J: PAPAY-HUNT (discussion)

DR. SENIOR: Julie, that was excellent. You focused on the positive rechallenge cases. I'm interested in the 400 negative rechallenges. First of all, were those rechallenges adequately done, and if negative to adequate rechallenge, were they safely put back on the drug and --

DR. PAPAY: It's a great question and --

UNIDENTIFIED SPEAKERS: What's the question?

DR. PAPAY: I'm sorry. John Senior was just asking about negative rechallenge, and if we felt that those cases were adequately dosed and had an adequate negative rechallenge.

It's a great question. Unfortunately, we did not adjudicate those cases to the same level of detail as we did for positive rechallenge. So within our automated GSK safety database, there is a way to retrieve negative rechallenge cases by asking it to find where negative rechallenge has been checked, but we did not go through and read 441 cases line by line to the similar degree that we did for positive rechallenge.

DR. SELIGMAN: Were they put back on the drug?

DR. PAPAY: Were they put back on the drug? Yes.

DR. WALLIS: Wallis from Seattle again. You indicated that about 14 percent of the cases of the 88 were from clinical trials and yet the listing of the various products implied only approved therapeutics and I'm

wondering if, in fact, part of the clinical trial experience reflects early phase studies 1A, 1B, where the toxicity of the drug is being first defined and, if so, were any of those in this data set?

DR. PAPAY: Great question. I think all but 1 of the 12 are FDA-approved. And so our data set reflected cases back to the eighties, some from the seventies, and it's a great question. I went back through in anticipation this question coming up. We had a clinical trial with cimetidine, a clinical trial with abacavir, you know, as the hypersensitivity reaction was being understood around 2000, 2001, but none of those drugs as I recall fell out of the drug development program. They are all marketed except for one oncology agent that's still in development.

DR. WALLIS: But does that mean that there have never been products that have been dropped out because of a positive rechallenge?

DR. PAPAY: None that we were able to find in our data set that met the three rigorous criteria that defined positive rechallenge were classified as probably or possibly drug related and, of course, they're medically confirmed because they're clinical trial cases.

DR. WALLIS: Thanks.

DR. PAPAY: Great question.

DR. ROCKEY: Don Rockey. This is fascinating and it makes me wonder whether actually it may be safer to rechallenge than we think as clinicians because, you know,

we're faced with the situation all the time where somebody needs a drug and we don't give it because we're concerned about rechallenge. And so my specific question is: even in the two patients that died, they both had congestive heart failure and they were on multiple medications. How sure are you that these were, in fact, true DILI cases? Could these patients have had passive congestion? As you know, hyperbilirubinemia is a classic finding with passive congestion.

DR. PAPAY: I think it is interesting that both patients had congestive heart failure and that's where the value of having a hepatologist, Chris Hunt, work on these cases, I think having her evaluate them and it meant her litmus tests were being included in this data set, but you raise a good point.

I would hope that the overwhelming message about this data review is that rechallenge potentially puts the patient at a very increased risk for a serious adverse event and potentially could be life threatening. There were, to me, an interesting and surprising number of cases who had Hy's Law in both the initial event and rechallenge. So I hope that the take-home message is rechallenge should only be done under strict supervision where the benefit clearly outweighs the risk, where you've got consent from the patient, they're well informed and they're buying into this.

DR. HUNT: And just to address the -- sorry.

Christine Hunt, GSK. Just to address this question. These patients between events -- before events -- well, we don't have much information before events, but between events actually the liver chemistry elevations were modest or negligible.

DR. BONKOVSKY: Herb Bonkovsky. This was a terrific presentation. Thanks very much, Julie and Chris, and your team. I just wondered about the sex thing. You commented on that. What about the denominator? Were there also more men, you know, in the total end of these trials or -- because you'd have to take that into account in saying that there truly is an unexpected greater frequency. I mean most of us think that actually DILI is somewhat more common, particularly immuno-allergic, you know, disease in general, more common in women than men.

DR. PAPAY: That's actually a great question and I'd have to go back, to be honest, to look at the total data set of let's say the 770 positive rechallenge cases to look at that male/female ratio to see if it's similar as to what was reported for the 88 cases.

DR. BONKOVSKY: I'm thinking the total number in the whole database. You know, especially in these older trials, women may have been underrepresented as subjects for the stuff.

DR. PAPAY: Interesting. Very interesting. That's something we'll have to take back and evaluate further. Thank you.

DR. COMER: Gail Comer, Wyeth. I have one question about the criteria that you used. You indicated that they had to have a positive dechallenge within one month, and we see many patients who have serious drug-induced liver disease that can take months to recover. Was this criterion really inclusive enough and would you not have had more cases had you looked for a longer recovery period?

DR. PAPAY: Yes. That's a great question and we had to pick a cutoff at some point to define positive rechallenge to rule out chronic liver disease in the subset. My recollection is that there were very few patients that we would have gained by using a longer window of time. But great question.

DR. LEE: I may have missed it but how did you get the 88 cases from the 648?

DR. PAPAY: So, yes. Sorry about that. So --

RECORDER: Can you repeat the question for the record?

DR. PAPAY: Sure. Yes. Sorry. Will Lee is asking, Dr. Lee is asking about how we drilled down to the 88 cases from the subset of 770. I ran through those numbers quickly and apologize, but the 770 represent where you can click in the database and say show me all cases of "positive rechallenge," okay, and then we ask the database, well, tell us only when it was reported by a healthcare professional or by a regulatory agency, and that drilled

down the 648 cases. And then what my colleagues and I did was we actually adjudicated those cases. We sat and read line-by-line, case-by-case, and we evaluated them with the following criteria: They had to have a clear positive rechallenge. It had to be probably or possibly causally related, and it had to be medically confirmed. That's how we got to the 88 cases.

DR. LEE: What were all the other cases?

DR. PAPAY: The other cases were either reported by a consumer, a non-healthcare professional. They didn't meet the rigorous criteria of the positive rechallenge that included the initial liver event, positive rechallenge and then having a liver event again. And sometimes when you click a box in a computer database, you could have positive rechallenge but it doesn't mean it was linked to the liver injury. It could have been a positive rechallenge for a skin injury, and you don't know that until you review the case. Great question.

DR. SELIGMAN: Would it be safe to assume then that in the 49-year history of clinical development, that in your database that rechallenge, in the context of a clinical trial, except for the HIV drug that you mentioned, either rarely or never occurred?

DR. PAPAY: Yes, I think it's fairly safe to say that within clinical trials, in the GSK experience, rechallenge happens very infrequently and is GSK policy not to rechallenge patients in clinical trials. Any

consideration has to go through a safety board and it also has to go through an ethics review board.