY: Well, you can only take that at base value because the positive rechallenge were rigorously adjudicated, meaning they had to meet the criteria that were highlighted earlier. We did not do a similar analysis on the negative rechallenge cases.

DR. STONE: Correct, but I'm just saying that I don't know where this 1 in 8 number comes from when, in fact, if you use the same level of specificity, it seems that only 60 percent come into it in the same way.

DR. PIERCE: Right. I did make an error. I think it's actually one out of five. I was looking at 648 and going down to 88 but I think you have to look over to the right and see that 441 of them were rechallenges, that were considered to be negative although you pointed out that you didn't examine those data quite as carefully. The point is that a minority of patients rechallenged will have a positive rechallenge. So you have to think about that the yield is somewhat low.

DR. STONE: But again, that's not true. If you have the same level of specificity, you have a 60 percent positive versus 40. If you went through the same adjudication on the right side, you might end up with 60 cases.

DR. PIERCE: Well, we don't know what that is because the adjudication level wasn't the same.

DR. STONE: Right. But that's why you can't make that extrapolation. That's my point.

DR. PAPAY: I knew I'd get in trouble if I showed numbers. (Laughter.)

DR. DONOVAN: Joanne Donovan, Boston. You had mentioned that most of the rechallenges were inadvertent. So an inadvertent rechallenge that was negative would never go into your database. So there's a huge denominator there that we would all be unaware of if they were rechallenged and nothing happened.

DR. PAPAY: And that's a great point. I think maybe the rechallenge must underreported because, you know, it's kind of like preventative medicine. Nobody came in and saved the day. So I think there is an underreporting bias for negative rechallenge.

DR. SELIGMAN: Any additional comments or questions? (No response.)

DR. SELIGMAN: With that, thank you very much and we'll take a break and reconvene at 4:00.

(Applause.)