DISCUSSION IB

DR. WATKINS: Okay. Now we're going to come to the discussion. I'm going to take moderator's prerogative to have a little fun. Where's Bob Temple? Don't tell me -- oh, there he is. Can you come up -- we need you permanently at a microphone here for this next section. I hope you don't mind, and also I think John Senior needs a microphone to respond, and can we go on to 12:30? Is there any reason we can't?

MS PAULS: No.

DR. WATKINS: We can't?

MS PAULS: Yes, we can go to 12:30.

DR. WATKINS: Oh, we can. Okay. Good. All right.

I think it's safe to say these two gentlemen had the heaviest hand in coming up with the Guidance document. Isn't that fair? Because one of the goals is to try to come to consensus and make sure there's agreement. So I would propose to ask a series of questions. We'll get their responses to them, and then for people who feel they have an important point or in some way have a point that needs to be made, I will run out to get you a “mic” unless you're near that mic there.

The first question is stopping the investigative drug in a Phase III trial when ALT goes over eight times. Are there any data for the eight times upper limit of normal? Do you feel that's reasonable? Where did it come from, the eight

times upper limit of normal in a Phase III trial absent eosinophilia, hypersensitivity, symptoms?

DR. SENIOR: I think that eight times was a figure you mentioned at the January 2007 conference. There're no data to support it. It's just an opinion-based idea. It was in that verbal response to the concept paper that you provided last January.

DR. WATKINS: Yes.

DR. SENIOR: I think the idea behind it was that maybe three times elevation is not enough of an elevation to be important always.

DR. WATKINS: Bob?

DR. TEMPLE: Well, there's also a consciouness that a fair number of people have a little bit of injury at onset, but then recover, and you want to get a chance to observe that, but you don't want to endanger people. So at what level you stop is arbitrary. I mean if someone said seven-fold, we wouldn't argue.

DR. WATKINS: Does anybody feel strongly that that recommendation should be changed in the Guidance? Mohamed? But these are questions related to the eight times cutoff only, no other.

DR. EL MOUELHI: Yes, how will the investigator stick to this tough criterion and how comfortable he will be to see the patient going that high in term of his liver enzymes and

continue the drug? That's a leading consideration.

DR. TEMPLE: You know, the Guidance presumes that individual investigators who are more nervous can stop earlier and an IRB could say, oh, heck, no, you can’t go on to 8-fold. So this is just our best guess. We're just suggesting what seems reasonable. Nobody would argue that there are data.

DR. SENIOR: There are no data and we need data. We ought to be getting away from opinion-based rules, which we hope to do by doing appropriate studies.

Now it should be appreciated that the height of the transaminase is not a very reliable measure because you measure transaminase at some given time. You don't know whether it was higher yesterday than it is today, or it might be higher tomorrow than it is today, but you don't measure it every day. You just measure it whenever you measure it. So we don't really know whether that's a peak value or not a peak value. We just don't know. And therefore to make rules about it seems to be a specious argument.

In order to make a true assessment, you've got to get serial data. You've got to measure it every day or two or three and watch which way the serum enzyme activity is moving. Otherwise, we can't get anywhere with this. We're just going to be arguing in circles.

DR. TEMPLE: It could also depend on how much prior data you have and what the drug is for. I mean your attitude

towards a new anti-HIV drug and an eight-fold elevation that is providing important treatment you didn’t have before, is going to be totally different from a drug with no identified major value. All of those things go into it. I don't think anybody was trying to say absolutely we know what to do.

DR. WATKINS: Jim.

Dr. FRESTON: That was my point. It depends on what benefit one is getting. If you're studying a new, for example anti-neoplastic, drug, and you're getting a clinical response, it would be ridiculous to stop at eight, for example.

DR. SENIOR: It took forty years, Jim, to resolve that issue for isoniazid. Isoniazid was very early appreciated to be an important drug to help save people's lives, yet in 1992, a very prominent liver consultant said it's too dangerous to use.

DR. TEMPLE: On the other hand, it's all relative. The MAO inhibitor iproniazid was long gone by then (as it deserved to be), because it offered nothing special.

DR. WATKINS: Okay. I'm going to go onto the next question, and I hope you can hear me. Yes

DR. SENIOR: Go to the microphone and give your name.

DR. WATKINS: The reason is it's being recorded.

DR. SENIOR: I want to emphasize that this is a public meeting. Everything shown and said is in the public domain. It's going to be on the worldwide web for everybody to

see. So it's a public meeting.

UNIDENTIFIED SPEAKER: Just a minor clarification. I assume that the threshold of eight times the upper limit of normal here implies that it's considered to be a drug-related elevation. So if you do a study in population prone to liver enzyme elevations, would you still consider stopping the drug at eight times the upper limit of normal?

DR. SENIOR: Well, I think Don Rockey just addressed that point. Just the abnormality of the test doesn't tell you what the cause was. The attribution of causality is critical. As Bob Tipping showed you, you can see elevations in placebo patients. They're not Hy's Law cases. It simply points out that what Hy observed was an important principle, that when you get enough liver injury, with elevated transaminase, or from any cause, whether it be viral hepatitis or drug, and it's associated with jaundice, it's an important finding. All of Bob Tipping's cases, all six cases, had elevated ALTs and bilirubins. They all had disease not drug-induced injury. They weren't Hy's Law cases because they weren't caused by a drug, but they exemplify the importance of the observation. The combination of enough injury to produce jaundice was important clinically.

DR. TEMPLE: I want to mention one other thing about Hy's Law. This is clear in the Guidance. Ordinarily, the small number of Hy’s Law cases arise on a background of a drug

that causes relatively large increases in transaminase rises to 3x, 5x, 8x the upper limit of normal in people on drug, e.g., more frequent 3-fold transaminase elevations, 2 percent on drug versus 0.5 percent on the control agent. That finding alone might not signal an important potential for severe injury. But if there are a couple of people with hepatocellular injury who also get elevated bilirubin, showing that the injury can be very substantial (Hy's Law cases), we take that as a highly sensitive and specific predictor of real trouble. There have been cases of drugs with fairly high rates of transaminase elevation, sometimes quite large, but without Hy's Law cases. Aspirin is a commonly cited example.

DR. WATKINS: Well, tacrine is another example of a clinical trial being treated up to ALT 20 times the upper limit of normal and some people went higher and the drug was stopped but other people turned around and came back to normal without stopping the drug. So they were asymptomatic.

DR. TEMPLE: But they had a lot of experience by the time they did that.

DR. WATKINS: Yes, that's correct.

DR. TEMPLE: You sort of knew that a lot of people got over it.

DR. SENIOR: Transaminase elevation is not proportional to the extent of the injury. It's important. Here's Dr. Kaplowitz who will explain.

DR. WATKINS: Neil, do you want to say something? I think we have to move on. So there won't be another comment after this. I'll just stop it.

DR. KAPLOWITZ: I would just say that, as a note of caution, I was impressed with one of the examples that was shown of a case where the patient was monitored and the ALT went up. The bilirubin was normal when they stopped the drug, but the patient went on later to develop acute liver failure. So the response or course of an individual developing DILI can vary. We saw that with troglitazone, and with ximelagatran. I've seen it with antituberculous drugs on occasion, and a combination of antituberculous drugs. And so although you can cite tacrine and statins and all these examples, my concern is that there may be situations where in the case of a particular drug, the train leaves the station and you can't stop the train. So that is just a point of caution.

DR. TEMPLE: Absolutely right. The definition of Hy's Rule really didn't give any time limit for the bilirubin elevation. If you get liver injury, hepatocellular liver injury manifested by transaminase elevation, and if the bilirubin rises later, that's plenty of trouble. So that counts in my book as a case and the timing varies as you said.

DR. SENIOR: They don't always go up together.

DR. TEMPLE: They don't go up together.

DR. SENIOR: You noticed it in the case that Kate

Gelperin showed. The transaminases went up first, and it was quite a while, a couple of weeks, before the bilirubin started to go up. So if you took an action on the transaminase by stopping the drug and observations, you would have missed the bilirubin rising. It was already happening.

DR. TEMPLE: That is why when the transaminase goes up a lot, and if you don't have enough experience to know what that means, you tend to stop the drug. Later on, if previous cases were all benign, then you might wait somewhat longer.

DR. WATKINS: Just to point out, the eightfold is in Phase III trials where presumably you already know quite a bit. It's just a guideline.

Let me move on. The next question is Hy's Law definition. And the first iteration of the draft Guidance, they talked about that it wouldn't be a Hy's Law case if there was a substantial elevation in alkaline phosphatase. In the current version it's two times the upper limit of normal or greater alkaline phosphatase and I'd like to hear thoughts on that.

DR. TEMPLE: Well, the trouble is you don't have a whole lot of data to develop rules from. The general idea is that Hy was talking about was a relatively pure hepatocellular injury but, of course, we all know that if you get enough hepatocellular injury, you get a little obstructive component. So how to deal with that is the problem.

But if what you're basically seeing is the drug that gives you a hepatocellular injury and now you have a case that is mostly hepatocellular injury, not much alkaline phosphatase elevation, you should be very worried, but we don't know how to say exactly how high.

DR. SENIOR: The ratio of 5 that Don Rockey mentioned was developed by that CIOMS group in France, and was meant to be applied to the initial elevations of transaminase and/or alkaline phosphatase. It was not meant to be taken at sometime much later, weeks or months later, when a person was already green. It's not applicable then. It's only the initial event. Is the initial event cholestatic (high alkaline phosphatase), or is the initial event hepatocellular (high transaminase)? If you don't have data on initial event, you can't use it very reliably, and often the onset of the liver injury is missed. You don't see the patient. The problem is not detected until weeks later. So we're not talking about onset. We're talking about the date of detection or diagnosis, whenever that may be.

DR. TEMPLE: The cholestatic finding is often an indication that the person has some other disease, some cancer that's growing or stone disease or something else.

DR. WATKINS: Any comments about the alkaline phosphatase? Jack? Any other comments about the alkaline phosphatase? Chris?

DR. HUNT: Christine Hunt from GlaxoSmithKline. I'm

just curious about whether perhaps more successful would be using the R value, the ALT over alkaline phosphatase ratio greater than five, and just sort of ignoring the other alk phos because it'll be factored in by showing hepatocellular injury. It's what the DILIN group uses, what we came to use and, you know, just using that coupled with the bilirubin greater than two and ideally, you know, greater than -- percent direct or, you know, predominantly not indirect.

DR. TEMPLE: I mean the reason for the bilirubin of two or thereabouts --

DR. HUNT: Yes.

DR. TEMPLE: -- is as a rough crude measure of how much liver you injured.

DR. HUNT: Right.

DR. TEMPLE: And what I observed is if you injured enough to make people yellow, it's ominous that some of those people are going to die. So the rule is just trying to do that. If some of the bilirubin elevation is because of obstruction, it doesn't carry the same implication.

DR. HUNT: Right.

DR. TEMPLE: So that's why you try to, in one way or another, minimize it. What the best way to do that is I don't know. Maybe the ratio is the best way. I don't know.

DR. HUNT: Julie Papay and others at GlaxoSmithKline looked at rechallenged cases that were Hy’s Law cases, and

looking at those, you could potentially exclude some patients that appear to have at least possible or probable drug-induced liver injury if you use the alk phos less than two. So the hepatocellular rule, you know, the ALT over alk phos greater than five that has bili greater than 2 or even greater than 3, seems to capture, the Hy's Law cases --

DR. TEMPLE: So this proposal is looking at the ratio of --

DR. HUNT: Yes.

DR. TEMPLE: -- transaminase elevation to alkaline phosphatase.

DR. HUNT: Yes, because if you have an ALT, you know, 40 times the upper level of normal, and alk phos, it's 3 times, and the bilirubin is 3, 4, or 5times. I think that's a Hy's Law case --

DR. TEMPLE: For what it's worth, usually the transaminase elevation is considerably more than threefold.

DR. HUNT: Right.

DR. TEMPLE: I think that the threefold level is a way to look at the rest of the population. If you look at the ratio, the rate of threefold elevations in drug, placebo, whether it's fivefold elevations or sevenfold, you find something there and then you find one or two Hy's Law cases that are plausible and then you've got a drug that historically is in trouble.

DR. WATKINS: Chris, are you showing those data this afternoon or not?

DR. HUNT: No. Julie Papay will.

DR. SENIOR: Well, we're going to look at the GSK data. Chris is right, quite right, but what we're trying to say in the draft Guidance is when you see any of these signals, whether it's threefold, eightfold, whatever, start watching the patient closely, serially. There's no one measurement on one day that's going to give you the whole answer. It's the time course. It's so critical and unless we collect that data, we're going to be arguing forever and never settling these questions. We must collect the data. We must watch the patient closely, serially, to find out.

DR. WATKINS: Okay. Next question is if you look at the definition of Hy's Law, there are three components. There's the background of a higher incidence of ALT, relevant to the other population. We heard Adrian Reuben mention the so-called “Rezulin Rule” of two percent. It's not in the Guidance. Should we just put it to bed and never talk about it again?

DR. SENIOR: No, no. Jim Lewis started to come up with a catchy phrase. I call it Temple's corollary, instead. It's the same idea. We're talking about the disproportion between the experimental drug and a control drug, whether it be a placebo or some known non-hepatic toxicant. If there's a

disproportionate, if there's a higher incidence of transaminase elevations with the experimental drug than in the control drug, look at it. It becomes a signal of interest and I threw up the term Temple's corollary like Bob said, and Jim Lewis called it Rezulin Rule because it was applicable to that drug.

DR. WATKINS: Well, he applies it, the absolute number of two percent to it.

DR. SENIOR: Well, there isn't any absolute value -- it's just a higher incidence.

DR. WATKINS: Okay.

DR. SENIOR: You saw it in the data there with the date that Ted showed, with the graphic, the ones in the right lower quadrant had elevated transaminases.

DR. WATKINS: Right, and clearly a difference between drug-treated and controls --

DR. SENIOR: There were seven times as many on the experimental drug as there were on the control. There wasn't some absolute percentage but it was seven times as much.

DR. TEMPLE: For all the drugs that I can think of that went very bad very fast, troglitazone and bromfenac, there was always an excess (2 or 3 to 1) of 3-fold elevations, and usually 5-fold, 8-fold, etc., elevations.

DR. SENIOR: It was 7 to 1 in the case shown.

DR. TEMPLE: Sometimes all you will get is the transaminase signal. If the rate of severe injury is low, say 1

in 50,000 with a Hy’s Law rate of 1 per 5,000, you may not see any cases in even a large clinical trial.You still might see some transaminase elevations. For nefazodone, there were no Hy’s Law cases but I believe there was an increased rate of transaminase elevations. With bromfenac, where the the serious injury rate was higher (perhaps 1 in 5,000 or 10,000, there were Hy’s Law cases, probably at a rate of about 1 per 1.000.

DR. WATKINS: Comments about that? Good consensus. Okay. Next thing. The third criterion for Hy's Law cases is that no other reason can be found to explain the combination of liver chemistry abnormalities, such as viral hepatitis or another drug capable of causing observed injury. It doesn't say that a more likely cause exists but presumably that's what's meant. Then there is question of who does the causality assessment? Does everybody now need to get expert panels or can they use the RUCAM? Comments please.

DR. SENIOR: The first thing you have to do is to decide whether it's disease or drug. Then after that, you often run into the vexing problem that there are many drugs being given and you don't know whether it's Drug A, Drug B, or maybe the combination of taking both drugs at once. We don't know the answer to that.

DR. TEMPLE: Remember the numbers. Any marketed drug may cause serious liver injury in well under 1 per 10,000, except maybe for INH. So in clinical trials, any given case of

hepatocellular injury is not likely to result from the drug. Now if they've just taken an overdose of acetaminophen, fine, then you have an alternative cause, but most of the time the fact that people were on something else with some potential for for liver injury is not a terribly good explanation. On the other hand, acute viral hepatitis is.

One of the things we found and I think the Bob Tipping analysis shows that, if you watch people somewhat longer, sometimes the reason turns up. They bounce again while off therapy. They drink lots over the weekend or who knows what, and so following these people longer to see if there's another cause is very, very important to deciding whether you really have a Hy's Law case.

DR. SENIOR: Yes, Bob's sixth case showed up later. There were five early cases: two were acute viral hepatitis. No problem. Two were gall stones in the common duct. One was an amyloid infiltration of the liver. The sixth patient was taken out of the study because of minor transaminase elevations before jaundice had appeared. Jaundice appeared later when the patient was off study and the data were not included in the study database. It turned out to be a carcinoma metastatic from the colon to the liver that killed that patient. It's a hard problem -- you've really got to get the data, and get the follow up. You can't just pick one set of numbers at one time and decide on that.

DR. WATKINS: Okay. So we do mean for number three a more likely explanation, right? And then we still haven't answered the question of who does the causality assessment and do they use an existing tool or we're just not there yet and so it does not belong in the document?

DR. SENIOR: Right now we've used the RUCAM and backed off the RUCAM, and the DILI network has decided that expert opinion is maybe better than anything at the moment, but we're still not there yet. And that's what Don Rockey was saying and Tim Davern, who is another one of your DILIN investigators. We need better tools, and we hope that the DILIN network reincarnation II, the next five years, will provide that.

DR. WATKINS: Okay. Comments. Herb?

DR. BONKOVSKY: I'm Herb Bonkovsky, one of the DILIN investigators, and I've served on a number of these expert panels reviewing things and just would like to make a plea. Maybe this is already being done commonly in pharmaceutical companies, but when we have these cases, I find that we really need to tell the investigators, the cardiologists, the pulmonologists, sort of the non-liver guys, what do you need to do if somebody has elevations, because it's very frustrating to us as hepatologists trying to review these cases not to have the data. Don mentioned this as being critical. So make sure that there's no acute viral hepatitis and hepatitis E,

particularly in Europe now, is going up in incidence. It's already quite prevalent in other developing parts of the world and it may turn out that we're going to need to be doing this in the U.S. as well. So in addition to acute hepatitis A, B, C, now we have E to deal with. Imaging is very, very important. Imaging at least with an ultrasound, if not with a CT scan, because again Naga mentioned that, in fact, gall stones can lead to these very rapid and striking elevations in transaminases. So as hepatologists, when we're trying to evaluate these things, we need to know other things. I would say those are the most important. We'd like to know other stuff like autoimmune markers and rule out other things and alcohol and possible other drugs as well, and the other one I would stress is these so-called herbal remedies which in our experience is an extraordinarily common cause, even more common in the Far East as a cause of liver injury.

DR. TEMPLE: Can I just add one thing?

DR. WATKINS: Sure.

DR. TEMPLE: There's an important distinction between a case that arises during clinical trials and cases that are found outside. In clinical trials, historically, individual cases that have led to non-approval of drugs like dilevalol and that showed a signal (e,g., troglitazone and bromfenac), were actually pretty clean. That was also true for many of the ximelagatran cases. Now in the real world outside of trials, to

try to figure out what a person has is much more complicated.

DR. SENIOR: Which is exactly why we've chosen to emphasize clinical trials, controlled clinical trials conducted under protocol with reporting, with good observation, as a much better area in which to discover what's really going on. And Arthur Holden, who is now leading the big consortium for serious adverse events, has agreed to that and the consortium has agreed to that. Clinical trials are the best way to find out what's really going on.

DR. WATKINS: Jim?

DR. FRESTON: Jim Freston, University of Connecticut. Many of us are still seeing in well designed clinical trials the problem that Herb Bonkovsky has raised, and that is an event has occurred and the opportunity was not fully taken to get the facts in real time. There are at least three companies here that I know of that have developed very sophisticated and user-friendly lists, checklists basically, that go out as soon as there is a signal to collect the data while it's hot, and then get it evaluated. So I suspect you may not be seeing these, Bob, because they're getting cleaned up before they get to you.

DR. WATKINS: Other comments? Jack, and any others could line up and I would know you're waiting.

DR. BLOOM: I would really underscore the comment about the night-and-day difference between the clinical trial

and the health care delivery setting, most of which has been addressed by the speakers this morning. But in that context, maybe a more important question than should we stop at eight times elevations of a transaminase, is should we continue when there's significantly less elevations than that? If, in fact, Hy's Law provides far and away the most predictive value (arguably the only signal with predictive value in premarketing setting for DILI), we may want to think about whether we're optimizing the opportunity to detect that signal. I know that there's controversy over how conservative we should be, as regards how patients with these lab values should be managed during clinical trials. However, should we not be encouraging a full exploration of such changes? For example, to not follow up on initial ALT elevations that may lead to a Hy's Law signal (by continuing treatment with careful monitoring) is probably not the greatest thing to happen.

DR. WATKINS: Right. Well, I think that's the intent of saying go ahead and treat up to eight times because in a Phase III trial, because in the real world people are going to get it and they're not going to know their ALT is up if it's asymptomatic.

DR. TEMPLE: It's a good question. I'm sure Sara is going to talk about that tomorrow. There's tension between protecting people and finding out what you need to know, and that tension won't go away. Eight-fold was picked because it

seemed moderately safe, not leading to harm and likely to get you what you want to know because you're not monitoring people every week. They have a chance between visits to go higher if they're going to go higher. I don't know what you tell someone whose transaminase is up to eightfold.

DR. WATKINS: Mohamed?

DR. El MOUELHI: Mohamed El Mouelhi with Novartis. Would it be helpful, since we know that in the premarketing situations and clinical trials in most of the cases, you try to get a blood sample for PK. That would help for causality assessment, especially if it's long term study, to make sure that the patient is taking the drug and also may help in term of mechanisms. Can we do that also for the post-marketing and maybe consider it in the Guidance?

DR. WATKINS: Well, the question is only premarket, right? That's the Guidance and do you have any comments about the role of PK in causality assessment or mechanistic insight?

DR. TEMPLE: Well, one of the things that we're very interested in is whether there's some characteristic of people that predicts who's at risk; who gets trouble, who gets big trouble, who recovers? That's what everybody's looking for, that sort of predictor. If you don't keep blood around so that you can examine it as you get smarter, you'll never find those things. So my dream is that the companies will keep samples of almost everybody (you've got to work through the HIPAA issues)

so that as we learn more and form hypotheses we can check them out. What we now call idiosyncratic presumably reflects some definite characteristic. We don't know if that's true but that's sort of our dream. We will never find out if it's true unless we have the cases and can go back and look. So it seems that as a practical matter, the industry ought to be trying to arrange to be able to do that as best they can.

DR. SENIOR: Even beyond going back looking, go forward with your eyes open. That's a whole different concept. You often can't go back because the whole problem has happened. It's over and gone. It's so important to look at what's happening as it occurs in real time. Collecting samples periodically as the liver injury evolves, so you can find out what's really going on.

DR. WATKINS: Next?

DR. CAI: John Cai from AstraZeneca. I have a single question regarding the criteria used in the draft Guideline, which are all based on ULN, such as ALT above eight times ULN. We know from the speaker this morning ULN is quite variable, and it depends on what reference population you choose. So my question is, will the guideline recommend what kind of ULN to be used for the sponsors? Is there a universal ULN or I mean what's the general approach here, because we are always trying to look at individual patients closely, which is to look at change from baseline. Like in the DILIN approach, one of the

criteria is five times above baseline. So I just wonder if the current draft Guideline has considered this issue.

DR. SENIOR: Dr. Cai, thank you for the question. Naga Chalasani tried to speak to this issue. Upper limit of normal is dependent on the population chosen as supposedly viewed as typically normal. However, we know from the studies done in the Milan, at the blood bank, that a lot of people who are thought to be normal are really not normal. They have fatty liver; they have undiagnosed hepatitis C. So depending on who you pick and how you pick them to be normal, will affect what you use as your range of normal. It used to be that we were worried about different tests that were used but Naga has shown that these tests have now become standardized. It's not the tests that vary so much. It's the population of so-called normals that varies mostly. Isn't that right, Naga?

And unless we get some changes beyond the Guidance for clinical trials, there’s a whole Guidance for the industry that does laboratory testing. They need to clean up the act. They can't allow individual laboratories just to take blood from a few technicians and call them normal. They’re not necessarily normal, but the populations from whom the samples are taken to establish the normal range, needs standardization. And that is beyond our Guidance, Paul, wouldn't you say?

DR. TEMPLE: Yes, but I wouldn't dwell too much on this. Remember, we're talking about studies that have a

control group. So whatever variability there is from one place to another, it ought to be similar for drug group and control. If you see more people in one group getting threefold, fourfold, fivefold elevations, local variations shouldn't matter.

DR. WATKINS: Can I ask for a clarification? You mentioned I think some guideline that's phrased in terms of fold baseline.

DR. CAI: Not guideline, I just heard from this morning's talk from DILIN's approach, there's a criteria used five times above baseline. So I'm very curious --

DR. WATKINS: No, that's not correct.

There is an issue when the baseline is above normal which I guess we'll hear when we talk about preexisting liver disease later, but I am unaware of any guidelines that're fold-baseline which would actually make a lot of sense, but there're no data I think to support some kind of change like that, unless anybody here knows of it.

DR. TEMPLE: It's not going to change the fundamental observation though.

DR. WATKINS: Right.

I think Dr. Gelperin is waiting to make a point, and then I think I'll go onto the next question.

DR. GELPERIN: Actually a question. I'm interested in feedback, especially if there are any study investigators

who are industry study directors, who may be feeling hesitant about continuing subjects after the traditional cutoff of three times the upper limit of normal. One of the things I was thinking about is if patients hit that point, might they be re-consented at least partially to determine whether they'd be willing to commit to come in for the more intensive lab tests, because I think people who have actually conducted clinical trials know that sometimes the patients can vanish or not come in for follow up. They go off to visit their relatives in the next state, and you just sort of hope and pray that they're not still taking the drug, that you wonder what their transaminases are doing.

So I'm just interested whether something formal like a re-consent process to continue subjects with minor elevations might increase the comfort level in some situations or would it just be too cumbersome?

DR. WATKINS: Okay. That question is directed at somebody in industry involved in only Phase III clinical trials. Do any of you want to take it? Are you going to address it anyway or just wait?

DR. HUNT: I think Phase III clinical trials specifically but in terms of the consent question, one of the things -- I'm sorry. Christine Hunt, GlaxoSmithKline. You can certainly prospectively inform patients that if they, as part of just informing them of the general protocol, that if you're

going to be doing this, that should be part of the initial informed consent, that if you have liver changes, that you'll have a conversation with your physician and you'll talk about the risk or benefit of continuing the study drug or stop it and do additional testing. So that should be part of, in my view, the original informed consent.

DR. WATKINS: Okay. We'll address that tomorrow. There's an ethics discussion then. Last question on this topic?

DR. LAMBRECHT: Raf Lambrecht, FibroGen. I'd like to ask clarification of the background ALT issue. A point has been added to the Guidance here in terms of defining Hy's Law cases, requiring it to come out of background of higher incidence than in the control group. It seems like this was not originally part of the Hy's Law definition per se. So I got the impression that the definition of Hy's Law has evolved into what is the risk of a DILI drug, because you actually need to have a database of some size before you can apply this. So how do you define a Hy's Law case when the database is still very small?

DR. TEMPLE: Well, fortunately or unfortunately you're not likely to have a case when the database is very small because there aren't very many for most hepatotoxins. Except for a couple of drugs we've seen recently, it would be extraordinary to find more than two or three Hy’s Law cases in

a several-thousand-patient database because the drug would have to be unbelievably toxic to do more than that, with a serious injury rate of more than 1 per 10,000..

I think the element of an elevated background rate of transaminase elevations, out of which a few Hy's Law cases would emerge was always there but we didn't necessarily think to write it down. The context for drugs that are serious hepatotoxins, whether you're taking isoniazid or whatever, is that there's a very high rate of modest injury and a very low rate, you know, 1 in 1,000 would be a lot, of more severe injury. So you always have that background there. Going back as far as I can remember, there was always a background rate of increased rate of threefold elevations. Actually there was almost always in addition a higher rate of very marked elevations, too, of up to 10, 20 and 30-fold. True, predictable hepatotoxins do that also.

This is not surprising. These are drugs that can do varying degrees of damage and in certain individuals it may be very great, but in a lot of people they do at least some damage. The main problem though is there are some drugs, and we know them, you know, aspirin, heparin, and tacrine is the classic example, that cause a lot of modest injury (just transaminase elevations) and don't, for some reason, kill anybody. I don't know why that is.

DR. SENIOR: The gentleman's quite right. Hy never

said all of this. Some 30 years ago, Hy made an observation. Now when Hy was at our conference in April 1999, within three months of his death, he could no longer speak because of his disease. I asked Hy about this. He refused to use the eponym, Hy's Rule, Hy's Law, Hy's Observation, Hy's anything. He just said it's what I have observed. He wrote it down. He couldn't speak it. So all of this business about Hy's Law and Hy's Rule, whatever, is all made up by Bob Temple and by us. (Laughter.)

DR. TEMPLE: You mustn't call it Temple's corollary.

DR. SENIOR: I won't call it Temple's corollary anymore.

DR. WATKINS: Okay.

DR. LAMBRECHT: Can I refocus the question then on the definition of Hy's Law? Would you then say that the case of an individual basis cannot be called a Hy's Law case until you have minimum database around it?

DR. WATKINS: The Guidance would suggest that.

DR. TEMPLE: You certainly would if you saw a case in the first 10 subjects, you'd worry plenty about how high the rate is and would watch very closely, but if nothing else happened by the time you had your whole database, and still with just one Hy’s Law case, you would look at it carefully as usual. What to do with such an early bad case doesn’t seem clear. In cases where we've seen early Hy's Law cases, it was

always in a setting where there were plenty of other people who had transaminase elevations.

DR. SENIOR: Bob Tipping just told us this morning about 6 cases out of 3248 patients observed who had laboratory findings but they were not Hy's cases. They weren't even on a drug. They were all due to disease. So just finding some laboratory elevations doesn't prove anything until you've done your causality assessment.

DR. WATKINS: Okay. Two more quick questions. We have just a few more minutes. Since Gilbert's syndrome is so common, why aren't we just measuring conjugated bilirubin rather than total bilirubin?

DR. SENIOR: Because it's not being done. We would be glad to have it if they would just measure it. They very seldom measure conjugated bilirubin. Besides, you're not talking about conjugated bilirubin anyway. You're talking about direct-reacting bilirubin. That goes back to 1916, when it was noted that when you add the diazo agent to the sera, some of them react directly and some of them you had to add methanol then to get the total bilirubin. So the direct reacting bilirubin is a very crude estimate of truly mono- or diglucuronidated bilirubin, conjugated bilirubin, a very crude measure. And it isn't routinely done anyway.

DR. WATKINS: Okay. And the last question actually in the Guidance, this is on page 7, it talks about retesting.

So if you have abnormal values, to retest within a couple of days, and it says the need for prompt repeat testing is especially great if the aminotransferase is greater than three times upper limit of normal or total bili is greater than two times the upper limit of normal. Can we assume that the drug should be stopped if the patient fits Hy's Law? There's no confirmation of that.

DR. TEMPLE: If the transaminase has gone up and the bilirubin has gone up, I would say definitely stop it. This represents substantial injury.

DR. WATKINS: Okay. So a no repeat verification in that case.

DR. SENIOR: Nobody today would have the courage to do what Mitchell did and let those patients continue on the drug for a year --

DR. WATKINS: Right.

DR. SENIOR: -- even though they all recovered. Right now nobody would do that.

UNIDENTIFIED SPEAKER: He didn't do it knowingly.

DR. SENIOR: Well, I know that. He didn't do it knowingly, but I say today we would be extremely nervous about doing such a thing. I guess that's the answer. We've learned something since 1975.

DR. TEMPLE: We know that some people who have both those things will recover, but we also know that some won't.

So you don't really want it.

DR. SENIOR: We don't know what distinguishes the difference.

DR. WATKINS: Yes.

DR. WATKINS: Any last words on the session, any review?

DR. SENIOR: Good session.

DR. WATKINS: If not, let's give a round of applause and we'll be back here after lunch.

(Applause.)