D:GELPERIN-GUO (discussion)

DR. WATKINS: Anyway, I think it may take us a couple of minutes to get the next presentation online. So I'd like people who would like to make clarifying comments to please come up to the microphone. An obvious issue is should eDISH be in the Guidance? Right now to my knowledge there's no mention of it. Should every NDA be required to generate one of these graphs and perhaps even more, have data available in a form that would allow you even to click on one of the potential Hy's Law symbols to actually get the ALT, bilirubin course for any individual patient and any other relevant data just as they showed us. Comments, please go to the microphone and introduce yourself please. Yes.

DR. COMER: I'm Dr. Comer, from Wyeth. Can you hear me? We've been looking at this graphic display from the slides from last year's meeting, and a couple of questions came in as we were trying to develop our own graphic display. One of them was do you look at peak bilirubin and ALT or do you look at the concurrent ALT and bilirubin?

In one of the studies we were evaluating, there was a lot of hemolysis and prior liver disease that were confounders. We found that looking at concurrent bilirubin with ALT was really more representative of the true injury.

The other thing we looked at was using multiples of

upper limit of normal on the ordinate and abscissa rather than the log because that was really more in keeping with the clinician review. It was more obvious to the medical reviewers what they were looking at rather than the log. We thought that this was a little bit more user-friendly, that we could roll out with our organization and have everybody understand it.

DR. WATKINS: Okay. Well, let me take a stab at those two. In terms of log or just using upper limit of normal multiples, I wouldn't think that would matter. The obvious advantage of using a log scale, which John first did, is you can put ALT, AST, TBL, all on the same graph, without visually suppressing the relative rises in bilirubin.

For the other question of whether you use concurrent maximum values or just the maximum bili and maximum ALT, my argument would be this. You're not saying those are Hy's Law cases. You're just using a visual tool to find cases to then hone in and try to explain. So from my perspective, the maximum ALT and the maximum bili does that even if it turns out the person had Gilbert's or some other problem and bili was elevated before they even started the drug. It just allows you to visually focus in on cases, and the goal of that kind of mapping is to focus in with the broadest possible in any case that might be a problem, not to just hone down to the definite Hy's Law cases. Remember, and this is a point Bob Temple -- well, I'll let Bob make his own point in a minute, but does

that answer your question?

DR. COMER: Actually we thought that they were both valuable, and we thought that as a screening tool, to have the peak was a broader map to look for cases. However, we found that if you look at the cases that were concurrent, they were more likely to be real cases of liver toxicity.

DR. WATKINS: So in other words, show both --

DR. COMER: Yes.

DR. TEMPLE: The last conversation raises one point that I'd like to emphasize. This is partly my own obsession but it's also a matter of the terminology we should use. When Bob Tipping presented his data, he said there were 5 Hy's Law cases. That is not correct. There were no Hy's Law cases because there was another explanation for all of those liver injuries, and they were not drug-related.

A Hy's Law case, if real, tells us that this particular drug has potential to cause serious hepatocellular injury. We want to be as sure as we can that it’s a real case of hepatocellular injury severe enough to cause bilirubin elevation. So if a person has an elevated bilirubin and a little bit of a transaminase elevation but clearly has an obstructive disease, the liver problem may not be due to the drug. That's not the Hy's Law case that predicts a potential for severe hepatocellular injury. So we don't count that.

The reassuring thing about the analysis of the

placebo control group is that in about 3300 patients, there were no false positives. That should be reassuring to the drug companies because if 1 in 1,000 people had a spurious Hy's Law case, and we believed the drug were likely to be a serious hepatotoxin, that would be a lot of dead drugs for no good reason. In fact, none of those placebo-treated cases suggested a drug-induced liver injury meeting the description of a Hy’s Law case.

Remember, Hy observed that pure hepatocellular injury that does so much damage that the bilirubin goes up creates a serious risk of death. That is because bilirubin does not go up until there is a lot of damage to the liver. The liver has a lot of excess bilirubin-excreting capacity. So if you get jaundice or elevated bilirubin, you must have wiped out something like half the liver, an extent of injury that will cause some of those people to go on and die. That was the observation and that's how we've used it. A drug that can do that much damage will sometimes kill people. I don't know whether it's 5 percent, 10 percent or 20 percent of people with elevated bilirubin, but that's why it's so important.

So a bona fide Hy's Law case is one that has the elevated transaminase and bilirubin elevation without any signs of obstruction and it doesn't have another explanation. I think that's laid out clearly in the Guidance, but it's very important to remember that. We're looking for drugs that can

do major damage.

DR. WATKINS: Okay. We may be discussing things for quite a while by the way. So think of good questions.

Well, Jim, you'd have to go to the microphone if you want to speak, and -- Ana.

DR. SZARFMAN: Ana Szarfman with FDA. As suggested by Dr. Jack Bloom several years ago, we need to start collecting data from placebo patients in clinical trials to help us understand the background rates of hepatotoxicity in patients with different diseases and demographic characteristics. As Dr. Bloom suggested, Clinical Laboratory data from Central Laboratory Services for Clinical Trials are an excellent source of standardized, easily reviewable clinical laboratory data. Unfortunately, these data resources are still untapped for this purpose.

We are moving away from a world where clinical trial data are not collected in a standardized way. After we develop data standards and the data are integrated into a common structure with common vocabularies, we will be able to more easily re-assess the data collected in the past and in future: http://www.cdisc.org/publications/interchange2007/session11/JayLevineJanusSafety.pdf (Dr. Jay Levine). This will improve our understanding of potential risk factors for hepatotoxicity, including the risk of congestive heart failure and other concomitant conditions, and the risk of drug-drug interactions.

When dealing with individual patients it would be useful to be able to graph using a common time line, not only the flow of lab results, but also the flow of concomitant medications (with their start and end dates), concomitant conditions (with their start and end dates) using the same time scale. Normal lab results can be shown in black, high warning and panic values in red and low warning and panic values in blue, to facilitate interpretation. With this type of display, we will be able to quickly identify missing data and potential risk factors in individual patients.

One more comment, I think that we may have clinical trials in house to assess the efficacy and safety of drugs to treat tuberculosis, I don't know for sure if we have such trials. If this is the case, we may want to review these data before we plan the next clinical trial to assess the hepatotoxic profile of isoniazid. Thank you.

DR. WATKINS: Okay. I think, Mohamed, you're next.

DR. MOUELHI: Mohamed El Mouelhi, Novartis. Within the eDISH, have you looked at the correlation of, instead of the bilirubin, to look at other liver function like INR for example?

DR. WATKINS: John.

DR. SENIOR: The answer is no, because it isn't usually measured. We can't look at it if it wasn't measured, and bilirubin is a routine measure. Transaminase is a routine

measure. We don't have studies done where INR is routinely measured. So obviously we can't look at it.

DR. MOUELHI: How about albumin?

DR. SENIOR: That would be valuable if it were done. Alkaline phosphatase is routinely measured.

DR. WATKINS: Albumin.

DR. SENIOR: Albumin is not. We can only deal with what sponsors do in their protocols. If they don't get the tests, we can’t do the analyses.

DR. WATKINS: Okay. I hear we're ready to go. We will take one more unfortunately and then we'll get back. There is in the document, there's one place where it mentions INR in addition to bilirubin but then there's no mention of it in terms of Hy's Law or any of those other issues. Okay. Last question before we move on.

DR. PIERCE: Ross Pierce, FDA/CDER. We've been looking so far at completed studies, large clinical-based Phase III trials for the most part. But we also have a responsibility to monitor the safety during the course of product development, while Phase III studies are going on, and while smaller Phase II studies are going on. So I have a particular interest in early signals and I'm curious, for example, whether different cut points for ALT, like 15 or 20 times the upper limit of normal, whether certain incidence of those is seen in smaller trials. We may not have the numbers to have Hy's Law cases,

whether those actually predict as you increase the sample size that you're going to start to get Hy's Law cases. So I'm curious if anybody has data on that.

The other point that I'd like to make is I think Bob Temple's point was very well taken but I don't think we can completely ignore in earlier stages of product development cases where there's a potential Hy's Law case but we find that there are alternative explanations for liver abnormalities. Going back to John Senior's presentation, we have to remember there may be unique factors in the individual that prevent that person from adapting and recovering during the course of continued treatment. So if they have another explanation we may be in a situation where there's a combination of factors, including the patient that's being tested and the underlying condition that together are making the clinical situation worse than it might otherwise be. So in the course of it, I think we have to investigate those cases and maintain our index of suspicion as well.

DR. WATKINS: Well, there're obviously some complicated issues there and maybe we can pick this up best in the discussion either right after our two speakers or later, but let me just go on.