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OPEN SESSION

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8:05 a.m.

Hilton Hotel
Maryland Room
Silver Spring, Maryland

PARTICIPANTS

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Cicely Reese, Pharm. D., Designated Federal Officer

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Richard H. Haubrich, M.D.
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C O N T E N T S

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P R O C E E D I N G S

Call to Order

DR. SHERMAN: Good morning.

Go ahead, Dr. Reese.

Conflict of Interest Statement

DR. REESE: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.

This meeting is being held by the Center for Drug Evaluation and Research. The Antiviral Advisory Committee meets to discuss clinical trial design issues and the development of products for the treatment of chronic hepatitis C infection.

The primary objectives for the committee deliberations are to discuss issues related to the identification of appropriate control arms, populations for study, endpoints and long-term follow-up.

Unlike issues before a committee in which a particular product is discussed, issues of broader applicability, such as the topic of today's

meeting, involve many industrial sponsors and academic institutions.

The committee members have been screened for their financial interests as they may apply to the general topic at hand. Because topics impact so many institutions, it is not practical to recite all potential conflicts of interest as they apply to each member.

The Food and Drug Administration has prepared general matters waivers for the following Special Government Employees:

Drs. Raymond Chung, Richard Haubrich, Janet Andersen, John Vierling, Douglas Fish, Kenneth Sherman and Karen Murray, who are participating in today's meeting, Karen Murray as of yesterday only.

Waiver documents are available at FDA's Docket web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all the waivers can be obtained by submitting a written request to the

Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussions before the committee, these potential conflicts are mitigated.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Eugene Sun is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Sun's role on this committee is to represent industry interests in general and not any one particular company. Dr. Sun is an employee of Abbott Laboratories.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with

any firm whose products they may wish to comment upon.

Thank you.

DR. SHERMAN: We are joined by another member of the committee today.

Dr. Paxton, do you want to introduce yourself?

DR. PAXTON: Good morning. I am Dr. Lynn Paxton. I am with the Epidemiology Branch of the Division of HIV/AIDS Prevention at the Centers for Disease Control and my particular specialty is antiretroviral chemo prophylaxis for HIV infection and microbicides.

Questions/Discussion

DR. SHERMAN: Thank you.

Today, we have a number of more questions to go through and try to arrive at some consensus response for the agency. We are in 1b and 1c and I am sort of going to combine these, because the first thing we need to do is make sure that we are all in agreement on a series of definitions in treatment-experienced populations.

The terms that I would like to describe are the issue of what is a null responder, which we talked about extensively yesterday, what is otherwise a non-responder, what is a relapser and what defines breakthrough.

Would anyone like to begin? No one has any energy this morning? Dr. Chung, we are going to start with you.

DR. CHUNG: I would think that a null responder--I mean I think we, based on our discussions yesterday, felt that it would be important to distinguish the non-responder, partial responder and responder relapser groups.

I think from the standpoint of defining the null responder, I think I would propose a reasonable definition might be the lack of reduction of HCV-RNA or HCV-RNA reduction less that 1 log at 12 weeks from baseline HCV-RNA.

A partial responder might be described as someone who achieves a 1 log reduction, but less than 2 log reduction by Week 12 of treatment, and a responder relapser might be defined as someone who,

of course, achieves clearance of HCV-RNA by Week 24 of therapy, but then subsequently experiences--excuse me--by end of therapy, Week 24 and end of therapy and then experiences recrudescence of HCV-RNA in the follow-up period.

DR. SHERMAN: Okay.

DR. CHUNG: And, of course, just any response we defined yesterday.

DR. SHERMAN: Could you clarify how you would define what you called the responder relapser at the end of therapy, because it seems that the test used would make a significant difference. In other words, a highly sensitive TMA assay or real-time PCR assay may give you a positive result, which would have caused you to classify the patient as a non-responder rather than as a responder relapser and, if that is the case, if it is simply an issue of the test, is there any intrinsic difference between those two?

DR. CHUNG: I think this gets into an extremely moving target and it would be hard for us or the agency to define what that target is at any

given moment in time.

It may be important to simply say that at least according to 2006 guidelines that we should try to achieve RNA undetectability at the end of therapy using a qualitative assay with a lower limit of detection of under 50 IUs per milliliter and that would subsume, of course, the higher sensitivity TMA and other assays including real-time PCR, et cetera.

I think we have to leave it a little bit open-ended or leave a little wiggle room for the fact that there is going to be ongoing and evolving variability of sensitivity of assays, so I would propose some slightly open-ended definition.

DR. SHERMAN: I am pushing on this question because we currently do define these relapsers as a different class and they have been excluded in many prior trials of non-responder patients.

I think we, as a committee, need to clearly define do they really represent a different class of patient, or is it just another type of

non-responder, because ultimately, the question is can we combine these groups and treat them the same in future trials.

DR. CHUNG: Well, I think you are defining them as kinetically different, right? I mean I think that the partial responder has a less steep curve and they may be on a path toward clearance, but it's a lot more attenuated path.

So, I grasp that this group could be lumped at some sort of fundamental conceptual level. But I think, moving forward, given the difficulty recruiting non-responder patients we talked about yesterday, I think it might be reasonable to consider potentially stratifying a non-responder study design to include certain--or stratify for these, what we would characterize as responder relapsers versus those who we would more characteristically classify as the more classic, you know, either partial or non-responders.

I think that the distinction should be made for the purpose of stratification, but I think it would be important to try to maximize

recruitment to non-responder trials and potentially consider including responder relapsers if we were to define them as being sensitive or positive by a very sensitive assay at the end of therapy.

DR. SHERMAN: Okay. Dr. Andersen.

DR. ANDERSEN: What I would want to ask is whether there is an anticipated difference in the EVR rate to second line treatment or a second round of treatment in these groups, and also SVR, especially in some of the proof of concept studies, it is likely the EVR is going to drive whether we think something is looking good or not.

So, if you have got one group that potentially could have a very high EVR rate and another group that could potentially have a very low rate, even with stratification you are going to get a very mixed message coming back.

DR. SHERMAN: Dr. Havens.

DR. HAVENS: The other issue, and these are brilliant definitions which outline it very clearly, but yesterday, the point came up that it is hard to get the data on patients who weren't

yours at the time of their initial treatment.

So, I think one thing that we could perhaps be helpful with in a very practical kind of way is when you are trying to identify people and where they belong in these groups, what data are you willing to accept, because the reality of trying to get data from another location, sometimes another city, is really a difficult burden I think.

So, as perfect as these are, and if you had the patient in your study, you could get the data perhaps, in a real world situation, is there a difference or is this the only way you are going to allow them to be defined?

DR. SHERMAN: I think that is one of the issues we need to wrestle with here, because in the real world, as Dr. Lindsay said yesterday in her open mike comments during the public session, in the real world, the majority of patients are experienced, but their exact classification remains unknown.

DR. HAVENS: Right, so given that, how can we identify groups that would be satisfactory for

interpretation of the study we are talking about with real world data, is there a way to solve that problem?

DR. SHERMAN: Dr. Haubrich.

DR. HAUBRICH: So, this is very similar to what we have been facing for the last 20 years with HIV therapy except there it is even more complicated because you have people coming in that have been on therapy on 15 years and have had 10 regimens and 15 different drugs and so the probability of even capturing drugs they were exposed to, more or less the order and responses thereof, is very little.

So, to some extent, the success of recent studies of new classes of agents has been successful, because all of this prior exposure history may or may not be relevant to the exposure to the new therapy.

Now, getting someone to undetectable, if you need interferon, then, it will be relevant, however, looking for early viral load reduction for proof of principle, it may be less. So, I think it

depends on the overall aim of the study.

If you are doing a study which is an endpoint study where you are looking for SVR, then appropriate controls that allows you to ferret out these various categories, I think is the way to go because you can spend a lot of time trying to get this data. In the end, all you do is really drive your study coordinators bonkers.

DR. SHERMAN: Dr. Seef.

DR. SEEF: We have generally accepted the fact that whole categories--the total null responder, the partial responder, the breakthrough while on treatment and then the relapser--I wonder whether the first three--the first three require that whoever has performed the treatment had to do regular testing during the course of the treatment and, if they hadn't done it, then, you cannot distinguish among those three.

I suspect that most people who treat individuals with hepatitis C get an end of treatment response and, hopefully, a relapse would be identified if they follow the guidelines by

checking six months later. I think the relapser is different from the others because I think the sense is that the relapser is more likely to respond, for example, to a second course, whereas, I don't know that there is really a distinction between the partial responder and the null responder with respect to retreatment.

So, I wonder whether it's worth lumping everybody together who hasn't responded except for the relapser, because the relapser, we should be able to I think in the clinical setting have much of the information that permits us to distinguish that one from the other three.

DR. SHERMAN: My experience, I think you would be surprised at how often that doesn't happen. For the practicing clinician in the community, frequently, the issue is at some point I want to know if the virus has gone, the patient will complete their therapy and come to the office 3 to 10 weeks later where a viral load is done and, if it's positive, they are told that they didn't respond, but, in fact, they may have relapsed, so

you don't have that classification.

DR. SEEF: You think that they should all be lumped together as one.

DR. SHERMAN: No, I am asking. I am not sure what to do here. I think there is the ones that don't completely achieve clearance and those that are relapsers probably are not that different from each other. They are just at a different point on an arbitrary 48-week curve.

Tracy Swan.

MS. SWAN: It is hard to chase precise treatment data around, but I think some patients' self-report can really be relied upon, like someone is going to know whether they were on interferon for 3 months or 12 months depending if they got discontinued because they didn't have an EVR, or if someone spent a year on interferon, I think they would really have a sense of what their response was at the end of treatment if they get tested then. That is the big "if," but I think maybe there is a simple self-report form that could be used to capture some of the things we are wondering

about.

DR. SHERMAN: Dr. Vierling.

DR. VIERLING: Well, I very much agree with Leonard's analysis that there are four groups and I think most readily identifiable from self-reporting, as well as from prior records, will be the relapser based on negativity as an end of treatment response.

I am very concerned that historically, there has been very little traction in the practice community of using an early virologic response for decision-making.

Therein lies a problem with applying the definitions immediately. I think you are addressing that, Dr. Sherman, by saying that maybe it's just delayed and perhaps we are going to end up needing to lump, but I truly think that the relapser is a different population kinetically and based on that end of treatment response and, therefore is more likely to be retreated, particularly if they are retreated with a regimen that contains interferon again.

The historical experience is they will re-respond and then we have the issue of whether the addition of new agent will then lead them to a sustained virologic response. We have obviously nothing that we can infer for the null responder at the opposite end of the spectrum.

I am also concerned about the flip side of what you asked about the lower limit of detection sensitivity of the assay, because to do an EVR, both in the trials and ultimately in practice, requires attention to the variability of the upper limit of detection, the dynamic range of the variable assays that are being used in clinical laboratories throughout this country, because one cannot calculate accurately an EVR unless you knew accurately where you started from.

Very often we have assays that may underestimate the viral load and thus now allow us to accurately define a 2 log or greater drop at 12 weeks. I think this needs to be addressed both in the studies but, ultimately, in the practice community.

DR. SHERMAN: Dr. Andersen.

DR. ANDERSEN: A modest proposal to throw on the table just to consider would be those who have an undefined history, so you are not sure where you are and those who you know have relapsed after end of treatment target those subjects for studies that have an SVR as the primary endpoint, those where you have a good knowledge of whether they are, in fact, a null responder or a partial responder, target those subjects for studies with an EVR endpoint, obviously, that would then go on to and SVR endpoint.

But otherwise I think it would be very hard to define what is going on with EVR and follow-up studies if those with either an unknown history or those where you expect a high EVR rate, because they have shown themselves to be responsive are included.

DR. SHERMAN: So, to clarify what you are suggesting, you are suggesting that the less well defined patients go into the larger trials with SVR as an endpoint, but that the better defined

patients are the ones that perhaps should be in the pilot trials, the Phase II trials because you can better guess exactly where they are.

DR. ANDERSEN: Well, clearly, the second group would also be eligible and invited to go into the large studies.

I wouldn't restrict them to not be able to at all, but more the other way around, restricting those where you potentially expect a very high EVR rate, but unknown, or have no idea what to expect, then, they came to you with virus, they did not get an SVR, so to then seek SVR, you know, seems to be a good endpoint there.

DR. SHERMAN: Dr. Chung.

DR. CHUNG: I think there are some merits to that proposal, Janet, but I would caution that using EVR as a primary endpoint for the new classes of compounds would be like setting a very low threshold to achieve in that we are seeing some pilot data and early phase data that many of these compounds are capable of achieving the traditional 2 log reduction in patients.

So, what I am afraid of is that everyone will surmount the bar, you will have 100 percent EVR, upwards of 100 percent EVRs among these populations because of the intrinsic properties of the antiviral compounds.

I think the idea is a good one. I still think SVR may have to still be the endpoint on that other group.

But, Mike, I wanted to comment on just this concern about recruiting patients for non-responder trials. I mean we have this vexing problem historically. I mean everyone has spoken to this, how do we get around that.

I think the practical way around it is to essentially have these patients retreated with a lead-in type of phase to redefine them as non-responders in a lead-in type of format of 12 weeks to set the bar and have absolute data to essentially pedigree them as such.

That is an expensive proposition for industry. The other possibility would be to take patients and having them, if you will, roll over

from other trials at which they were deemed to be non-responders or non-EVRs from those trials, well defined.

That would require some degree of cooperativity between industry sponsors to define such patients where there are two or more companies involved, for instance, but I think there is going to have to be greater effort to try and identify just those types of patients in an effort to maximize recruitments for these non-responder trials.

DR. SHERMAN: Dr. Seef.

DR. SEEF: To get back to the issue that I raised with you, just to remind ourselves we have RVR, which is 4 weeks, we have EVR, which is 12 weeks, we have ETR, which is the end of treatment and then we have SVR. All the trials that were done did not have EVR or did not originally have RVR, and at end of treatment response that was the issue.

Now, when I say to you that I thought that's the distinction between the relapser,

because the relapser is the person who gets to the end of treatment, is negative, and the relapses--and surely, your comment about the fact that many people don't know, it seems to me when I was treating people at the VA, and I treated hundreds, by the time they got to 6 months, they sure as hell wanted to know where they stood at that point.

It's not the same as an EVR or an RVR or an EVR where it is up to the investigator or the physician to test for that, but end of treatment response is something that the patients want to know, and most of them also want to know, and you tell them that really, we can tell you at this point that you have reached an ETR, but we can't tell you you have an SVR until we see you six months later. Virtually, all my patients, those two tests were the most important tests for them.

So, I think that there still is the ability--you know, I think it is going to be very difficult to distinguish among the other three, but I think lumping the first three from the ETR, and

relapse is possible, at least in my experience. I think there are a lot of clinicians here who probably have other experiences, that I think that patients who have taken six months of this very difficult to treat, to accept medication, want to know what their response is at the end of treatment.

DR. SHERMAN: Dr. Fish.

DR. FISH: I agree with Dr. Seef in that sentiment. I am just thinking if I am a patient and I am offered this trial to rego through this rigorous treatment and what are my chances of getting placebo, what is going to entice me to do that strenuous treatment, again, be it for 3 months or 6 months or whatever, to go through another round of treatment if I am a non-responder or a partial responder with the likelihood that that is going to fail again.

So, I am just thinking how the challenge of getting people willing to participate in those trials, you know, if it's 2 to 1 or 3 to 1 randomization, that will help in terms of

recruitment, because they have got a better chance of getting the new drug. But if I am one of those people who doesn't get the other drug, and I go through all that heartache again, you know, I would want some assurance that I had a better chance the second time around.

DR. SHERMAN: Other comments? Okay.

To sum this up, it appears that overall, the committee feels that the definitions, as initially expressed by Dr. Chung, are appropriate, that a null responder is someone who has less than a 1 log drop by 12 weeks, a partial responder is between 1 and 2 log by 12 weeks, that responders who relapse do represent a unique class and should be kept separate because of that, although studies should be done, that if patients are not well defined coming into centers doing studies is to consider a formal lead-in.

Dr. Fish has raised concerns that this may not be something patients would desire to do, but, in fact, may be the only way that such patients can be clearly identified and stratified.

We will then go back to the inclusion in treatment experienced non-responder patients and we will start with the issue of previously treated with 1 or more interferon-containing regimens that include PEG interferon and ribavirin.

I suspect there isn't a lot of discussion in that group. That pretty much defines what we just said would be a working definition. Is there anyone who has an issue with that? Okay. So that would be an appropriate group.

Failure to achieve a greater than or equal to 2 log reduction in HCV-RNA at Week 12, or HCV detectability at Week 24 or beyond while on therapy confirmed by a repeat test. That again fits in with the definition that we just described. Everyone is okay with that?

DR. CHUNG: Do we need to set a lower limit of detection for that Week 24 test? I mean detectability is what is stated there.

DR. SHERMAN: Well, you indicated that in practice it is now the standard PCR, which is approximately 50 international units. That

certainly does represent a challenge in terms of it being a moving target and something that we can't anticipate.

We know we have assays that go down to 5 now and I think that is something that both the sponsors and the agency have to examine when they look at the entry populations.

Dr. Havens.

DR. HAVENS: As you pointed out before, many people who were treated in practice might not have gotten a Week 12 test. They certainly wouldn't have known what test was used and confirmed by a repeat test.

This is how you would write it if you were writing a study protocol and had the patient in your hands. But I think the question remains how we would define this in practice, patients self-report or you are not going to have all this.

DR. SHERMAN: Well, these are very specific. So, if we accept that these are what is needed, and if a patient doesn't have this type of documentation, then, the only response is to go to

that lead-in type study, which would better define them again.

DR. HAVENS: So, in order to have a patient population sample that is big enough, since people aren't going to want to get interferon for another 12 weeks unless maybe they are--well, I don't know, do you think that interferon-based lead-in study to define who you are is an acceptable requirement?

What we are talking about here is what is the pedigree, the term that was used, and how far do you go to exactly define somebody's response.

Is patient report good enough, or do you have to require a lead-in study, or I think your point was very well made that maybe it depends on the kind of study, you know, what you are trying to study, what kind of drug or what you are going for.

DR. SHERMAN: Dr. Munk.

DR. MUNK: Give my pedigree?

DR. SHERMAN: No.

[Laughter.]

DR. MUNK: I really would like to purge that word from our lexicon. I think we can use

"treatment history."

DR. HAVENS: Point well made. Thank you.

DR. MUNK: But I think, you know, we are talking about a lead-in study as though it's a separate one. I think we have to be open to the possibility that some drugs may be tested in the patient population and at 12 weeks, we could then sort people into a follow-on phase depending on their response based on those first 12 weeks.

So, I don't think that patients' self-report is ever going to be accepted in clinical trials. But, you know, rather than looking at a separate 12-week study as a lead-in, to look at that as kind of the Phase I, and that is the treatment naive patients, and then the non-responders go on to a certain treatment phase.

DR. SHERMAN: Okay. Just to make a comment, I have been involved with several studies where there is such a lead-in that continues on through the study and enrollment has not been an issue in terms of that being a barrier to patients getting in.

I am curious from Dr. Seef, that was also the model used in HALT-C, and was that ever perceived as a barrier to enrollment?

DR. SEEF: I don't remember whether--I mean I think that we depended upon the information that we received both from the patient and from the charts that we got to see what had happened to them.

But certainly we treated the individuals, all the people who came in and found that there was a difference between those who had received the ideal standard of care treatment versus those who had not, but I think it was a barrier.

Could I just ask a question? You know, you guys are the experts about this business about TMA versus second-generation PCR. Do we know really what the meaning of it is at the moment?

You know, those that are TMA-positive PCR-negative, what really is the meaning? You know, where is your gold standard and what do we know about this.

I mean we do know that in the studies that

have been done using the PCR, and in which there has been an SVR, 10 years later most of these people are still negative, so has the TMA at this point taught us about those who are--you know, those 2 percent who may reappear with a virus came 15 years later.

So, I don't know whether we need, at this point, to struggle with this issue of TMA, because, as you say, this is a moving target and we are still learning about this.

DR. SHERMAN: The literature, as I know it, has not shown anything different in the patients otherwise classified as an SVR.

The place where it has been important has been at the end of treatment, the ETR, where a high proportion, although not all, of the patients that ultimately relapsed in the first 8 to 12 weeks, in fact, were positive by TMA when being negative by standard PCR.

DR. SEEF: But not with SVR.

DR. SHERMAN: No, but not with SVR.

Dr. Chung.

DR. CHUNG: Regarding lead-ins, I think that our history of success with lead-ins has been predicated on the fact that the patients mostly have been treated with interferon or interferon ribavirin, standard interferon ribavirin, and had at least the enticement of getting current state-of-the-art, which was PEG interferon ribavirin, so there is a little bit of an apples and oranges dimension to that perspective.

Nonetheless, I would say, though, and perhaps amplify on what Bob was saying, that I don't think that it would be problematic for patients to enter a lead-in phase if they knew that there was a decent chance that they could get active compound in the follow-on, or even in those who got the placebo arm, potentially, a crossover could be offered after the conclusion of their therapeutic arm.

But I don't see that recruitment as being hugely problematic to allow us to redefine the non-EVR, for instance.

DR. SHERMAN: Dr. Andersen.

DR. ANDERSEN: One thing about lead-in studies is those with either inadequate treatment previously either through drugs or duration potentially are going to achieve an EVR on the PEG-riba and going to shunt off probably on that study for continued treatment.

So, that does increase the size of the study at least at that step one. The tradeoff here is the efficiency in bringing a group that is well characterized into that second phase of the study of the new treatment and, when you have got a group that you are convinced is highly non-responsive, those are going to be very efficient studies in terms of sample size. You are not going to have to see the huge sample sizes to get signal in this population.

DR. SHERMAN: Tracy Swan.

MS. SWAN: I think there are going to be some insurance coverage issues with maybe the repeat test at Week 24. I don't know how many people out there in the real world are getting those. That is the one little bit of sticking

point.

As someone said, this is really, it's like classic clinical trials definition, not clinical practice definition. I think we have to watch it a little bit, but as far as the lead-in, I think for now with the drugs we have at the moment, it makes a lot of sense.

But I would hate to see us chain ourselves to having people have to be on pegylated interferon and ribavirin for 12 weeks, when we have more agents that could be combined in a different way, so it might be good to think about what is coming down the pipeline, too.

DR. SHERMAN: I think that as standard of care changes, what is defined as the baseline treatment will change, as well.

Dr. Birnkrant.

DR. BIRNKRANT: Just to clarify, so with regard to all of the groups we identified, the null, the partial responder, the relapsers, does it also depend on whether they received interferon or pegylated interferon?

DR. SHERMAN: My sense from this group is that it is pegylated interferon defines the standard of care, which is why a lead-in with appropriate agent is important.

DR. BIRNKRANT: Thanks.

DR. SHERMAN: Dr. Haubrich.

DR. HAUBRICH: I guess I am confused by this discussion. If we are talking about lead-in to help characterize the patient, so you have a more homogenous group of people than randomized, the study design again, unless something happened while I was sleeping last night, that was proposed for at least the early studies here is standard of care PEG ribavirin plus or minus the new agent.

So, in that context, sure, you can homogenize the population presumably by excluding the people or including the people that you want be they non-responders, partial responders, but then haven't you done a disservice to everybody, because essentially, what you are doing is you are missing the benefit of the full new 3-drug regimen upfront, which is we have learned of 20 years of

antiretroviral therapy the way that people respond best.

So, although we gain by homogenizing the population and it might make sense to do that in early Phase II studies where we are really looking to see and want to have a much better idea of responses.

In the bigger registrational trial, it wouldn't make sense to do that because then even the best of responders have already had 12 weeks of therapy and now you are adding on after that where they may have had even a better response if you had combined them from the beginning.

So, I think we need to separate out what we are talking about and when in the series of study designs we would use this lead-in phase.

DR. SHERMAN: I think that it becomes a way to classify into these definitions, but there would be nothing to stop a sponsor from going after the group that had a drop that did not meet the criteria, and were they non-responder, but not a null responder, for example.

So, those patients could be studies in trials. It is just then you probably don't want to mix those with the ones that would have responded and cleared by the end of therapy, the relapsers, or whatever. It is a way of classifying into different groups and then focusing on those definitions as to where you apply your new agent.

DR. CHUNG: In an ideal world, we wouldn't have lead-in things. If we could easily identify 100 patients, we would get them all in for non-responder trials and start them on the comparative regimens right off the bat.

But I think we are speaking to ways to augment and enhance recruitment of these patients to such trials, because we know that is going to be challenging given the difficulty in characterizing them.

If we could change practice and make people document RNA declines better and, if we could make that happen, you know, in the real world, I think this discussion would be moot. B**ut I am afraid that that is just not the way the

real world is operating.

DR. SHERMAN: Dr. Havens.

DR. HAVENS: And it seems to be that the people who have the greatest experience with these trials and with treatment of patients with hepatitis C have a strongly held conviction that each one of these non-responder groups is biologically different enough that the exact characterization is very important for certain types of studies.

That is what I hear you saying, that this characterization is so critical for some types of studies that you would absolutely think a lead-in with all these criticisms that have been raised is important to do.

DR. SHERMAN: I wouldn't think so.

Dr. Chung.

DR. CHUNG: But Janet said it best. I mean there are going to be some patients who we thought were EVRs previously in the real world, who under a study protocol are actually full of EVRs.

DR. HAVENS: Right, and depending on the

study you are doing, the efficiencies that are obtained by exactly defining the population that you are studying outweigh or pay off in doing the lead-in study. So, since it is important for some studies to gain that efficiency is worth the extra work is what I hear.

DR. SHERMAN: Dr. Andersen.

DR. ANDERSEN: Addressing Richard's point, large studies can make up for imprecision in definition of the patient population. But that does increase the sample size, because if, as a statistician, I have a group coming in where I don't know if they are likely to respond or not, I am going to assume that they are going to be in, to me, the least--to them probably the most favorable high rate of response in both arms, so it is going to be difficult to see a difference in that group.

That is going to increase the sample size of the study. But then it would avoid the lead-in phase, so there are different ways to approach this. Both have different kinds of sample size implications.

DR. SHERMAN: Dr. Havens.

DR. HAVENS: And this got to something that Dr. Sun said yesterday, which is then that is actually in the best interest of the person running the study to most exactly characterize the groups in some settings, because then you know exactly what you are doing. I hope I didn't paraphrase you badly.

DR. SUN: I just wanted to clarify whether the lead-in design element here is being proposed as a requirement for this type of study or as an optional tool. I think a required element here would be--

DR. CHUNG: I don't think that we are proposing a requirement here or at least I wouldn't propose a requirement.

I am suggesting it as a recruitment tool to enhance enrollment into non-responder trials, do you could have a direct enrollment, a direct pathway into the trial for bona fide responders and another pathway for the nebulous non-responder.

DR. SHERMAN: In some ways doing the

stratification does permit at the end if patients in all groups received a particular agent to actually define differential response across well-defined groups and it may be used as an exclusion if someone wants to limit to a population or not.

Dr. Fish.

DR. FISH: I am just thinking, too, in terms of where these patients might be coming from. I wonder how many will be kind of the real world patients versus how many will have been research world patients, so patients that we already know about. So this data would be well documented and they would be fairly well characterized.

We would probably get a significant number of patients from that pool, I would think.

DR. SHERMAN: I think it depends upon the center doing the study and the mix of types of patients that they see.

As we get into more and more new drugs, there is going to have to be probably an expansion of the number of sites doing these types of studies

because there is a lot of things in the pipeline right now.

DR. SEEF: Again, in the HALT-C trial, some of the patients came in having participated in previous studies, they were well characterized, and they came in as what we call express patients. They didn't have to go through an early phase treatment, a lead-in phase. They went directly into the randomized trial.

So, I suspect that there may well be, since there have been so many trials now, many patients out there who would fit that category.

DR. SHERMAN: I think that that second point regarding what is the definition is an appropriate definition. But that that can be used to provide strata and that the best way to do it is either well characterized patients coming out of trials or lead-in phases in trials.

The last item is compliance documented over the first 12 weeks of previous therapy to confirm receipt of at least 80 percent of the prescribed ribavirin and PEG interferon dose, in

other words, using the issue of the 80:80:80 rule to say that someone before you classified them, in fact, achieved adequate drug to be classified appropriately.

Is there discussion from the committee? Tracy Swan.

MS. SWAN: Given that there is problems getting all this other information, it seem like it would be virtually impossible to retrospectively document somebody's compliance over 12 weeks and that may be the first two categories seen sufficient.

DR. SHERMAN: Other comments? Dr. Fish.

DR. FISH: I would agree that I think this would be a pretty challenging bar again unless they would come from another trial. But even that necessarily doesn't guarantee unless it was built into the trial, you know, some kind of adherence assessment.

I certainly think it's a call for trials moving forward to include this as part of their analysis and follow-up of patients.

I would just like to also volunteer the use of the term "adherence," which we use in the HIV world as opposed to compliance as a better term.

DR. SHERMAN: Other comments? Ray Chung.

DR. CHUNG: Let me just throw out an example. If a patient was a non-AVR, but had taken 50 percent of their doses, if we didn't have some kind of provision for compliance or adherence with the medication, that patient would qualify for a non-responder trial. Then would I suspect there would be issues in terms of the reasons for the patient not to have been taking, I think that 50 percent of doses.

You may be enriching that trial for patients who are not just noncompliant, but potentially intolerant. There may be plenty of reasons for the lack of adherence to the regimen.

I am just raising that as an issue. I think, as we define these patient populations, I think there is the conflict between precision and practicality. I think it would be challenging

enough, as Tracy said, to get the first two criteria met, but I just caution that we would have a mixed bag of patients if we didn't have a sense of what their adherence to the regimen was like.

DR. SHERMAN: Dr. Fish.

DR. FISH: Perhaps counterbalancing that might be that if we worked harder with those patients in the new trial and guaranteed their adherence and their tolerance and, you know, worked with them to stay on their full dose of ribavirin, et cetera, that they might do better. But it is true that you don't know which kind of group you might be preselecting in terms of some of these characteristics.

I agree, though, that for practical matters, it is impossible for us to impose this restriction.

DR. SHERMAN: Dr. Andersen.

DR. ANDERSEN: Again, this goes to how the actual new studies are to be designed and some of that can be incorporated into the design. If, in the design of the study, somebody tells me that

this group is guaranteed not to respond, I always build in some amount of response, because I know that is going to happen.

So, this can be accounted for in the study design depending on the level that you think might be there, you can certainly work your designs on that.

DR. SHERMAN: Unless there are other comments, I think the general feeling is that it is probably not appropriate to have documented adherence rather than compliance as a factor for enrollment based upon the first 12 weeks of prior treatment.

Okay. Selection of Controls. Since we are moving nicely along here, we will stay with this.

Are placebo controls or delay of initiation of therapy acceptable and, if so, what duration? Consider the following patient populations: the treatment-naive versus the treatment-experienced and the compensated versus decompensated.

Let's start with that question, in the treatment-naive and treatment-experienced populations, and the issue is placebo control, treatment-naive. Let's start with that to keep it fairly narrow.

Dr. Haubrich.

DR. HAUBRICH: I guess it depends on the design of the study that you are talking about. If we are talking about a standard of care plus the new agent, and the placebo control is the new agent, then, that would make plenty of sense. You have a standard of care with or without the new agent. It is better to have it be placebo controlled, particularly since a small molecule might be more facile in generating a controlled substance.

DR. SHERMAN: Other comments? I see some heads nodding. Is there general agreement? Dr. Havens.

DR. HAVENS: Yes, I would certainly support that. There is plenty of information to show us that placebo controls are important in that

context.

DR. SHERMAN: Dr. Vierling.

DR. VIERLING: I thoroughly agree with it and, as emphasized yesterday in my remarks, I think placebo control not only has the advantage of the double-blindnesses as we look for extraordinary or different issues of AEs or SAEs. But it also would be important for retaining patients in the trial, because those that are actively seeking new therapies, were they to know that they are receiving only standard of care, I fear we won't retain them in the trial and then we do not have the power of our analysis.

DR. SHERMAN: Okay. So, it appears as if there is pretty much general agreement that in the treatment-naive patients, we should have placebo controls trials available. It is important scientifically and it may help in retention in the trials.

Is the same thing true in treatment-experienced populations? Dr. Chung.

DR. CHUNG: I would make the argument that

it is even more important in treatment-experienced populations to have the placebo control.

I mean at least for the naive population, they are facing antiviral therapy for the first time, they are getting standard of care minimum to get the non-responder into the trial, again for the same reasons that Dr. Vierling was just stating.

I think they need to know that there is a very good chance that they will be getting active agent and standard of care.

I think we also talked--I think Dr. Fish talked about a weighted design and that, too, would, of course, enhance attractiveness of such a study.

DR. SHERMAN: Dr. Munk.

DR. MUNK: Yes, if you could remind us about those first phase viral kinetics, it seems that that stage of placebo control could be relatively short and still give us valuable information.

DR. SHERMAN: Dr. Andersen.

DR. ANDERSEN: Maybe I am confused, but if

there is a lead-in where subjects have just failed to respond to standard of care, it seems like more standard of care with the placebo, what is that gaining?

DR. SHERMAN: So, you have some concerns in the treatment-experienced population.

Dr. Havens.

DR. HAVENS: That is not a criticism of a placebo, that is a criticism of a lead-in design maybe. It would seem maybe perhaps, sorry, maybe I shouldn't have been quite so aggressive about that.

DR. SHERMAN: Tracy Swan.

MS. SWAN: I think we have to really look at designs, because there is pretty much zero incentive for someone who has already failed standard of care to go into a long trial where they are going to get what didn't work possibly with one other agent.

I definitely think crossover designs and multi-agents--and the paradigm might be more looking at a regimen rather than the effect of one specific drug in treatment-experienced people.

DR. SHERMAN: Dr. Haubrich.

DR. HAUBRICH: So, I will come back to my point of the value or necessity or ethical issues of the lead-in design, so I can understand how it would help you find those non-responders. Then, what do you do with them, are they randomized to one drug placebo versus nothing?

That would be great to characterize the viral kinetics activity and particularly resistance of the new drugs, which is a great way to do that, to add monotherapy to a failing regimen, or do you just take those people and give them all the drug. I mean it doesn't make sense.

I suppose you could continue interferon and ribavirin and see if longer periods are more effective. But it seems like from the consensus here in the non-responders, that doesn't make sense either.

So, why do you want to do a lead-in to identify a group of patients that you have nothing to offer?

DR. SHERMAN: Dr. Seef.

DR. SEEF: Let me just raise another issue with regard to placebo and non-placebo and that is the issue of the common fact that many of these patients are taking herbals.

We have actually just looked at the HALT-C trial, which I am extremely amused about this, because here are a group of people who have been treated at least once before, sometimes twice before. They now commit themselves for four years of interferon. Twenty percent of them are taking silymarin in the belief it works. I call this the belt and suspenders approach.

So, the question would be when they design these studies, should you be saying that people should not be using herbals, this is a placebo.

I know that people have strong feelings one way or another about this. You may know that the NIH is doing a study looking at silymarin now, once and for all, to see if this thing works, but I wonder whether, in designing these studies, you should ask the question about whether people are taking herbals and either exclude them or make sure

that everyone else is doing it.

DR. SHERMAN: Dr. Chung.

DR. CHUNG: I think to get to Dr. Haubrich's concern about the lead-in for non-responder population, I think, and Tracy spoke to this as well, I think you are going to have to structure that design for those lead-in patients specifically.

I should say the standard of care plus placebo, again, in a weighted manner but with the provision that they could be crossed over to receive active compound after completion of their arm.

I think you have to offer something for that patient and the possibility that they just might be getting standard of care plus placebo.

DR. SHERMAN: Yes?

DR. PAXTON: Forgive me, I missed yesterday's discussion, but it sounds to me like we are also talking about there is the group of I guess the 12-week lead-in, we find that they respond or they don't respond. But we are also

talking about the group that will be coming in from other treatment trials and which we already know that they don't respond.

So, isn't this an issue that is going to affect, not only the 12-week lead-in, but also the people who come in from the other trials that we know that they are not responding, so then randomizing them to placebo-controlled is the same thing. You know, it is not just this lead-in.

DR. SHERMAN: That's right, at least some proportion of them would get PEG-interferon ribavirin presumably.

Other comments?

So, I think that this group is a little bit more difficult and the sense of the group is that while there is some information that may be useful to obtain by having placebo arms in the treatment-experienced population, that there are some issues that would need to be addressed because you are taking patients who presumably have been well classified as a failing agent.

There is biological implications in terms

of essentially treating them with a single agent therapy and that perhaps shorter term elements of response evaluation with some sort of a crossover design, as suggested by Tracy Swan, might be appropriate in dealing with some of these issues.

The next group is the compensated and decompensated and, I suspect, since we have been talking mostly about compensated patients, there won't be a lot of discussion there, because that has been sort of the assumed baseline for pretty much what we have been discussing up to this point in the last little bit.

Unless someone has a specific comment, I would like to turn to the more vexing issue of the controls in decompensated patients. Everyone seems to be in agreement.

In the decompensated patients, we have the issue of use or not use of a potentially life-saving agent in a setting of high risk and should placebo controls be used in that setting.

Dr. Havens.

DR. HAVENS: If I were trying to develop a

drug and bring it to market in this very high-risk group who has lots and lots of health care problems, I would not want to do a study without a placebo control, because if I didn't have a placebo control, I wouldn't be able to identify the background risk of medical problems in the population for adequate comparison with my experimental drug, which I think would act to make the experimental drug potentially look more dangerous than it really is.

So, I would argue for placebo arms given that there might be ways to shorten the time of a placebo or to get people into an active treatment arm at the end of a certain, you know, 12 or 24 weeks, but I think placebos are very important in these sick patients.

DR. SHERMAN: Dr. Vierling.

DR. VIERLING: I would agree with that. I think the issue also starts with much more emphasis on safety than efficacy, which is underlying what you are saying. I think therefore part of the design in this particular group with their known

intolerance to standard of care regimens and, in fact, a contraindication to their use in decompensated individuals, requires the focus of attention beyond safety. That, in turn, requires the placebo.

I think that therefore I would look at this as almost a dual stage population for study once establishing some parameter of safety to then have larger access or crossover design in mind.

I would also re-emphasize that in the choice between using a Child-Turcotte-Pugh score in which 2 of the 5 elements are subjective, but one of those elements, namely, the issue of ascites is now detectable, subclinically detectable using imaging, which all the patients are having with decompensated cirrhosis is probably less advisable than using the MELD score.

I further emphasize that with respect to safety, that your safest patient population would be the MELD score population of 14 to 17 range, the low end of a UNOS-listed transplant candidate, because there is a safety net where you can really

see an unexpected SAE.

DR. SHERMAN: Dr. Havens, do you have a question?

DR. HAVENS: No.

DR. SHERMAN: Okay. So, it appears there is general agreement that in the decompensated population, that a placebo control is necessary and valuable to separate out the other things that may be happening to these patients, but that complete understanding of safety issues is paramount and extremely close monitoring is indicated.

Okay. We are now going to turn to Endpoints.

The question says, Considering the patient populations identified in Question 1 and the necessity that endpoints for registration be clinically meaningful, answer the following:

a. Which primary endpoint(s) should be used in clinical trials with a focus on the histologic, viral and biochemical endpoints.

I am not sure that at this point, until we get into this discussion, there is a need to

separate all of those groups unless has a particular relevant issue with one of the subgroups and using alternative endpoints. But let's start with the simplest, I think, viral endpoints because we have had considerable discussion already. The starting place is SVR, I think everyone would agree is the definite endpoint.

In a few minutes, we will talk about what is SVR, is it always 24 weeks, but we don't need to talk about that now.

Does everyone agree that SVR is the primary viral endpoint? Are there other surrogate endpoints using virus quantitation that should be considered in an approval process, not necessarily that they shouldn't be gathered in the course of a trial, but for an approval process, is there any other relevant endpoint?

Yes, Dr. Haubrich.

DR. HAUBRICH: So if you take patients that are complete non-responders to interferon and ribavirin and put them on essentially monotherapy with compounds, the likelihood of an SVR is

probably going to be pretty low even if they have 4 log drops, although the studies haven't been done, maybe they will work by themselves.

So, in that patient population, that might be a clinically meaningful endpoint, if you reduce viral load for some period of time, maybe you would improve some of the other parameters. So, in that small subset where you are not getting anything out of interferon and ribavirin and perhaps a viral load change might be relevant.

DR. SHERMAN: So, I think that raises the question, then, and I will pose it initially to Dr. Seef and Dr. Chung, but, of course, everyone can chime in. Is there a clinically definable suppression endpoint that has meaning in terms of clinical outcomes of patients that can be identified short of eventually analysis of HALT-C data?

DR. CHUNG: I think that is respectable effort to take the HIV paradigm and apply it to the HCV paradigm. I am afraid there is little to defend, at least thus far, the idea of using a

viral surrogate endpoint for the--short of SVR--for clinical benefit in patients.

I will just say--Leonard can chime in, as well--but I will say data certainly from HCV-HIV coinfection trial where we looked at Week 24 histologic responses in patients who were receiving PEG interferon or standard interferon ribavirin therapy. We saw that histologic improvement, meaning a 2 point or better reduction in histologic activity index was observed in about 35 to 37 percent of patients, but did not relate to the degree of HCV-RNA reduction.

We had hoped to see at least a partial response predicting a histologic improvement, so we could justify it is a surrogate. But we did not observe that, so that this concept of histologic improvement without a virologic even suppression to a great extent was not demonstrated.

Now, that was a small subset of the trial and I certainly would not view that as gospel. Clearly, there is a coinfection and monoinfection maintenance studies being done, as has already

alluded to, that will help address that subject to a greater degree. But for now I don't think we have the evidence to use a suppressive threshold as indicative of clinical benefit.

DR. SEEF: Why do we use SVR as a surrogate? I mean as a surrogate for what? It is a surrogate for the hope that this is going to lead to a lower incidence of cancer or lower likelihood of going on to end-stage liver disease.

We believe implicitly that that is going to be the case with SVR although I am not even sure that we have 100 percent data to support that. I mean I think it's reasonable. We have argued this point and achieving an SVR I think is extremely important. It may take some time yet before we know that for certain.

But what happens if you treat and cannot eradicate, in quotes, the virus, but you can lower it? You know, I guess the Japanese have got some data to suggest that the incidence of cancer is a little less in such people but I am not sure that we can translate into what is happening here.

I think we need to wait for the trials that are ongoing. Our study comes to an end early next year. I suspect we will have information that will be very important before some of these trials will begin, so we will have some information in that regard.

I mean we are all poised to get all the appropriate papers written. You know, we have done all the baseline reporting on this study. Now we are about to do the end of this and I think we will know then.

But I don't know that there is evidence at the moment that reducing it really had made an impact. We have to wait to see the trials that have been designed to answer this question, not only ours, there are a couple of other trials, as you know.

DR. SHERMAN: Dr. Birnkrant.

DR. BIRNKRANT: One of our concerns, however, with regard to using SVR for the new molecules is that the trials on which we now use SVR as the basis for approval were interferon

based. So, if interferon is removed from that regimen, can we still rely on SVR?

DR. SHERMAN: Dr. Havens.

DR. HAVENS: I think that Dr. Seef's points are very well made especially in this context, that you are using SVR in interferon-based studies because you think it is a reasonable surrogate endpoint for prevention of later complications of the infection.

Now, if you are saying that small molecules are going to prevent later complications of the infection without an SVR, you have just dramatically raised the bar, the level of difficulty of showing that these drugs are useful, because then you have to link use of these drugs with the later complications of infection.

So, if you can't even show an SVR, you are going to have to wait for decompensated liver disease or hepatocellular carcinoma as an endpoint, which is an impossible endpoint.

There is already a therapy, standard of care, which leads to SVR and that needs to be the

comparator against which new agents are measured.

DR. CHUNG: I think that is an important area to look at endpoints that are relevant to interferon-free or interferon independent regimens where we are talking about combinations of small molecules.

This gets us into classes of molecules, because if they are predominantly antiviral, then, the primary endpoint should be a viral endpoint in SVR, because of some of the arguments that Peter has already made. But I think it would also be important to collect secondary endpoint information from those trials in the event they fall short of the SVR given this two- or three drug regimens, for instance.

I would be very I think interested in seeing that the histologic endpoints be also performed in those populations. In case you fall short of your SVR, we can at least demonstrate whether these drugs function and get to Dr. Haubrich's possible suspicion there could be benefit provided by long-term suppression for

disease progression and that would be best measured really by histologic progression.

So, I would be strongly in favor of collecting information about both of those very important endpoints with the idea that imposing an SVR endpoint on primarily antiviral compounds is an important thing to do, but actually, also documenting whether we can also see disease suppression or slowing.

DR. SHERMAN: Dr. Havens.

DR. HAVENS: Maybe we need to go back to how we are using the term SVR. SVR, in this context, is 24 weeks after you have stopped the drug. Now, if what you are saying with the small molecule is I can suppress and continue and it's easy to take the drug for a longer period of time, then the histologic endpoint is fine. That documents the absence of progression of disease while on your drug, or, in fact, improvement in the liver disease while you are on the drug. That may be an adequate endpoint for the study in the absence of even though the virus may come back

after you have stopped the drug.

That is why I was kind of broadening out instead of just hepatocellular carcinoma later in the future, but rather the complications of the virus infection, which could be shown by histology during therapy.

So, maybe you need to think about--right now SVR is we stop the drug, you would clear the virus and it didn't come back and that is a surrogate endpoint for improvement in liver histology and prevention of later complications.

If what you are trying to do with small molecule compounds is say while you are on this drug, your liver gets better, then, the endpoint is proving that your liver gets better perhaps even in the absence of this 24-week post-therapy clearance of the virus. But histology would then be an important endpoint in that kind of study.

DR. SHERMAN: Dr. Vierling.

DR. VIERLING: I think the primary versus the secondary endpoints that you have just characterized get to the root issue of whether we

are going to analyze these drugs for capacity to terminate infection and then the secondary question is, is termination of infection sufficient in these previously chronically infected individuals to modify their disease.

That Point No. 1 in the SVR, I think does translate for all data that we have to date in essence to a cure in terms of viral replication largely based in the liver. I think we know that that can potentially be achievable, so that becomes an endpoint, if you will, for infection.

When to start to talk about things that may relate to longer term chronic care management, analogous to the treatment of hypertension of diabetes or other chronic diseases requiring ongoing therapy in the modification of those diseases, it is much more important to look at inflammation and the capacity specifically of the inflammation to generate fibrogenesis.

Truly, if we were going to step back and say historically, we have an interim marker of ALT, and it is not a bad marker of injury. We can

debate its relative levels in terms of what should be or should not be the normal range, but it does have that capacity and its change is meaningful.

If we look at histology, we clearly have conundrum, because the kinetics of inflammatory responses, the generation of new cells from memory basis and lymphoid tissue, the trafficking in the circulation, the chemo attraction to allow them to congregate and to signal one another is a very dynamic and long-term process.

You can terminate diseases and not change histopathology for quite a while and we may wish, if we are going to focus on the issue of hepatic inflammation, to be more creative than we have been in the past, because we do have the capacity--and some of this is coming from the studies of Cardiovascular diseases--to look more at the issue of the inflammatory state of the body, in this case the surrogate for the site of inflammation being the liver and to add even in the analysis of histology, techniques that allow us to define whether we are actively in the state of

fibrogenesis have proliferating stellate cell mass, things that are relevant to the development of chronic liver disease.

So, I am an advocate of histology. My worry is based on all our prior experience that we have never achieved the usefulness of that endpoint in part because the timing of the use of that endpoint has been so variable and, in my opinion, has been too early in the course of therapy to have a meaningful chance at defining the effectiveness of the drug.

So, if we are going to go for inflammation and fibrogenesis, it would be part I believe of a larger analysis of inflammatory state and the reduction of that state in test drugs.

DR. CHUNG: Points well taken, John, but I would simply make the case that even if you are thinking about downstream histologic markers, I think there is still even benefit to the idea of end of treatment or even perhaps in the case of the interferon-based regimen, six months off treatment. But a short term histological measurement has

certainly at a minimum demonstrated improvements in that inflammatory activity.

I have also drawn the example of hep B and nucleoside analogue therapy there in terms of those are one-year trials predominantly that looked at histologic improvements and we saw the majority of patients experienced histologic improvement in necro-inflammatory indices.

So, I would say that would be kind of floor, which a minimum benefit can be at least observed. There may be longer term benefits, as you suggest, downstream, but I think even shorter term histologic endpoints are still a reasonable first start for evaluating--

DR. VIERLING: I don't disagree with that. My point is simply--and I think you just stated it--if one were going to look for registration purposes, this endpoint, particularly the end of treatment, assuming that we haven't gotten to these designs of whether that may be, say, a 48-week course of therapy, maybe in some it is going to be shorter.

I think you have to have at least a 24-week period if you are going after SVR as an endpoint in which you delay your biopsy to consolidate the degree of improvement that you might see.

Otherwise, you will likely see the same kinds of benefit in 30 percent to 50 percent and I believe that the other half probably is still capable of achieving and demonstrating the benefit, but the timing of the biopsy is not adequate for their kinetics of inflammation in the setting of an SVR in hepatitis C trials.

DR. SHERMAN: Tracy Swan.

MS. SWAN: I think we may have overlooked the question of liver histology as a safety issue. We might have a great antiviral that has unintended effects that are not so good and that we may need to really closely monitor that, not that someone should have a biopsy every two weeks or something horrendous like that.

I also think there are real issues with retaining people and the kind of data we would all

love to see is just no one is going to want to come back for a biopsy after biopsy and that we should really look at inflammatory markers and other noninvasive markers to prospectively validate some of these studies with, so that we have better ways of really assessing liver histology without the biopsy.

DR. SHERMAN: Dr. Chung.

DR. CHUNG: I would just sort of cone down a little more on the point about timing of the biopsy, only that if we are talking about combinations of antivirals, novel molecules that are purely antiviral. We are not talking about interferon now, we had suggested I think yesterday that we are going to see rebound, we are going to see it immediately based on the fact that these are mechanistically inhibitors of replication and, in the event of failure to achieve complete suppression, we should see a recrudescence very soon.

So, delaying that biopsy to six months after conclusion of therapy may actually obscure

any benefit that those drugs my have provided during the 48 or whatever, during the treatment duration of the trial.

I think it would be useful to switch the paradigm to an end of treatment biopsy in this context, to maximize our ability to demonstrate a meaningful clinical improvement should you even fall short of the virologic endpoints we cited earlier.

DR. SHERMAN: Dr. Seef.

DR. SEEF: I am thinking through the process. There are two parts to this. One is the virus and one is the disease. We are trying to get rid of the virus for two reasons.

One is obviously people from the point of view of society, the less virus there is around, the less likely there is to spread this disease, although it is already beginning to drop.

The other one is our belief that there is a relationship between the presence of a virus and the development of liver disease. We obviously want to do that and that is what we have focused

our attention on.

So, the question is, is this how these drugs are going to have their impact, is it through its antiviral effect, or is there something else that's going on. I think that clearly, the number one endpoint is SVR. I don't think anyone is arguing that.

The question is do we get any benefit in the registration trials by also looking at other markers. I think everyone is going to do an ALT for sure and we are going to look at ALT. I can't see how you can do any study without doing an ALT in addition to the SVR.

The question is would there be any benefit in a short-term treatment, for example, with respect to liver histology. Now, clearly, fibrosis is not going to change in a very short time. That is not what we are interested in. The question is if we use the HAI score, when you say it drops by two points or whatever it is, is that a really meaningful endpoint at this point.

I think that the histology is extremely

important over a long period of time. I mean I think it becomes very important to know whether, in fact, you change the histology. But, in the short time of treatment, I am not sure that that is going to be helpful immediately for registration purposes.

I think, as a hepatologist, I can't live without a liver biopsy, I mean I think everyone should have a liver biopsy in the elevator when they go up between the second and third floor--and I would love to see liver biopsies. But the question is do we need it as an endpoint for the registration trials. It is absolutely an endpoint on a long-term basis, there is no question about that in my view.

DR. SHERMAN: So, we have short of shifted into this issue of histology as being the primary issue and I think that it is probably reasonable to then broaden this discussion because ALT is just another measure of inflammation, as well.

If we were looking at this as endpoints, is there any role other than as a secondary marker?

Dr. Havens.

DR. HAVENS: Dr. Chung has already brought up the comparison with hepatitis B treatment. I think that abacavir [?] and lamivudine are useful drugs, but don't attain SVR in the majority of patients.

Now, I don't like comparisons with other diseases, so I apologize for this a little bit. But inasmuch as there might be small molecules that would be useful only while you are taking them than the 24 week after therapy SVR might not even be the goal of therapy within the drug for hepatitis C. Then we might look to the hepatitis B model to say, well, then change in ALT or biopsy at 48 weeks on therapy is the appropriate endpoint.

I am very supportive of what you said about the expectation that virus load may rapidly increase after you stop the drug, so it has to be an on-therapy, at end-of-therapy view of liver damage rather than waiting.

So, in an interferon-less treatment, the paradigm may need to change for many drugs in which

you are not really expecting perhaps to eradicate.

DR. SEEF: Well, let's assume that you are looking at three endpoints. One is the vital importance. Second, the serum enzymes, and not liver function tests, by the way. One of the things that when I teach, I taught that the ALT and AST are not liver function tests, which is a term that everyone seems to use. ALT and AST are found in many other tissues, they are not liver function tests at all.

But anyway we use that term ALT, SVR and histology. Let's assume then that the SVR is not achieved. The ALT falls a little but the liver histology shows a 2-point drop in HAI. What is your interpretation of the study now, is that good enough to say let's register this drug, or use this drug?

DR. HAVENS: Well, you might register that drug to be used on a continuous basis rather than for a single year or for 24 weeks.

DR. SEEF: Well, of course, this is exactly like hepatitis B or like HIV. You know,

it's a question of suppressing the virus, if we find that suppressing the virus really has a long-term impact. I am not sure that the fact that it comes down by 2 points and nothing else changes, that that is a meaningful thing for treatment.

Particularly, at the moment, the treatments that we are using for hepatitis B are a lot easier to take than interferon ribavirin over a long period of time.

Maybe it is going to be true also of these small molecules if they are the only ones that are being used. But if you are going to use them in combination, we have to have I think fairly good evidence that there really is an impact in order for us to suggest that this be used for a long time and that may take decades.

DR. HAVENS: Well, or may take 600 days I think was the suggestion from the kinetics discussion yesterday, so depending on what you are trying to get from your drug, the endpoint, the primary endpoint might be histology. The secondary endpoint might be SVR, or the initial study might

be for histology at 48 weeks, and the secondary endpoint might be for SVR in the subgroup that goes for 3 years on therapy.

DR. SHERMAN: Leonard, I would like to tease this out a little bit more in your thoughts. Would you argue that one of the issues that hep-C differs from hep-B and HIV is that, in fact, we can cure some proportion of patients with some regularity and, therefore, that changes the paradigm a bit, whereas, in hep-B, we really have not been able until very recently to start to see some HBSAG losses and that, in fact, if you go for what you can already achieve, it's a different measure, it's a different way of approaching this disease.

DR. SEEF: There is no question that we can cure some people. I think that this is an extraordinary event that we have recognized that very few viral diseases can be cured. It appears that we can cure it, maybe can cure it. But what is the cure that we have at the moment is that the virus disappears using except perhaps TMA. But it

disappears and it seems to stay away for a long time. Histology seems to get better, enzymes get better, so I think, yes, they can be cured. But I am not sure the questions, in what way--

DR. SHERMAN: We do accept histologic improvement in hep-B as being an approvable endpoint that has been used in the past with viral suppression. But in hep-B, this concept of cure has been a rare event.

Does the ability to cure change the paradigm for this treatment?

DR. SEEF: Well, the cure then is SVR.

DR. SHERMAN: Right.

DR. SEEF: The question is if SVR is not achieved, but you see some reduction in inflammation, because over a short period of time, you are not likely--you may get I guess some reduction in fibrosis depending on where you are.

I mean I am not arguing against the use of the liver biopsy. I think liver biopsy is part of the evaluation of this without question.

The question is, is it needed at the end

of a given treatment period for registration purposes if indeed the virus doesn't disappear and the ALT remains elevated. I doubt that you are going to have a 2-point reduction, but you may I suppose.

Is that enough to say that this has been a positive effect? The only way you are going to find that out is following these people for the next 20 years to see whether, in fact, that really has had an impact.

Let me put it this way. If we treat now genotypes 2 and 3, I don't think we need a liver biopsy. Genotypes 2 and 3 have an 80 percent response rate. We no longer are suggesting that this is required, because we think we are getting rid of the virus, and we think that the virus is so good a surrogate marker of what the ultimate outcome is going to be, that we don't need a liver biopsy.

I don't know where you are doing a liver biopsy for genotypes 2 and 3, but genotypes 1 we are doing it partly because we are trying to decide

should we, in fact, be putting people onto these very difficult to manage treatments when, in fact, they have minimal fibrosis and they have had this infection for 30 years and the likelihood that they are going to progress is probably low. So that is good reason to do it, it helps you make a decision as to whether you treat or not.

The histology is very important obviously, because what we are trying to do is not only get rid of a virus, but to improve liver disease and the question is can we do that.

DR. SHERMAN: I am pushing you on this question, it is really for all members of the committee. So, if we accept that there are null responders to interferon, and we realize that as time goes on, we hopefully will be dealing not just with interferon-based therapies, but with perhaps combinations of small molecules, and histology improves over some period of time, so in patients for which cure with an interferon-based regimen is not possible, is there a path to drug approval that could be met by a viral suppression combined with a

histologic endpoint and, if so, what is the endpoint, where is that, a year, two years?

DR. SEEF: It will be a lot easier for me to answer this when we see the results of the HALT-C trial, because there, we are not, in fact, focusing on the virus, we are focusing on perhaps the mechanism somehow antifibrotic effect, because it is the fibrosis that is responsible.

The inflammation is important, of course. But the inflammation presumably is the path by which fibrosis occurs and ultimately people who die from this disease die because of fibrosis, progressive fibrosis to the time to cirrhosis, end-stage liver disease and develop into liver cancer, which is largely, but not--we are now beginning to see in the HALT-C trial not necessarily absent the requirement for liver cancer in hepatitis C.

But I think it's the progression to fibrosis which is the issue. The question is can we get that answer in a short time, or are we using in the short time of treatment, are we using then

reduction by HAI as another surrogate marker, a surrogate marker of the likelihood that we are going to reduce the development of portal hypertension or reduce the development of liver cancer.

I just am uncertain whether that can be used in a short period of time. I think it has to be used in long-term follow-up, there is no question about that. But I will have a better way, I think I will be able to answer the question a little bit more comfortably when I see what comes out of the HALT-C trial.

DR. SHERMAN: Dr. Chung.

DR. CHUNG: I would like to take a somewhat different view of that particular question, and I think it's important for us to be open-minded about the potential long-range benefits of new strategies that are about to be introduced.

First of all, from a needs standpoint, there are many patients who are sidelined from the benefits of interferon and the whole promise of SVR that go with interferon-based regimens because of

intolerability, contraindication, et cetera, et cetera and we all know, we all have many patients in our practices who meet those criteria.

There are also the non-responders, as you already suggested, in the maintenance trials ongoing to look at, as you suggested, the antifibrotic benefits of interferon.

I think when we talk about these novel compounds and these interferon-free regimens moving forward, I think we must be open-minded about not just looking at the virologic benefit, which simply, you know, the SVR standard should be imposed on. But I think we need to collect that histologic information as a secondary endpoint on the premise that we might be able to identify a clinical benefit moving forward even in the short term.

If that is HAI, I think there are reasonable studies that show that inflammatory indices among patients with hep C do correlate well with subsequent fibrosis progression, that the more inflammatory the index is, using the same pathway

description you have defined, which is inflammation promoting, ultimately collagen deposition fibrosis.

So, I think we shouldn't impose these long-term trial requirements right off the bat. But I think this needs to be studied incrementally and to the extent that end of treatment data and from histology will give us information. I am not suggesting that is the primary approval tool.

I am suggesting that information be collected as the basis for saying there is promise here for this combination of agents, using it as a suppressive strategy with histology.

DR. SEEF: I completely agree with you, Ray, I completely agree with you. I am not saying that we should not collect this. I think we should get that information. Obviously, this is part of the whole process.

My issue is if nothing else improves but the--you know, the improvement of histology, is that enough for registration purposes or is this simply saying, well, it looks as though something is happening and that is where I am uncertain.

I think that we have to collect it, of course, I don't disagree with you.

DR. CHUNG: I think we collect it. I think we impose the SVR bar first. That is what we are asking an antiviral to do in the first place. But I think if the data are promising enough about histologic improvement, I think we should think nimbly about potentially creating a potentially composite endpoint or histologic endpoint for subsequent trials.

DR. SHERMAN: Dr. Havens.

DR. HAVENS: Actually, you are not suggesting that all these drugs will have SVR as defined, which is off drug for 24 weeks, there is still no virus and you just eloquently outlined the patient populations for whom a purely suppressive regimen might be their best hope.

So, I would say that histology rather than just being something important to include in all studies, might, in fact, act as the primary endpoint for some patients, because it is better than what they can get now, which is nothing.

So, if you have failed you lead-in or if you can't tolerate interferon for whatever wide range of reasons, so these are the patients who are the most difficult to handle right now and, for them, they can't get to the ribavirin endpoint of off drug and no virus. An improvement in their histology at 48 weeks might be enough for initial registration or might be considered that way because that is an important group who need this therapy.

DR. SHERMAN: Dr. Vierling.

DR. VIERLING: I think that most of us are reaching a point of agreement. The problem I am having regarding this group and the concept which I definitely agree with is ultimately the potential for noninterferon-based, probably based on HIV experience combination therapy and suppression is whether a histologic endpoint early on with a virologic endpoint within these study, I think we would want to obviously see histology combined with some antiviral impact during study.

Whether short term is long enough to then

be advocating the long term use of suppressive therapy, to me that is getting into yet another trial design and I think that, in my mind, it is a bit of an apple and orange.

If we are trying to see whether SVR is achievable, clearly, we have the time frame in mind. If we find that we can suppress virus but there is recrudescence early, which is your point, and definitely with single agents may be more anticipated than not, we would like to know what translated into histologic and ALT change, in my view secondary endpoints, along with the viral suppression endpoint within the trial, maybe then giving credence to longer follow-up on therapy and moving toward a chronic treatment paradigm, very analogous obviously to HIV, which is not something we have actually ever studied in hepatitis C. I think we have to acknowledge that.

We have been blessed by the SVR and by the original trial designs to be so focused on this we haven't really looked until HALT-C and others in the very advanced histologies in terms of

maintenance.

DR. SHERMAN: Dr. Havens.

DR. HAVENS: Now, we get into the discussion that we were having yesterday perhaps about what is required at the time that you go for registration versus what is good enough to be in a promise from a company for a follow-on study.

So, if you have 48 week liver biopsy data showing virus suppression and good outcome and then go for initial registration and then say, well, and we will do the 96-week follow-up to show continued improvement in histology, you know, that might be a way to balance the kinds of issues you are bringing up with the need to get drugs out to people who might benefit from them.

DR. SHERMAN: Dr. Chung.

DR. CHUNG: I agree with that because I think the company has a stake in all of this, and if they fall short of the SVR goal, and you have only got a 48-week histology improvement and no approval on those grounds, it's a tough day.

I think the idea of continuing that

therapy onward, if the 48-week secondary endpoint for histology could be met, I think would be an important way of allowing the momentum to continue and evaluation to continue of a new strategy for those new classes of compounds.

DR. SHERMAN: Dr. Birnkrant.

DR. BIRNKRANT: It seems like we have a thorough discussion on the noninterferon-containing regimens with regard to histology, what about in the setting where it's the standard of care, which is interferon based, plus a normal agent, do we want histology data in that setting as well, because this is a common area of negotiation with the pharmaceutical industry, that is, the use of histology versus non-histology. For the hep-C products we have gotten away from it. Hep-B, we are still using it.

So, to go back to it for hepatitis C will take a great deal of negotiation unless we hear something positive from you.

DR. SHERMAN: Dr. Havens.

DR. HAVENS: Well, the context within

which the importance of histology was raised, was in development of a drug for which you were not trying to get an SVR as defined as 24 weeks off therapy, no virus found.

So, in any interferon-based regimen, SVR defined that way is the standard by which such a regimen should be measured. Since that SVR defines good histology already in interferon-based regimens, by studies that have already been done, that's a reasonable surrogate endpoint.

Biopsy data might be less important in those kinds of studies. Does that make sense? We are kind of ranking the endpoints. If you are going to get an SVR, then, you can do that without histology.

If you are not going for an SVR, but rather a suppressive regimen in a whole different paradigm, then, histology and suppressed virus control might be an important way to look at it.

Now, this is as little bit tricky to me. The point was already raised that some of these drugs might actually make your liver a little

worse, so then I don't know how to balance that kind of safety issue, as well.

DR. SEEF: This is obviously very difficult. I actually like what John has said, which is the fact that when the studies are designed, there is going to be a given period of time of treatment, let's say 48 weeks.

We get to the end of that period of time, we find that the virus has either come a little bit, has not gone, the enzymes may have come down a little, but there has been a two-point improvement in histology.

So, the FDA now are going to say on that basis we are going to approve this, and if we are going to approve it, are we going to approve it for 48 weeks, are we going to approve it on the basis they need to continue to treat for a given period of time until we find that this has had a real impact over a long period of time.

I find that difficult, I really do. I think that while I grant you that these drugs may not work in the same way and that suppression of

virus or eradication of virus may not be the answer. I am just not sure that basing a decision to release the drugs to the public, and you are very worried about who is going to use these drugs when we start talking about all the other complicated cases, what does the FDA say on the basis of this response, that there has been some improvement in the histology after 48 weeks, what is the recommendation now with regard to treatment?

I find that difficult. I think that histology is critically important, obviously, and I think this is information in any trial of liver disease where infected is the disease that you are worried about, that you need to get that information.

But to base it solely on that may be very difficult I think.

DR. SHERMAN: Tracy Swan.

MS. SWAN: I am just wondering if we are looking at approval for an antiviral drug it makes sense that histology should be checked for safety and perhaps for a benefit, but that we wouldn't

want to limit other drugs like antifibrotics and immunomodulators to the same sort of contained set. This is all coming from such an antiviral context and I am just wondering if we are missing something else here.

DR. SHERMAN: This is the Antiviral Committee.

MS. SWAN: True. Thank you.

DR. SHERMAN: Dr. Chung.

DR. CHUNG: I think we are all in agreement actually, Leonard. I think we are in agreement that we wouldn't approve a compound regimen based on 48-week HAI improvements. I think we need to collect that information as grounds for subsequent follow-up, perhaps even within the same trial, use that data to perform follow-on histologic improvements with continued therapy.

It is important I think to separate out the antiviral goals from the disease management goals. I think to Dr. Birnkrant's question about PEG and novel agent regimens, I think it all again depends on if the intent is liver fibrosis

suppression, if that is the intent right out of the box, then, that ought to be a long-term trial using parameters similar to those outlined by HALT-C and other suppression trials or maintenance trials using those criteria, i.e., longer term histologic indices rather than the shorter term ones that are under discussion now.

I mean I agree with Leonard and John that you can't go to the bank for long-term use of a compound with 48-week data with HAI. If it is disease management indication that you want, that you are seeking, then, you ought to impose a disease management study design on that particular compound or compound combination.

If you are shooting for antiviral effect, of course, we have already said the SVR and an SVR study design should be pursued, but I don't think we should be mixing. I think the intent should be laid out right from the outset by the company.

DR. SHERMAN: Dr. Haubrich.

DR. HAUBRICH: So, it seems that the standard approval particularly in naives ought to

be the SVR. But particularly in the experienced patients, especially those that include the non-responders, following those patients would be critical for developing hypotheses about what antiviral changes lead to inflammatory scores and what the long-term consequences in those studies ought to be continued until we know more. But I agree completely not as the basis for approval for the drug, you have to have SVR.

DR. SHERMAN: I would like to raise the issue that one of the reasons to consider doing histology at the end of studies with the addition of a new drug to an interferon-based regimen may be that there may be an added synergistic effect that has not yet been defined. You won't know that if you don't look and that having such evidence could be an important factor in swaying a future committee decision that, in fact, there is usefulness in this agent that is demonstrated in multiple facets of the response.

DR. HAUBRICH: But it could be a subset.

DR. SHERMAN: Sure. Dr. Andersen.

DR. ANDERSEN: That is where I was going is a potential to do those as a substudy or more importantly perhaps, in the initial "n" of a large study, because that gives you a chance to make a mid-course correction if you need to either to collect more data or to analyze those data themselves.

DR. SHERMAN: The problem generally in a substudy is a real world consideration. If you ask a patient you have an option of getting a liver biopsy or not, most would say no.

DR. ANDERSEN: I think that's why my point was the first end into the study are committed. That is a condition, that is the study design when it opens.

DR. SHERMAN: I think to sum up here the general feeling is that SVR remains the standard for an approval using the virologic definitions that have been in place to date, however, the use of histologic endpoint or histologic evaluation is encouraged because it may permit determination of other changes that could be added, synergistic

improvements.

It may identify safety issues that Tracy Swan pointed out to us and provide information that might, particularly when the HALT-C data matures in the not too distant future, provide a path to licensure based upon suppression that is different than the traditional path of SVR and could be very important for the long-term considerations of this committee and the agency.

I think it is time to take about a 20-minute break. Thank you.

[Break.]

DR. SHERMAN: The next issue on our agenda, Dr. Laessig.

DR. LAESSIG: I am sorry. Before we leave that question entirely, I would like to muddy the waters and ask the committee if there are any endpoints other than SVR which would be acceptable as the basis of an accelerated approval, for example, ETR.

DR. SHERMAN: Okay. Let's throw that open to the committee and see if an end treatment

response is an acceptable approvable endpoint.

Dr. Havens looked like he was ready to respond.

DR. HAVENS: I didn't want to go into that first, though. I think the SVR is a surrogate endpoint for the virus is gone and the liver looks good. Virus suppression on therapy, there were histology at the end of 48 weeks would say that at least at 48 weeks, we have done pretty well, similar to studies in hepatitis B.

Now, you are taking us back to the virus is gone at 12 weeks or it's a quick step to say the virus went down by 4 weeks if you are having that discussion and what that study says is I have a drug that can bring down the virus load. But it doesn't say anything about more, so that might be a prerequisite for ongoing studies. It certainly wouldn't tell you anything about the progression, that would be improvement, of disease at 48 weeks, which the prior discussion argued was a minimum requirement to show better histology at 48 weeks.

So, I would argue that showing that you

can bring the virus down by 12 weeks is a sort of a prerequisite to identify a reasonable drug that you might want to move forward. But absent data showing benefit to the liver or the patient with the liver it is certainly inadequate for a registration trial.

DR. SHERMAN: Dr. Chung.

DR. CHUNG: I would say that for an antiviral compound that is going to bring about meaningful HCV-RNA reductions during therapy, that end of treatment response simply cannot suffice as a benchmark.

I think we would all envision at least in naive patients that we are going to see excellent response rates on therapy. The real question is are they durable. I think it's the SVR that should be applied under those circumstances and, for histologic endpoints, there is a histologic endpoint to use. But for an end treatment virologic response, I just don't see that that is a defensible primary endpoint.

DR. SHERMAN: Is there any dissension to

this view on the committee? None. Oh, Dr. Fish has a comment.

DR. FISH: I just had a question in terms of would we think differently for a non-pegylated treatment where you might expect it would be a model that, you know, you go up there thinking the viral load is going to go back up.

DR. CHUNG: Well, I think we addressed that argument in the previous question in the discussion, which is that yes, I mean we could again anticipate even these combinations of antivirals could bring you to end of treatment responses. But we would certainly be concerned about the high relapse rates that could occur under those circumstances. I think we would have to apply the SVR or benchmark under those circumstances, as well, again with all the other caveats stated earlier.

DR. SHERMAN: The next question we face is we accepted SVR is an appropriate primary endpoint. It is currently defined as 24 weeks after cessation of therapy. But there was some data

shown that suggested that the majority of patients who relapse, in fact, relapse within the first 12 weeks following completion of therapy.

Do we have sufficient evidence and are we at the point of being able to recommend that an SVR 12 might be an appropriate endpoint in terms of redefining what at SVR is with the understanding that this does somewhat accelerate the approval process if you only have to follow a patient for a period of 12 weeks following completion of therapy?

Dr. Havens.

DR. HAVENS: No. Twenty-four weeks is the gold standard by which standard of care is measured. If you are developing a drug that you want to meet that current standard, it has to meet the standard of SVR-24 after the end of therapy.

Now, for me, partly to get to the question of should it be 72 weeks after the start of therapy and a shorter therapy, something I am happy with.

DR. SHERMAN: That's the next question.

DR. HAVENS: Then, I will stop there.

SVR-24, because you don't know what is going to happen with the newer compounds. It seems, while the data might be there for current therapy, it is possible that there would be a different pattern of recurrence with new drugs. I would stick with this.

DR. SHERMAN: Dr. Seef.

DR. SEEF: I came here with the view that I would accept the 12-week. But that was when we were talking about the virus as the item that we were looking at. Now, we have extended this to say it may not be an impact on the virus, but may have another impact which may not be identified by, for example, an SVR. So I also tend to accept the fact that I think that I would stick with 24 weeks rather than 12 weeks at this point.

DR. SHERMAN: Tracy Swan.

MS. SWAN: We need to do a huge amount of education if we were switching to SVR-12, because I don't think people are as familiar with that. I think it is really important to prospectively validate SVR-12 in future studies, so we could

maybe move towards it if it is applicable and relevant.

DR. SHERMAN: Dr. Haubrich.

DR. HAUBRICH: I think actually Tracy said exactly what I was going to say.

DR. SHERMAN: Dr. Chung.

DR. CHUNG: I wonder, I think SVR-24 is going to have to be the benchmark for final approval. I wonder if in mid-phase approvals, when moving from Phase II to III in the development process whether in terms of speeding transitions, data on SVR-12 could be presented and used as a 98 percent surrogate at least on PEG ribavirin-based regimens for the movement into a Phase III study design.

So, in other words, just applying that to drug development prior to preapproval steps.

DR. SHERMAN: Don't you face the same issue of the potential of missing? Back in the Phase II, it seems that you would want just the opposite, you would want to know more, not less.

DR. CHUNG: Ninety-eight percent

correlation with SVR-24, I think you would get a pretty clear sense of whether you could make a go-no go decision. That is just a practical consideration. I mean again none of this is for licensing purposes per se and that's Phase III.

DR. SHERMAN: Dr. Vierling.

DR. VIERLING: I came also like Leonard with a sense that giving this as an RNA virus and what we know about its major hepatic sites of replication at 12 weeks may be sufficient. You ascertain whether it was present or absent and it should be replicating within that period.

I think also the 2 percent that we arguably may have missed with the 12-week point on the retrospective studies, none of which are actually that robust, may have been a phenomenon of the lower limit of detection of the PCR assays at the time.

You have already addressed this, Dr. Sherman, that if you look carefully at those relapse rates you may find with sensitive assays or 50 IU per Ml assays are lower, that they were

actually viremia at the end of treatment and therefore may be not achieved in end of treatment response.

However, I think Dr. Havens has really introduced the other issue and that is whether you could have post-drug period of suppression with any particular combination of agents that would obscure the time frame in which the replication could occur and, if that were to just by the nature of the drugs or their distribution or their intracellular gene effects, have a longer duration post treatment, then, the observation period might not be appropriate at 12 weeks. I can see the merit in using 24 weeks as the gold standard. But to collect in these studies 12-week data, because if it is validated at 12 weeks, is the surrogate, then, I think that is very appropriate.

Obviously, at 12 weeks ends up with further relapse, it is very important that we would know that, so I think you need both.

DR. SHERMAN: I think the response is clear that at this point, 24-week SVR is

appropriate. It would be useful to suggest collection of data that might ultimately change that paradigm in light of the new classes of agents.

The next one is the one that Dr. Havens was anxious to work on and that is the issue of the duration of the treatment arms. We discussed this briefly yesterday, as all, and I had asked the agency to prepare a good response to this.

The basic issue is should patients be followed, if we accept that the SVR evaluation time is 24 weeks while in completion of therapy, is the 24 weeks following completion of a particular arm that may be shorter than the traditional standard of care for that particular genotype, genotype 1 or perhaps genotype 2-3, should the evaluation be made at the 24 weeks, or is there a reason to, in fact, require those patients continue to be followed to the end of the standard of care treatment time, which would mean that, for example, a 24-week treatment period compared to a one year standard of care, those patients would have a follow-up of an

additional 48 weeks before a definitive evaluation is made.

I would like to hear the comments of everyone at the table starting with Dr. Birnkrant.

DR. BIRNKRANT: We had discussions yesterday and what we felt was that this really wasn't a statistical issue per se, because that could be handled in that way, however we thought it was more of a clinical/interpretability issue, that is, if you treat someone for a fixed period of time and follow them 24 weeks and compare that to another group that is treated for a different period of time, with 24-week follow-up, then, there would be a lack of data on that first group if the were treated for a shorter period of time still with the 24-week off treatment endpoint. But then we wouldn't know what happened to them between the time of their 24-week off treatment endpoint and then the 24-week off treatment endpoint for the standard of care arm.

One solution to that is obviously to measure multiple time frames and, as you said, just

follow them longer. But we thought that it was more of an interpretability issue. We just wanted to make sure we didn't lose anyone in that intervening 24-week period.

DR. SHERMAN: I would actually like to use the Chairman's prerogative to call on Dr. Andersen, who is a statistician and clinical trials person, to maybe comment on the issues related to this longer duration and a shorter treatment arm.

DR. ANDERSEN: Let me separate it, strata versus arms, because if there is a uniform clinical decision, for example, separate genotypes 1-4 from 2-3, so that in the PEG paradigm, for example, potentially 2-3 is being treated with 24 weeks of therapy, not 48, making the distinction within strata is perfectly reasonable to come up with a uniform decision there.

In terms of treatment arms themselves actually having very different end of study times within arms gives statisticians, makes them uncomfortable. There is a concept call the guarantee time that just to take it to its observed

point, let's say everyone shall fail at 14 months if one arm is looked at, at 12 months, everything will look great and the other looked at, at 18 months, everything will look terrible. That is highly unrealistic, but it is out there and it's something that makes people nervous.

So, with that context, generally, we really would like to see a uniform decision time. It doesn't mean the decision time can't be made earlier in one arm, but for everyone to have a uniform time of evaluation is ideal for our standpoint.

DR. SHERMAN: Dr. Alter.

DR. ALTER: I am not sure I want to ask a question, but I am going to ask it anyway, because while I understood exactly what you said, and I understood exactly what you said, it is still measuring two different things.

In other words, if you measure 24 weeks after you finish 6 months of therapy, and 24 weeks after you finish 48 weeks of therapy, that, to me, is an identical endpoint in that both arms have

been off treatment for the same period of time, if I said it correctly, and now I don't even remember what numbers I said. But, in other words, your follow off therapy SVR is defined as how many weeks?

DR. SHERMAN: Twenty-four.

DR. ALTER: Thank you, 24 weeks. I am afraid to say any number now. SVR is measured at 24 weeks after therapy ends, so you have a short arm and they are followed 24 weeks after therapy ends and you have a longer arm and they are followed for 24 weeks after therapy ends, which obviously are different lengths of time. But they are both measured 24 weeks after the end of their therapy.

That is the part that is bothering me.

DR. ANDERSEN: What if--and again we are dealing in hypotheticals here--what if one arm was 7 days of treatment and the other arm was 48 weeks of treatment, so now we have essentially 48 weeks difference.

DR. ALTER: What you are saying basically

is that you are saying that the shorter duration of therapy was defined based retrospectively really and that the shorter duration of therapy might actually--they might take a longer time to relapse.

DR. ANDERSEN: Potentially.

DR. ALTER: Potentially. They could be exaggerated versions.

DR. ANDERSEN: They potentially could be fragile responders and by not having that uniform period of observation, then, to some extent, while it is not apples and oranges, it might be varieties of apples being compared here.

DR. SHERMAN: I am going to ask you the question, what about differential dropout in the long-term untreated arm and how does that affect analysis?

DR. ANDERSEN: That is definitely an issue, it has always been an issue with studies. The problem is obviously, if you are doing an intent to treat analysis, then, dropouts, if you are looking at dropouts as failures, that is a problem.

Studies like that can also be analyzed using failure time. Methods can be either sensor dropouts to look at the estimate proportion still in SVR at the uniform time point, can also do competing risk type analyses to begin to work with those issues.

DR. SHERMAN: So, there would have to be clear criteria because it seems that if you simply did intention to treat, which is the traditional approval mechanism, you could end up with lack of finding an effect when, in fact, a very significant effect was present at the appropriate time point if dropout was sufficient in patients untreated for a full year of time potentially in this setting.

DR. ANDERSEN: You do run into that issue, but, on the other hand, you run into it if you are doing an intent to treat analysis and also presenting an as-treated analysis, which is very often done in any approval process.

If those are mismatch, then, we need to stop back and look at the data. So, what you are saying here is I think the same thing, that if you

have got an extended follow-up period, again, we are not talk about 4 or 5 years of follow-up here, we are talking about 72 weeks, which is standard for all studies, at least at this point in the ribavirin era, PEG riba.

So, if all people entering the study know that they are going to be followed for 72 weeks, this does not put an undue burden on the arm that has potentially stopped treatment earlier.

DR. SHERMAN: Dr. Haubrich.

DR. HAUBRICH: I agree with everything Dr. Andersen has said. I think we have to bear in mind here that we are doing studies in people and the one thing we can realize will happen is that people will drop out.

So, purely by basis of that, there are reasons for dropout, for toxicity, there are reasons for dropout because people move to Kansas, which is hard to understand from San Diego.

So, some of those are important and biased and some of those are not important and hurt the study. So, having different lengths of follow-up,

you can envision all sorts of things that could happen that could bias the results one way or another.

In my mind, it makes sense to have uniform follow-up, just state that upfront, and then have sensitivity analyses after the primary endpoint to make sure that the way you analyze it, however you choose, is not influencing unduly the overall outcome assessment.

DR. SHERMAN: Dr. Chung.

DR. CHUNG: I think we are making this a little more complicated than it needs to be. The definition of SVR is virus negativity, HCV-RNA negativity 24 weeks after completion of any regimen of therapy. So, the fact is that the clock should start at the discontinuation of therapy whether it's the planned 48, the planned 24, or premature discontinuation of the regimen.

That is the time the clock should start and it should be uniformly maintained for the 24 weeks after that clock has started. The data collection should take place at the 24 week after

completion of discontinuation of therapy and that should be the benchmark for SVR definition whether they got 48, 24, or 4 weeks of treatment.

The intent to treat principle is covered. I mean dropouts are non-responders by standard criteria and I don't think we need to--I understand the statistical considerations, but if you start the clock at discontinuation of therapy, then, there is a uniformity there among all your study subjects.

DR. SHERMAN: Dr. Vierling.

DR. VIERLING: I agree with Dr. Chung and I think that there is a biologic basis, because as Dr. Seef said yesterday, the long-term follow-up data strongly suggests that we are looking from a virologic standpoint that SVR long term is a cure and, in fact, the largest study, and I presented just briefly, it went by on the slides yesterday, that that was essentially 98 percent. Of the 100 percent of patients, they had undetectability by PCR using sensitive assays in the serum. The detectability in the 2 percent that were detected,

one was in peripheral blood mononuclear cells and 4 out of 5 out of 217 patients were in liver biopsy tissue.

I have a prejudice that that was probably peripheral blood mononuclear cells which are part of the normal resident inflammatory cell mass in the liver, so the issue here, if you think in terms of cure, if you defined cure and you are dealing with an RNA virus, which is capable of replicating at extraordinary rates as have been shown with the viral kinetics and, basically, if present and in the right environment, doesn't have a choice about whether to replicate or not, I think its presence really in the right environment will dictate replication that you are able to find and defined in 24 weeks.

So, biologically, I believe that 24 weeks of follow-up post any treatment regimen can be considered to currently sufficient. I think we have the data to support that view.

The question that was raised earlier, what if you had a therapy that for 7 days could achieve

a cure. I would love to see that therapy and I would love to be able to monitor it and understand it. Would long-term follow-up be necessary as we have already done to define SVR as a potential cure? Of course. But I think that it's 24 weeks post therapy and, in this era, keep in mind that not only do people drop out for moves and other considerations, they may drop out to try any number of things including the herbal products, anything else that they think might advance their health and, within that period of time, they also have an increasing liability of being treated or diagnosed with other comorbid conditions that weren't at the initiation of study apparent in terms of inclusion and exclusion criteria.

So, I am worried about an off-therapy extension of analysis, because biologically, I don't see the data validate its necessity. Statistically, I can understand the way in which it could be used. But, biologically, I think an SVR is a cure at 24 weeks.

DR. SHERMAN: Dr. Alter.

DR. ALTER: I am still on the fence here, I could go either way. What if the treatment was--let's just say we were treating genotypes 2 and 3, let's just say, using standard of care and standard of care plus some other drugs, so that the standard of care is a shorter length of therapy, and then the 24 weeks. Now, would 24 weeks be okay? And that was the study, it was just for that, so there wasn't another arm that was longer.

Would that study also have to have extended follow-up? No, okay. So, it is only when you have different lengths of therapy within the same study.

The other issue that I can't quite decide one way or the other has to do with the fact we are dealing with new compounds. We don't know if they are going to act in the same way as the antivirals that we currently use, at least I don't know that we know that.

So, is there something that could happen with these including resistance that might be measured at a longer time than we are currently

measuring, which would go along with why you would follow them longer if you had a longer treatment arm.

DR. ANDERSEN: One approach would be to be not completely prescriptive or restrictive, to pick one and say in general and however there might be circumstances where either differential follow-up is obviously the way to go in a certain circumstance or where the agency, the company see a reason to have a uniform follow-up period of time.l

DR. SHERMAN: Dr. Sun.

DR. SUN: It seems like people are applying the word "uniform" and reaching different conclusions. I think fundamentally you have a situation here where you have differing lengths of therapy. So there is no way to make it all uniform.

So, I think you have to choose which principle you want to apply your uniformity to. It seems to me that SVR-24 is primarily a measure of durability and, if that is the case, then durability is defined as how long it lasts from

when you stopped. So, in that regard, I kind of agree with the comments about applying the uniformity to the duration of follow-up from the end of therapy.

As an example of that principle, you could say, you know, we typically follow drug safety for five half lives of the individual compound and so that is a uniform application of a principle that leads you to different periods of follow-up depending on the half-life of your drug.

I think one can get comfortable with the idea of uniformity if we think about it in the right way.

DR. SHERMAN: Dr. Havens.

DR. HAVENS: I would argue that maybe the duration of follow-up being either uniform from the end of therapy or uniform from some other time point depends on what outcome we are really looking at.

So, this discussion would only really apply to regimens that we are arguing are going to be virus curative and then, if it's virus curative,

the time from end of therapy to some uniform duration of follow-up time showing it is still gone then is appropriate, I think. But, if you have a different outcome, then, the liver biopsy 48 weeks later might be 48 weeks from starting a one-week therapy versus a 6-month therapy, liver biopsy 48 weeks later might be the outcome of interest.

So, inasmuch as we believe that the SVR-24 weeks off therapy is any important surrogate marker for good liver outcome, then, that is an appropriate endpoint in a way that I think everyone has been kind of arguing.

If we are looking at a suppressive therapy rather than a curative therapy, virus suppressive therapy rather than a virus curative therapy, the answer might be different. I think this is applied only to the virus curative therapies and then I think 24 weeks after end of therapy is the appropriate time.

DR. SHERMAN: Dr. Chung.

DR CHUNG: I think we are in agreement. It should be 24 weeks after completion of a

measurement of therapy. That defines SVR. I think for virus-specific agents, and that is certainly true for interferon-based regimens of any sort, for virus-specific regimens, novel combinations, whatever else, if those are antivirals, we can define whether longer term collection for the sake of ruling out resistance be done. But, for the time being, I think we should also impose, at a minimum, an SVR endpoint for those combinations as well. I think we have spoken to that already.

DR. SHERMAN: Dr. Fish.

DR. FISH: I agree with Dr. Chung and Dr. Vierling, and also just for purposes of comparing historically two existing trials, and so on, of keeping the same as the side I would come down on.

DR. SHERMAN: Dr. Andersen.

DR. ANDERSEN: Although I am going to go back to Dr. Sherman's point about dropout, that if again, if we have a very short period of treatment plus 24 weeks of follow-up, potentially, we have less than a year where somebody has to be in the study.

Whereas, another arm that takes quite a bit of time and then needs more follow-up, if there is a uniform dropout rate over time, then, the arm that takes longer is, by default, going to have a higher dropout rate, which in the intent-to-treat is going to mean a lower SVR rate.

DR. SHERMAN: Dr. Seef.

DR. SEEF: Let me begin by saying that I am in awe of biostatisticians. I am also in awe of immunologists, virologists and epidemiologists.

I would tend to support the 24-week virologic response, as Dr. Havens and others have said here. The question about whether there is a difference, if we are saying that the drugs that we are looking at may have an impact other than antiviral effect, might have an antifibrotic effect, if we decide it's 24 weeks after cessation of treatment regardless of how long the treatment, is that a time to do the liver biopsy, or might that be too short and should that be perhaps, as Dr. Havens suggested, at the same time, say, 48 weeks.

The problem is in do we go to the 48-week one and say, well, it maybe should be at 72 weeks, I don't know, but I think that I would personally stick with the 24 weeks for the virus. I am uncertain about the liver biopsy. I think the liver biopsy should be later.

DR. SHERMAN: Dr. Havens.

DR. HAVENS: I agree that is the issue kind of that a different outcome may have a different timing, that the virologic outcome is an end of therapy, durability of the virus is gone. But, for a different study, suppressive study, it may be that a biopsy at a given time point after study start would be an appointment endpoint. But that is in a different non-PEG kind of world, I think.

DR. SHERMAN: Dr. Haubrich.

DR. HAUBRICH: So, I won't disagree with my esteemed hepatology colleagues as that has brought me nothing but grief so far. So, clearly, I think everybody agrees that the 24-week evaluation for the SVR makes the most sense. But

let me at least raise one point for consideration.

If, say, you are designing a 24 versus 48 and your designing is not inferiority, because you are hoping that a shorter therapy will be at least as good as, which makes sense if we are using interferon.

Let's say, then, you have a 10 percent margin of non-inferiority, the true success rates in your trial is 10 percent in the long therapy and 20 percent--sorry-- failure rates, 10 percent and 20 percent just for argument in the two groups.

So, just by looking purely at that, you would conclude there is a 10 percent difference, so you failed to conclude non-inferiority. Now, let's add to that 5 percent dropout per 24 week. That means in the long therapy, you have added 10 percent dropout. The cumulative failure rate is now 20 percent.

In the 24-week group, it's 25 percent. You now conclude non-inferiority of the 24-week therapy purely based on moving to Kansas.

Obviously, you can never handle all of the

extremes. I just caution that although I completely agree that the 24-week endpoint makes sense from the standpoint of the virus, administratively, I think there are concerns about having differential follow-up and that if there is even a uniform dropout between groups, it could lead to a different study answer.

I don't know how to solve that, but that is where my conundrum is.

DR. SHERMAN: Dr. Andersen.

DR. ANDERSEN: We have an opening. How does Boston sound?

[Laughter.]

DR. SHERMAN: On that note, I think that after considerable discussion, the committee has come around to the consensus that, in fact, differential treatment follow-up times are appropriate as long as we use the 24-week mark for a virologic response.

If other elements are a key part of the protocol, such as histologic evaluation, there may be a need to modify the durations of follow-up,

that the agency and the sponsors need to be aware that, in either case, the potential for dropout biases one arm or the other and that analysis needs to take that into account as you move forward in making decisions about the approval of not.

Is everyone okay with that? Okay.

The next issue is Study Design. We have a variety of choices to discuss. Some have already been discussed almost with the assumption that that is going to happen, but I think we need to at least briefly consider each one.

This is not a this or this necessarily. It may be that all of these are appropriate design considerations but we will consider each one individually.

We will start with the one that has been discussed the most in light of what we currently have and where the current trials have been going and that is adding the investigational agent to the standard of care.

Is there any disagreement that that is an appropriate study design? None. So, that is an

appropriate study design.

DR. LAESSIG: I just want to clarify something I thought I heard yesterday regarding a discussion of non-inferiority versus superiority. What I understood was that the committee was comfortable with a non-inferiority design, for example, studying treatment-naive genotype 1 patients using a standard of care arm for 48 weeks versus a triple arm for 24 weeks and demonstrating non-inferiority.

DR. SHERMAN: So, now we are not talking specifically about the design, but how the design is analyzed at the end of the study.

DR. LAESSIG: Right.

DR. SHERMAN: In terms of what is the goal, so I guess that is a reasonable question. Using an add-on to standard of care study, where is the bar, is it non-inferiority with this current standard of care, or is it that it has to be better?

DR. HAUBRICH: Isn't that the next bullet?

DR. SHERMAN: It may or may not. The

question, though, may be relevant to other areas, but it is still relevant even here in a simple add-on. Someone may choose to define non-inferiority over the same treatment period, perhaps with less side effects.

DR. LAESSIG: I guess I would ask wouldn't you want an arm, a triple arm out to 48 weeks to possibly demonstrate superiority? I mean it really doesn't change the duration of the study. You have to go out to 72 weeks anyway.

DR. SHERMAN: So, again, the agency issue is, is it sufficient at this stage to accept non-inferiority even with shorter treatment perhaps, or should the bar be set at trying to find a superior agent.

Dr. Andersen.

DR. ANDERSEN: One thing I would like to point out is that with non-inferiority studies, all I can say is there is no free lunch, it does have a smaller sample size than potentially an equivalent study with the same tolerance.

It's a toss up as to whether it has a

smaller or larger sample size with respect to superiority study. But, by using that design and using a one-sided test, you are giving up a lot of information that can be gained at the end of the day with what could still be a very large study.

The other point with non-inferiority studies where the primary endpoint is efficacy, is safety potentially still should be a two-sided test because you don't know whether safety could be worse with the new agent.

So, in this case, non-inferiority might better be done, I will throw out, as sized so the two-sided test can and should be done, but with a non-inferiority target for it.

DR. SHERMAN: Dr. Chung.

DR CHUNG: Let's try to draw on some concrete examples. I think, where you have got a substitution strategy like a better tolerated ribavirin, where you would be talking about essentially an equivalence duration of therapy, but a measurable toxicity that might be minimized, a non-inferiority design I think would be reasonable

in that context because you have a demonstrable objective measurable toxicity or AE along with a non-inferiority for the primary endpoint, which would be SVR.

That kind of a substitution sort of strategy we were talking about compounds that act in place of one of the active regimens, active compounds is reasonable.

For these PEG plus ribavirin plus active agent X, I think we have to demonstrate the efficacy of that agent in a superiority design against standard of care, PEG rather plus control, placebo control.

It is reasonable to add in the PEG and ribavirin plus X for a short duration, for instance. But I don't think that a separate study for non-inferiority before you have shown the efficacy of that compound as superior to standard of care is advisable.

So, I would say that you could vary that arm in the context of a larger superiority study design or once you have shown that superiority, do

a non-inferiority design for substitutions or a shorter duration. I know I am getting into the second question.

DR. SHERMAN: Actually, they are clearly related.

Dr. Alter.

DR. ALTER: I hate to be simplistic, but aren't we supposed to decide before the study begins, when we design the study, what the objective of the study is? So, the study should be designed to meet that objective.

Now, sometimes you get secondary objectives, because of what happens with the study. But you have to decide in advance whether you are designing a study to show efficacy, superiority, or just you want to meet the standard of care because this is oral, and not injectable, that would not be the first one. Right?

So, that has to be decided upfront, not afterwards. You don't decide that the study design is okay because--

DR. SHERMAN: But that is the question we

are being asked now.

DR. ALTER: That is not what I am hearing. I guess that is not what I heard. I heard something different. So, I am saying, you know, I mean if you design the study upfront, what I heard was people talking about, well, you have to determine, you have to show superior efficacy first. Then you can show non-inferiority.

Well, you don't know what is going to happen, so the question is--we are talking about study design, we don't know what is going to actually happen once the study is concluded.

So, when you design the study, you have to decide if you are designing it to show superiority or not, you know, using, for example, a two-sided test.

But maybe you don't want to show superiority, maybe in terms of efficacy, maybe it is because the drug regimen, which I know is not No. 1, is easier to take, which we talked about yesterday, in which case you don't necessarily want to show superior efficacy, although that would be

great, you just want to show it is just as efficacious, but easier to take.

So, I don't see anything wrong with that design either as long as you design it appropriately upfront to meet your objectives. So, if your objectives are to show superior efficacy, then, the study design should--and, Dr. Andersen, please feel free to tell me I am full of it.

I am looking for, I mean you decide before, when you design the study, what the study is intended to measure.

DR. SHERMAN: Accepting that, I am going to push you further, though, because the question really is, as a member of this committee, where is the bar.

Is it appropriate at this point, looking at new generations of drugs, to be designing trials for primary approval for shortened courses of therapy that may be somewhat better tolerated, with equal efficacy, or is the bar, let's find out in at least one arm of this study, before approval, if it's a superior agent.

That is the question, not can you or should you. Yes, we can design studies that answer either question, but at this point, looking forward at approval, which is the relevant response.

DR. ALTER: Both of them.

DR. HAVENS: At approval, you need to know the drug is safe and efficacious. Dr. Andersen, could you please come back to your statement, that for safety, you need a two-sided p-value.

DR. ANDERSEN: I had put this out for consideration. I think it is study-specific and has to be looked at that way. The issue is that if safety is designed as a one-sided test and, at the end of the day, something went wrong, you now are underpowered for the two-sided question.

DR. HAVENS: So, the unexpected side effect might be missed in a study that was designed to show efficacious non-inferiority. Is that how I understand your statement?

DR. ANDERSEN: Potentially, yes.

DR. HAVENS: So, for new drugs, since we are really looking for both safety and efficacy,

safety might best be analyzed only with a two-sided test.

DR. ANDERSEN: For a new agent, I am offering that to the committee, yes.

DR. HAVENS: Therefore, if I understand you correctly, the safety evaluation crucial in these deliberations mandates that we not use a non-inferiority design.

DR. ANDERSEN: Non-inferiority for safety. Your effect size may be different. What I was bringing up and Dr. Alter I think is bringing up, as well, this could depend on the phase of discovery with a given drug with a given strategy.

Some of these will be strategy studies, in which case the different things are going on. Shorter duration of therapy, you are not going to expect to have more safety problems than with the longer duration.

DR. HAVENS: But for new drugs, to show safety you need a two-sided p-value, which is not a non-inferiority design.

DR. ANDERSEN: Exactly, yes.

DR. SHERMAN: Dr. Chung.

DR. CHUNG: We are approving drugs based on efficacy. I mean the safety is important information to have but we are ultimately going to approve the drug based on its efficacy.

So, I want to pose the question. If we have a 24-week study design PEG riba plus agent X, 48 weeks, compared in a non-inferiority trial design to PEG riba for 48 and we have numbers that show non-inferiority, does that tell us that drug X is effective against HCV to a reasonable degree of certainty?

I mean that is really what this comes down to. I think that, you know, scientifically, the most attractive concept to demonstrate efficacy of a compound is to show that it, when added to a backbone, is better than the backbone. To me, that is the best control type of study to demonstrate efficacy of that compound, I mean if you can't do monotherapy studies, which is what we are facing here.

Are we satisfied with that shorter term

duration showing non-inferiority under that design, is that robust enough for us to say that this is primary data that justifies its approval as a compound? Personally, my feeling is no. But I would like to hear what others have to say about that.

DR. SHERMAN: Tracy Swan is next.

MS. SWAN: I agree with you, Dr. Chung, and I would also like to add that if we are going to be looking at multi-agent trials, the more superiority data we have on a particular agent, the better we will be able to use them in combination.

DR. SHERMAN: Dr. Haubrich.

DR. HAUBRICH: I actually agree with Dr. Chung, but for different reasons. I think that we could design a study 24 weeks plus the new agent and show non-inferiority I think that would be scientifically justified that if, that were the case, then, it would provide additional benefit.

However, I don't think that should be the first study, because we don't know if that is going to work and I think it might be unethical at this

point to use shorter interferon ribavirin in genotype 1 if we don't know that that is really going to work.

So, standard plus or minus the new agent seems like the first study. Once that is established that you can use a new agent and increase the efficacy, then, the next studies can be non-inferiority. So, I agree it should be a superiority plus of minus.

DR. CHUNG: I agree with that staging.

DR. SHERMAN: Dr. Havens.

DR. HAVENS: Just that I think efficacy is important. But safety is crucial, especially if we are looking at special patient populations and safety is an open question. It is not a non-inferiority question, it could be completely unexpected and requires a bigger sample size because of that.

DR. SHERMAN: Dr. Andersen.

DR. ANDERSEN: I think where we are iterating to is in most circumstances, the first study is a superiority study with a new agent, in

which case my issue is dealt with here.

If the next study is a non-inferiority study with reduced duration, you have got a lot of safety information with that first superiority study. This is now yet more information on the same agent, shorter course, that could have different parameters.

DR. SHERMAN: I see a lot of head nodding around the table. I think that we have arrived at the consensus that the bar is superiority and that other studies, based on non-inferiority, probably will follow and may improve the treatments. But the first goal is to get approvals based on superiority.

That actually I think largely addresses the issue of the second point, the use of a dose of PEG interferon lower or shorter duration with the investigational agent added, because the concept is the same, that equal is not the goal at this time.

So, the third item on the list is ribavirin substitution and how would one design a study with ribavirin substitution. I would

actually query the agency. By ribavirin substitution, do you mean another agent similar to ribavirin or do you mean the removal of ribavirin and that the investigational agent with PEG interferon is sufficient, or are you asking to consider both circumstances?

DR. LAESSIG: I think the intent was actually the latter.

DR. SHERMAN: So the removal of ribavirin.

DR. LAESSIG: Right, the removal of ribavirin--

DR. SHERMAN: So Peg interferon plus the experimental agent, and how would that study be designed and what are presumably the standard of care comparator arm.

Comments?

DR. SEEF: I think it would be a problem for the naive patients. I think it would be less of a problem for the non-responders. I think that in the naive patients, you have to have the standard of care and, until we know that one of these new products is equivalent or superior to

ribavirin, I am not sure how you can, in fact, replace it at this point.

DR. SHERMAN: But isn't that the purpose of the study, is to see if you can replace it?

DR. SEEF: Of course, it is. It seems to me, though, I would be uncomfortable at not having ribavirin, knowing the impact of ribavirin, that the addition of ribavirin had a real impact on the response rate, how is it possible to treat naive patients with what is now not the best treatment available. I would have some difficulty with that.

I would like to see how we could find a way of doing that, but I am just not smart enough.

DR. SHERMAN: Dr. Birnkrant.

DR. BIRNKRANT: I just wanted to clarify what we have heard. I understand about doing the first study design--that is, adding the investigational agent to standard of care. But is that sort of like the hierarchy. We start out with that and then we move to these other explorations, unless, of course, there is ribavirin molecule that is so close to already approved and we can just

substitute that in.

But other than that, we would approach then this hierarchical type of fashion. Is that the understanding we should take away?

DR. SHERMAN: Yes.

DR. HAUBRICH: I will make one caveat to that, for approval, yes. But for Phase II exploratory studies of maybe early viral dynamics, then, you could have room to be more experimental if you have a short duration study of 4 weeks, 12 weeks, where you are looking to see if with the new agent you can get as good a viral dynamics to plan future studies. But not at this point for approval.

DR. SHERMAN: Dr. Chung was next.

DR. CHUNG: I think that the idea of removing ribavirin is operating with your arm tied behind your back. You have two agents that are absolutely critical to the activity of currently approved therapy for HCV. Ribavirin brings an entirely different mechanism action that is complementary to that of interferon, that is, it

marked diminishes relapse rates.

To actually hamstring yourself by adding, by trying to substitute an antiviral drug, for instance, just to throw out an example, for ribavirin, would be essentially asking I think, you know, that is an uphill battle to ask an antiviral drug plus interferon to act in every way the equivalent of ribavirin and then some.

I think it would be largely unwise to do those types of studies right off the bat. I agree, I think, with Dr. Haubrich, that those should be secondary trials and should absolutely be looked at, but not as a primary approval goal.

I think we still have to demonstrate efficacy and the move into the move sophisticated substitution type strategy.

DR. SHERMAN: Dr. Havens.

DR. HAVENS: Now, there is two questions on the table, so if we go first to the ribavirin substitution question, do you have any patients who you have not been able to treat, even take into treatment, because they have an absolute

contraindication for ribavirin? Dr. Chung.

DR. CHUNG: Yes, all of us do.

DR. HAVENS: So, would it be reasonable for those patients who have an absolute contraindication for ribavirin to treat them with interferon plus a new comparator agent, because they can't get the current standard of care therapy?

So, it would be a special population that you are studying, but it would get around the ethical issues of not studying standard of care because they can't get standard of care.

DR. CHUNG: But that would be PEG plus compound versus PEG. That is not substitution per se, right?

DR. HAVENS: Well, no, no, no. I might study that as PEG plus compound versus PEG plus ribavirin.

DR. CHUNG: But that is an intolerant population you just said, your study population is intolerant to ribavirin.

DR. HAVENS: The people you would use the

new compound in. Oh, don't glare at me like that. When you are opposite Dr. Andersen and she gives you that face like, oh, Peter, how could you say that. Okay, go ahead then.

How is she going to get around it, Dr. Andersen?

DR. CHUNG: Are you done?

DR. HAVENS: Only if Dr. Andersen takes the floor now.

DR. SHERMAN: In a moment, but Dr. Vierling came first.

DR. VIERLING: I will yield to Dr. Andersen on this one.

DR. ANDERSEN: Having been put on the spot for a study I didn't design here, to summarize and buy myself a little time here, what I was hearing is take the population that cannot tolerate ribavirin, use them in a single-arm, Phase II-ish study, adding, so it's PEG plus new ribavirin analogue and the question is would that be a registration study.

DR. HAVENS: No, that is not a

registration study obviously, but it might be a way to get enough data to let you move ahead.

DR. ANDERSEN: Yes, it would be a very viable Phase II study for proof of concept, because if it doesn't work in that population, you have at least got some information. If it does, it helps you move forward.

DR. HAVENS: So, then, you could do a ribavirin substitution study as a Phase II study and, if the data looked good enough, potentially, then, would that allow you--so then we come back to the question, would that allow you then to do a bigger study, Phase III, with a substitute versus PEG riba?

DR. SHERMAN: I was just going to say to be specific, you are talking about something like a dialysis population.

DR. CHUNG: That is what I was going to get at. You could study that in renal failure. You could do PEG plus compound X and then learn what you could from that.

DR. SHERMAN: That would be a very

interesting study.

DR. SEEF: Or people with cardiac disease that you worry about. The problem is that I don't know how you would use that afterwards, because what is your control to that, is this a historical control?

DR. CHUNG: You would have your PEG interferon.

DR. HAVENS: We are talking about separate issues.

DR. SEEF: That is what Dr. Haubrich was talking about doing in a small group, not for registration purposes, but simply to understand more about it to see if it works.

The problem there, though, is that you have to compare it to the standard and you can't compare it to the standard, because you can't use ribavirin, so it would be a historical control, I guess.

DR. HAVENS: No, no, no. Dr. Andersen had said that you would do it, this is a Phase II, and then the question then I am proposing is after you

had some Phase II data in special populations who could not tolerate riba, then, would you feel comfortable with that, going to a Phase III, or how much of that data would you need to be able to do a ribavirin substitution study in patients who could actually have tolerated ribavirin.

Is that a possible phased approach?

DR. SHERMAN: Dr. Andersen.

DR. ANDERSEN: I think it could be part of a phased approach. Obviously, I am not a clinician. In my opinion, to take just special population data and then go into a large Phase III study in naives, I would be uncomfortable.

On the other hand, to use that as a phased approach, combining with data potentially in subjects who have proven themselves to be resistant to PEG riba, they are coming off it as non-responders, give them PEG plus new X, something like that, beginning to build the picture that could be part of the picture. If it doesn't work in them, the question is, is it invalid in a population with intact renal function, things like

that.

If it worked spectacularly in that population, that is a different piece of information.

DR. SHERMAN: So, I think the answer is not at this time ribavirin substitution for a pivotal trial, but there is considerable interest in focusing on small group, special populations in a Phase II type trial that might give us information that would lead us to future drug development.

The next one is use of two or more investigational agents. Again, we have discussed this.

Dr. Munk.

DR. MUNK: I would like to speak strongly in favor of this especially from the patient point of view. It begs the questions that we have raised earlier about early work on drug interactions. But I think this is a highly promising study design.

Of course, also the questions of teasing out the differential contribution of each

individual agent.

DR. SHERMAN: I suspect, and people can tell me otherwise, there is not disagreement about would people like to see trials in this. I think the issue is really the study design of trials and when those trials would occur based on where we are at today.

Are we talking about following appropriate Phase IIB trials. But, before we get to a Phase III, that maybe two, IIB trials of individual agents could lead to a IIB of a combination, or is there some other stage and approach that would be appropriate? Dr. Chung.

DR. CHUNG: I think we are in the era where we can try to learn from I think the misfortunes of our steps in the HIV era. I think that from the standpoint of being able to get out and investigate combinations of agents in a more timely manner prior to Phase III approval of each of the individual monotherapy agents, I think it represents an opportunity for us to change the paradigm a little bit.

I think that as long as there is adequate safety data from the Phase IIB of each of those respective agents and that there is obviously enough promise of antiviral efficacy, I think we should move quickly toward looking at those novel combinations for the reasons we talked about earlier, both their antiviral activity with SVR as an endpoint, but even disease modification or disease suppression as another potential endpoint.

I mean I think it's not axiomatic that the use of these agents, even if virus is not completely undetectable, i.e., there is resistant form of virus present, I don't think it's axiomatic that that leads to an adverse outcome for the patient per se.

I think mutation is something we have to be concerned about. But it is not absolutely clear that those resistant strains will be either more competent or more pathogenic than their wild type counterparts and that over time, this must be evaluated for the potential benefit of suppression albeit it with residual virus on ultimately

measures of liver disease.

So, I therefore think that the opportunity to move forward with two, IIBs approved compounds is something we should really push for.

DR. SHERMAN: Dr. Haubrich.

DR. HAUBRICH: I would strongly second that, as well, and I think that in addition to the IIB safety and efficacy data that is generated, if individual dynamic data is available on both agents individually, you could then combine them and look for differential dynamic effects and so could very quickly at least potentially in theory quickly tell if you are getting additive, synergistic or potentially antagonistic activity.

We have learned with HIV that not all combinations of things that make sense together work well, i.e., the triple nucleoside abacavir, tenofovir, 3TC are most potent agents with the best log reduction was a dramatic failure. So, doing careful, small, staged, dynamic studies could be very interesting and informative.

DR. SHERMAN: Dr. Havens.

DR. HAVENS: This begins to get to Dr. Birnkrant's earlier question, which I think remains on the floor, of are we really saying that everything has to go from the top down on this list. But could we start from the bottom up, and what is the duration of these studies that would be required and, if so, if you start with a short duration monotherapy, I showed dramatic change at 4 weeks, in three small molecule compounds. Then you want to go to combine them, that leads you to actually a pretty long time of you have to figure out the drug-kinetic interactions, the potential additive or synergistic or inhibitory interactions against the virus, which might be unexpected.

Now, we are getting to the point where we are looking at starting at the bottom and moving up, these would be shorter and have a different focus on issues related to drug exposure and pharmacodynamics perhaps that would allow you to do them sooner.

In the way that the FDA has gotten so great in what they require of studies for

antiretrovirals in terms of drug interaction studies both with antiretrovirals and other drugs that people are going to be on, this leads to a pretty long list of other things that will be required of drug manufacturers.

You have got to start looking early on at what you think you are going to couple your drug with and how you might want to do it, so that those appropriate studies are done early on.

DR. SHERMAN: I think the answer is the committee encourages use of two or more investigational agents probably following Phase IIB level studies, that safety needs to be established, that we need to have drug interaction studies done early, which I think you would have required anyway and that we may be able to learn quite a bit from short-term viral and viral kinetic-based studies, viral kinetic and pharmacologic studies that give us information that may inform the larger study designs and that earlier rather than later would be a good choice to get those studies going.

The last question was on monotherapy. I

suspect that the issues of monotherapy are going to be driven by issues of mutational resistance with a single new agent.

In theory, it may be able to design agents that have multiple hit sites that you have to have a series of collective mutations before resistance emerges, but that, in general, what we have learned from the world of HIV is that single agent therapy is not a good choice for direct antiviral agents.

Would anyone on the committee like to further that discussion?

DR. CHUNG: I would only say that the evidence we have thus far from single agent, early phase studies has borne that out, that we have seen emergence of, or selection of, likely pre-existing variance that are resistant both in vivo and in vitro.

While we can be reassured thus far by the fact that most of these, if not all of these, appear to be interferon sensitive, I think that this is a cautionary tale for any monotherapy study design.

DR. SHERMAN: Dr. Birnkrant.

DR. BIRNKRANT: Briefly, how do we feel about like an induction maintenance kind of picture where we start with the monotherapy. It is extremely potent, but perhaps there may be some safety issues. But we get the viral load down, then, we hit them with the PEG ribavirin. How do we feel about that model?

DR. HAVENS: Well, is the question how long can we do monotherapy and still be safe from a resistance perspective?

DR. BIRNKRANT: The idea of getting the viral load down really low initially and then we add something else on. I know it's a different question, but you were here.

DR. SHERMAN: That was addressed yesterday as a potential study design that may have validity. I would think that as long as significant resistant emergence was not a problem in the time that was selected based upon the early studies of those drugs, that that is a reasonable approach.

DR. CHUNG: To the extent that the

appropriate preclinical work was done on those isolates and demonstration of subsequent interferon sensitivity, for instance, in a replicon or other assay, was demonstrable, then, that could be a defendable design.

DR. BIRNKRANT: Sort of a modified monotherapy.

DR. HAVENS: But the issue of how much work needs to be done in terms of the safety, the safety of monotherapy primarily is in development of resistance and, as long as that is uppermost in the agency's mind when they consider these studies, that an important adverse event is development of resistance.

DR. ALTER: I wouldn't call that monotherapy, I would call that sequential therapy.

DR. SHERMAN: Yes. The next question is something we also discussed a little bit yesterday, so I would like to just bring everyone up to date to what the discussion was.

We talked about treatment of decompensated liver disease and what type of meaningful endpoints

might be available. Dr. Vierling commented on this and said that use of the child's Pugh score or variations of the child's Pugh had many subjective elements and probably wasn't the best choice, that MELD is fairly well validated and that there seems to be a cutoff in the area of a MELD to 15, that defines more rapid progression to death without transplant versus less rapid progression to death without transplant and that if one can change the outcome in terms of risk using a well validated model, that might be a reasonable approach.

I think that the outcome of transplant would certainly have to be included in such an endpoint devaluation, because some patients will come to transplant for one reason or another.

Dr. Vierling.

DR. VIERLING: I want a point of clarification. When I was using the MELD score discriminate at MELD score of 15, it wasn't regarding the long or short term risk. What I was defining is that based on the scientific registry of transplant recipients, a very robust database,

analyses that have come from independent groups, it appears clear that if you ask for the benefit of a transplant in order to achieve a survival potential for an additional year of life, that there is no benefit for a transplant beneath a score of 15 itself or lower.

Hence, we do have some MELDS, opportunities in different regions of the country where patients with lesser scores can be transplanted and the data analysis would suggest that they have a high survival probability one year after with medical care than they do with transplant, so I wanted to define that cutoff.

DR. SHERMAN: Important clarification, yes.

DR. VIERLING: The other important issue is whether or not, because of the serious concerns of adverse events in this population, that studies should be limited to those patients that are UNOS-listed for transplant as a safety net.

The third point would be that the proof of safety in particular and efficacy obviously in

these trials, I believe, would be best done in the group right around a MELD score of 15.

They are not approaching in most regions of the country organ donation, because of the short supply. Most places are transplanting in the mid-20s in terms of MELD scores.

There are exceptions on either side of that statement but it does allow you to establish safety and efficacy at an at-risk population already defined by the UNOS listing and to, I think, protect them.

If then you had data that were positive, it could be extended into higher MELD score arenas where your efficacy endpoint would be the reduction of MELD score. Keep in mind that the MELD score is giving you the best information about the probability of 30-day subsequent survival.

It is sort of a rapidly changing endpoint and that is how, with sickest first policy, we federally allocate organs to those with the highest risk of death within that time.

So, the reduction that you could achieve

in a MELD score would certainly have a target I believe of efficacy to achieve 15 or lower for ultimately those populations that were substantially above that.

Everyone also needs to keep in mind that the MELD score has been very carefully validated and using receiver operating curve analyses, various other aspects have been added to the model, things like encephalopathy, hyponatremia, other things.

They do not add very much to the robustness. But the MELD score with respect to the need for transplantation is quite good for the cirrhotic decompensated patients with the average complications of portal hypertension that we are looking at.

It is not good for a variety of other patients and it doesn't adequately serve in circumstances of patient at need, about 17 percent of transplant-eligible patients, therefore, we have MELD exemption points and we have recently had an international conference.

In press is the paper talking about the delivery and recommendations for exception points to move people that have diseases that otherwise wouldn't qualify.

The most appropriate example is that we have come to increasing grips with the hepatocellular carcinoma occurring in the setting of cirrhosis being awarded extra MELD points, not on the basis of the deterioration of the hepatic disease, but because of the risk that this could be nontransplantable tumor if allowed to grow indefinitely to achieve those points.

So, I believe that that becomes another issue particularly in C, because 24 percent of the patients we are transplanting with hepatitis C have either a know or an incidentally identified hepatocellular carcinoma.

So, in the transplant listed patients, this is an enormous consideration and would have to be factored in to design.

Thank you.

DR. SHERMAN: I want one clarification.

You are suggesting that a MELD with a categorical cutoff be applied as an endpoint meaning a specific score, because the other way to design this would be to take the average mean MELD between two groups and look for the appropriate difference in change over the study time, the study period.

DR. VIERLING: I could certainly look at both as being very valid considerations for study design. My point is simply if one would ultimately have safety and efficacy data and extend, say, treatment into MELD scores in, say, mid-twenties where they are approaching eligibility for transplant, I am not sure as I would be as comfortable with what we had achieved if we had moved it down one or two points and no further down the scale.

We may have modified something even at a metabolic level. Perhaps we had helped indirectly renal function and changed the serum creatinine, which is one of the three elements in the MELD score and really have done nothing to the intrinsic liability of their liver disease or carcinogenesis.

If, on the other hand, you were to take patients with MELD scores of 25 and moved them substantially down the scale, particularly to areas that I have discussed, would not necessarily be benefitted from transplantation. You have achieved literally the grand slam.

I would again go back to historic example. That was achieved in hepatitis B-treated patients with severe decompensation with some measure of success. Therefore, the hope would be with new agents that we might recapitulate that.

That is why I emphasize that your ultimate goal would be to come to a point where medical therapy would have a superior survival potential than transplant itself.

DR. SHERMAN: Ray.

DR. CHUNG: So, you could look at two potential endpoints. One would be the mean reduction, let's say, taking your 16 through 20s, your mean reduction and a more binary endpoint, your threshold endpoint of achieving a MELD under 15.

You could look at it both ways. But I would also caution that when you are evaluating MELD, because bilirubin is part of the MELD, you wouldn't want to look at him on therapy because if they are on ribavirin, they are going to bump the bilirubin, so you would have to take direct bilirubin as your measurement, or just be cautious about you use that score in its timing relation to the agents being use.

DR. VIERLING: That is an excellent point and I it went by very rapidly on slides. I think this is a population in particular where one wants to scrutinize the opportunity for elimination of ribavirin from the regimen for this very reason, or a substitute that is not productive of bilirubin load, because that is the highest weighted component of this equation and would have, by definition, an adverse consequence on your analysis based on MELD score.

So, this is a group that is very unique in terms of its need in your drug development.

DR. SHERMAN: Other comments from the

committee? If not, the response is that MELD appears to be a reasonable outcome in the decompensated patient awaiting transplant, listed for transplantation.

It's 12 o'clock. There is one question remaining on the list. Do you want me to address that? Okay.

It's long term follow-up. Beyond the assessment of the primary endpoint for registration, what is the appropriate duration of follow-up for chronic hepatitis C infection and what kind of information should be gathered?

Please discuss duration of follow-up for different patient populations, especially pediatrics and, in particular, when an investigational agent is not added to standard of care.

So, we are essentially talking about the issue of durability, which we have discussed at length in terms of long term follow-up.

DR. BIRNKRANT: Not just durability, though, let's say complications, ACT, end-stage

liver disease, et cetera, should we go that far.

DR. SHERMAN: Committee?

DR. SEEF: Aren't there two parts to this? One is the virologic and the other one is the nonvirologic, so that for the virologic, we certainly need the typical SVR. I suspect that we should probably have a follow-up at another time just to be sure that the SVR means the same thing. This group has a dozen people who are receiving pegylated interferon.

So, whether that be a year or two years later, I guess we would have to decide. But the other part of it is, of course, you are talking about the fact that there may be another component to this and that is if we, in fact, focus our attention on the histology, is this a long-term effect and do we need to follow up even further if, indeed, that is the only outcome that is achieved.

The virus doesn't disappear but the histology improves, in which case we would need to continue to follow these people and repeat liver biopsies at a further time.

DR. SHERMAN: Other comments? Dr. Munk.

DR. MUNK: I think that the learnings from HIV are instructive here, that there are side effects that showed up much after the drug effect and certainly much after five half lifes of the drug.

The question really is the primary endpoint for registration and the necessity of follow-up for registration compared with the data that we are going to want to see given the etiology of hepatitis C and especially the histologic endpoints or benefits that may accrue from some of these agents.

DR. SHERMAN: Dr. Vierling, you look like you were ready to say something?

DR. VIERLING: I think that Leonard is exactly right about the distinction between the virologic and the disease endpoints, as well as the long-term safety concerns. What I am grappling with is the concept that in order to evaluate that at a distant post-therapy time, that we do or do not need a biopsy, and, of course, that relates also to

the stratification of the entry level of the study.

There are some people who will enter this study who will never even without being part of study or ever having therapy, not progress over times in terms of histopathology, and, of course, those that are already cirrhotic, we do not anticipate that they will necessarily lose their cirrhosis.

From a practical standpoint, if you propose to a patient that at a certain distant point we would like to see you again for a biopsy, it is almost a guarantee that you won't keep that particular visit and appointment. That is just not likely that they would do that.

It gets to the issues of whether, when we do look at histology as a secondary endpoint, we could encourage the use of all potentially available surrogate markers and this was a point that had been made by Tracy Swan earlier in order to try to inform ourselves of their potential validity and comparability. That would be more desirable I would think.

Equally important although we are using ALT as the surrogate marker of liver injury and, although in this disease that relates to inflammatory-based liver injury, it can come from injury that is not inflammatory as we know.

Also, persistence of ALT normalization could be a more easy marker to have for follow-up and maybe interrogation for persistently abnormal ALT in long-term follow-up could be a clinical justification to relook at biopsy where we are not subjecting everyone to the concept that long after therapy would be required to have a biopsy. I just believe that is not going to occur in the real world.

DR. SHERMAN: Dr. Havens.

DR. HAVENS: The absence of virus in blood at 24 weeks after stopping therapy is a surrogate marker for the concept that your liver is going to be all good. Is that a fair statement or not?

DR. VIERLING: I look at it as a cure.

DR. HAVENS: With PEG ribavirin, the absence of virus at 24 weeks is considered to be an

adequate surrogate marker for all these liver outcomes that we are talking about not going to happen.

DR. VIERLING: That still is a debate point. I think that Leonard has made that point repeatedly and it is equally problematic when you look at the age group, this cohort effect where we are going to have more derivation of patients for study, are also increasing by age and the issue of metabolic syndrome and body weight in the United States at risk for many other issues, not the least of which is the metabolic syndrome in nonalcoholic fatty liver disease, but also hepatotoxicities due to a variety of multi-pharmacy that we treat one another with in the United States.

So, the fact is that it is not just you have restored the liver and put it on a pedestal as being pristine and unaffected. It is still doing its function in the context of all that goes on subsequently and we are going to have to ultimately tease out and know whether ending the viral disease does absolutely everything downstream as a help to

the patient.

I would submit that the working hypothesis is that you are correct, that you have ended the viral disease and as long as there is not some secondary insult that all consequences of the immune response to the viral infection should have been terminated, too. But I don't believe we have the data to actually say that.

DR. SHERMAN: I would like to address that, as well, because there is some data with long-term liver biopsy follow-up where there has been evidence of regression of fibrosis, something that hepatologists years ago thought didn't happen at all and, since we have been able to achieve SVR or cure hepatitis C, it has been observed and described in a number of circumstances.

What is less clear is in a patient with more advanced fibrosis where the physiology of portal hypertension has developed whether at that point eliminating the virus is going to change the physiology back to normal, because there is many, many adaptive changes that occur at that point and

the virus may be the smallest part of the issue at that time. But I mean I think there is evidence.

DR. SEEF: I agree that there is evidence, that we were talking about it earlier, that some time ago we used to believe that once you have cirrhosis, you have always go cirrhosis. But now we know I think that in some instances, this can reverse.

I think we should also remember as part of all of this that taking care of these patients is not only using drugs. There are other things that are responsible or helpful in the disease progression, so that, for example, we have to be sure that they stop drinking alcohol.

We have to be sure, in my mind, that if they are obese, that they lose weight, because fatty liver is going to be very helpful in advancing the disease regardless, so I think that there are other factors, as well, that need to be taken into account in the general care of patients with this disease that may have a long-term impact. The best is likely to be the drugs, of course.

DR. HAVENS: So, in a PEG riba-based therapy, there is reasonable agreement that SVR-24 is a surrogate marker for benefit to the liver and long-term potentially continued improvement given those caveats.

Now, we are one step away from PEG riba when we are talking about these studies, because we are talking about newer agents, some of them potentially non-PEG-based. So, in a non-PEG-based therapy, we don't know that even SVR-24 is an appropriate surrogate marker for either no progression or improvement in the patient at longer term.

Now, this says beyond the assessment for registration, so we are assuming you would get drug approval before we are suggesting this. But I think even if newer regimens, especially non-PEG-based regimens, achieve SVR-24, it is very important that the FDA require postmarketing studies to prove the relationship of SVR-24 reached in a non-PEG-based regimen to show that that is the same as SVR-24 in a PEG-based regimen with longer

term follow-up.

DR. SHERMAN: So, what you are talking about, I think the agency is referring to is the issue of these rollover long-term follow-up studies where patients may be seen at intervals of as little as once a year where basic laboratories, virology, synthetic function of the liver and other systems like renal function may be assessed.

If a patient is found to have died in that interim period, that is reported appropriately, because the patient is involved in a study, so that a database can be developed, and, if so, how long should that be, is it 2 years, 4 years, 5 years, longer? Am I correct that that really is the essence of the question?

DR. HAVENS: How long did you require before you were satisfied that SVR-24 was okay for a PEG-based therapy, PEG riba?

DR. SHERMAN: I would ask Dr. Birnkrant, what were the postmarketing requirements for the PEG interferons?

DR. TAUBER: Actually, we didn't make that

one of our postmarketing commitments.

DR. SHERMAN: Right, they weren't part of the registration.

Dr. Munk.

DR. MUNK: I think the FDA is going to have to look at this almost case by case depending on the length of the agent that is being used in addition to PEG riba. If this is a life-long agent, that has implications for the length of the follow-up, not that it is life-long follow-up given the problems of doing so. But it increases the importance of trying to ascertain what is going on a few years down the road.

DR. SHERMAN: My sense is that there is some interest in some type of follow-up. It is not clear what that duration should be.

Dr. Andersen, do you have any light to shed on this?

DR. ANDERSEN: Well, one thought would be to partner with one of the institutes. I mean I am thinking in terms of a registry because right now part of the discussion here has been about the

nested surrogates, that X is a surrogate for Y, which is a surrogate for Z, which is a surrogate for the other thing.

A question is whether this is an opportunity to start building a registry that at least looks at end-stage liver disease and survival and potential some other targeted effects that could be combined with what the agency itself needs for postmarketing surveillance.

DR. SHERMAN: Dr. Haubrich.

DR. HAUBRICH: I certainly don't feel qualified to know how long we should follow people. I think we would all agree we would want to follow people. I think a registry is a great idea. Databases are great ideas but, having worked with both clinical trial data, as well as cohort data, even with electronic medical records captured at the point of care, the clinical trial data always is more informative because the patients are clearly more carefully characterized.

So, my only point would be, and I might be saying this both to the agency and the companies in

the field of HIV, the companies that have followed their trials for long term have reaped great rewards in terms of advancing the field, but also advancing their own special interests in terms of presenting long-term follow-up data, which has been very informative and I think very useful for their marketing colleagues.

So, if you need to take that back to your colleagues and get them to fund those long-term studies, that might be helpful. But I think it is very informative, particularly here where we just don't know what these endpoints mean when we start using new agents. I think it is important that we all follow them.

I think we are all in agreement that it is not 24 weeks, that it is probably some number of years.

DR. SHERMAN: I think that very nicely sums up the answer.

Dr. Havens.

DR. HAVENS: I think the issue here is that even though in earlier studies, the FDA may

not have mandated long-term follow-up, we are in a different world. The requirements for antiretroviral registration are dramatically different now than they were in the early 1990s and we know lots more now.

We have got surrogate within a surrogate within a surrogate, an postmarketing surveillance is crucial. We are very supportive of the FDA in requiring those studies to be done at the time of registration of a drug, or at least I am, sorry.

DR. SHERMAN: Dr. Vierling.

DR. VIERLING: There is one group in particular that I feel strongly you would want to have input and follow-up and that is the cirrhotic patient with respect to surveillance for hepatocellular carcinoma. The liability in this disease is with cirrhosis. This is a very important long-term endpoint in that treated population to understand whether we have modified this. But more importantly, were we not to modify it, and these patients not be under appropriate surveillance, the window of opportunity for a

curative procedure of liver transplantation would be missed.

I would to give these patients a false security that the absence of virus has translated to out definitive understanding that they have been protected against hepatocellular carcinoma, which is the longest term, most devastating risk and that is what I would definitely want follow-up on for that cohort.

DR. SHERMAN: The best studies from Japan looking at cirrhotic patients and the issue of prevention following interferon therapy have been I believe four- or five-year follow-up, so that seems to be the window that it is reasonable to do the study in and make that determination.

I think we have answered all of the question. This concludes the open session of this Antiviral meeting. This afternoon, the committee members should be next door, Potomac Room, for a closed session update. Invited consultants are excused from that meeting.

I would like to end by saying this is my

last committee meeting. I have been with this group four years and for the record, I want to say I appreciate the opportunities I have had to interact with the colleagues that have been on this committee and, in particular, the opportunity to work with the professionals at the FDA under Debra Birnkrant.

They have been a terrific group, they have integrity, honesty and they are incredibly thoughtful about all of the issues that are raised and it has been an honor to work with them. Thank you.

This meeting is adjourned.

[Applause.]

[Whereupon, at 12:20 p.m., the meeting was adjourned.]

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