DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE

OPEN SESSION

VOLUME I

Thursday, October 19, 2006

8:00 p.m.

Hilton Hotel
Maryland Room
Silver Spring, Maryland

PARTICIPANTS

Kenneth E. Sherman, M.D., Ph.D., Acting Chair
Cicely Reese,

MEMBERS:

Janet W. Andersen, Sc.D.
Douglas G. Fish, M.D.
Richard H. Haubrich, M.D.
Peter L. Havens, M.D.
Robert J. Munk, Ph.D., Consumer Representative
Eugene Sun, M.D., Non-Voting Industry Representative
Ronald G. Washburn, M.D.

CONSULTANTS (Voting):

Miriam J. Alter, Ph.D.
Karen F. Murray, M.D.
Raymond T. Chung, M.D.
Tracey Swan, Patient Representative
Leonard B. Seef, M.D.

CONSULTANT (Non-Voting):

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FDA STAFF:

Debra Birnkrant, M.D.
Katherine Laessig M.D.
William Tauber, M.D.

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PROCEEDINGS

Call to Order and Opening Remarks

DR. SHERMAN: This meeting of the Antiviral Drugs Advisory Committee is now called to order. We have a few housekeeping issues to discuss.

First, for members of the committee, there are mikes and you do need to hit a button when you speak and turn it off when you are done speaking or there may be feedback in the system.

If you have interactive communications devices, please turn them off so that there are no communications during the meeting.

There are scheduled breaks and, in addition, people can feel free to get up and use the facilities. There are restrooms straight back behind this room.

With that, we will go through introduction of members of the committee. Let=s see, we can start with Karen Murray.

DR. MURRAY: Hi! Karen Murray, pediatric hepatology in Seattle, Washington, University of Washington.

DR. HAVENS: Peter Havens, pediatric infectious diseases, Medical College of Wisconsin, in Milwaukee.

MS. SWAN: Tracy Swan, Treatment Action Group, New York City.

DR. WASHBURN: Ron Washburn, infections diseases at the Shreveport VA and LSU Medical Center in Shreveport.

DR. REESE: Cicely Reese, designated federal officer.

DR. HAUBRICH: Richard Haubrich, adult infectious diseases, University of California, San Diego.

DR. FISH: Douglas Fish, adult infectious diseases and HIV medicine, Albany Medical College, in Albany, New York.

DR. SEEF: Leonard Seef, liver disease research, NIDDK National Institutes of Health.

DR. ANDERSEN: Janet Andersen, statistician, Harvard School of Public Health, in Boston.

DR. SUN: Eugene Sun, clinical development,

Abbott Laboratories.

DR. VIERLING: John Vierling, Baylor College of Medicine, hepatology and liver transplantation.

DR. TAUBER: Bill Tauber, medical officer, Division of Antiviral Products.

DR. LAESSIG: Katie Laessig, Deputy Director, Antivirals, FDA.

DR. BIRNKRANT: Debra Birnkrant, Division Director, Division of Antiviral Products, FDA.

DR. SHERMAN: Thank you. Cicely Reese will now read the conflict of interest statement.

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 infections.

The primary objectives for the committee=s 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 general 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, Karen Murray, John Vierling, Doug Fish and Kenneth Sherman are participating in today=s meeting.

Waiver documents are available at FDA=s

dockets 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 exclusions 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.

This statement was prepared by our conflict of interest staff.

DR. SHERMAN: Thank you. We will begin with Dr. Debra Birnkrant, who will present FDA introductory remarks on the hepatitis C perspective on drug development issues.

FDA Introductory Remarks

Hepatitis C: Perspective on Drug Development Issues

DR. BIRNKRANT: Good morning. Before we begin the discussion on today=s topic of hepatitis C I would like to acknowledge some of our members of the advisory committee who will be rotating off.

With that, we would like to bestow the Advisory Committee Service Award to three participants, Dr. Fish, Dr. Washburn and Dr. Sherman. Individually, if you could come up here,

we will give you your plaques.

Dr. Fish, from Albany Medical Center. Thank you very much for your guidance over the years.

DR. FISH: Thank you.

DR. BIRNKRANT: Dr. Washburn, thank you very much for your input and help.

Dr. Sherman, this is for you. Again, thank you for helping us with very complex issues.

Good morning again. For the next day and a half we will be discussing issues related to drug development of hepatitis C products. I would like to put this topic into perspective.

[Slide]

These figures show the increased burden of hepatitis C in the U.S. population as well as globally. Approximately 40,000 new infections occur each year. These are estimates, by the way. There are approximately three million patients with chronic infection and there are up to approximately 10,000 deaths per year as a result of hepatitis C infection. It is the most common

indication for liver transplantation, and worldwide almost 200 million are chronically infected.

This slide points to the need for development of new drugs for this indication and highlights that this endeavor will likely be a global one. Dr. Sherman will be presenting more updated figures.

[Slide]

Currently there are five interferon alpha products on the market that are approved alone or in combination with ribavirin. However, the standard of care is a combination of pegylated interferon with ribavirin. Why is this the standard of care? Because in clinical trials this combination has produced greater SVR rates than other combinations. But even though this is the standard of care, there are issues with it, that is, there is limited efficacy in certain subgroups, with attendant intolerability or toxicity issues and cost.

[Slide]

I show this slide to remind you why we are

here today. That is because our pipeline for hepatitis C products is filling up and we are seeking advice so that we can be able to provide consistent advice to sponsors of hepatitis C products.

So, today we are reviewing and commenting on INDs and pre-INDs related to the following molecules: polymerase inhibitors, protease inhibitors, interferons, cyclosporin A analogs, tau-like receptor agonists, antisense oligonucleotides and others.

[Slide]

What is the scope of this meeting? Well, we are here today to discuss drug development issues, and the basis for this meeting stems from questions that we sent to 15 IND holders where we asked questions about issues related to clinical trial design. Namely, we inquired about what patient populations should be studied; what should be the controls for Phase 3 studies; again, clinical trial design issues; which endpoints should we select; and how long should follow-up be

of patients enrolled in clinical trials. Dr. Bill Tauber, of the FDA, will summarize the industry responses.

[Slide]

Specifically with regard to patient populations at the time of initial approval, we asked whether there would be naive or experienced, or both, in the marketing application; whether the application should contain data on compensated and/or decompensated subjects. What about genotype? Should it be one and four, two and three or all? What about co-morbidities? Should there be data about pre and post liver transplantation in these marketing applications? We need to know whether you think that there should be data on pediatrics when a product is initially approved, and what should the representation be of certain racial of ethnic subgroups.

[Slide]

With regard to controls, we inquired about placebo controls; whether the standard of care, pegylated interferon and ribavirin should serve as

the control, of should there be a design where there is deferred therapy versus immediate therapy? Clearly, this depends on the patient population under study, that is, treatment naive or experienced.

[Slide]

With regard to trial designs, we have a number of this slide and we posed the question to the IND holders whether they thought these were appropriate trial designs. They are, adding an investigational agent to standard of care. Again, this would be dependent upon the patient population because it would be possibly concerning to add functional monotherapy in a failing regimen in a treatment-experienced subject with hepatitis C, similar to the HIV paradigm.

What about lower dose and a shorter duration of pegylated interferon plus an investigational agent? We thought about a ribavirin substitution. And, we questioned our IND holders about the use of two or more investigational agents, and we were obligated to

ask about monotherapy.

[Slide]

With regard to endpoints, we questioned our IND holders with regard to histologic, virologic or biochemical endpoints as well as the timing of the endpoints. Should they be SVR12, 24 or something else? Again, this could be patient population dependent.

[Slide]

With that, I would like to briefly review the agenda for today=s meeting and tomorrow=s meeting. Dr. Ken Sherman will be presenting updated epidemiology, natural history, viral kinetics and impact. This will be followed by a talk by Dr. John Vierling on trial design difficulties. Jules Levin will present the community perspective, and Dr. Bill Tauber will summarize industry responses. There will be an open public hearing at one o=clock today and we will have ample time for questions and discussions both today and tomorrow.

Thank you very much. I would now like to

introduce Dr. Ken Sherman.

Hepatitis C Epidemiology, Natural History, Impact and Viral Kinetics

DR. SHERMAN: Thank you. I notice that we have some additional members of the come in since the initial introductions and, before I speak, starting with Ray, could you introduce yourself?

DR. CHUNG: I am Ray Chung, director of hepatology at Massachusetts General Hospital, in Boston.

DR. MUNK: Bob Munk, consumer representative.

DR. ALTER: I am Miriam Alter, director, infectious diseases epidemiology, University of Texas Medical Branch, Galveston.

DR. SHERMAN: Thank you.

[Slide]

As Dr. Birnkrant said, I was asked by the agency to provide an overview of epi., natural history, the impact on society and some discussion, at least a brief discussion of a complex area, viral kinetics because all of these subjects will

come up and serve as the background for further discussions today. This is really meant to just get everyone up to the same page on what we will be talking about.

[Slide]

I will start with this picture of an iceberg. I would just like everyone to keep that in mind because, in terms of both the epidemiology and in terms of the impact, the world of hepatitis C is much like this iceberg with some parts visible and other parts still hidden or unaddressed. Hopefully, this meeting is a big step forward in addressing some of those issues as we move forward.

[Slide]

If we look at data on causes of death in the United States, we see that chronic liver disease comes in as number 12, fairly significant. Among people between 35 and 54 years of age, it jumps up to number 5.

[Slide]

The etiology of chronic liver disease in the United States is shown here. If one combines

the hepatitis C with hepatitis C and alcohol use we see that roughly two-thirds of the chronic liver disease in the U.S. is associated in some manner with hepatitis C infection, emphasizing the importance of this virus.

[Slide]

Briefly characteristics of the virus, it is a single-stranded RNA virus, a positive strand. Its classification suggests that it is related to pestiviruses and flaviviruses. There is one serotype with multiple genotypes and replication has been demonstrated in both liver and in lymphocytes. There is some question about replication in other tissues as well.

[Slide]

The viral genome is approximately a 10,000 nucleotide RNA. There is a 5-prime end which represents the internal ribosomal entry site or IRES. There are structural proteins, a core and envelope proteins, and then the rest is functional proteins involved with the replication of the virus. It is those areas that primarily serve as

targets for some of the drugs that we will be discussing.

[Slide]

The virus appears to replicate at extremely high levels. Modeling suggests that greater than 10 trillion virions per day is not uncommon. Numbers up to 12 trillion have been reported. The RNA-dependent RNA polymerase lacks the ability for error correction which leads to drift of the virus. The drift is observed in two forms. Within an individual patient we see multiple species arising and we call those quasispecies. In populations, particularly populations isolated over time, the virus adapts across the population with changes in the master sequence that leads to the classification scheme that we call genotypes.

[Slide]

This is a phylogenetic tree. There are different phylogenetic trees based upon different mathematical algorithms for assessing how close agents are to each other. In this particular tree

there are actually nine different genotypes. Many people talk about six genotypes. There are schema that have 11 genotypes in them. Again, it is largely related to the algorithm used for determining how close neighbors are to each other and where the branch points are.

That said, it is clear that at some point there was probably a common ancestor and there has been divergence. When we talk about quasispecies we are talking about the small branches that might exist in an individual patient at the end of one of the longer branches that represents a genotype and a subtype.

[Slide]

In the real world we see that there has been a distribution of genotypes with varying predominance in different places. In the United States 1 is the most common. In Southeast Asia we see genotype 6. In the Nile River Valley genotype 4 is the most prevalent. So, because this virus was isolated in time, probably historically about 500-600 years ago, we have seen a divergence in

various populations. The clinical significance of this will be discussed at length but is primarily related to differences in responsiveness to interferon-based products.

[Slide]

Debra mentioned that there are at least 200 million chronic infections worldwide, at least 4 million in the U.S., and these infections are highly associated with the development with both cirrhosis and hepatocellular carcinoma or HCC. Again as Dr. Birnkrant mentioned, this is the leading etiology for liver transplant in the U.S.

[Slide]

Recent data from the CDC--and I would like to thank Dr. Alter for updating my slides--shows that we have peak prevalence now in this group here. The age has been moving forward with a bolus in the population so the population that is most commonly infected with hepatitis C tends to get older. There is an over-representation among non-Hispanic blacks, which is shown here. And, this graph really defines the center of this

epidemic process.

[Slide]

This is an updated slide again from what Dr. Birnkrant showed. New infections per hear have dropped dramatically from this period to an estimate in 2003. Deaths from acute liver failure are very rare but they do occur. The CDC estimated that about 4.1 million people in the United States have been infected. A very significant percentage remains undiagnosed, hence, the iceberg analogy in relation to this particular infection. While some people clear, many develop chronic infection and these estimates suggest 3.2 million with, again, 8,000-10,000 deaths directly attributable per year.

[Slide]

Dr. Brian Edlin presented some work last year suggesting that the rates may be a little bit higher than that based upon the nature of the NHANES III study, from which most of the U.S. estimates are derived. He did an analysis and his group did an analysis looking at populations that were not well characterized within NHANES III,

including homeless, prisoners, military, people who are in nursing homes and hospitalized patients. It is important to note that the data from some of these subgroups came from very limited studies so estimates may or may not be accurate. But his conclusion at the end was that the CDC estimate is slightly low and that, in fact, there was 4.7 to 5.1 million infected and 3.4 million with active disease.

[Slide]

Based upon risk factors, the CDC has issued guidelines for who should be screened based on increased risk for infection: Those who ever injected illegal drugs; those who received clotting factors prior to 1987, which is the year that clotting factors began to undergo a heat treatment process which turned out to eliminate the hepatitis C virus; those who received blood and organs before July 1992; patients on chronic hemodialysis; patients with evidence of liver disease; and those who are HIV positive. In terms of screening based on need for exposure management: healthcare and

emergency personnel after exposure and children born to HCV-positive mothers.

[Slide]

Now, there are other groups that the CDC recommends do not need routine screening but may undergo screening at individual discretion. Confirmed risk factors who prevalence is low, healthcare workers, emergency medical, public safety workers; patients with history of STDs or multiple sex partners; long-term steady sex partners of those who are HCV positive where the risk is low but appears to still be a contributor to the total burden of disease, in which case individualization, counseling and testing may be useful.

Unconfirmed and prevalence groups include those with intranasal cocaine use history or other non-injecting illegal drug use, and history of tattooing or body piercing where, again, individual decisions should be made.

[Slide]

There are multiple tests for hepatitis C.

They fall into these main categories. We are not going to review all of the tests now, though I am sure there will be some discussion later because it is relevant particularly in the decision process. Enzyme immunoassays are often used as the primary screening test. These tests have been claimed to have high sensitivity at the loss of specificity. Recombinant immunoblot assays which give you confirmation but are not as sensitive as the enzyme immunoassays; qualitative HCV RNAs by a variety of amplification methods, either signal or target amplification; similarly, quantitative HCV RNAs; and, finally, measurement or evaluation of HCV genotype based upon the overall structure of the master sequence in key portions of the genome.

[Slide]

A number of years ago Joe Hoofnagle published the typical course of a patient with chronic hepatitis C following exposure. We see often a bump in liver enzymes that may or may not be associated with symptoms that are identifiable as a hepatitis infection. In fact, more often than

not it is not recognized as being a hepatitis. The patients do not come to the attention of a healthcare worker that would do the appropriate testing the define the acute infection. We see eventually emergence of antibody, though the lag time is based upon the tests. The median time is now about seven weeks with third generation ELISA assays. HCV RNA becomes positive very early, usually a few weeks after infection. There may be periods where it is transiently negative. Similarly, liver enzymes may drop into normal ranges, bump up, go down. So, liver enzymes at any given time, as we get to the point of establishment of a chronic infection, defined as greater than six months of infection, may be normal or may be abnormal and should not be the sole screening criteria.

[Slide]

Stewart Gordon published this paper a number of years ago. I show this because it is relevant to some of our upcoming discussions. It followed a group of patients that were not treated

and looked at variation in HCV viral load. Most of the assays available measuring viral load have a range of variability of up to half a log. If we look at this and then cancel out those within half a log, we find that once chronic infection is established, in fact, there is a great degree of stability, following patients for five to six years out, in a patient=s typical viral level. There are large epidemiologic studies, particularly in hemophilic populations, that do suggest there is a slow increase in viral load over an extended period, over decades, that may occur in patients.

[Slide]

With that, I would like to introduce the concept of viral dynamics. If one has a pool of virus in their bloodstream that virus may be cleared by mechanisms that are still poorly understood, or it may go on to contact an uninfected hepatocyte and cause a productive infection. That hepatocyte, again, may become productively infected or it itself may quickly die, usually at some given rate. Remember that the

liver has great capacity for regeneration so there is also a constant regeneration of uninfected hepatocytes going on. Among those that are productively infected, they will produce virus which adds back to the infectivity pool, or they will die at some point and no longer produce virus.

This is a picture of the dynamic process, simplified in cartoon form, that you should keep in your head as we talk about the issue of viral kinetics.

[Slide]

A little bit of terminology, we have viral loads, V; we have production; we have clearance. When production equals clearance we have equilibrium. At equilibrium the viral loads remain the same, similar to what is seen in chronic infection as demonstrated in the data provided by Dr. Gordon=s group.

So, what does the viral at steady state tell us? Well, in the world of HIV infection the viral load at a steady state is highly predictive of risk of progression for HIV disease. In the

world of hepatitis C viral load by itself does not seem to be an independent marker of disease severity. Instead, its main role is to predict response to interferon-based therapy, with high viral loads being less likely to respond. The modeling data actually does help explain why that is.

[Slide]

So, you can begin to develop mathematical equations of steady state at equilibrium. It is way too early in the morning to do a lot of math but, briefly, you can develop a basic differential equation that virus over time is the result, and at steady state results in production, minus the clearance of the virions equals zero because there is no change in the steady state. So, at steady state this equation calculates to zero.

[Slide]

Now, if one intervenes in the process by whatever method one intervenesB-interferon, interferon with ribavirin, other immune modulators or specific small molecule antiviral agents, you

presumably have a perturbation from the steady state.

[Slide]

So, if production is stopped, in other words, if an agent is able to bring viral load to zero, then we can change the equation. The production part goes out of it and the end result is that you are simply left with the clearance of the infected cells. So, there is no production; viral load would drop accordingly until ultimately all of those cells are infected are, in fact, cleared. That clearance rate is probably the same for infected and uninfected hepatocytes, meaning that that is a constant. It is thought to be a constant rate of clearance that is associated in any individual at a particular time with the loss of those hepatocytes.

[Slide]

Now, the problem is most drugs are not 100 percent effective in blocking production. Interferon partially blocks viral production and we can then begin to evaluate-Band I am not going to

go through the more complex math that leads to this, but we do use a parameter, the epsilon or efficiency or efficacy of the early response in blocking production and make some changes in the equation again, and what we see is that there is a new parameter added that is 1 minus the epsilon, the total amount of production of virus that is shut down. That could be 60 percent, 70 percent, 90 percent, 99.9 percent, whatever that particular agent can do in that individual.

[Slide]

So, what does this do for us? Well, it leads us to a situation where if we plot and then do the mathematical modeling that involves, again, some much more complex set of equations but starting where I showed you where we have a perturbation, we see an initial rapid decline in viral load, which is called phase 1 kinetic decline. It doesn=t go to zero. If it went to zero we would have 100 percent efficient drug but we don=t in most cases. So, we are left with a pool and that leads to a change in the slope with

clearance of infected cells. Again, we are not sure exactly what is happening during this clearance phase. We know that if production is largely stopped, then new infection is not occurring and that there is clearance of both virus out of the serum by the clearance mechanism and clearance of infected hepatocytes. This is often called the immunologic clearance phase because it is thought that various immunologic mechanisms have a role in the normal clearance of senescent hepatocytes. But whether drugs affect this slope at all remains unclear and really much of the action seems to be occurring in these early stages, here.

This first phase is usually complete within the first 72 hours up to perhaps a week before one goes into the second phase decline curve. There are reports from a few centers describing what is called a third phase decline. That has not been observed in all studies and remains sort of a controversial aspect of doing this type of viral kinetic modeling.

[Slide]

So, why should we look at this and what does it mean? Well, it does begin to give us some predictive ability. If you start at a given viral load and have varying amounts of efficacy, of efficiency or epsilon and you can see that very, very minor changes of going from 0.9 or 90 percent to 99 percent, starting at the same place, would theoretically result, out at 120 days here, in a fairly significant difference in the viral load level. The more efficacious, the closer you get to 1, which would be a straight decline down to here. The further you drop initially in the lower level, you reach this point of inflection that then leads you down into this second phase decline slope.

Another way of looking at it is to flip the same data around and say at different levels of epsilon how long would it take to clear virus? What you see here is that, again starting with the same viral load, if you had 90 percent epsilon, 90 percent efficiency, it would take close to 600 days to clear virus in that particular patient. If you

can take it up to 99.9 percent, then you have decreased it down to about 400 days. At 99.99 percent you are down in this range here, between 300 and 400 days. So, very, very minor differences in the efficiency of the early decline significantly affect the predicted clearance time of that virus.

So, does this stuff work? Well, I am going to show you some data from actual patients and some pooled data that I was involved with. There are several groups in the country that do this kind of work.

This is an HCV/HIV coinfected patient treated with pegylated interferon and ribavirin. We collect multiple samples in the first few days and then we collect other samples to see what happens. But the models are actually generated in this case in the first 14 days of therapy. The line shows the prediction and the dots show the actual, and what was predicted by the model was that there would be viral clearance below detectability by a sensitive assay in 64 days. In

fact, the patient cleared at 56 days, which is a pretty good predictive model.

[Slide]

Here are two patients. They are actually matched with each other, an HCV mono-infected and a coinfected patient. Here we have a patient that did not experience two phase kinetics. This patient had virtually 100 percent efficiency, actually 0.997, and cleared virus almost immediately; did not show second phase kinetic drop. They were negative, negative, negative very, very quickly in their actual numbers. Therefore, the model actually fails because the patient did not exhibit that type of kinetic response.

[Slide]

The model fails for other reasons too, including if early on there is actually an early blip in actual measurement, in the first 72 hours particularly. It really messes up the mathematics that are currently involved in putting these models together. Here is a patient that actually had this little blip but then appears to be declining, but

the model predicts no response at all.

[Slide]

We can use this type of modeling information to look across groups. This is a coinfected population treated with standard interferon.

[Slide]

We can then look at what happened in a matched population when PEG interferon was used as the comparator and it gives us an agent-to-agent comparison showing a much steeper decline curve in the first phase and a greater slope over the first 14 days, suggesting that this is a more efficacious agent.

[Slide]

We can then look at the comparison of different populations. Here it is HCV infected versus coinfected with HIV. It is good at generating hypotheses and raising questions. Her, unlike what was suspected, we saw no difference in the early responses whether patients had HIV or not. Both the early decline curve and the early

phase 2 curve are actually parallel, very similar, suggesting that coinfected patients do respond similarly to interferon-based therapy. Yet, we know from clinical studies that the responses are not as good and this is where that issue of viral load comes in.

So, you might say, Aboy, that=s less than a log, how much difference could that make?@ But, in fact, by using this modeling we learn that there could be a differential time to clearance across the group of coinfected patients over two months. As I am sure Dr. Vierling will discuss in the next talk, as we develop paradigms it is not just the time to clearance but something happens after virus is gone that leads finally to what we call a sustained viral response.

[Slide]

The window for that may be as short as 4-8 weeks and may be as long as 30 weeks, and we haven=t really clearly defined what creates that window between clearance and cure. However, if one uses a fixed stopping point parameter one would see

that in the coinfected patients you would expect less response because the group as a whole didn=t clear until much later in the infection process.

[Slide]

So, how does all this help? Well, modeling characterizes the effect of an intervention. It permits comparisons between different agents and different groups, as I demonstrated. It introduces prediction capabilities and it creates a hypothetical framework in which different hypotheses can, in fact, be tested, often very efficiently in a short period of time.

[Slide]

The part I want to focus on is this concept of prediction and stopping rules. Back in the early days of interferon use all we had pretreatment predictors. We knew that men didn=t respond as well as women; that generally people who are big didn=t respond as well as those who are little; that genotype 1 doesn=t respond as well as genotype 2 or often 3; that patients with cirrhosis

are less likely to respond than don=t that don=t have cirrhosis and that is probably tied to duration of infection and immunosuppression seems to affect treatment outcome. So, those are pretreatment predictors. They don=t tell you who to treat or not treat. They simply give you an idea of who is more likely to respond.

What we have evolved to is predictions of response during treatment. The main one that has been used as a paradigm for a number of years is that if you are not virus clear by 24 weeks, then with a course of therapy you are unlikely to clear or achieve an SVR. That is based, again, on a fixed period of therapy.

Now, when a lot these rules were created they were sort of done post hoc, following the data from the clinical trials and then looking to create rules. But if you think about the viral kinetic data, the actual models really explain all of these prediction rules that were developed before we knew anything about the viral kinetic modeling.

In recent years-Band we will look at the

data on thisB-12-week non-response parameters have become the standard for use with base 48-week treatment therapies. To decide whether to continue, in recent literature there has been considerable discussion about 4-week rapid viral response predictors. And, there are suggestions using the viral kinetic I showed you that if you are able to do enough sampling in at least some patients you should be able to predict who is going to respond or not respond, at least in terms of viral clearance, within a period as short as 72 hours.

[Slide]

This shows from one of the pivotal trials, with Mike Fried as the first author, the negative predictive value at the 12-week mark basically saying that if you did not achieve a two-log drop from baseline or negative HCV RNA by 12 weeks, then it was extremely unlikely that you would, in fact, clear virus, and further treatment may be considered futility and you should stop.

[Slide]

There is similar data available from Gary Davis= paper, in data derived from the PEG-interferon alpha-2b pivotal trial again showing that similar sense of futility if you don=t achieve those parameters by 12 weeks.

[Slide]

So, we have predictive rules. They do provide use in a clinical setting. Again, they are based upon the viral kinetic modeling that I showed you that we don=t know when those rules were created and, in fact, they are based upon arbitrary and fairly strict cutoffs in terms of how long a patient should be treated, which is often a necessity in a clinical trial. You have to stop some place.

So, the variabilities in this modeling if we actually go back to the mathematical modeling, well, there is assay variability in how you determine how much viral load is there at any given time, both in terms of how tight the number you get is, there is variability around the numbers and then the sensitivities of the test; different

agents, for example interferon alpha-2a versus interferon alpha-2b. They pharmacologically behave somewhat differently, which can affect your modeling equations. For example with PEG-interferon alpha-2b work from Andy Talal and Alan Perleson showed that you can derive better models if you include some information about drug levels because of loss of drug towards the end of the week and the small rebounds that occur. Sampling frequency, sampling times and frequency make a big difference in the outcome of your model. Like all models, the more sampling, the better the result. The patient population chosen and the controls used clearly make a difference. What you do with outliers in your analysis is very important because we see different results even in the viral kinetic modeling from different groups around the world. However you deal with the issues of non-response and rapid responders, and what do you do because in the real world sometimes you can=t get the sample at six hours because the patient was in the bathroom and didn=t come down at the right

time when you have blocked some kind of unit, and that affects outcomes. So, in the real world even things like missing data points affect the quality of the model.

[Slide]

Why do models fail? Well, they fail to account for all the parameters. They all assume that clearance is constant, that the clearance parameter is constant. It may not be. It assumes a fixed rate of new hepatocyte formation but, in fact, it has been suggested that following early clearance there is a burst of hepatocyte regeneration that may occur. It assumes a steady state of viral load prior to treatment, which is true in most patients but not, certainly, ones with earlier infection. It assumes infected cell death rate is constant. Again, we don=t know that that is true; we think that is true and not modifiable. We are not 100 percent sure. It assumes there is only one viral compartment so if there is infection going on in different places with variable rates of clearance, you can=t tell that from the current

models as they exist. A process may be going on that the early virus cleared may be less fit virus, meaning the virus left that is causing infection infects more efficiently than the virus that was in the general pool at the start, which leads to potential errors.

Why am I saying all this? What is the point here? The point is that these models are extremely important tools and we, and I think many pharmaceutical companies, have found them very useful in generating hypotheses and I think those hypotheses then need to be tested with the recognition that these models are still imperfect and have many areas of potential variability that let us generate effective hypotheses but may not give us, at this point, definitive answers to treatment outcomes.

[Slide]

A few words about natural history of HCV infection. This slide from Adrian Di Biceglie has been commonly shown in our community. Patient]s are exposed. Some percent resolve. Depending on

who you are, the resolution rate may be higher than 15 percent. Some populations, particularly young women and children, may resolve at much higher rates following acute infection. But some percentage goes on to chronicity. Of those that have chronicity, a subset go on to cirrhosis within a fixed year period, understanding that this is a continuing dynamic process and the longer it goes on, the greater the chance that any one individual may progress through the various stages of liver disease to cirrhosis, and when you are cirrhotic the second clock starts. Patients can develop end-stage liver disease, manifest by ascites, encephalopathy, bleeding varices that one sees in end-stage liver disease, or simultaneously development of hepatocellular carcinoma. Those patients undergo transplant or die in a relatively short period of time after that point.

[Slide]

The progression of fibrosis is highly variable. So, there is not a rule. We are looking at individuals. We have patients that progress

slowly over many years and we have patients that progress quickly. There are modifiers that we know about. Alcohol is an important modifier. HIV coinfection is an important modifier. In patients with obesity steatosis appears to be a modifier in terms of fibrotic progression. So, there are external factors that can change this in a given individual and some may be modifiable.

[Slide]

This is a study from Ireland, looking at a large group of women that were infected so you had young women, non-alcoholic, non-immunosuppressed, not coinfected with other viruses, and after 17 years only 2 percent had gone on to cirrhosis. This is not to minimize the severity of this disease process, but to tell you that clearly there are factors that affect progression and not everyone progresses to a point of cirrhosis rapidly.

[Slide]

For those that don=t think about or look at liver biopsies, I just want to show you that this

is a normal biopsy or semi-normal biopsy. There is a little bit of fat in here which is all those little white circles. Generally, we say that on this stain blue is bad and when the liver lobule, the functional unit of the liver, is surrounded by scar we call that cirrhosis. Cirrhosis is a histologic definition. There are clinical ways that we recognize patients who have cirrhosis, although most patients at any given time with cirrhosis may be clinically inapparent even with imaging-based studies.

So, cirrhosis is a histologic finding and when people talk about it today as an endpoint or a group that we think about treating, or the stages before that where we have beginnings of bridges between portal areas, you need to keep this picture in mind. It is when we get to cirrhosis that we see altered blood flow in the liver and it is the physiologic changes associated with altered blood flow that lead to what we call end-stage liver disease.

[Slide]

Once a person is cirrhotic, there is a rate of decompensation to the signs and symptoms of end-stage liver disease. It is approximately four to five percent per year and an additional couple of percent per year will go on to develop hepatocellular carcinoma once they achieve cirrhosis.

[Slide]

What does all this have to do with health? Well, there have been predictions made that say that we are in the increased phase where we are at now in terms of both hepatocellular carcinoma and liver-related mortality. Based upon those numbers that I showed you on the bolus of patients and where they are at relative to their estimated times of infection, we see that we have peaks in about a decade from now in terms of mortality. That mortality is mirrored by increase in societal costs that can get quite dramatic in their estimates.

[Slide]

Some specific predictionsB-future HCV-related mortality may double over the next

10-20 years, with up to 208,500 deaths related to hepatitis C.

[Slide]

The cost of this is estimated to be between 2010 and 1029 11 billion in direct medical care costs, with societal costs of 21 billion dollars. So, again, we are dealing with an important issue here.

[Slide]

There have been predictions from Gary Davis, looking at issues of complications based upon the likelihood of treatment and what happens there, and suggesting that effective treatment in this model leads to decreases in the number of cases of decompensated disease and, presumably, then a decrease in the long-term costs and societal costs that are associated.

[Slide]

I will leave you with this quote, paraphrased from Robert Frost and parenthetically from Miriam Alter that we still have Amiles to go before we sleep.@ I began working in this field in

1980, so 26 years later we are entering now an extremely exciting time. There have been amazing advances I a relatively short time and now we are about to embark on a whole new generation, and I think that this meeting is absolutely critical to setting the stage for the future. Thank you.

Next we will hear from John Vierling, who will be discussing clinical experience and difficulties and issues in trial design and what we need to think about in populations as we move forward.

Clinical Experience: Difficulties in Trial Design for Therapeutic Products to Treat Chronic HCV Infection

DR. VIERLING: Thank you very much.

[Slide]

It is a pleasure to be here with all of you as we look to see our next steps and to peer over the horizon, with the ultimate therapeutic goals in hepatitis C infection of making it a vaccine preventable disease, and to develop a safe and effective pharmacologic cure for both acute and

chronic infections, terminating the hepatic and the extrahepatic disease manifestations, allowing dissolution of fibrosis in those cured patients, and to reduce the incidence of associated metabolic and malignant diseases.

[Slide]

To orient this discussion, I would like to first begin with briefly summarizing what we know about the clearance of HCV infection or lessons learned from our studies of pathogenesis, and look at interferon and ribavirin mechanisms of action in sustained virologic response since the standard of care of therapy is very crucial to the design of our new trials with single antiviral agents in development.

I want to look then at the relevance of the prior clinical trials and the study of the new therapeutic agents, and then end with selection of patient populations for clinical trials of new agents and some of the new clinical trial design and endpoint controversies and opportunities.

In the latter two segments of the talk I

certainly wish to disclaim that I am speaking for anyone other than myself from an experienced clinical point of view, and really am not here to usurp in any way the discussion of this advisory group.

[Slide]

Well, it is important in HCV pathogenesis to recognize the difference between infection and hepatic disease. The HCV virus infects a variety of cells, as you heard hepatocytes and lymphocytes in which it can replicate. Possibly it is existing in other tissues but replication is unproven. But more importantly, when it infects hepatocytes, except in very special circumstances of immunosuppressed patients, it is not a cytopathic virus. Hence, the disease is mediated by an immune response.

Very importantly, that immune response leading to the inflammation, which was the blue part of those histology slides you saw from Dr. Sherman, has a variable ability to cause fibrogenesis, perhaps mediated by the difference in

the cytokines, a difference in the responsiveness in the stellate cells and their activation or the differences in the host=s ability to clear collagen once it is made. But the advanced fibrosis ends up, as you have seen, to be at variable progression state and, therefore, variable problem for individual patients.

[Slide]

That is illustrated on this slide, in which you see, to the right of the screen the spontaneous clearance where the person=s immune response gets the upper hand. That upper hand is a response that we know something about and will discuss. But in the chronic infection state, about 85 percent of adult infected patients, one sees the variability of outcome where ALT, L-aminotransferase, a readily available blood screening measure, looks at the surrogate-Bit is a surrogate marker for the inflammatory state. You see here that there are differences in those that have persistently or intermittently elevated ALT and those that don=t. That does have an impact on

the histological outcome, as you see here, at least a ten-fold difference in the rate of cirrhosis at 20-30 years. Hence, knowing something about who is going to progress and what their stage of progression is, is a key role for liver biopsy. So, we have the issues of viremia for which we have tests; the biochemistry for which we have a readily available test; and then the biopsy for histologic outcome.

[Slide]

Well, the end result of cirrhosis starts the second clock, as Dr. Sherman has just shown you. To the left is a slide that you saw in the decompensation rate of about five to six percent per year in the cirrhotic population, and an elevated rate of hepatocellular carcinoma, with the newest estimates being three to five percent per year.

If you look to the right you see that once you have cirrhosis a process, which needs to be reemphasized, outcome truly an endpoint, that if you remain well compensated life expectancy is not

terribly blunted. But once you have elements of decompensation, shown in green, you drop to a 50 percent life expectancy by five years. Hence, the existence of cirrhosis is an extremely important clinical target population.

[Slide]

The immunopathogenesis of hepatitis C infection results, as I said earlier, from the immune response to a well defined set of epitope peptides in both the structural and non-structural proteins of the HCV virus, leading to a CD4 T-helper response and a CD8 cytotoxic lymphocyte response which is vigorous, polyclonal and multispecific, and still a conundrum compared to other viral diseases of the liver as to why this is so robust and so few people actually clear this virus spontaneously.

[Slide]

We think that there is an important role of the dynamic balance of CD4 T-helper lymphocytes in this, and this may be a subject of therapeutic intervention as we develop new drugs. If we have

presentation of the viral peptides to a naive CD4 T-helper knot cell, it then has the ability, depending upon its cytokine milieu, to become a T-regulatory cell, at which time it will be an antigen specific immunosuppressive cell, or to become one of two mutually exclusive types of helper cells, to your left T-alpha-1, to your right T-alpha-2. These are defined by the gene switching that allows for a mutually exclusive set of signature cytokines to be produced. Those produced by T-helper-1 augment a greater immunopathology and, hence, a greater capacity to attack a virally infected cell or to clear it. Indeed, these cytokines are not only mutually exclusive but they cross-inhibit each other=s cells, involving in decreased production of the contra lateral cytokine, as well as decreased replication of the contra lateral cell. Hence, a balance is achieved and may be ultimately perturbed therapeutically.

It is important to note that the greater immunopathology at CD4 Th1 is the characteristic of those people who spontaneously clear this disease

without therapy. In fact, in their blood stream 20-30 years later they have high frequency of responsive cells.

[Slide]

Well, the immune-mediated clearance of the infected hepatocyte is largely the purview of the cytotoxic T-lymphocyte. That causes an apoptotic change in the infected cell. It is both cytokine and cytotoxic protein-mediated and leads to the clearance.

[Slide]

However, we now know that at several sites, illustrated here by the star bursts, hepatitis C virus itself has the capacity to antagonize this cytotoxic response and, hence, promote viral persistence leading to an ineffective clearance where there is a constant new barrage of infected cells and a constant ongoing inflammatory attempt to clear them.

[Slide]

Well, you have seen this slide in Dr. Sherman=s talk that looks at the dual mechanisms

that may underlie the biphasic HCV kinetics on therapy. This slide is derived from analysis of daily interferon monotherapy in which that first slope drop of the serum levels of HCV is due to the efficacy of replication termination induced by the interferon. You then see that second slope. That slope has been characterized in much of the literature as immunologic clearance of hepatitis C infected cells. Dr. Sherman pointed out to us all that, indeed, there is a controversy that in some patients that slope may coincide with the natural half-life reduction of the hepatocytes themselves and not necessarily evoke immune clearance.

But I will call attention to Dr. Sherman=s nice demonstration that when you are at 0.999 percent epsilon, you might still take 300-400 days to clear cells. We have to contend with the explanation, which is still I think a hypothesis, that the fact that we can get a sustained virologic response at 24 weeks in genotype 2 and 3 infections and 48 weeks in genotype 1 infections suggests that there must be something augmenting this, and the

immune response is the candidate.

[Slide]

Well, the antiviral mechanisms of action of interferon-alpha are probably important because, again, we are looking at designs that may use standard of care within their arms. We know that hepatitis C infection will cause a production in hepatocytes, as other epithelial cell models, of interferon-alpha and, of course, as shown in the middle, we can give it exogenously as a drug to simulate the alpha/beta interferon receptors. Working through the Jak STAT and interferon response elements, then signaling a whole host of interferon-regulated proteins, there can be a reduction and ultimate termination of replication which is responsible for that first look kinetic I showed you in the prior slide.

[Slide]

The antiviral mechanisms are resplendent within the cell. Something to keep in mind is that interferon adds a sort of multi-specificity, which is not necessarily HCV specific, compared to some

of the drugs that we are going to be advancing into clinical trials that are highly HCV specific and mono-specific.

[Slide]

We know that interferon-alpha also affects the immune system, and particularly affects natural killer, the innate immune component of the system as well as the adaptive CD4 T-helper-1 response. It does show, as shown here, that the HCV-infected cells making interferon-alpha, as well as other cells that make it, are stimulatory of the innate immune response. Time doesn=t allow me to go into all the ways that it stimulates but I am showing here that with the production by NK cells in a localized environment of interferon-gamma it skews the response to a T-helper-1, increasing the immunopathology and in some models, unfortunately, increasing even the capacity for mediated fibrogenesis.

[Slide]

Well, hepatitis C is crafty in this regard also because it can antagonize interferon-alpha

effects. Here we see that in the structural as well as non-structural proteins there are a variety of ways that the virus can subvert the effects, some of which relate solely to the effect of the interferon on the virus within the hepatocyte and some that relate to the immune response.

[Slide]

It is also I think instructive to not that interferon-alpha has the capacity to inhibit hepatic fibrosis. It can do so by decreasing mRNA expression within livers, as proven by biopsies and gene analysis of HCV-infected, interferon-treated patients with monotherapy of many of those factors that promote fibrogenesis. It will decrease, therefore, the surrogate markers of fibrogenesis in their serum levels, and it will actually increase the capacity of the liver through collagenase and metallo-matrix protein production to dissolve preformed collagen. This may be important when one looks at the long-term issues of the administration of interferon.

[Slide]

Well, we are less sophisticated and knowledgeable about which among the putative mechanisms of action of ribavirin are pertinent to its augmentation of interferon=s capacity to achieve an SVR.

[Slide]

We know that ribavirin entering hepatocytes is phosphorylated in its monophosphate form has the capacity to interfere with ionosine monophosphate dehydrogenase important for the purine synthesis necessary in this infection. Its triphosphate form has the capacity to interfere with the replication of flavivirididdate and it can be, in certain viral types, including HGV flavivirus family member, mutagenic. Whether or not all of these are completely pertinent to our understanding is still debated.

[Slide]

It is also true that ribavirin, as shown on the left, can augment within the liver the production of interferon-gamma with the capacity to help direct and to augment a T-helper-1 environment

within the inflamed tissue and, by so doing, contravene the T-helper-2 population and its cytokines. It is also true that ribavirin, to the upper right, may inhibit the proinflammatory cytokine production, changing the milieu and perhaps changing the capacity of the effectiveness of the immune response.

[Slide]

Let=s turn then to the hepatitis C therapy with interferon-based regimens and the concept of the sustained virologic response, which is illustrated here using a lower limit of detection for the viral load within the serum of an infected individual. We have the initial period of treatment in which we have some rapidity of that drop to some time point, and we have heard about rapid virologic response, early virologic response and a 24-week response, but here we have an individual that really terminates the replication of virus under therapy. It is consolidated in this period which is still debated as to how long it should be so that there can be, in theory,

clearance of all the infected hepatocytes and, hence, when we stop therapy at this point this is a sustained virologic response.

Twenty-four or more weeks has been the god standard for defining that after therapy. But it is important to know that if you look at this SVR it is quite durable. In fact, it can be durable in some patients. The estimates now are approaching 20-27 years for some individual patients treated early on with monotherapy. It also has the issue of how long does one have to wait to define it. As I am sure we will discuss more within the committee, that is important in terms of perhaps condensing our trials. I leave you with the data point that 98 percent of those SVRs can be determined by the 12-week post therapy analysis.

[Slide]

Unfortunately, not everyone gets the SVR. We wouldn=t be here. Consequently, we have to look at the four patterns of non-response which are also illustrative of patient populations concerning to us for treatment with new agents. The most

important to define, and we do not use the words currently in a say to define this group, is that group which under therapy, despite compliance with the therapy, really has no virologic response. They are truly the non-responders.

We have the group here, shown in red, who achieve their early virologic response and the end of treatment response but then they relapse. That is the group that is going to occur 98 percent of the time within 12 weeks and 100 percent by 24 weeks.

We have a very small group, shown here in green, which under therapy, presumably with excellent compliance, have a breakthrough phenomenon. They are rare and for purposes of clinical trials are less likely to be identified.

Then we have an increased population in which we are using the early virologic response, principally at 12 weeks, to actually take patients off therapy and tell them that they have only a one to three percent chance that they would achieve an SVR and that that is not sufficient for them to

continue. So, this is the group that we still know least about in terms of the non-response categories.

[Slide]

We have talked a bit about genotypes. From a practical standpoint, I only show you these data based on a very large number from Larry Blatt. It emphasizes the point that 70-75 percent of the studies will show genotype 1 infection in North Americans and the residual 20-25 percent are comprised of equal components of genotypes 2 and genotypes 3. Thus, if one wanted to design studies that will have the greatest impact in applicability to North American populations, these three genotypes dominate.

[Slide]

Here we look at the issue of liver biopsy. We pointed out its utility in telling us how patients on an individual basis are advancing in the progress of their disease through its duration. You have seen these slides before. Here is cirrhosis, characterized by the nodular

regeneration within an inflamed scar. We have excellent systems to assess grade of inflammation and stage of fibrosis. We have arbitrarily taken significant changes to be those that in a relatively short period of time achieve 2 or greater change principally in inflammation.

The caveats are important if we are going to regard biopsy as a potential tool for endpoint utilization. First, we have to have adequate specimens. In fact, this is the major problem in analyzing large series. We have specimens that are not large enough to contain an adequate number of portal tracts to grade and stage with accuracy.

We need to use large needles. This is particularly problematic because many biopsies are done now by our interventional radiology colleagues that use 18-gauge needles and use a gun technique. An aspiration biopsy is much more productive of larger amounts of portal tract tissue than is a gun technique, which actually in fibrotic individuals can trim the biopsy and take in more of the fleshy parenchyma and trim on the outside edges these

portal areas.

We need to consider optimal timing where we can use biopsy, and that is before and after comparison. The problem here is the half-life of inflammatory infiltrates. If you were to terminate replication and if you were to continue to have the immune response inflame the liver and hemotract to the liver in order to clear the cells, those cells will have a very long half-life, and biopsies that are done immediately at the end of therapy are only partially informative of what may be forthcoming if you were to extend that period.

Conversion from fibrogenesis to collagenase activity is less well understood but thought to take even longer. So, expectations that biopsies with relatively short duration between pre therapy and post therapy will show changes in fibrogenesis, that has not actually been forthcoming in the data sets.

[Slide]

Well, we have talked a bit about non-response and Dr. Sherman outlined for you a

number of aspects regarding the variability of achieving an SVR, shown here in the yellow and the blue, based on genotypes 2 and 3 and the robust SVR potential compared to genotype 1. And, viral load, the low amounts of virus, arbitrarily look as about 800,000 IUs/ml versus higher viral loads having a differential response. Weight is playing a role, perhaps based on the dosing of the drugs, and the stage of fibrosis. The earlier non-fibrotic stages of inflammation have a higher response rate than do those that have advanced fibrosis or cirrhosis, which is the F4 grade.

But shown here in green is also the variability in the populationsB-the percentages are shown here-Bof those that are not responsive to these therapies in these different categories. So, one finds, obviously, in genotype 1 with high viral load that you are going to have a cluster of your largest population available for study in non-response. The same is true for the higher weight individuals and the group, here, with cirrhosis. So, with non-response one needs to take

into consideration what type of risk factor profile led them to be non-responsive if we are purely going to address non-response rather than surrogately address the reason that they were non-responsive to the standard of care therapy.

[Slide]

This slide from Ferenci and colleagues addresses the issues of the rapid virologic response, negativity or two-log drop at 4 weeks of therapy, the early virologic response and then the negativity of the PCR test at 24 weeks of therapy. It shows that when one has the earliest virologic evidence of response at four weeks and it is persistently negative, the most robust response leads to a very high probability of an SVR. This I think are the data that inform us as to how we would like to gauge a trial and to interpose stopping rules or abbreviations of therapy.

[Slide]

Well, all therapies are predicated on the ability of the patient to tolerate the adequate amounts of drug, as well as to be compliant in

their use. These data, although solely with the alpha-2b pegylated product and fixed dose ribavirin or weight-based ribavirin illustrate, from John McHutchinson, the issue of adherence. We have the overall response rates of SVR shown here in the yellow. We have those that do not have the ability to achieve at least 80 percent of the ribavirin dose, 80 percent of the interferon dose, and to use both for 80 percent of the duration of therapy, shown as a statistically significant decrement. In contrast, we see a statistically significant increment in response for those that can achieve an 80-80-80 rule. We are going to present data later this month that the same thing holds true for post liver transplant patients.

[Slide]

The differences are also involving groups that can be analyzed and predicted on the basis of race. Here we see the differences in SVR for African Americans versus non-Hispanic Caucasians in the most recently published NIDDK viral hep. C study. Along this axis we see the undetectability

of RNA at weeks 4 through weeks 48 of that. This was limited to genotype 1 infection. It is quite clear that although in this early virologic phase of response there is an increase that occurs in both groups, it is always higher in the non-Hispanic Caucasian group and it leads to a disparity in response of nearly 50 percent lower response.

Now, the subset studies to explain the mechanisms for this response are incomplete. But those that have been preliminarily presented show that there may be deficits in the innate immune responsiveness and the interferon-based signaling, perhaps on genetic bases, that are dictating their response to the alpha interferon. Hence, the need for this particular population for new drug development and inclusion in studies.

[Slide]

HIV and HCV coinfection has been mentioned several times and it is an extremely important subpopulation. We know that the survival rate for the coinfected population differs from that of the

HIV population that is not infected with hepatitis C, and this is owing to the effectiveness of a highly active antiretroviral therapy that is now causing a revolutionary health response in the HIV population. Indeed, when one has the effectiveness of that therapy and looks at cohort years here, just illustrating one of many studies I could show you, one finds that in liver disease related deaths are now principally because of death in the coinfected population. So, there is an urgency in this population.

[Slide]

Finally, we look at the fact that the studies that have been done with standard of care pegylated interferons or ribavirin-Bfour studies shown here-Bshow that for your tougher to treat genotypes duration required is longer for treatment 1 and 4 compared to 2 and 3. You still see the disparities in terms of SVR rates but you also see very high discontinuation rates within the trials so that the doses used have not been well tolerated. Clearly, important work.

[Slide]

Finally, we have the accelerated progression and increased mortality of recurrent infection in the transplant patient where 10-30 percent may develop cirrhosis not over 20-30 years, as you have seen with the natural history of infection, but in 5-7. Within a given year almost half of them may decompensate.

[Slide]

We look at national data, from Lisa Forman from the STR database, and one finds that those transplanted for non-C indications versus the hepatitis C, which is the principal indication for all transplants in the United States far better, largely due to this impact of recurrent disease.

[Slide]

With that information in mind, let me turn very briefly to the issues of candidacy and, again, not to usurp but to inform and orient our discussion. We clearly can have the treatment-naive population and, remember, this particular population could be segregated to those

that are at major risk for progression based on ALT and based on liver biopsy. The group at greatest risk would be that it has elevated biopsy, has active inflamation and an absence of contraindications.

The treatment-experienced has at the top of a list of those that would be candidates for achieving response with new agents, those that relapse from standard of care, and at the bottom those that were non-responders or the absence of any virologic response. Then we have a host of special populations.

[Slide]

Let me just give you a personal sense that the priority populations I think for many in the clinical community include the treatment-naive populations and would be inclusive in study designs for whites, African Americans and Latinos. The elevated ALT and the ability to stratify on the basis of our three most common genotypes, accounting for 95 percent of the infections in the U.S., may be productive of the highest priority,

and that it be stratified on histopathology because we know that the advance histologies fare poorly with standard of care.

The treatment-experienced, those that are non-responders documented at these various times, could be considered inclusive because those patients, a large number of them, were stopped from therapy because of the absence of an ETR. The relapsers with documented end of treatment response I think would be second. Again, to try to be inclusive, one could argue the inclusion of all three major ethnic racial groups.

The special populations, I think for many of us treating these patients, coinfected populations, those with HIV at the top of the list, those with decompensated cirrhosis and those post transplantation are very high on our priority screen, but recognizing that these populations are most perplexing for the analysis of adverse events and serious adverse events due to the impact of their underlying and advanced diseases. Then, of course, we have the issue of chronic renal failure

where the prevalence of disease is quite high.

[Slide]

What could be done? Well, there are many study designs and one can entertain a whole host of those. I entertained one here for purposes of informing the discussion but not directing it by any means. I will point out a debate here about the utilization in standard of care plus active new drug regimens and the inclusion of placebo. Personally, in talking to many patients, I feel that the inclusion of a placebo is going to be very productive in keeping patients in these trials because many that are seeking new therapies, if it is known to them that they are not receiving anything that is new are subject to leaving the trial and I think this could hurt our data analysis.

I think that with these trial designs the primary endpoint that we can probably most advocate would be an SVR and then the debate would be how long post treatment does one extend the trial to achieve definition of SVR?

[Slide]

For the treatment-experienced patients, also for your consideration advocate the inclusion of the placebo because of the variety of extended high dose and other availabilities for their temptation while on trial, in the absence of knowing they are on active drug, the primary endpoints being similar.

[Slide]

For those that are special populations, I think the coinfected HIV population still is the most important for us. There we have, obviously, considerations that will be discussed by others regarding the patient selection and treatment duration. But I think that one could make a strong argument that eh endpoints would be identical for those that are completely controlled in the HIV infection by the HAART regimen.

[Slide]

Decompensated cirrhotics, those that are listed for transplantation afford the greatest ability for rescue were their disease to progress

independent of any impact of therapy. Thus, one could be looking in the United States at a pool of approximately 17,000 individuals currently on the UNOS waiting list.

One can look at a variety of designs here of controlled trials for superiority. I think in this particular group since decompensation in particular has been a contraindication we really don=t have an issue of comparability or non-inferiority. Here we have to really start to look at the issues of what do we do with ribavirin, which is very problematic in this group of patients. What do we do with potential substitutes? What do we do in terms of the potential utilization of placebo or the lack of a placebo control group.

Primary endpoints would be robust to have this termination, but second endpoints may be very important here, particularly improvement of the MELD score, a highly validated measure of short-term probability for mortality and improvement of synthetic functions and

manifestations of decompensation ultimately I transplant-free survival and, very importantly for long term, patients who had achieved an SVR in a decompensated state, whether or not this would achieve an absence of hepatocellular carcinoma on long-term follow-up. This is a group that clearly needs long-term follow-up.

[Slide]

What about recurrent infection post OLT? Again, this is a very important population to the transplant and hepatology community, one that we recognize is problematic for new drug development but that we urge that it be strongly considered at the earliest possible opportunity where safety and efficacy data allow it to be moved into clinical trials of this group. Here randomized designs have the same issues as the decompensated cirrhotics. I think the endpoints are, however, similar.

[Slide]

Finally, chronic renal failure patients on dialysis who are incapable of taking anything other than monotherapy with interferon because of

ribavirin=s renal clearance and the severe anemias and toxicities with its use. Here we have the subgroup that brings into our consideration what would be the best of the ribavirin substitutes, or are we capable of dosing a ribavirin prodrug in a manner that allows a ribavirin effect without accumulation leading to hemolysis? Again, the endpoints for consideration would be similar.

[Slide]

That leads to just the last two points. That is the potential that we are moving I think inexorably toward of clinical trials of two or more agents, new agents. Certainly, the rationale is important because it potentially could eliminate the need for interferon and/or ribavirin in the regimen, and we have heard about the tolerability; we have heard about the cost and that is important if we were to expand our thoughts about truly treating all infected individuals.

It could retard or prevent resistance. That would be based on the modeling for the cocktail therapy represented by HAART. It could

have a possible adverse event and SAE profile that is favorable for chronic treatment where we could allow the natural half-life turnover of infected cells no longer capable of generating a virus to infect a neighboring cell to take care of the ultimate clearance of the virus. The primary endpoints would be those that are virological. The secondary endpoints would, hopefully, be the predicted improvement of histopathology, the prevention of any progression of disease, the reduced incidence of hepatocellular carcinoma, obviously requiring long-term follow-up, and improved health-related quality of life.

[Slide]

With that in mind, we really are up against I think the old and the new paradigms. So, from a personal perspective, our concerns, which are going to obviously engender a great discussion regarding the selection of patients for HIV therapy currently and with new therapies emerging, are very reminiscent of the conundrums regarding the use of arsenicals for the treatment of syphilis due to the

variable efficacy of arsenicals and the severe AEs and SAE profile.

However, we are all aware that once penicillin was proved to be safe and efficacious that therapy was essentially offered to all and there was no further consideration as to which group we would treat. The question before us, with the Amany miles@ left of Dr. Sherman=s slide, is when with the new developments and knowledge that we have will we have a similar success achieved in HCV infection? Being an optimist, I would suggest it is not if we will have that success, it will ultimately be when and we certainly want to be planning for it. Thank you very much.

DR. SHERMAN: Thank you, Dr. Vierling. The next speaker before our break will be Jules Levin. Jules is the executive director and founder of the National AIDS Treatment Advocacy Project, NATAP. He will be presenting a community perspective.

Community Perspective

MR. LEVIN: Well, thank you for inviting me to speak. Thanks to the FDA. I am glad to be here

today.

[Slide]

I am glad the FDA is holding this hearing today. I will try and cover what I think is important from my perspective today. I think the table was set pretty nicely by Ken Sherman and Dr. Vierling, discussing a lot of issues that I don=t even have to mention, although some of them I will select to talk about.

[Slide]

I want to give a little bit of background on myself first. I found out I had HIV. I have had HIV for 20 years, 23 years. I founded NATAP in 1995 in my living room and it was a very small organization. I spent six years on the ACTG and on the HIV RAC as a community representative from NUY and Bellevue. I think I am actually probably the first coinfection cure with PEG and ribavirin. I was the first person to enroll in a PEG-ribavirin coinfection study. So, I have been cured, or whatever language you want to use. The virus has been eliminated--I like the word Acure@B-for about

three years now.

Actually, I started working in this field in about 1995 when a couple of drug companies did not want to provide drug, protease inhibitors, for expanded access. I worked, actually, pretty closely with the FDA. The FDA held a hearing that they worked with me on at the time where all the protease manufacturers were invited and, as a result of the public attention that that received, within a couple of weeks after that public hearing those two companies agreed to provide expanded access. And, I worked with tAttAt he FDA on putting protease inhibitors on a fast track. At the time it was Kessler and Feigle, and we have come quite a way since then.

Now I think we are at a point where hepatitis C finally has come to where maybe we were ten years ago with HIV, but it is quite a bit different because now we have a standard of care which I think is going to change perhaps in three years. So, I am wondering if everything that we are going to talk about here today might change in

three or four years if we have a new standard of care.

[Slide]

In 1996 of March after three protease inhibitors were approved, my organization, NATAP, held community forums around the country, in New York for about 900 people, in Los Angeles for about 900 people, the first community educational events on protease inhibitors. Our website is I think the other arm of what NATAP does. It is a leading resource on the internet. The volume of traffic on the NATAP website and through the email programs that we have reaches, I estimate, over 150,000 people every year. I think it probably has as much, if not more, traffic than any other website on the internet in terms of providing conference coverage, time sensitive, overnight often from conferences, journal publications, full text, and the latest news.

So, what I do is essentially provide scientific information to the medical community, as well as providing treatment education to patients.

So, what I want to say is that over the past six years I have traveled all over the country to every major city and met with patient populations in all major cities, as well as departments of health in all these cities and offices of AIDS, as well as with community organizations. Our forums have had about 15,000 attendees in 25-plus cities and about 80 events in the past five, six years around the country, probably closer to 100 or more. In New York City it is probably double that.

So, over those years I have become very well acquainted with patient issues and the situation in coinfection, as well as mono-infection. I have to tell you that I strongly believe that there are two diseases here. There is mono-infection and there is coinfection with HIV. I have separate recommendations for both of those diseases and I think that it is important to recognize the compelling nature of HIV coinfection and the compelling nature of certain subpopulations in mono-infection, and not all populations in mono-infection.

As was mentioned by some of the presenters, maybe 15-20 percent of people with moninfection on average have the risk or do progress to cirrhosis and serious complications, while in HIV we think it could be everybody. So, I think that creates a situation that we need to consider in designing our approach to study design.

Now, included in that seriously affected population are certain subpopulations of mono-infection. That includes cirrhotics. It includes people with decompensation. It includes pre and post transplant. And, all these populations were highlighted in our talks before.

The last point I want to mention on this slide related to coinfection is the Ryan White Care Act. As many of you know, two billion dollars goes to HIV to support clinics and agencies and community-based organizations. It is pretty much one of the major sources of care and treatment in HIV and up till now it has not addressed coinfection with hepatitis C or hepatitis B at all, and still doesn=t.

Well, four years ago I launched a project to get hepatitis C and hepatitis B coinfection into the Ryan White Care Act. So, the current Care Act, as it is now languishing in the House and the Senate, does contain language including hepatitis C and hepatitis B coinfection. If it passes with this language in there, it will change the world of coinfection. You can read the language that is in there. You can speak to me at the break and I will tell you some of the language that is in there. But if it passes as it is, it will change the world of coinfection.

[Slide]

So, why are we all here today? Well, I think the good news is that we are at the precipice of many, many new drugs for hepatitis C. Is hepatitis C an immune-based disease? Is hepatitis C an antiviral-based disease? I have had this argument with Ray Chung a couple of times on my radio show in New York when I insisted it was an antiviral disease and he argued with me that it is more immune-based. I think that is one of the

issues. As we move ahead we will be addressing so many issues. Many hepatologists think this is not a viral disease, and maybe we need to look at the HIV model. So, I think this is an ongoing argument which is not that relevant today actually.

So, the good news is we have all these drugs that we are ahead of us, and the difficult task is how do we develop all these drugs in a way that makes the most sense for the patient population? We have a couple of counterbalancing populations here, if you will. We have the companies that want to get their drugs on the market, and I think that that is very important, to have access in development and have the drugs on the market. We have the patient populations that need certain data at a certain time.

[Slide]

So, I think the two main points that I want to makeB-because I think a lot of points have already been made and I will make a few more, but the two main points I want to make are that I think we need to consider the HIV drug development model

as we proceed ahead here with hepatitis C drug development. I think that we need to strongly consider fast track for hepatitis C drugs, particularly considering the populations that are seriously affected here.

I want to make a case here that before drugs hit the market we have an adequate amount of data, not just drug interaction data but safety and efficacy in certain populations because once a drug hits the market I think you all know that people are going to use it. So, if it approved with a certain amount of data and a certain indication in mono-infection, that doesn=t mean that its use is going to be confined to that population. For example, you have a hep. C protease inhibitor, the vertex protease inhibitor and let=s just say for the sake of speculation that it looks like you can cure hepatitis C in a high percentage of mono-infected people, with 12 weeks data with a vertex protease inhibitor and PEG interferon-ribavirin, well, we all know that interferon and PEG interferon or ribavirin does not

work the same in coinfected people. It doesn=t work the same in certain populations. So, that 12-week indication does not necessarily predict how coinfected people and others may respond. But when that drug hits the market it is going to be used by everybody. I pormise you that.

So, my case is that it is very important that the companies haveB-and I am not going to define what adequate is because I don=t know exactly. You know, when I was thinking about what to say here today, I really started giving thought to how to design studies. When I seriously started to think about what I was going to put on my slides about four, five, six days ago, I really became overwhelmed because I think that we have a tremendous task here on how to design these studies. It is very difficult. So, I am not going to stand here today and in 20 minutes tell you how to design these studies, and I don=t get paid for that but the FDA and the companies do.

But I want to tell you that I think it is very important that we have an adequate amount of

data in certain populations, safety and efficacy and how to use these drugs in certain populations, and in particular HIV coinfected patients, people with decompensation, people who are cirrhotic and pre and post transplant. I think it would be wrong to come to market with a drug without an adequate amount of data in those populations.

So, I want to recommend that we consider fast track for hep. C drugs because I also think that we need to give incentive to the drug companies if we are going to ask them for a lot, and I want to ask them for a lot. I want fast track drugs. I want to consider expanded access and accelerated approval in hepatitis C as we do in HIV. And, I think ultimately it would look different because, you know, obviously HIV is lifetime therapy so far and hepatitis C will not be. So, I think that the utility of expanded access and accelerated approval will look different in hepatitis C. I am not going to stand here and define it, but I think you can all appreciate how different it would look. You probably would not

have as large a population going into expanded access as you would in HIV, but it needs to be discussed and ironed out.

The other key subject that I want to focus on here is multiple investigational drug studies. I think this is crucial. Again, I am not going to tell you how to do it because I don=t know how to do it, and I am not sure that anyone here understands how to do this but I think that a lot of people have a mind set that we can=t do it, that we cannot have multiple drug investigational studies because the model that was presented here in some of these slides was standard of care plus/minus the new drug. That is what we have been doing in HIV. So, PEG-interferon-ribavirin plus VX950 plus polymerase. What about combining these agents before they come to market? I understand the challenges involved, or at least some of them. One of them is toxicity if you combine two oral agents in Phase 2, and if there is toxicity whose drug gets blamed?

So, I don=t have the answers to these

questions but I think that it is extremely important that we consider this and try and design a new model to approach this, to take this one step beyond HIV. HIV has changed the paradigm in all diseases I think, and that is reflected by the fact that I am speaking to you today and we have people from the HIV community sitting on these panels. There probably was never anything like that before. Well, I challenge you to take this to the next level and deal with hepatitis C in a better way than we dealt with HIV. We made a lot of mistakes. I don=t want to criticize people but we made mistakes along the way in HIV. Let=s try not to make the same mistakes in hepatitis C.

I also want to mention drug resistance. Clearly, I think with hep. C protease inhibitors, until proven otherwise, and with polymerase inhibitors we are facing a challenge of drug resistance and how do we address that? Well, I think we need to really keep that in mind and when sponsors come to the FDA with drugs and when there are hearings for approval we need clearly defined

resistance and cross-resistance characterizations and we need data so that we can move ahead with that data and understand how to move ahead. I think that needs to be required.

[Slide]

I think we need to consider how we can accelerate animal and human safety and efficacy studies. Obviously, that is one of the issues. We need to do animal safety studies and human safety studies and efficacy studies before we can move ahead into larger clinical human studies. I think part of the problem in accelerating research and in doing multi-investigational drug studies and in getting these drugs out in a timely fashion, which is just as important, is how we can design these studies; what the FDA needs to require of companies in terms of data for animal and human studies, not cutting short the need to prove safety and efficacy. I want to make sure that we have that safety but I don=t want to be languishing in long processes that hold up the development and access to these drugs. Again, I don=t know the answers to

these questions, and these are also very challenging questions but it is for the FDA and the companies to try and figure out.

So, when can we start multiple investigational drug studies? Well, I suggest perhaps Phase 2b is not too early to start combining oral agents. I want to suggest that we have resistance assays and databases for resistance for the drugs for hepatitis C. That is something that we can improve upon from HIV, where we can start collecting resistance data now instead of databases.

I think the point has been suggested but I want to really hammer this home in terms of coinfection, that at this point I don=t think there is any doubt, with all the published studies and all the discussion, that today in HIV hepatitis C is the leading cause of death and hospitalization in HIV, except perhaps for AIDS, and it depends where. In certain cities in the United States, certain urban areas, you could make a case that the leading cause of death in HIV is hepatitis C. In a

recent article in The Annals of Internal Medicine they made that case, that hepatitis C is perhaps the leading cause of hospitalizations and death amongst people with AIDS in New York City. So, I make that point to make the case that we need safety and efficacy data in the coinfected population before a drug hits the market.

[Slide]

A little bit about study populations, it has been touched on regarding African Americans and Latinos. We are in the area now in HIV of pharmacogenetics and we know that there are some populations that may not respond as well or respond differently. Considering that and other issues, it is important to study African Americans and perhaps Latinos adequately early on to characterize the response to therapy. I mentioned a lot of this already and some of it has been discussed already.

As you know, hepatitis C I think is a little unusual, and coinfection even more so in the sense that the most affected populations tend to be marginalized communities. These are communities

that are marginalized in many ways, injection drug users which is the leading cause of infection today; substance abusers; alcohol users; people on methadone; poly-drug substance abusers. Certainly, amongst coinfected people these are the most prevalent populations. We need to consider that as we move ahead. I don=t have all the answers here today. I am just telling what I think we need to consider.

[Slide]

So, I think in terms of endpoints, as I mentioned, I think the endpoints will be different in coinfection. I like the slide that was presented by Dr. Vierling in terms of endpoints. I don=t know if we are going to cure everybody, but we can certainly have endpoints of improvement in terms of improved histology, in terms of biochemical endpoints and other endpoints of that nature, softer endpoints. I think in the coinfected population the endpoints may be different. It may be 12 weeks in mono-infection or 12 weeks in mono-infection; it may not be that in

coinfection. It could be but we need to study that before we come to market.

[Slide]

I want to mention durability a little bit. We know, I think we have a pretty good track record, as was mentioned already, that in mono-infection 24 weeks post treatment follow-up and the clinical experience, despite some controversy about reservoirs, the clinical experience is that those people can=t consider themselves cured. Well, we know that with PEG and ribavirin or interferon and ribavirin, but do we know that with all agents alone?

I know the goal is to move into multiple oral agent therapy over the years and maybe eliminate interferon or ribavirin, and that might happen but we are not there yet and we may not get there. We may need PEG interferon on board in light of considering what was said about the immune applicability of interferon and its effect. We may get there, we may not. We need to prove that we can do it without interferon and ribavirin. We

might, but we are not there and we won=t be there for a little while. But at some point we need to consider will oral agents alone get us to where interferon has taken us. And, we don=t know that yet. I know people would like to think that two or three oral agents alone will create a sustained response and a cure 10, 20 years down the line but how do we prove that? You can=t have Phase 3 for ten years. Well, I am not sure what the answer is to that but I want to raise that as a consideration.

I also want to mention that it is clear, I think, that biopsy is the gold standard for evaluating the stage of liver disease. So far, non-invasive tests have very limited utility-Bnot very limited but limited utility. The point is that I want to place emphasis on is that we need to realize that and maybe we can move forward with non-invasive tests but we are not there yet. Perhaps one of the things to study would be correlations between SVR, biopsy and non-invasive tests.

[Slide]

I just want to emphasize again resistance, the importance of characterizing resistance for the new drugs so that we don=t make mistakes; so that we understand because we will, I think, be looking forward to serial usage. There will be, we hope and we think, a number of protease inhibitors, a number of polymerase inhibitors and we need to characterize resistance and potential cross-resistance and understand that and talk about it so people in the community, patients and doctors, understand the risk that we face with resistance and cross-resistance. The mistake that was made in HIV was early on people jumping on a protease inhibitor and all the resistance that occurred to protease inhibitors as we came out of the chute with HIV. Now we are still paying for that with salvage therapy and with people dying because they ran out of options. Let=s keep that in mind. So, we need to characterize resistance and cross-resistance in hepatitis C drugs.

[Slide]

I guess what this slide says and what I mentioned is that in three, four years we may have a new standard of care, with it is VX950 plus PEG and ribavirin or maybe one of the other protease inhibitors in development, and there are no guarantees that any drug makes it to the market. We know that. But there could be a new standard of care. So, I think that we might have to meet in another couple of years to talk about, well, now how do we design studies from that point on.

I want to suggest 7-14-day monotherapy studies and consider the concern about resistance. It appears as though HCV protease inhibitors are more prone to resistance until proven otherwise than HIV protease inhibitors. So, I just want to raise the concern about doing monotherapy studies for too long a time. I know we have to establish efficacy but I just want to raise the concern that we also don=t want to make people resistant too soon or at all, or try and avoid it as much as possible.

[Slide]

In terms of follow-up, I think three years of SVR follow-up is adequate, and I am sort of shooting in the dark because, again, I don=t know what oral agents mean. I know from experience of 10, 20 years what PEG and ribavirin mean in terms of we have a track record.

I want to suggest that we need long-term cohorts. We need to follow people with hep. C and coinfection for years. We need to set up long-term cohorts to follow people to learn a lot about not just efficacy and safety but lots of things, like diabetes, like in coinfection, the metabolics, the effect on cholesterol, triglycerides and other things. We know that people who have coinfectionB-I have been saying this for years and there was the first poster I have seen on this at ICAC that people who had coinfection, their lipids remained lower. Well, my personal experience is my lipids weren=t too bad untilB-and this poster said the same thing and that is why I was saying it, that when people were cured with PEG and ribavirin the lipids shot through the roof. That is what

happened to me. My lipids were controlled and then my lipids shot through the roof. I think because my liver was now able to synthesize lipids they shot through the roof. That is just an example of the many things that need to be followed with long-term cohorts.

I want to suggest a hepatitis C study consortium. Years ago there was the ICC which was a collaboration of HIV drug companies that was a group that got together to share drugs and to talk about collaborating on study designs. I think we need a hep. C study consortium now that would be independent, not necessarily in the ACTG, not necessarily NIH, something independent that would be able to move quickly and that would have membership of the companies and researchers and community to design studies and try and figure out how we can do multi-investigational drug studies before drugs come to the market, and help set up rsistance databases.

[Slide]

I think that is pretty much everything I

have to say and I hope I haven=t spoken too long. Again, thank you for listening. Thank you.

DR. SHERMAN: Thank you. We will take a break. Let=s reconvene at 10:35. Thank you.

[Brief recess]

DR. SHERMAN: Let=s get started.

Summary of Industry Responses and Regulatory Perspective

DR. TAUBER: Good morning and welcome back. It is my task this morning to sort of form a segue to the discussions of the advisory committee.

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As you can see, the title of my talk is a summary of industry responses and regulatory perspective. It is actually a two-part title. The industry responses deserves some explanation. By way of explanation, in March of this year IND holders of clinical trial protocols for the treatment of chronic hepatitis C were contacted and questions were posed to them that basically resemble but are not identical to those that are placed before the board today.

Of those IND holders, 15 responded to our questions and their responses form the bulk of what I am going to be saying today. As you might expect, among that group there was congruity of some responses and disparity in other areas. It is one of my goals today to represent the majority opinion but also give voice, where possible, to all the voices that might have had other, differing opinions.

The second part, you notice, is regulatory perspective and I am going to use that like salt, somewhat judiciously. So, the bulk of what I have to say represents what the 15 respondents, the IND holders, submitted to the agency to the questions that were posed to them.

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Presentation outline: What you just heard was a preface, not the introduction, I am sorry. There is going to be an introduction. It will be short. I am going to go over consensus definitions, again, to assist interpretation of what I have to say. Then I would like to plunge

right into a summary of responses. As you can see, there are six main areas which have been previously brought to your attention. At the end of that part of the talk I will then quickly move to concluding remarks in which I am going to summarize what I believe to be the salient points of the feedback from the IND holders.

[Slide]

Here is the introduction. You have heard it before, 170 million, 200 million. Your assembly here indicates you acknowledge this is an important disease. The good news is the incident infection, as Dr. Birnkrant indicated, is decreasing. The bad news is those who are infected are aging. Their disease is progressing and the opportunity to see hepatocellular carcinoma, end-stage liver disease and cirrhosis is increasing.

Why is that? Well, we know that this disease has a long latency. We know that it has lack of spontaneous resolution, and we know that the population, as was shown earlier, has aged and is more likely to have the complications of chronic

hepatitis C infection, as was shown earlier. As has been said, but repetition is the mother of learning, chronic hepatitis C is already the most important common reason for liver transplant in this country so it is already important.

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Current standard care of treatment is, as everyone knows, interferon-based. If you have genotypes 1 and 4 you will receive 48 weeks. If you have genotypes 2 or 3 it will be 24 weeks. We know this therapy is expensive and we know this therapy has considerable safety issues attendant to it.

It is effective in 30-80 percent but clearly based on genotype and population characteristics, some of which we understand, some of which we do not. It is clear new treatment strategies are needed and the good news is they appear to be on their way.

[Slide]

This is my wall of benefactors. These are the 15 respondents who responded to the questions

that were posed to them.

[Slide]

What are the consensus definitions? You always have to start with definitions. Starting up, on the left upper corner, you can see what is chronic hepatitis C for the purposes of the definitions that we are going to be considering. Well, obviously you have to have evidence of ongoing liver damage and hepatitis C replication for greater than six months. I don=t think that is controversial.

Moving over, again to the top line, to what is compensated liver disease, I am going to be discussing what I am talking aboutB-all chronic hepatitis C patients, including those who have compensated cirrhosis. Well, what is compensated cirrhosis? Well, compensated cirrhosis are those patients who have cirrhosis but do not have evidence of consequences of liver disease such as ascites, encephalopathy or variceal bleeding, and also have normal synthetic function as demonstrated by albumins, bilirubins and prothrombins that are

in the normal range.

Lastly, the decompensated cirrhosis are those patients with cirrhosis who clearly don=t meet the specifications to the right.

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Our first question was regarding study populations, stage of disease, compensated versus decompensated. As has been said many times already this morning, decompensated is an area where the need seems to be quite great. Is that an area that should be initially studied?

Again, these are questions posed to the IND holders. What about the treatment-experienced versus treatment-naive? Which group should be in the cohort that is initially studied?

Genotype 1 or 4? Well, we know that for genotype 1 the standard of care has the lowest response rate. Perhaps we should focus on that. The IND holders were opposed to this question. Should we confine this to the hard to treat genotypes or look at the entire spectrum?

What about liver transplantation, both pre

and postoperative? Pediatrics? We know that pediatric patients usually are infected in terms of the maternal route; that generally they have milder disease. But that being said, severe disease does occur. Should they be part of the initial presentation?

I did not mean to skip over HIV and HBV. As you heard moments ago, HIV coinfection with HCV is a very devastating disease. HAART has been able to staunch HIV but hepatitis C is continuing to ravage the community. HBV is a bit of a separate issue. We know that hepatitis B is sensitive to interferons and it is possible that you treat people with hepatitis B/hepatitis C coinfection which, untreated, again, advances more rapidly. If you treat them together with interferon you have perhaps a better response.

Lastly, this has been touched on. I would like to spend just a moment on the racial and ethnic groups. As was demonstrated by Dr. Vierling=s talk, African Americans, even with the same genotype, appear to have lower response to

interferon-based treatments. Should they be a part since their options are fewer? We already have a standard of care. Should we be looking at them?

[Slide]

What was the response from the IND holders? Well, the IND holders were basically divided into two unequal camps. One camp identified that the ideal population would be the treatment-naive with early stage histologic changes, high baseline viral load, and genotype 1. Well, it just so happens that is the greatest population in the United States at this time. It is also the most homogeneous as far as we understand that and the current treatment response in this group is 40-50 percent.

The other camp said, well, the greatest need is in the treatment-experienced non-responders. They are the fastest growing group. They, on average, have more advanced histologic changes and they have a more urgent need. They did agree that the initial population should be compensated liver disease. They could

include cirrhosis; no co-factors, in other words no coinfection. The initial population should be adults only and all genotypes should be represented rather than focusing on genotype 1.

[Slide]

They did comment, however, on African Americans and Hispanics. They did want them as members of registrational trials in the general population, with the understanding that in the past at least these groups have been difficult to enroll and are often under-represented, leading to questions that need resolution at a different time. They suggested that perhaps investigator trials of Phase 4 post-marketing studies would be the way to further understand if there is disparate response, as has been seen in the interferon-based treatment.

[Slide]

Well, what about the post-approval period? This is where everyone else would be dealt with on average. In pediatrics there was some concept that access to promising agents in Phase 2 or 3 development might be a good way to go, but they

wanted to reserve pediatric study until the drug has already demonstrated efficacy in the other population. This is the group of the patient population that is historically difficult to enroll, as previously mentioned. This is where those patients that are coinfected with HIV or HBV and hepatitis C, this is where they would like to see them studied. Lastly, of course, the decompensated and those patients in the transplant period.

[Slide]

Another definition, we posed in our questions to the IND holders their opinions of the following definition of non-responders. Non-responders are obviously a very difficult group. It is a very heterogeneous group. We are looking for at least some agreement on what constituted a non-responder for enrollment.

As you can see, a non-responder would be that person who was previously treated with one or more interferon-containing regimens that included pegylated interferon and ribavirin. The same

patient would have failed to achieve a greater than or equal to two log reduction in HCV RNA at week 12 or were detectable beyond 24 weeks. Lastly and very importantly, compliance would be documented in these individuals, who are now called non-responders under this definition, that their compliance was documented in the first 12 weeks or previous therapy to confirm that they received at least 80 percent of the prescribed ribavirin and pegylated interferon.

[Slide]

The IND holders were in agreement with these definitions. Does that basically end the story? Well, of course, outcome. As was said earlier, the non-responder population is heterogeneous. I notice that Dr. Vierling=s groups are somewhat different than mine. I had differentiated them as the patients with no response, the true non-responders; the AASLD refers to these as the null responders. There are partial responders. There are relapsers. There are relapsers/rebounders. Again, these are all

definitional.

Is this anything other than a curiosity? No, it has some bearing. We do not know why these patients behave in this way. Does this represent a difference between these populations? Is it only confined to interferon? Will it also intrude into our development of new and novel agents? Will these patients behave differently? I certainly am aware that newer technology has indicated that perhaps even the relapsers, over 50 percent, are positive at the end of treatment. So, maybe it is not so mysterious. But even so, we have differential responses. What does that mean?

One of the charges to the committee is to provide on how do we handle this apparent heterogeneity among these populations. If they are going to be compared to interferon-based treatments as the comparator arm, that clearly will have an impact. We know that in relapsers a sustained virologic response is far more likely, 30, maybe 40 percent, where a non-responder, a true non-responder would be less than 10 percent likely

to achieve an SVR with retreatment with pegylated interferon and ribavirin. These are obviously issues that we really solicit your input on.

[Slide]

Moving on to controls, the IND holders held that for the treatment of naive compensated chronic hepatitis C patients the consensus was that the most appropriate control parenteral pegylated interferon and ribavirin for 24 or 48 weeks depending on genotype, in other words, the standard of care.

They did concur that placebo or deferred administration could be acceptable if crossover to active treatment was assured. They did feel that an acceptable delay duration, in other words using the new drug, could be as much for 4-12 weeks.

One of the themes that is going to emerge is the concern about viral resistance that has been brought up earlier and fear of monotherapy, and no parenteral placebo received any endorsement from the IND holders.

[Slide]

For the treatment-experienced the major difference was that they tolerated longer durations of placebo control and delay up to 24 months. Again, the reasoning here, as articulated by IND holders, was that the treatment-naive are essentially on their first shot at success and you should give them their best shot, whereas, patients that are treatment-experienced have already presumably seen treatment and their chances are somewhat different and a longer duration of placebo might be acceptable.

For both populations novel monotherapy would be acceptable for short periods, typically two weeks. There were someB-again, giving voice to the divergent viewpoints, there were some who felt that monotherapy with novel agents for longer periods than two weeks might be acceptable.

A few commented on patients with decompensated liver disease, but one brave soul did venture that placebo control or treatment delay might be acceptable.

[Slide]

What about endpoints? Again, I have differentiated this into compensated liver disease and I will speak to decompensated later. What I want to cover is primary endpoints for viral clearance goal, and to avoid the confusion, clearance in this instance I am using it as a surrogate for eradication but that needs an asterisk. As everyone knows, as technology marches on we become less and less certain that we have achieved total eradication even with an SVR. Primary endpoints, viral suppression goal for those instances where eradication or clearance is not possible and, lastly, I would like to talk to what the IND holders thought were reasonable secondary endpoints.

[Slide]

Well, the king of the show right now is the sustained virologic response, the SVR. It is defined variously actually, but is most commonly defined as HCV RNA undetectable, that being less than 100 copies or 50 IUs/mL 24 weeks after untreated follow-up.

It is a preferred endpoint for all populations. Everyone loved SVR. It is considered to be a surrogate for viral clearance. The definition of 24 weeks treatment duration becomes more problematic however. This is where the IND holders and the Division may have had some difference of opinion. The IND holders believe that once the patient stops treatment the clock starts and 24 weeks later you sample it and that is the SVR. For the agency that is a source of concern because then you have patients with differing regimen durations and you are having multiple endpoints that you are trying to compare. So, we would certainly value the input of the committee on this particular issue. When is the SVR appropriate to be measured?

What about the timing of the SVR measurement? As was said eaerlier, 98 percent, if they are going to relapse, they relapse within the 12 weeks. Maybe that is fine. Some IND holders said we can go to an SVR 12 rather than 24 but they hedged their bets by saying but we will confirm

that with an SVR 24. Well, that would give them an extra 12 weeks to change directions or proceed with protocols perhaps. But none of the IND holders, and there may be other opinions that I didn=t come across, felt completely confident that the SVR 12 was in and of itself the end of the sampling; we are done.

One of the important features, and this is another recurring theme, and the IND holders are in agreement on this, that the SVR currently is only based on interferon-based treatments. We do not know if we move away from interferon-based treatments what it means. We may need to re-prove that, that the SVR in non-interferon-based treatment has the same validity as the one that we currently feel comfortable with for the interferon based.

[Slide]

Moving on to primary endpoints, now you know about SVR, what is the primary endpoint for viral clearance goal? Well, SVR in both groups. I have differentiated these into treatment-naive and

treatment-experienced. In both cases all the IND holders said, gosh, if Santa would bring me an SVR, that is what I want! It is not always possible, however, obviously with the treatment-experienced. For the treatment-naive there were IND holders who suggested that perhaps, as was shown earlier, the RVR 4 could be, which is defined as an undetectableB-again, using the 50 IUs. I know there is technology that can take lower but the one that was used among the IND holders was the 100 or 50 IUs at 4 weeks. There were IND holders who suggested that perhaps we could make that a co-primary, that those patients who get both the RVR4 and the SVR would be the answer.

On the treatment-experienced side it was less definitive. SVR would be best. Early virologic response, and you have heard about having a negative predictive value in the treatment-naive, in the treatment-experienced it is recorded as being 100 percent. Again, these are interferon based. The SVR, the EVR, the RVR currently are all interferon-based tools. It should be remembered

and we have to be careful if we try to apply them. They may be applicable for non-interferon-based treatment but we do not yet know that.

There was one IND holder that I need to give voice to, that offered the EVR12 as a primary endpoint with a promise for a post-market commitment to prove that it was correct.

Lastly, I put that for novel agents the viral clearance may be slower. I think we have to be sensitive to that. Again, we do not yet know this disease well enough to predict if a novel agent is being employed in an interferon-free regimen whether or not the time points are as accurate. Perhaps an EVR12 is premature.

[Slide]

What about viral suppression? Well, the hypothesis here is that if you suppress the virusB-you can=t eradicate it but you suppress it, you still have the benefit of decreasing incidence of end-stage liver disease or cirrhosis and hepatocellular carcinoma.

The non-responder population with lack of

response or intolerance to interferon would be the most likely for this to be employed. In those cases, there were three endpoints that were offered, one being the histologic improvement, usually a 2 grade HAI stage change, the Knodell Ischak score. Biochemical improvement as in normalization with be considered for this group to indicate that your agents are working. Lastly, the analogy to HIV was brought up earlier, there were those who suggested that perhaps we should adopt that model that has been applied to HIV and viral suppresion of a certain degree would be considered to be a success. Nobody offered me a number though. Basically, it was Awouldn=t it be nice.@

[Slide]

Lastly, secondary endpoints for both treatment-naive and non-responders except as noted above, histologic and biochemical endpoints were considered appropriate for secondary endpoints. The reasons cited were lack of specificity and the penchant for sampling type issues with histology.

[Slide]

Moving on to decompensatedB-it is hard to keep repeating myself, but few IND holders wanted to talk too much about the decompensated liver disease pt. I think it is a mistake for us to believe that patients are going to march into doctors= offices with compensated liver disease and we will catch that before they get to be decompensated. This disease can be occult enough to present for the very first time with decompensated. We know that without transplantation, as was said earlier, there is five-year survival.

Where I am going now is mostly from the literature because, again, I didn=t have too much from IND holders to go on. So, what I gleaned from the literature as the primary goals were transplant avoidance; slowing of progression, improving hepatic function; reversing complications; and reduced need for transplantation. Well, that seems straightforward.

Secondary goals would be preparing the patient for the transplant that is inevitable. We

know that those patients who have HCV viremia at the time of transplantation, essentially 100 percent of those individuals will relapse in the transplanted liver. Reduction of the viral load, if not to undetectable levels but reducing it would also reduce the severity of post transplant liver disease.

[Slide]

So, why is there so much silence with decompensated liver disease? It is not spoken; it is silent. But the reason probably is that interferons are relatively contraindicated for the decompensated patient due to bone marrow risk and the worsening of liver function, causing lethal hepatic decompensation.

Where it has been attempted, SVR again is the favored primary endpoint. In one study at least, and I saw a study that commented on this study, saying, well, those were really mildly decompensated patients. So, at least in some soul=s attempts a 22 percent SVR rate was achieved. Interestingly, and possibly very importantly, of

those that did achieve SVR, none of those patients had resumption of HCV viremia, at least as of the publication. Even in the post transplant period SVR does seem to carry benefit. In another study, an SVR was achieved in 36 percent of patients and in those, the very same patients= rate of fibrosis progression decreased sharply with the achievement of an SVR, which the authors took to mean this is doing something. Other studies, however, obviously are not as favorable.

[Slide]

Well, if SVR can=t be achieved can we do something else? We do have some scoring systems that might be possibly used to develop endpoints for the decompensated. We already have the Child Turcotte Pugh and the model for end-stage liver disease, the MELD. These were developed to prioritize transplantation, but they basically speak to residual liver function. Could the reversal or improvement of residual liver function make a difference?

Well, we know that in the transplant

centers if you go from a Child Turcotte Pugh C to a B, for whatever reason, your transplant priority becomes less. So, the transplanters believe it. It has been used for chronic hepatitis B, and published in the literature from Hong Kong where chronic hepatitis B is a significant problem. We would consider improvements in the Child Turcotte Pugh or MELD score to be endpoints. However, no threshold values were offered. I know that Dr. Vierling offered 15 and if it could possibly be supported, substantiated, that would be a reasonable endpoint and we value that input.

One soul did suggest a composite endpoint, that being a serum HCV reduction of one log with histologic improvement. This was offered as a possibility without any literature support.

[Slide]

What about study design options? There are five and I am going to go over each one in turn. The first of these is a study design option adding an investigational agent to the standard of care.

Well, the IND holders were in general agreement that adding a third agent to pegylated interferon-ribavirin is the preferred clinical design for treatment-naive patients. Essentially, this is one of those areas where there was congruity.

Other suggestions included for the treatment-expreienced using the RVR for an EVR12 to prevent extended monotherapy. A great concern to the Division, and I believe to everyone here, is the development of viral resistance. I think we would be very concerned with extended periods of monotherapy. The RVR4 might be useful, using that just as a definition, but the EVR12 we would have to talk more about.

If the investigational agent is oral, an oral placebo is great. In fact, it works very well. Depending on the safety or efficacy characteristics of the novel agent, three ways of using it in addition to the standard of care were offered, one being that you essentially add it as agent number three and you treat for a course of

treatment and then you stop and see what you got. Another would be that you use the investigational agent for a fraction of the time and continue on the standard of care and, lastly, in a way very analogous to the way we use interferon-based treatments, you give the agents for a period of time and then you follow-up with off-treatment follow-up.

[Slide]

Moving on to use of a dose of pegylated interferon lower than the standard of care and/or a shorter duration, in other words, taking our interferon treatment and manipulating it, making it a little shorter, a little lower, perhaps reducing toxicity and adding an investigational agent to that.

[Slide]

Well, the consensus was, yes, okay. There wasn=t a lot of enthusiasm but they said okay, that would be possible but they were insistent that pivotal studies should include the standard of care comparator arms with and without the novel agent.

In other words, we are going back to adding a third agent to the standard of care.

[Slide]

What about ribavirin substitution? Well, I guess everyone was concerned among the respondents that ribavirin=s mechanism is not yet understood. We know that it appears to work but we don=t know exactly why. So, there was a bit of resistance essentially, at least as they articulated to me in written form, to substituting a different agent unless that agent already has demonstrated itself to be efficacious. If it has, if you have a novel agent that appears to have anti-HCV activity, then it potentially could be compared I a head-to-head competition with standard of care, and it might prove to be approvable as non-inferior or possibly by virtue of its improved toxicity or safety profile.

To test the additive or synergistic effects of a novel agent, administration as monotherapy was suggested up to 12 weeks. Again, this causes pause in the Division. Could we get

away with 12 weeks? Is it reasonable to expose a new agent that potentially the virus will figure its way around quickly? Do we do that? I think we would like your input.

[Slide]

Lastly, using two or more investigational agents.

[Slide]

Ideally, they should have differing mechanisms of action, therefore, different resistance patterns. Prior to combination studies, each novel agent would need to demonstrate antiviral activity over a specified period up to 14 days and, again, there were those who were optimistic and said longer could be done if resistance was satisfied.

Drug-to-drug interaction studies might be considered if the metabolism profile of the drugs suggests that an interaction might be potentially happening.

Novel investigational agents with two-plus novel agents with complementary mechanisms would be

considered important in the so-called difficult to treat chronic hepatitis C patient populations.

[Slide]

Who are these patients? The patient populations that are most likely to benefit from this approach, as has been said earlier, are the standard of care non-responders where multi-drug could be compared to retreatment standard of care or deferred treatment with a novel regimen to establish a placebo-like control period. Concurrent pegylated-interferon-ribavirin treatment period with an EVR12 was recommended to be incorporated into these studies to prove that you actually are dealing with a non-responder so that basically you have more interpretability of your results. Obviously, the decompensated liver patients might fall in this category, those for whom standard of care interferon-based treatment might not be recommended or might be contraindicated. To minimize safety concerns, an RVR4 could be used depending upon the viral kinetics of the products.

[Slide]

Lastly, monotherapyB-agreement for limited monotherapy treatments in clinical trials. The major concern is a high daily turnover of HCV RNA and low fidelity of the replicase and the development of resistance. This is a genuine concern articulated by the IND holders, and certainly one that concerns the Division. There was no support expressed for more than short duration of interferon monotherapy, except in those special populations as was mentioned earlier with end-stage renal disease.

[Slide]

What about long-term follow-up? Well, there was great confidence in the durability of SVR for interferon-based treatments. The literature is replete with articles that indicate that the SVR is, indeed, durable although, as technology marches on, we are finding bits and pieces of HCV hidden in areas we didn=t expect them, in other cells. But that being said, patients aren=t recurring. We aren=t seeing large viral load rebounds in these

patients years out. This is greater than 95 percent likely to be a valid endpoint. Whether or not it will translate out to less end-stage liver disease and hepatocellular carinomas is unproven but we are optimistic and so are the IND holders. There were some who said Ayou=re done; no follow-up. You don=t need to do anything more.@ Others said 5-10 year follow-up would be a good idea.

What about the non-interferon-based treatment? That is where the IND holders really felt that there should be ongoing-Blet=s validate this. Let=s follow these ALTs and these HCV RNAs for a period of three years at least, and if they start showing up positive we may change our minds. It was felt by the IND holders that those patients who are cirrhotic, transplant recipients, those who are coinfected, those with immune deficits should probably, just on the basis of intuition, be followed longer. We don=t have any data yet but it is possible that if anyone is going to have an SVR that isn=t as solid, it is going to be these folks.

[Slide]

What about long-term follow-up for patients who fail to achieve an SVR and who basically do not opt to continue treatment? The recommendation wasB-and this was sort of a clinical recomendationB-that these patients be seen twice a year for routine follow-up. For those situations where the patient elects long-term suppression, as there are studies out there looking at this, you should intermittently demonstrate that your treatment is doing something and you should probably see them every four to five years for that purpose.

[Slide]

Now I am moving to my concluding remarks. Inclusion candidates for initial IND approval, the IND holders say that they should be adults. They should have compensated liver disease. They can include cirrhotics. Minorities should participate but with the full knowledge that their participation may not be of sufficient breadth to answer all questions. All genotypes should be studied but no patients that are coinfected. The

treatment-naive have their advocates because they are the most homogeneous and, therefore, the data would be most interpretable. The treatment-experienced are more heterogeneous but, that being said, they are the fastest growing and probably have the greater need. Inclusion candidates post approval, basically everybody else.

From our perspective and the regulatory perspective, to write a label we need to have a representative population. So, it is important that a good sampling of the patients who will receive the drug be part of registrational trials.

[Slide]

The non-responder population needless to say is an important challenge. It is a substantial opportunity, however, for novel drugs or new treatments utilizing currently approved products. It is heterogeneous. The inclusion criteria that we offered was considered to be acceptable. But we would like to bring to the committee questions regarding the heterogeneity that we know of, the differential responses. How do you conduct a

clinical trial where you have relapsers and you have non-responders? Basically, how do we handle that and make it interpretable?

In terms of controls, the standard of care comparator is recommended wherever possible. Placebo or deferred treatment is possible with shorter durations for the treatment naive, again, the differential for the treatment naive being shorter.

[Slide]

The primary endpoint is SVR, SVR, SVR. But it also needs to be remembered that it is only validated for interferon-based treatments. The timing of the endpoint, there is some discussion. The IND holders want to say 24 weeks. As soon as the last shot of interferon is given, 24 weeks later is when you do your sampling. The agency would prefer to have a more uniform response.

EVR12 and RVR4 are great tools but their interferon=s tools and we don=t know whether interferon will share them. It is possible that they will be validated and that we can use them, or

perhaps there will be different tools developed with newer agents. Histologic and biochemical endpoints are useful as secondary endpoints, except in those instances where you have decided that viral suppression is your only option. Clinically meaningful levels of viral suppression and change in the CTP and MELD were not offered by the IND holders and we certainly would be very interested if you, as a committee, can help us with that. Can you help us to find clinically meaningful changes in MELD or viral load?

[Slide]

There is general agreement among the studying design options that adding a third agent to the standard of care treatment was preferred in the treatment naive. The RVR4 and the EVR12 may prevent prolonged monotherapy if you are treating the treatment experienced. Ribavirin substitution should be with an agent that has already demonstrated activity. Two or more novel agents, standard of care non-responders or contraindicated, that is, the IND holders saw the novel agents as in

the folks where interferon is not as likely to be successful but they, again, wanted to make certain that they were, indeed, interferon non-responders. Monotherapy limited time. If you are going to use interferon it should be in the special populations, otherwise there was no enthusiasm for interferon monotherapy.

[Slide]

Last slide, there is confidence in the SVR with interferon-based treatment. This confidence ranges between no further follow-up necessary to every five to ten years for those who are cautious. The SVR with novel agents is of unknown durability and retesting is recommended up to three years, perhaps longer. Special populations may need more frequent follow-up. For those patients who do not achieve an SVR, do not elect to receive further treatment at that time, follow-up twice a year was recommended. For those patients for whom long-term suppression was opted in those studies, they recommended that those patients should be monitored on a periodic basis, and suggested every four to

five years just to demonstrate that your drugs are providing benefit to the patients.

That concludes my talk this morning. Thank you very much for your attention.

Questions/Clarifications

DR. SHERMAN: Prior to the lunch break we have some time to begin to address the long list of questions that were brought up by the agency. But prior to doing that, I think that we should start, and we will see how long it takes, to give the members of the committee an opportunity to question the four speakers we have had this morning if there are elements that remain unclear or need clarification. So, we can start with that. A number of people came to me in the break and asked for some clarifications. So, they may be committee-wide and we should have an opportunity to discuss those. Anyone want to start? Dr. Alter?

DR. ALTER: Well, I think in order to address some of the questions, there is some information that might be helpful so that we are all on the same page. We are all familiar with

SVRs in naive-treated patients with genotypes 1, 2 and 3 for 24, 48 weeks with the current standard of care. But I don=t think we are all that familiar with the rates after retreatment, which would affect how we might discuss whether or not there should be a control arm, a placebo arm, what the standard of care should be when we are looking at new drugs either for retreatment or for naive patients. Also, perhaps some differences in the response and safety of current standard of care in more advanced liver disease since those are the patients most likely to have an immediate issue in terms of therapy. They are also the most difficult to treat and many times we can=t treat them with the current standard of care. So, those were some issues that came to mind.

DR. SHERMAN: Dr. Vierling, would you like to address the issue of response to retreatment in a non-responder?

DR. VIERLING: I think that we have heard and probably have embraced a consensus about the desirability of SVR if we look at it in terms of

viral clearance, as Dr. Tauber has said, that either the eradication of the virus or the compartmentalization where, under the immune control and the good health, it does not reemerge as an active disease state in the liver or elsewhere.

One issue there is clearly the stalking horse of our question, and that is if the virus remains present what biologically is the consequence? Can an RNA virus, the cytoplasmic site of replication, remain protected and dormant and reemerge at a later date? The data would suggest, in terms of the largest study, the one that we discussed and shown, that that might happen around two percent of the time, discounting the possibility that through risk factors and subsequent exposure and even reinfection. I think that is a difficult point.

So, one of the questions is, is there really a difference in SVR? If you take out a patient post treatment long enough and there is no detectability of viremia, using very sensitive

techniques, is there any chance really the virus has the capacity to have been altered by therapy and still be residual and living? So, I think that is an important question that we still don=t have an answer to.

You mentioned also the issue of the decompensated patients and how to look at the issues of safety and efficacy. I certainly don=t have a sense of an answer. If we did, we would all be trying to enjoy its use now and treat more patients with this serious condition. It is a population that I believe we have to strategize for and it is going to be different I believe than our strategy for individual agents that we are going to be talking about in terms of the study design. So, the immunologic is giong to be different and some of the inhibitors of polymerase and protease.

I would comment, however, that part of the endpoint analysis, and Dr. Tauber had mentioned this and I had the slide-Bwe can at least look with MELD scores which, remember, are only applicably fundamentally to our cirrhotic population.

Scientific registry of transplant recipients database analysis unequivocally showsB-we and others have published this-Bthat looking at survival for an additional year from a point in time and the benefit of being transplanted shows that transplantation has no survival benefit for a MELD score of 15 or less. Consequently, moving a MELD score to 15 or lower from a higher and, therefore, more at risk population in need of transplant, may be a valid endpoint for those reasons.

So, I have dodged most of the issues that you asked about, Miriam, because I don=t know the answer.

DR. ALTER: Actually, right, you didn=t answer. So, that was excellent as a politician!

[Laughter]

But I do think it would be helpful to actually talk about, if someone has some data that they could discuss, particularly perhaps unpublished data from some of the larger trials we know are going on, or whatever, assuming we are

using SVR, just for the moment, you know, that the person is virus negative for a defined period of time and that is what we are measuring, but in people who don=t respond or relapse which, as was pointed out, are different groups, what is the response to retreatment with the current standard of care? That was the first question.

DR. SEEF: Can I respond to that?

DR. SHERMAN: Yes, certainly.

DR. SEEF: Miriam set me up actually. I think people know that the NIDDK has been involved in a study which is still ongoing, the HALT-C trial, and the information from this trial has been published.

For those who don=t know, the HALT-C trial focused on individuals with significant fibrosis. They had to either have fibrosis or cirrhosis which was compensated. So, perhaps the downside with respect to the figures is that we are talking about one end of a spectrum. We are not talking about people who have minimal fibrosis. These are with significant fibrosis or compensated cirrhosis who

have been treated previously and had been non-responders.

To do the study we brought people in and we began the study about seven or eight years ago, at the time when pegylated interferon was not widely available. So, people who came in who had been treated in the past may have had either interferon, or interferon monotherapy, or interferon monotherapy with ribavirin but not pegylated interferon. Anyway, these people came and were treated if they had not received the ideal treatment. They were treated and the response rate, as published by the group, headed by Schiffman, was that there was am 18 percent overall response rate, 18 percent of people who had previously not responded to treatment now responded.

But when you look to see who these people were, it was largely people who had genotypes 2 and 3, people without cirrhosis. The fibrosis were better than the people with cirrhosis and individuals who had not received standard of care,

in other words, pegylated interferon. When the data were looked at, the individuals who had received standard of care, namely, pegylated interferon plus ribavirin, the response rate was six percent.

So, I think that what this study saysB-the study, of course, is ongoing now. Those who were non-responders eventually went into a long-term treatment trial for four years. They were given only interferon without ribavirin to answer some of the questions that have been raised here now, what in fact is the impact of treatment, long-term treatment on outcome even if the virus has not disappeared. Do we have, in fact, reduced progression? Have we reduced the likelihood of development of cancer? We can=t give you that answer yet. The study will complete early next year and at that point we will be able to look at that information.

But I think what we can say is that individuals who have had standard of care before, when retreated, have a very, very low likelihood,

in fact, of responding. This, in fact, then raises the issue of what kind of a control we have, whether we have a placebo or non-placebo control. I guess that is for discussion as we go on with this conference.

DR. SHERMAN: I think your second question was the issue of safety of interferon-based therapies in the decompensated patients.

DR. ALTER: People with more severe cirrhotics and how to evaluate that.

DR. SHERMAN: As Dr. Tauber said, safety is an issue because of marrow suppression and risk of actually worsening decompensation. The study that he referred to, I believe, was Greg Everson=s study where he used a low dose, accelerating dose regimen, with increasing doses over time. Those patients, unfortunately, though they met the criteria he defined in his study, were less sick than what many of us are seeing on a regular basis in the transplant setting. They did tolerate it, though dose reductions were often required and many patients were not able to complete a full course of

therapy. That has been kind of the experience in treating. Ray, you have been involved in these treatments as well.

DR. CHUNG: Yes, and the counterpoint to Everson=s article was, in fact, reports from Jeff Crippen and others where there was a high mortality rate associated with the use of PEG interferon or interferon-ribavirin based regimens in the more decompensated population. So, I suspect the state of decompensation really does matter here. So, minimally decompensated patients may be better candidates than the MEL greater than 15 that John was referring to.

DR. ALTER: Will different types of drugs, in other words, now we are looking at completely different types of drugs, nucleocide analogs, protease inhibitors, etc., would they have less of an adverse impact on individuals with more severe disease, or is there no reason to believe that?

DR. SHERMAN: I think that is certainly the hope and that is something that will be discussed further, but until tested it remains to be seen.

DR. SEEF: Could I just also add to this? That is, you are right, in Greg=s original study a number of these patients were cirrhotic but they were class A. They were CTPA. Just to let you know, and I think you probably do know, there is another study that is looking at this now. There is another trial that the NIDDK is running, called the A-2-ALL study. This is a comparison of living donor and deceased donor liver transplantation. Obviously, many of these people have got to this point because they have chronic hepatitis C.

So, as an ancillary study, as a part of this, we are trying to, in fact, do a trial of treatment again, with Greg actually leading the charge, to focus attention on these individuals who are destined presumably for liver transplantation with the usual hope, as you say, of perhaps reducing the likelihood that they will end up having a liver transplant; certainly reducing the likelihood that they will be reinfected subsequently. So, there is a study that is looking at it. But it is obviously not with these novel

treatments.

DR. SHERMAN: Dr. Vierling, any comments?

DR. VIERLING: I think with respect to the hope, only careful studies and analyses will tell us whether reduction in viral replication that might be forthcoming with a protease or a polymerase inhibition strategy, alone or combined, would have a salutary impact in this patient population or be free of side effects we don=t know. But we do know that when we introduced nucleocide/nucleotide analogs for the treatment of hepatitis B in advanced cirrhotics on the waiting list, we were gratigied to see that those patients responding to that therapy often did improve the status of their health and often actually were removed from the waiting list for more prolonged therapy. In the severely diseased population, largely decompensated patients but also some earlier cirrhotic stages treated by Liauw, and published in The New England Journal in 2004, he had a distinct benefit towards survival and even in that small cohort some indication that he might

have been retarding or preventing hepatocellular carcinoma.

So, I think that those give us the inference of what we might anticipate. The question is will the agents achieve that degree of termination of replication and will they be safe in doing so.

DR. MURRAY: If I could ask a question of Dr. Tauber really to set the stage maybe for future discussion, that is, do you have some insights or can you elucidate further the reluctance by IND holders to include children in earlier phases of study as opposed to waiting till post-marketing?

DR. TAUBER: Actually, I cannot. The nature of the data survey was basically to request response to questions. In most cases it simply was that this would not be a group that they would want to approach early. There was no justification as in we wouldn=t do it because of the following aspects of pediatrics that we would not trespass there. It really fell into the category of we acknowledge that these are important patients and

perhaps there are ways of dealing with them but we would see them after we have gotten our drug to market.

DR. SHERMAN: I have a question for Dr. Tauber as well. We are going to actually have a group discussion about this later, but as a point of clarification you made a comment that the agency would prefer a more uniform response time for evaluation following treatment, which presumably means that if you had two treatment arms, one 48 weeks and one 24 weeks and with a 24-week follow-up, you would prefer that the evaluation be made at 72 weeks for both groups, if my interpretation is correct. Can you comment on that?

DR. TAUBER: Your interpretation is correct. I don=t want to speak to the statistics all that deeply since it is a field somewhat foreign to me, but certainly for clarity of endpoints using the same endpoint for all treatment arms is preferred. We have had occasion to discuss this with sponsors that come in with this very

question and that is the response that we have given them. Sometimes compromises can be made where both the 24-week they prefer and the 72-week that we prefer are performed, but that is on an individual basis. But you are correct, we do actually prefer to have that rigor to the sampling.

DR. SHERMAN: Then, for purpose of discussion when we get to that point, I think you should be prepared to perhaps answer that in a little more detail in terms of the statistical issues because it is obviously an important issue and we need to understand exactly why that is. Dr. Havens?

DR. HAVENS: Could I have a follow-up on that same question for Dr. Tauber? In your excellent talk, which I appreciated, your introduction slide suggested that the current standard of care is interferon-based, that the duration was 48 weeks for 1 and 4 and 24 weeks for 2 and 3. It sounded like the agency was satisfied that the SVR endpoint measured 24 weeks after stopping was an appropriate endpoint. Now, if the

agency is satisfied with a 24-week endpoint after stopping for current standard of care, I share the misunderstanding about why the agency would want to change the endpoint in newer studies. I don=t know if we want to talk about that now but it is the same question. If you are happy with where we are now, why wouldn=t we continue to be happy later?

DR. SHERMAN: We will give the agency a chance to respond. Again, we have a whole discussion on this subject but, you know, for clarification if it wasn=t a straightforward answer I think that we should give you time to think about that response and discuss it.

DR. BIRNKRANT: The other point I can make now though is that that determination was made after clinical trials had been conducted for longer periods of time and we could go back and say, well, perhaps we only need to treat this group for this fixed period of time and then look 24 weeks later. So, up front it wasn=t designed that the 2 and 3 would be studied for shorter periods and followed for 24 weeks. That was after the fact.

DR. SHERMAN: Dr. Chung is next.

DR. CHUNG: I actually really wanted to echo Peter=s comments.

DR. ANDERSEN: Just to add one more, to consider the evaluation time for studies where you are staggering when you actually start treatment, when to start studies because those then have a differential endpoint time.

DR. SHERMAN: Dr. Haubrich?

DR. HAUBRICH: I would like to throw this out to anybody who would care to speculate with new agents, two issues. One is defining when is an SVR really an SVR given that particularly when there is no interferon-based regimen we have no idea. So, using our knowledge of viral dynamics or other things, how will we really know? That is question one.

The second is a little bit related. Given that this virus doesn=t integrate like HIV, is resistance forever? Is it a one-way street or is there possibly some washout period in the middle and then retreatment with the same agent that is

possibly going to be beneficial since the resistance may have disappeared with time?

DR. SHERMAN: Well, I think those are excellent questions and I am not sure that we have the answer to those particular questions at this point.

DR. CHUNG: But I suppose that is worth speculating on. I think with interferon-based regimens insofar as interferon is the backbone of that therapy, I suspect that the SVR, in traditional definitions of an SVR endpoint, ought to continue to hold, i.e., the 24 weeks after completion of therapy because adding on specific antiviral therapy is only add-on to an interferon-based regimen.

I think what you are really referring to are the specifics of solely antiviral-based regimens, the novel regimens of one or two or more agents. There, I have to wonder, based on your kinetic discussion earlier, Ken. You were talking about first phase declines with direct antivirals so you were talking about rapid declines in these

patients that we hope are sustained, but if sustained during the course of therapy, one would imagine that if one were going to relapse that relapse would occur extremely early in the sense that you are talking about a direct antiviral effect without immumomodulation per se. So, that virus is present in a replicating compartment and that should be evident immediately after completion of therapy that wasn=t sustained. So, I wonder whether the three years or some of the other durations that have been mentioned really isn=t so much of an over-call on the definition of SVR using these novel combinations of agents. I would expect that relapse actually occurs quite early.

DR. SHERMAN: I think that is true as well, though clearly one of the factors would be the half-life of these drugs, and we think that the small molecules typically will have fairly short half-lives. We know in the transplant setting that recurrence occurs in a new liver, and visible viremia in the blood very quickly. So, in addition to the current treatment models in transplant

settings without specific antiviral interferon-based therapy recurrence is often a matter of weeks and detectable viremia occurs. So, we would assume that that, combined with a short half-life, would lead to a similar presentation. Dr. Vierling?

DR. VIERLING: In the spirit of speculation, I think that the question you are asking is excellent and gets to the fundamental issue of whether you terminate therapy in order to enjoy and assess a sustained virologic response, or for some of these agents that deeply suppress replication, perhaps terminate replication, that you go with the concept of a sustained treatment for sustained remission of activity, virologic and immunologic.

I think Dr. Sherman=s analysis and those epsilon modeling figures inform us that if we want an SVR when only the agents solely terminate replication, that is fundamentally going to involve the heterogeneity of the half-life clearance of the infected hepatocyte mass that has residual and now

drug-suppressed virions, and that issue is two-fold, the half-life of normal hepatocytes, as well as the ongoing immune response of that population which may also vary in terms of disease state.

Ken, you had figures there that you might have to go out at the 600-700-day treatment to have some sense of confidence that in that circumstance you could have eliminated the potential that stopping of drug would allow re-emergence within a hepatocyte of a suppressed viral load. So, I think that it really is very fundamental to our discussion of whether we are going to be going for long-term suppression in such circumstance, and then maybe termination late when we infer that this has reduced and cleared all infected cells or not. It is a very different paradigm than what we have come to regard as 24- or 48-week regimens in interferon-based or combination interferon-based.

DR. SHERMAN: That is absolutely correct, and I think that that is another totally different approach to potentially an approval for viral

clearance for long term.

DR. CHUNG: I suppose the analogy there is hepatitis B where we are talking about long-term antiviral regimens that offer in some cases a clearance, or near clearance, but are clearly viable strategies for disease management as compared to sort of swinging from the fences with interferon in that very same population and the occasional very durable clearance achieved there.

DR. HAVENS: I want to switch to the other end of the discussion a little bit, the question of how long would monotherapy be safe at the beginning perhaps. The flip side of that is really for you, what is the shortest time that you could use monotherapy, with perhaps daily testing of virus load, to be able to sure that you had predicted the response at week 4 or 12? That might go to you.

The second part of that question would be would that allow an analysis of an exposure-response relationship that would be later meaningful, trying to move away from a dose-response relationship since we know that

weight, for example, is an important predictor of failure. And, this speaks to the issue of pediatrics where you can measure an AUC or a Cmin that would allow you to understand the drug exposure. So, the question is, is a week=s worth of daily data adequate to predict week 4 or 12 response? In that context, can you measure kinetics in a way that allows you to better understand the drug exposure-response relationship which would then allow you to inform pediatric use later when you just get the kinetics?

DR. SHERMAN: I don=t think that daily sampling would permit you to develop the kinds of differential equation-based models that we now have. In other words, you can use daily sampling to begin to develop an approximation of just a simple slope, which is not the same as developing these complex multi-phase decline models.

It is important to remember that the models don=t work in some patients. In some of the published literature using the differential equation-based models they threw out up to 40

percent of patients to show the patients it worked in because the model was not applicable, for various reasons, in the other patients. That is an important consideration if you are then going to translate that into a true treatment decision model.

The other thing is that while all of those time points or RVR, EVR, are based upon levels of viral decline, it makes sense that if you decline below a certain level you are more likely to develop an SVR, and if you don=t do that you are less likely to. But, beyond that, they don=t tell you who is going to develop an SVR. In other words, dropping your viral load is a necessary feature of eventually setting yourself up for SVR, but it is not the only feature available and simply clearing virus doesn=t mean you are going to have an SVR. The literature is replete with patients that drop down to undetectable and come back.

DR. HAVENS: But it would give you some sense of the potency of the drug for example.

DR. SHERMAN: Yes, in drug comparisons

early potency can be assessed with such modeling.

DR. HAVENS: So, then the question is can you do that by a week, or do you need two weeks or do you really need four?

DR. SHERMAN: Using the more complex models with frequent sampling, you can do it in as short as a week with a fairly high degree of confidence. The four-week is really just, again, an arbitrary cutoff that makes sense in a clinical setting; that it is reasonable to bring a patient back in a month which most clinicians do anyway, and develop some type of a decision tree based upon that. Dr. Fish?

DR. FISH: My question also relates to kind of minimal amount of therapy. Among virologic non-responders, do we know the minimal length of therapy with our current standard of care therapy required to confer benefit in terms of decreasing fibrosis or inflammation or decreasing the risk for hepatocellular carcinoma? And, might this then impact our secondary endpoint determinations and alter the algorithm instead of stopping treatment at 12 or 16 weeks when we get that viral load back

and continuing on in our trial designs?

DR. VIERLING: I am going to defer to the update of the data that Dr. Seef has from the HALT-C. There are three trials of maintenance of at-risk patients with advanced fibrosis stage 3 and 4. None of the data from these three trials is yet complete. The interim analysis showed a reduction in the portal venous hypertensive complication of variceal bleeding in the co-pilot study.

The issue of the long-term effect of prevention of stage 3 becoming stage 4, any remodeling of stage 4 or reduction in stage and the serious issue of hepatocellular carcinoma risk is still unknown. But these studies I think are powered and should be capable of giving us that answer, although I would say that it would be very desirable if we were able to persuade those in appropriations to extend the HALT-C study to truly be able to answer this important question.

DR. SHERMAN: Dr. Seef, do you want to comment?

DR. SEEF: The study terminated. The final

follow-up will be early next year, at which point we will be able to look at this information in detail. We have managed to extend it for an additional two years without treatment. So, the patients will be followed for an additional two years for outcome, with a particular interest, of course, in hepatocellular carcinoma. We have a number of ancillary studies looking at biomarkers, etc., to try to see whether we can predict hepatocellular carcinoma early. So, it will be extended for an additional two years, to 2009.

DR. SHERMAN: I think another way of responding to this is based upon the data we have from a series of studies in Japan. The question was what is the minimum time, and we don=t know the minimum time but we know that there are a few studies with 24 weeks and several more with 48 weeks or therapy in non-responders where, in cirrhotic patients, there was a reduction in risk of subsequently developing hepatocellular carcinoma. I am not aware of any benefit that has been shown for shorter 12-week therapy in terms of

those types of endpoints. Based upon the time that it takes inflammation to resolve following viral clearance, I suspect that there probably is little long-term benefit for shorter treatment periods. Dr. Andersen?

DR. ANDERSEN: To some extent, going back to questions about early drug discovery, the question is if you had data on the first 4- or 12-week kinetics and then added a new agent to standard of care in that setting and saw another bump down, would that be beneficial and is that information you can use?

DR. SHERMAN: That is a very good question. I am not aware that to date anyone has studied that type of sequential therapy. It raises some interesting possibilities because, clearly, once you know the decline curve, if you were able to impact that you might be able to make some very interesting predictions about what would happen after that, and perhaps starting with a lower viral load when you come in with an antiviral agent would significantly reduce the possibility for developing

mutations that are more likely to occur when viral replication is high. So, that is an approach that has apparently not been suggested to the agency through their responses from industry, but I think is something that is worthy of discussion as we go along here. Dr. Vierling?

DR. VIERLING: I think when you consider the modeling that could be done and what information can be derived or extrapolated, I believe it is important to keep in mind the analysis, very careful analysis of the half-lives of the drugs and the capacity that their half-life and/or effect may be changed as the infected hepatocytes may become less impacted by an inflammatory milieu over time. These early responses and termination and ultimately inflammation and the cytokine environment may influence these, especially those drugs that are already known to be metabolized by the hepatocyte. So, a return of health, if you will, of the hepatocyte may also impact subsequently on the adequacy of the dosing and duration of therapy.

DR. SHERMAN: That is an excellent point and we are adding layers of complexity to the answer the agency is looking for.

Well, it is twelve o=clock. We will reconvene here at one o=clock, at which time there will be an open public hearing. Several people have signed up for an opportunity to speak. Following that we will jump into the specific questions that the agency has posed to this committee. We will adjourn for lunch.

[Whereupon, at 12:00 noon, the proceedings were recessed for lunch, to reconvene at 1:05 p.m.]

A F T E R O O N P R O C E E D I N G S

Open Public Hearing

DR. SHERMAN: We are going to have an opportunity for an open public hearing. There is a statement that I am going to read that is required by law. Following this, there are two people who signed up for an opportunity to speak and we will

give them ten minutes each. Then, following that, if anyone else wants to make commentary, we are going to ask that they go to the desk outside and sign up. In the interest of time, we will be limiting them to a maximum of five minutes for any speaker, maybe less depending on the total number that register, but we will determine that after we see how many people wish to make commentary. Those people should actually go out now, after I read the statement.

The Food and Drug Administration and the public both believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of an individual=s presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is

likely to be impacted by the topic of this meeting. For example, the financial information may include a company=s or a group=s payment of your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

For the purpose of recording, we would also ask that you spell your name if you haven=t provided it in writing in the back. So, will those who are interested in making a public statement, please, now go to the back, in the hallway, and sign up for this? With that, I would like to call the speakers that have signed up. We are going to start with Dr. Janice Albrecht, and please state your affiliations and conflicts as well. Thank you.

DR. ALBRECHT: Mr. Chairman, ladies and

gentlemen, my name is Janice Albrecht. I am vice president of clinical research at Schering Plough Corporation. My focus is hepatology and, in fact, I have been head of the group at Schering Plough since we initiated the first trials with Intron-A for the treatment of chronic hepatitis C really in the mid 1980s.

There have been a number of discussions this morning about where we are in the treatment of chronic hepatitis C and I would just like to show you this slide because, as Dr. Sherman mentioned this morning, we have had quite a decade of progress. We have gone from not being able to treat this disease in the early >90s to depending on the strategies that we use with our patients to go as high as 50-60 percent in the genotype 1, the very difficult to treat patients.

I think we are entering a new era that is very exciting and I think we need to have two focuses when we look at that. One is can we achieve these response rates with less intolerance? These drugs are very poorly tolerated. I think we

all know that, but it is a serious disease and we are willing to, if you will, deal with the intolerance to get the kind of response we do. So, can we get these same responses with better tolerance or can we improve on our responses if we have to use interferon as the backbone?

I think this morning we talked about our primary goal being viral eradication with these new therapies and, certainly, I believe, and I think that most everyone else does, that we have to concentrate on this as our primary goal. We are not willing to go to suppression with these new drugs. We have to meet our criteria. I think we have shown with the interferon therapies that, indeed, we do have sustained loss of virus. In fact, we have done two very long-term studies of five to seven years in which 97-99 percent of our sustained responders at six months after treatment actually remain HCV RNA negative.

One of the things that would help us, if we could have the committee=s opinion, is we tend to lose patients over the years. For three years

we can probably hang onto about 80 percent of our patients but as we get to five and seven years these patients become tired of coming back. They know they are essentially cured, if you will. So, we would be interested in what constitutes valid data.

We believe that for the near future we are going to end up having interferon as the backbone of our new therapy when we add our proteases, our polymerases, simply because from the in vitro data in the Replicon system and early clinical trial data we tend to see resistance if we don=t have interferon there. However, I think we all have to focus on-Band this is another thing that would be very interesting to hear the committee=s opinion onB-is how are we going to get to our ultimate goal of an all oral therapy to eliminate interferon and its toxicity. That is our ultimate goal. I guess we need to understand when we are going to be able to move to that point, or what are the criteria for moving to that point.

A couple of words, as one of the companies

that is very much involved in this area, about how we feel what it would take to register one of these new products. We feel that there has to be in the dossier broad populations that have been characterized for safety, efficacy and predictors of response. We believe that for an initial regulatory approval at a minimum we need to have characterized both the treatment-naive and the treatment-experienced patients.

Having said that, we don=t feel that regulatory approval of promising therapy should be delayed pending definitive data for higher risk populations, and we talked about those populations this morning. However, again, we feel that from, if you will, the company=s point of view the plans for larger studies in these high risk populations have to be in place. When I say in place, I mean they have to be initiated and ongoing at the time of approval. So, we are taking, if you will, about a stepped approach to this but saying that the companies are committed to doing these studies and have got them going at the time of approval.

I think we talked a lot about the treatment-experienced patients this morning and we are particularly concerned about these patients. Obviously, our therapies that we have licensed have, in a sense, created these patients because half of the HCV 1 patients don=t respond. I think it was raised this morning and I think it will be very interesting if the committee can discuss with us how we define these non-responders.

Dr. Tauber mentioned how we define these non-responders, except I have one question that I would ask if the committee might consider. There is a pool of patients that are known as non-responders but we have very little information about them. We know they were treated. We know they are positive now. But that is all we know about them. We are doing some very large non-responder studies right now and we have had a very difficult time pedigreeing these patients. Investigators do the best they can to get the information about when they were treated, how they were treated, did they have their dose reduced, did

they stop early, but in many patients that is not available and it would be a shame to exclude these patients if we can find a way to subset them.

We also think that the committee could help us understand better when we stop the addition of single-agent new therapy in these non-responders. We think that in patients that have had suboptimal interferon-based therapy adding another single agent on may be a problem. So, we are going to need to monitor for resistance and the question is when do we call it quits in these patients and say that this is not a viable option.

Finally, I would like to say that Schering Plough does strongly support early initiation of clinical trials with multiple investigational agents. Probably we are going to need to use interferon as the backbone, but we certainly feel that one or more of these drugs that have different kinds of safety profiles or different kinds of mutational profiles could be combined in these treatment-experienced patients, which are certainly the greatest unmet medical need. Thank you very

much for this opportunity.

DR. SHERMAN: Thank you, Dr. Albrecht. The next speaker is Dr. Apelian.

DR. APELIAN: Thank you, Dr. Sherman, and good afternoon, everybody. By way of introduction and in the spirit of full disclosure, my name is David Apelian. I am the chief medical officer at GlobeImmune, an immune therapy company based outside of Boulder, Colorado.

We have ongoing programs in cancer and chronic viral disease with an active Ib study in chronic hepatitis C infection. Before joining GlobeImmune I served on the development teams for the Rebitrone sNDA for pediatric HCV, as well as the Baraclude NDA for chronic hepatitis B infection.

I would like to applaud the committee for these very constructive discussions today. It is clear by Dr. Sherman=s presentation about the viral dynamics that there is a basis by which we can start analyzing novel therapies. Dr. Vierling=s presentation of host and viral characteristics also

points the way to enable us to better predict which types of therapies might have impacts on certain endpoints. Clearly, Dr. Tauber=s summary indicates and illustrates the complexity of development issues we face today during these exciting times in hepatitis C development.

While I recognize that this committee=s focus is on the category of antiviral drugs, I do have some concerns about perhaps an unintended negative impact on novel therapies that utilize a different mechanism of action. Specifically, I am addressing the case of therapeutic vaccines which clearly will have different kinetics of response for various host and viral markers of disease.

It is instructive to look at the immune responses in patients who naturally are clearly exposed to infection and become chronically infected. In this case, this graphic illustration is of an ELI Spot immune test which shows the killer T-cell or cellular immune response that a patient can elicit in response to acute infection. As was mentioned earlier, about 20 percent of

patients that are acutely exposed can actually clear the infection without treatment. What we notice in these types of patients is that they have a robust magnitude of cellular response with a broad HCV epitope coverage, which is characteristic of patients that can actually clear infection without treatment.

What we observe in patients that are chronically infected is a stark difference in the immune response. The cellular responses are quite weak in amplitude and there is actually very narrow epitope coverage for hepatitis C specific peptides. So, we look at these data as an indication that if one can develop an immune therapy that can convert this weak immunologic cellular response to one that is the type of response that allows an acutely exposed patient to clear infection, this type of tool could be of therapeutic as well as prophylactic utility in the clinic.

In fact, we are aware of about seven other companies that are developing immune therapies with this goal in mind, to harness the cellular immune

system to enhance the ability of patients to respond to their ongoing infections either in the acute setting or in the established chronic disease setting.

We anticipate that the viral kinetics will be quite different for immune-based therapies compared to antiviral therapies. As Dr. Sherman pointed out very elegantly in his presentation, what has been observed in the setting of interferon-based treatment is a biphasic viral load curve when measurements in the serum are taken during the time course of therapy. When you consider the mechanism of action of the direct antivirals, they are going to inhibit the production of virus which then will reduce the release of free virus into the peripheral blood. So, it is not surprising to see this rapid and robust decline early in the course of treatment. This represents the rapid peripheral clearance of virus from the blood.

As he pointed out, there is this stubborn second phase of viral load clearance which

represents hepatic clearance, and this is really what we believe is the unmet need in hepatitis C treatment. If we can improve this rate of response the patients will more readily achieve SVR and potentially other long-term benefits.

In contrast, immune therapies likely impact disease by clearing infected hepatic cells. This has been shown in various models looking at antigen-specific targeting of in vitro or xenograft models of hepatitis C presenting tumors. What we believe will happen here is that we will see an enhancement of this stubborn second phase of viral load kinetics and, thereby, address an unmet need by the current armamentarium of treatments. And, if we can improve the slope of this hepatic clearance, we can perhaps shorten treatment, reduce doses of these antiviral agents, and perhaps make treatments more efficient.

For these reasons, we believe it is very important that a clear distinction be made by the committee between therapies that inhibit viral replication directly as opposed to the class of

immune therapies which act by mobilizing HCV-specific cellular immune responses. It would be of tremendous benefit to HCV drug developers if the findings and recommendations from this committee and future committees could be very clear about which drug classes are being addressed during those recommendations.

It is highly likely that the complementary mechanism of action of immune therapies and antiviral therapies will lead to near-term combination trials using these agents. So, you can understand that HCV drug developers would greatly value input by this committee on the types of endpoints and trial designs that might be more relevant for those types of mixed modality combinations. Guidance regarding which of the agency=s centers would be taking the lead role in those kinds of mixed modality approaches would also be greatly appreciated by the drug development community.

I would like to thank the committee for giving me some time to address some of these

high-level issues about immune therapy and why we think these distinctions will matter even for the antiviral drug development going forward. I am hopeful that the Division of Vaccines will also follow the lead of the Antiviral Division in setting up a similar committee to dig deeper into these complex issues surrounding immune-based therapies for chronic hepatitis C. I thank the esteemed committee for your time and attention.

DR. SHERMAN: There have been two individuals who signed up requesting time. We will start with Mr. Philip Anthony. Five minutes, please. He is affiliated with the Adult AIDS Clinical Trial Group.

MR. ANTHONY: Thank you, Dr. Sherman. As you said, my name is Philip Anthony and I am affiliated with the Adult AIDS Clinical Trials Group. I am a member of the community advisory board, having served as the past co-chair, and currently sit on the hepatitis committee with a number of colleagues.

I am one of those unfortunate people who

was tri-infected. I have been infected with hepatitis B for 22 years, HIV for 19 years and hep. C is relatively new for me, only about six years.

My points for the committee to consider are based on our conversation with the community in our arena and basically lie around the area of the study population. As noted earlier today, hepatitis C tends to be more rapidly progressive in patients with HIV infection, and end-stage liver disease has become an increasingly common cause of death in HIV-positive people. Once the HIV infection becomes advanced, complications become more difficult and response rates tend to be less.

So, in contradiction to what you heard earlier from the drug industry responses, that they would prefer to do co-infections later, we strongly advocate that the study of co-infections occur early, preferably to do it simultaneously with the mono-infection studies.

Additionally, we would advocate that we need to study early drug-to-drug interactions and to identify the efficiency of the product against

specific genotypes of the hepatitis virus, and to identify the demographics that carry that genotype and how it is affected.

In the real world a number of us have a number of different co-morbidity issues. When you study us, we feel that you need to realize that those issues impact how we survive and what we deal with and, therefore, you must recognize those issues when you study them. Specifically, I would mention diabetes, cardiovascular abnormalities and metabolic abnormalities.

We also advocate very strongly that you consider the inclusion of both genders so that it is recognized that women and men have different responses at different times to the drugs, and that must be taken into consideration.

One of the things that we have run across and you have recognized today, and we must continue to recognize, is that the study population must reflect a diverse ratio in ethnic group populations. Particularly, we are concerned about the inclusion of the African American black

population at the earliest stages possible.

One last point on the realistic inclusion criteria for this co-infected population is that we have to realize and deal with the real-world lifestyles of many of our co-infected peers. Therefore, the committee has to recognize that individuals with alcohol and drug abuse issues, individuals with mental health issues, and individuals lacking stable housing should be included in the study populations.

We have a number of concerns regarding the toxicity of the drugs being considered for development. Basically, we understand that most of these are to be tried with the current standard of care regime, which we understand but we would prefer to do away with because of the toxicity issues. It is very difficult with some of the current standards to continue productive employment when you can=t go to work because you are sick with the medicines that you are taking. So, we would advocate that you work very carefully to ensure that the new medicines under development are no

less effective and are better than what we have right now.

Monotherapy we have discussed a number of times this morning. Particularly, we do remain concerned about drug resistance. We have learned from HIV and from hepatitis that resistance develops and we need to avoid that. We do not want to continue to relearn that old lesson.

Finally, the committee has already addressed, and I think it is quite well aware of the issues surrounding non-responders and relapsed patients. And, I commend you for that work and recognition of that population, and ask that you continue to be aware of those in the future. Thank you. I appreciate the time.

DR. SHERMAN: Thank you. The next speaker is Dr. Karen Lindsay from University of Southern California.

DR. LINDSAY: Hi! I came here not really prepared to speak but the talks this morning were so outstanding and the clinical science so outstanding, I just wanted to make a couple of

comments.

As Ken mentioned, I am at the University of Southern California in academics and I have worked in the design and conduct of clinical trials in non-A/non-B and now hepatitis C since 1985, funded both by industry and by the NIH.

Just on the spur of the moment, I don=t feel confident that I could describe in detail all of my potential conflicts of interest so I will submit those in a document in the next couple of days.

I think that we are all assuming that interferon is going to remain part of the regimen of treatment with the new agents and that treatment failure, as Dr. Albrecht and the speakers this morning pointed out, at this point is the big gemischt of patients. It is a large group of patients and they are extraordinarily poorly characterized in terms of their initial response to whatever treatment they received, and whether or not they received adequate 80 percent dosing. Obviously, we can expect that if they had a flat,

no virologic response to interferon-based therapy, retreating them with interferon is not likely to be of benefit and we need to understand those patients and their response to retreatment separately from those who have had a partial virologic response or responded and relapsed. Then, of course, we have a great deal of lack of understanding of the mechanisms.

So, in order to deal with this issue I would like the committee to consider a couple of proposals. One of the most difficult things in clinical medicine in this area is treating a patient all the way to 48 weeks and then have them relapse. Obviously, these patients are at this point going to be part of the trials as controls. My suggestion is that efforts be made to try to identify those individuals early, individuals at risk for relapse and early relapsers, so that they can be pooled into a separate, distinct trial to evaluate longer duration therapy. There is a lot of evidence that that might be of benefit. That can be done, obviously, by using more sensitive

assays when they are on treatment and then testing, starting at weekly intervals, immediately following treatment.

As far as the flat and partial virologic responders, I really do think that it is important to include substudies in these patients, looking at issues such as interferon resistance because if interferon is going to remain part of the regimen and we don=t understand who is an interferon-resistant patient we will keep spinning our wheels and adding to this group of non-responders.

The other thing is that because these patients are so difficult to identify as well-characterized patients, and it is impossible to require that all retreated patients be well characterized, I think that the issue has to be addressed in the way of requiring that some subgroup of the population that is being retreated be well characterized, certainly not all of them.

The second issue that I just wanted to address was an issue that was raised this morning

in the presentation on the IND holders. I think we all agree that these non-responders, or more appropriately treatment failure patients, deserve extraordinarily high priority in terms of new regimens and alternatives. But the concept of the ideal patient is an excellent concept. There was a statement in there that these patients with lesser degrees of hepatic fibrosis are actually the majority of patients. I don=t think we have any evidence for that. The natural history studies that have been done have been in very well selected patients who are mainly participants in clinical trials, which we know are not the average patient.

This disease is a disease primarily of individuals who, because of the risk factor profile, are in lower socioeconomic groups. A high percentage of these patients are incarcerated. They are in publicly funded healthcare institutions. I work in one of those at the county hospital and the frequency of cirrhosis and more advanced fibrosis in our population is much, much higher than what is reported in the natural history

studies.

So, I really think that we have to consider placing this group, the patients with cirrhosis who are at risk for hepatic decompensation and liver transplant and liver cancer, in a special group and give them priority. Some of the questions that we don=t really understand about are that we know cirrhosis has, in general as a retrospectively analyzed factor, patients with more advanced hepatic fibrosis who have a lower likelihood of SVR. Or, is that because the drugs aren=t adequately reaching the liver? Is it because they have portal hypertension and impaired hepatic blood flow? I think that that is an important question that needs to be addressed in substudies.

Finally, I just want to quickly make a plea that again deals with some of the issues that others have mentioned. Today we are really kind of focusing on the addition of agents to interferon-based regimens. But a large percentage of our patients are really unable to start

interferon therapy because of projected side effects, co-morbidities, and so forth. I think that it is really important, and I know you are going to address endpoints for virologic suppression or for other histologic endpoints, inflammatory endpointsB-as John pointed out, there are a lot of potential targetsB-to improve hepatic histology in patients who are really unable to even start interferon-based therapy.

So, I think you have a huge task in front of you and I really appreciate the fact that you are working on this. I think it is a really important area for all of us who are interested in the treatment of this disease and certainly for the patients. Thank you.

Questions/Discussion

DR. SHERMAN: That concludes the public commentary section of this and we are now going to turn to the specific questions that are being asked of the committee and have discussion. We are going to start with which patient populations are strongly recommended for inclusion at the time of

initial approval. We are going to take this point by point for a series of questions or subgroups that need to be discussed. We would like input from as many members of the committee as possible so that we can see what you think. At the end of each of these I will try and summarize what the general feeling is. So, we are going to start with the issue of stage of disease, meaning compensated and decompensated cirrhosis. Again, the question is not whether studies should be done, but what patient population should be studied for inclusion at the time of initial approval of the agent so not, yes, we should do it some day. Anyone here want to begin to address this issue or should I call on someone? Tracy Swan, please.

MS. SWAN: I will be brave. I like Dr. Albrecht=s idea that studies should be launched prior to approval as a prerequisite for approval. I don=t see a population here where I don=t think that is a good idea unless there is a compelling safety reason that a drug is going to kill someone with decompensated cirrhosis.

The way I would reframe that question is how much do we need to know about a drug=s safety before it goes into a person with decompensated cirrhosis, and since I am not a medical expert I am not the person who is going to be able to answer that. Thank you.

DR. SHERMAN: Dr. Seef?

DR. SEEF: Before I express my opinion let me say that I discovered this morning that one of the IND holders that was contacted was the NIH. I had no idea that this was the case. I don=t know who it was, outside of Jay Hoofnagle I presume if it went to NIDDK, or it went to NIAID. But it certainly was not me. So, I would like to, first of all, say that whatever I say does not represent the NIH. I am not talking on behalf of the NIH; I am expressing my own personal views.

DR. SHERMAN: That is on the record.

[Laughter]

DR. SEEF: The second thing I would like to say before I get to my answers is that I am very pleased that Dr. Tauber spoke about response rates

ranging from 30-80 percent among genotypes 1. The reason I say that is, as you well know, somehow we keep on losing the fact that almost a third of the people in this country who are infected with hepatitis C are African Americans and, therefore, I think to talk about a 40-50 percent response rate does not speak to the issue. We know that in the studies that have been done African Americans do not respond as well. So, I think that should be stated up front. The response rate is somewhere between 30 and 80 percent, depending on race, depending on genotype. So, that is an issue.

So, who should first be treated? Clearly, we are talking about an aging population. We are talking about people who are moving further and further towards serious liver disease. So, I think that this is a serious issue that needs to be dealt with as quickly as possible and we need to get these drugs, if they are effective, out into the market as quickly as possible.

Obviously, as Tracy was saying, I suspect that everybody on this list deserves to be treated

if these things works. If they work, if there are fewer side effects and if there is no viral resistance, you know, we need to know more about all of these things before we can make an absolute, definite decision.

So, the question is who should be treated in order to get an answer as quickly as possible so we can get this out into the market and, if possible, move to second-string studies? My initial impression was that the group that really warrants treatment are the non-responders, true non-responders. That was my first thought. These are the people who are at highest risk of ending up with serious disease potentially imminently. So, I think we need to find that out and I honestly believe that we have to include African Americans in this.

Now, one of the questions that was asked was how do we overcome the barriers? Well, you know, it is not easy but it takes work and it can be done. I mean, the aim of the viral hep. C study was to compare treatment response in African

Americans versus whites and we ended up with approximately 200 people in each of these two strata so it was doable. If you have minority physicians it makes it easier and that can be helpful. But to say that we should exclude these people because it is difficult to get our hands on them I think, personally, is unconscionable. That is my view. I think we need to get African Americans involved just as much as we get whites involved.

This, of course, raises the issue about gender. Should we be doing the same thing with gender? Of course, that is possible. You should certainly get women as well as men. We need to get the group who are at risk.

So, I think that the first group that really needs to be treated are those people who are clearly non-responders to standard treatment and I would stratify them on the basis of histology, whether they have cirrhosis or not cirrhosis.

The easiest group would be the naive patients. Again, this is my own personal view;

this is not NIH. Naive would be the easiest to do. I think that while it is probable that we should include all genotypes, we really need to focus attention on genotypes 1 and presumably 4 because we don=t see much 4 in this country but this is going to be something that is going to be used throughout the world so I guess we need to think about genotype 4, which is said to have the same relatively poor responseB-not relatively poor or, I guess, it is the way you see it; it is not as good a response as genotypes 2 and 3.

DR. SHERMAN: Leonard, can I interrupt for one second?

DR. SEEF: Yes.

DR. SHERMAN: I am sorry, but I would really like to do this by the stage of disease. We are going to cover every single one of those issues--

DR. SEEF: All right. You are asking about compensated--

DR. SHERMAN: And decompensated.

DR. SEEF: I would not at this point, as

the first series of studies, involve people with decompensated liver disease. I think this is just too complicated at this point and I think we need to know whether these things are going to be effective in compensated patients. Excuse me.

DR. SHERMAN: That is okay. All of your points are excellent and are all going to come up in the next few minutes. But you would start with compensated patients with cirrhosis.

DR. SEEF: Yes, I would include patients with cirrhosis. Certainly, they need to be included and, while they respond less frequently, they are appropriate I think to be treated.

DR. SHERMAN: Dr. Vierling is next.

DR. VIERLING: I would agree that the stage of disease should be inclusive of necroinflammatory and all stages of compensated disease through cirrhosis. I think that that has been our standard and we know the responses. We know the management of the side effect potentials.

I disagree with respect to holding off on studies of decompensated individuals, and would

like to see the entertainment of selected studies done in patients who are decompensated and listed for transplantation in specific regions of the country where, were they to have deterioration due to the natural process of their disease or unforeseen SAEs, they would have the rescue potential of transplantation. The reason I say certain regions of the country is that we have a great disparity of what MELD score will attract an organ donation. So, if you are in the Southwest that might be a MELD score of 35-40. In other areas of the country it may be in the low 20s. Clearly, you wouldn=t want to set these studies where they are between 15 and 20. They would all be transplanted before you could complete the study.

But I do think that we have a way to protect the patient, to do the study and to have the evidence of potential benefit in those who are decompensated with respect to their synthetic function and, most importantly as Dr. Lindsay pointed out, have shunting phenomena due to the

hemodynamic consequences of portal hypertension. There is no way, short of studying them, to know whether we are advancing therapy that could be of benefit.

DR. SHERMAN: Dr. Alter?

DR. ALTER: Actually, I misunderstood because I thought we were dealing with the whole list so I will wait. Thank you.

DR. SHERMAN: Dr. Haubrich?

DR. HAUBRICH: I will make a general comment that would apply to all of these and then discuss this particular one. I think that we will probably get a variety of opinion on all of these but there is one thing I think we will agree on, and that is whatever we can do to get these drugs approved the quickest will provide access to the most people in the most timely fashion.

So, my bias in looking at any requirement for approval of a drug is going to be tempered by what is going to get the drug approved in the most efficient manner, the caveat being having enough safety data available so that when it is approved

people will use it in populations that may not have been studied yet, so we at least have some safety data.

With that in mind, for each of these categories I would like to see safety data or at least PK data to some extent. But if a particular category could actually hinder the development by introducing toxicity complications or others that have to delay studies of, say, a naive population that might be more easily accrued and developed, then I would probably take the strategy of setting the studies up but not necessarily requiring that they be done at the time of approval. So, from my limited vantage point, I would say the decompensated patient would be one that may be ready to go but not needed for approval.

DR. SHERMAN: Dr. Alter?

DR. ALTER: Yes, I changed my mind! Are we assuming there is going to be one-stop shopping, so to speak? Like, one formula is going to do it for everybody once we develop these new drugs? The only reason I say that is I am concerned that our

assumption is that, you know, we get the drugs to the marketB-I am just playing devil=s advocateB-we get the drugs to the market as soon as possible so that there is the greatest access for the most patients but, in fact, it is not appropriate for these groups. Yes, they are going to be licensed therapies and, therefore, physicians can use them as they choose and whoever they choose but, on the other hand, maybe they won=t be useful in that group of patients. I honestly don=t know what the forecast is and how generalizable these treatment regimens are going to be between these different patients. Certainly current therapies aren=t very generalizable.

DR. SHERMAN: Well, I think initial approvals can be very specific or very broad depending on the studies that support them. Dr. Havens?

DR. HAVENS: Thank you. Can I step back a little bit to ask what kind of studies you are asking about? Specifically, are these experimental drugs on top of standard of care,

interferon-ribavirin, in which case the answer might be a little bit different if you think that that therapy is dangerous in decompensated cirrhosis, or is there some flexibility in the type of study that you might apply to different patient populations?

DR. SHERMAN: Your opinion can include flexibility, if that is what you wish for. We are going to address what it will take for approval later, but the question is at the time of approval do you want to see data in compensated and decompensated cirrhotics, regardless of what that regimen is which doesn=t have to be the same for both of those states?

DR. HAVENS: Are you asking my opinion on this?

DR. SHERMAN: Yes.

DR. HAVENS: I will come back later.

DR. SHERMAN: That is why we are here!

DR. HAVENS: Well, partly it is hard for me to give an opinion without being able to conceptualize the study that you would be satisfied

with because if the study is more dangerous to do you would potentially go with sort of the Haubrich approach, which is to say, well, let=s do it in a safer population and then move ahead with what might potentially be a more dangerous population in as much as monotherapy with a drug that has a rapid development of resistance as an important deleterious side effect, then it is harder to see how to do a single-agent study in the decompensated cirrhosis patient. You would have to do it potentially on the backbone of standard of care. So, in that context, I suppose I would be saying compensated cirrhosis where the standard of care therapies would be approachable, but decompensated cirrhosis, being such an important population, would be good to do if you could design the appropriate studies.

DR. SHERMAN: Dr. Chung?

DR. CHUNG: I share certainly that the cirrhotic population, especially the compensated cirrhotic population must be addressed at the time of initial approval. This is the population

perhaps most at need among all the populations described here and, of course, overlap with many of the other groups that you have on this list.

I would like to see, as John mentioned, perhaps a limited sampling of decompensated cirrhosis in the setting of the transplant center where the patient perhaps has the safety net of transplant listing under them.

I suppose it is worth raising the point that may apply to other groups as well, and that is should a toxicity attributable or potentially attributable to the new compound arise in that high risk population, I think it is important for the agency to perhaps take a new stance on forgiveness, if you will, or a little bit of a leeway. I think this has probably been a pharmaceutical concern historically, for an adverse event to arise and essentially put the kibosh on their naive protocol or program. I think that has certainly been a concern in certain high risk treatment populations. I think we need to give some thought to the idea of being careful to create a little bit of leeway

on evaluating adverse events in high risk populations.

DR. SHERMAN: Yes, Dr. Birnkrant?

DR. BIRNKRANT: We are in agreement with Dr. Chung=s last statement. That is, if we did something in a more advanced population, obviously it would raise concerns for us but then we could take what we learned from that population and perhaps increase monitoring in a naive study. So, we wouldn=t necessarily halt development in a naive group.

DR. SHERMAN: Tracy?

MS. SWAN: This is just a more general point of clarity around the question. For me, the line between a completed phase III registration trial looking at the data and being studied is a little fuzzy. So, I am wondering if this question means the study has to be completed or the study has to be under way before approval.

DR. SHERMAN: I think we are gathering opinions at this stage. So, your thoughts on that are the most valuable element here rather than the

question that is up. What would you do?

MS. SWAN: There may be some populations where I feel there is a more logical sequence. I wouldn=t want to start an experimental therapy on someone who had decompensated cirrhosis, rather than someone with less liver disease, right off the bat. But I think having a study under way at the time of approval with some of these populations once we have collected more data in later phase trials seems like a more reasonable way to get the data we need without things being used in the clinic and people not having a clue about drug interactions or safety issues, and without a lag in post-marketing commitments.

DR. SHERMAN: Dr. Andersen?

DR. ANDERSEN: Basically, taking a middle point here might be asking for pilot data to be available in a number of these populations to avoid having something going into general use that is clearly dangerous in one of the populations, to separate it from having equal safety issues with some of the more easily treated populations.

One thing, as a statistician, to bring up is the difference between having a stratified study with some of these populations. You probably would not combine compensated and decompensated. With some of these others what we would be looking at is to separate studies that are stratified for purposes of balance in power from studies that have targeted population sizes so you can do substudy analyses with sufficient power to see something you want to see. I will stop there.

DR. SHERMAN: Dr. Alter?

DR. ALTER: I am walking on the other side of the street now. If you had a group of patients with decompensated cirrhosis who were going to die because they couldn=t get a liver, would you offer them an experimental therapy--obviously with appropriate informed consent, if there is such a thing--that could be potentially dangerous so they are going to die anyway? I mean, how did we do the first transplants? How did we do a lot of things that are actually life-saving? It is either that or death. You didn=t do heart transplants on

people who were less seriously ill, so to speak. So, you know, I have just been sitting here, thinking, well, you don=t want to have a safety issue but, on the other hand, is there a way to actually do such a study ethically? That is really, in my mind, the issue, the ethics. Other than feasibility, money and a variety of other things there are the ethics, the safety ethics. So, maybe they are the group that should be right up front. Now, there could be stages, like you can start with the therapy before, in fact, they were in the hospital waiting to see if they were going to get a donor. That might make a difference as well. So, it is justB-I don=t know, food for thought.

DR. BIRNKRANT: We do have means of making investigational therapies available to patients who desperately need them. So, if that were the situation, clearly they would be made available as long as the company agreed to provide it. If we received multiple requests for that type of population, at that point we would ask the company

to develop some sort of protocol to actually actively collect the data.

DR. ALTER: I know that you have a process, like, for orphan things. I understand. But in this case I am actually thinking prospectively, that you would actually have the study design to meet that need. How many people die every year waiting for a liver?

DR. SHERMAN: Thousands.

DR. ALTER: With hepatitis C?

DR. SHERMAN: Yes.

DR. ALTER: So, that is the group I am talking about and, therefore, you know, maybe in fact there is an ethical obligation to initiate a study up front on those individuals.

DR. BIRNKRANT: So, maybe we can divide things into categories. In other words, for the original marketing application or the initial marketing application what would we need included in the application versus what do we need to have ongoing at the time of approval? At the time of marketing application, in addition to the Phase III

studies, please tell us whether you would like to see these patients completing a pilot study or would you like to have the studies just ongoing at the time of approval. That would help us a little bit.

DR. SHERMAN: Dr. Fish was next. Do you have a comment, Dr. Fish?

DR. FISH: I was just going to say that I would agree with including the compensated cirrhosis, as I think most everyone does, and to the question just posed to Dr. Birnkrant, I would be satisfied for approval if they were at least ongoing. I think that would be an important piece and give us the confidence that we are going to get some information in this high risk population.

DR. SHERMAN: Dr. Vierling?

DR. VIERLING: I can certainly see room for compromise in ongoing studies as I advocated, but I would like to underscore what Miriam Alter has stated, that we do have list, in 1997, of 7,200 dead people, Americans, waiting for a transplant. It approaches 17,000 because of a variety of

issues. Maybe about 13,500 are actively listed. We are maxing out in the number of transplants we do and you, Dr. Sherman, showed us unequivocal data of the cohort effect of this aging population which is going to accelerate decompensation, the need for transplant, the burden of hepatocellular carcinoma and the cost. So, it is unavoidable that this population will be expanding were we not to succeed in our efforts for better therapy, and I think for that reason should be included early on.

With respect to those 10 percent on the waiting list who are dying currently without an organ or where it can=t be any longer offered, it would be I think reasonable to focus our sympathetic attention on them. But that is the group that is so far removed from all standards of medical care and the option for transplant that I would submit it is the worst group in which we want to study new therapies. Therefore, I would respectfully advocate if we do have pilot studies ongoing at the time of drug approval in naive- or experienced-treatment compensated patients that it

be those listed for transplant but to a lesser severity of decompensation to understand whether we can change the trajectory of their disease, not those that are near death.

DR. SHERMAN: Dr. Sun?

DR. SUN: I just wanted to play off the comment somebody made about the one size fits all because I find it a little difficult to generalize for a lot of these categories, although I understand the desire to do that. Ideally, the simplistic answer would be, yes, ideally we would like to see data on all these patients in randomized, controlled trials in very pristine, rigorous kinds of studies but I think there are tradeoffs.

Dr. Haubrich referred to one type of tradeoff which is time. I just think it has to be pretty individual. If you just take this first category and you say should we study new agents in decompensated cirrhosis and have that data available at the time of approval, I would submit that it really depends on the individual drug. You

could have drugs that are more or less potent and, therefore, have more or less potential to make a difference in that, understandably, desperate medical state. You could have drugs that have differences in hepatic metabolism which could make them more or less dangerous in a decompensated hepatic state.

I would say that for that particular situation I think it would be desirable to have the hepatic metabolism of all drugs characterized because it is likely that somebody will try to use them in that state, but I find it a little difficult to generalize on many, if not most, of these categories. So, maybe the better thing to do is to try to come to some articulation of principles to try to abide by.

DR. SHERMAN: Dr. Seef, you had a comment?

DR. SEEF: I am really struggling with this decision. It is not only the patient with decompensated liver disease who is waiting for a transplant but the other people who are at risk, such as the HIV/HCV, where we would want to do

something quickly because these are the people who are at risk of progressing to death or whatever.

The question is will this in any way hold up getting the information we need if we did this on people who are more likely to respond and to get the answer? I actually liked, if I understood what Jan Albrecht said which is to say stop the studies and at the same time make an absolute commitment that all the other groups that need to be studied have studies in processB-is that correct, Jan?

So, I do agree that we need to have this information from all the groups, decompensated and not decompensated. To me, the question is how quickly can we get information about effectiveness, viral resistance, etc., so that we can get this out to a large number of people who need to be treated soon? I don=t have the experience of John Vierling or perhaps Ray Chung about actually treating people pre transplant, other than the studies that the NIH is doing but I am not particularly involved with that, but I understand, with Trial C, that it is terribly difficult to treat them. Since we are

suggesting that they can continue to be treated with interferon-based drugs in addition to whatever the new molecule is, it is a problem. It is very difficult. It is complicated. It is hard to do. You often have to use drug factors in addition and it may hold things up.

So, while I think it has to be done, and I think there has to be a commitment to do it, the question is what are the priorities? And, my sense at the momentB-and, of course, if I had someone who was waiting for a liver transplant, I mean, might I have a different view about this. I don=t know. But I think that we want to get these drugs when they are effective as soon as possible and, at the same time, commit ourselves to all the others that are very, very important such as the co-infection group, such as the pre transplant or even post transplant group, etc., etc.

DR. SHERMAN: Dr. Havens?

DR. HAVENS: One approach is to do the large registrational trial in the group in which it is easiest to do it, where you are likely to have

the fewest side effects, and to do smallerB-the term here was pilot--studies of kinetics, especially in the cirrhotics, and toxicities in patients with more advanced disease so you would have some feel for at least the PK and perhaps special toxicities that would occur in those groups, which might act to bring the drug out most quickly because the registrational trials had been done in large groups that were going to be straightforward and other people would have at least a feeling for how to treat them because they would understand the PK and potentially the pharmacodynamics if those studies were done initially.

DR. SEEF: I think you paraphrased me better than I can do it. This is what one of my thoughts is. I think that there is the possibility of compassionate use in those people who are waiting transplantation, for example, for whom there is no liver. And, why we may not learn a great deal from it, that is what has been traditionally the fact in cancer studies for

example.

DR. HAVENS: Right, but the problem is compassionate use is a mistake if you are using the drug at the wrong dose--

DR. SEEF: No, no, I grant you. I was just hearing about the fact that there are peopleB-I mean, Miriam raised the issue of how about people who are waiting for liver and they don=t have a liver? There is no donor, and they are at the end of their disease. What do we do about that? Should they be, in fact, part of the people who are being treated initially? I am reluctant. I am reluctant at this point.

DR. HAVENS: It would be hard to include them in a registrational trial, but it is important to get information. Their drugs kinetics are dramatically different and their toxicities are--

DR. SEEF: I agree with you completely, absolutely.

DR. SHERMAN: Dr. Vierling?

DR. VIERLING: I think your comments, Leonard, crystalize something in my mind, and I may

have made an assumption incorrectly. The assumption I think you were addressing is whether or not to include the decompensated patients as part of registration would, and I think you used the words Ahold things up@ or make it more difficult as if it was one trial just extending into the decompensated arena. I think the decompensated arena is a separate trial. I would not think that its duration or even its outcome should have a dramatic impact on the trial design in the compensated individuals, including the cirrhotics that we are all trying to say would be the fastest way for an accelerated discovery of safety and efficacy and ultimate approval.

I don=t see these things as being incompatible. I do believe that you would want a lead time to understand pharmacokinetics and dynamics, toxicities and drug interactions before you took on the challenge of this population, but to have it ongoing, to my mind, would not adversely impact the original trial that could add an element of acceleration for this very important group that

is enlarging.

So, maybe I had it wrong that I was being constrained to saying just broaden the trial design and add the decompensated groups. I would not do that. I would have decompensation only in transplant centers, only with certain MELD scores, only in regions where transplantation can virtually be guaranteed by organ access in a very separately designed study, but to do it near as concurrently as possible after safety issues are identified in a larger trial.

DR. SHERMAN: Dr. Havens?

DR. HAVENS: So, if the question we are being asked to answer is at the time of initial approval, then it sounds like there is some agreement that we are not really saying that decompensated cirrhosis needs to be included in the groups that would be studied completely at the time of initial approval but, rather, you would expect a registrational study in a target population that was easy to get basic information on, perhaps with PK and safety data, in smaller groups of the

special populations, for example decompensated cirrhotics.

Now, the question would be are we satisfied with what Dr. Haubrich suggested and what we heard from before that people are planning to do this? So, give me the FDA approval and I promise. Or, are we going to require that the smaller studies are done before the FDA says it is okay? That is a critical issue because there aren=t a lot of real teeth in the post registration, post approval and a post approval promise is dramatically different than requiring PK and safety before the initial approval. So, I would ask which of those are we talking about. I think we got some consensus.

DR. SHERMAN: Well, I would ask which would you vote for, which one would you support?

DR. HAVENS: Well, Dr. Haubrich has his hand up but I will come back.

DR. HAUBRICH: Let me clarify my point and say exactly what I would feel comfortable with, and that is having at least pilot data in certain of

the categories. So, what that pilot data is, of course, is probably a whole another two-day session. But for the sake of argument at least, let me throw out that that could be something like a PK/PD study with four-week data to show that you have dynamics that would indicate in the registrational trials that you would be likely to have a sustained response. So, if you have as a subset in the registrational trials dynamics studies and then have pilot data in these groups, meaning data not just promise; I would like to see data not just a promise of PK studies.

For the HIV population that means having a whole lot of data on pharmacokinetics if the drugs appear to be metabolized in the 3A4 cytochrome system. So, I would like to have that data in hand, not enough data to show full approval for that group but at least data to show that it looks like it is going to work and you understand the pharmacokinetics and drug interactions at the time of approval.

DR. SHERMAN: Dr. Vierling, do you have

something to add?

DR. VIERLING: Well, my preference would be to see the initiation of a large-scale study in compensated liver disease and information derived in terms of the safety and the kinetics, and soon thereafter initiate a decompensated liver disease study as I was advocating. The design would obviously be the subject of great debate.

When we talk about post approval, assuming that even if things are superb with respect to safety and efficacy and they are fast track, that approval process is a long process. As I say, there are going to be 1,700 deaths on the waiting list this year. As the waiting list grows, and it will grow, it has been growing, we will see about 10 percent, maybe up to 12 percent deaths on the waiting list, especially if it gets completely unbalanced with respect to our ability to transplant. So, I think there is a time urgency here that is of public concern to our healthcare system and the reliance on transplantation for the decompensated individuals infected with hepatitis

C. They are the largest indication and I believe strongly that we should consider moving forward in a deliberate way soon after we have the original data so that the time frame to understand its impact and to apply it and, hopefully, the safe and efficacious evidence of its usefulness will be shortened.

DR. SHERMAN: Dr. Andersen?

DR. ANDERSEN: In a way, it was just one phrase from Richard, which was that the pilot data and the special populations need to show some signs of efficacy. I would like to bring up that it might be that the pilot shows that it is not safe in a specific population or not efficacious. It might be that there is a genotype in which it would work and a genotype in which it would not. The pilot data would guide future studies but might not have to be positive in order to be part of a successful registration.

DR. SHERMAN: Yes?

DR. MUNK: Yes, I think we are veering off the one-by-one discussion of these points, but it

seems to me this is putting a burden on FDA to characterize what is the necessary content of these pilot studies for each of these special populations. In HIV we would have to have interaction data through the CYP 3A4 enzyme family before we would know if it is even worth applying the drug in that population. Liver disease I think is the second largest cause of death in people with HIV after HIV disease. As Jules Levin commented, once it is approved it is going to be out there and I share the skepticism about Phase IV commitments.

So, I think the idea of these pilot studies is, if we can characterize them population by population, what do we need to know so that we don=t unduly delay the overall approval of the drug is very important.

DR. SHERMAN: Dr. Seef?

DR. SEEF: I think we are all coming to the same conclusion that there has to be somehow an absolute commitment that the more serious kind of disease that we are dealing withB-if we are concerned in the post-marketing period that people

do not do these studies--I think we have to do something about it ahead of time. If we were going to use these and completely get rid of interferon, which is a terrible drug to have to take, with all due respectB-it works and I think it is an absolutely marvelous thing because here is one of the few viruses that can be treated and cured so I think it has been terrific but it is not pleasant to takeB-if we get to the point that this is an infectious disease and we get rid of the infection in a 100 percent of instances, then the whole thing is moot. We don=t have to worry about this. I mean, we are still dealing with the fact that this is a liver disease and this is what we have to deal with.

You know, to increase the response rate in genotype 1 in people who are compensated and have minimal fibrosis from 50-70 percent is terrific. But more important are the people who are seriously ill who are likely to die fairly soon from this disease, the HIV co-infected people, the people who are waiting for transplants because they have

decompensated liver disease. So, in my mind, there has to be an absolute commitment that that is part of the process, but I would like to see us getting to the point where we see that this thing works and, at the same time, have all these other studies either in process or at least clearly planned.

DR. SHERMAN: I would like to summarize where the committee stands and phrase it as a recommendation and then there can be additional commentary if needed.

I think that the committee=s consensus is that patients with compensated cirrhosis should be included in the original primary registration trials; that patients with decompensated cirrhosis represent a high risk population that, if effective treatments are available, in fact, needs to get this treatment the most but that there are concerns about safety and that it is important, probably at the Phase IIb to early Phase III development, to initiate trials and not wait until Phase IV. There should be, in fact, a strong recommendation or requirement that such trials be initiated to begin

to look at drug metabolism in patients with decompensated disease; to look at early safety studies, other drug interaction issues in addition to the primary drug metabolism; and that those early studies can begin to assess treatment outcomes, though not necessarily those that would lead to a specific indication but, in fact, those studies should be started and ongoing in this population at the time of approval. Fair enough?

The next question is treatment-experience, naive and interferon-ribavirin experienced patients. So, here we are dealing with should the initial approval be based on naive alone, interferon-ribavirin experienced alone, or both populations at the time of consideration for registration. Comments? Dr. Seef, I am going to pick on you because you look thoughtful.

DR. SEEF: Why don=t you start with Ray Chung for a change?

DR. CHUNG: I think we have just heard, both this morning and in discussion this afternoon, that while the naive treatment population is an

easily identifiable one and in many ways a neat treatment population, I think those who are at greater need include the treatment-experienced group that are the interferon-ribavirin or PEG-interferon-ribavirin experienced patients. So, I do believe that we should have data regarding both naive and treatment-experienced populations at the time of initial approval.

DR. SHERMAN: Tracy?

MS. SWAN: I would advocate for both, and I know pricing isn=t within this group=s purview but it is a huge concern in the community. Insurance coverage is changing. Publicly funded coverage is changing. And, the indication is going to make a huge difference in what gets paid for. So, the more broadly the population groups the drug is indicated for and well researched in, the more drug is going to be sold and it just makes sense to do both.

DR. SHERMAN: I want to make a comment here because one of the issues that we really haven=t discussed yet, and there will be discussions later,

is about issues of mutation but it is relevant here and I just want to raise the thought that when we deal with a true interferon-ribavirin non-responder population, and if the plan is to add another agent to this very important group, we may in fact be dealing with something that is akin to single-agent therapy, and the risk of mutational emergence is likely to be much higher in this group than treatment naive and that should be part of the thoughts when discussing what should be approved or what is required for the initial approval. Dr. Chung?

DR. CHUNG: Perhaps it is worth clarifying the experienced population or grouping the experienced population among the response categories we talked about earlier. That would be the so-called non-responder group versus perhaps the partial responder and the responder relapser. For the sake of just simplifying the argument, I would put non-responders in a very distinct group because they are the group that we are the most concerned about, the group for whom this kind of

treatment is going to appear, for all the world, like monotherapy of these agents because if we are talking about perhaps three to four log reductions we are reducing them to 102, 103 and increasing the risk for resistance, as you just suggested.

I think we are going to have to define virologic endpoints from a resistance standpoint in that population and study that population distinctly. The challenge is obviously going to be defining these groups. As Dr. Albrecht said earlier, finding these patients who are well pedigreed, well characterized from the previous experience is going to be a very important challenge facing us, but I think they should be divided based on their pattern of response.

DR. SHERMAN: So, treatment-experienced doesn=t necessarily mean just well pedigreed non-responder, clarifying what you said.

DR. CHUNG: No, no, I would advocate that we should look at non-responders. We should look at partial responders but they should be done distinctly.

DR. SHERMAN: As separate populations. Dr. Seef?

DR. SEEF: First of all, I agree with you that both populations, the non-responder population and the naive population, should be part of the registration trial. I agree with you completely that there is a real distinction between those who are clear-cut non-responders who had been treated 80-80-80 previously and had not responded from those who relapsed, in which the response rate and retreatment is much better, and those even, I guess, who have a reduction rather than a total loss of virus.

So, I do agree with you that somehow or other they have to be stratified and I agree it may be difficult to identify those populations. There are some studies, of course, where these may have been done already. But I do agree with you that they need to be separated into the three groups.

I had another point and I have forgotten what it is. I will remember again tonight and I will call you at 3:00 in the morning.

[Laughter]

DR. SHERMAN: We will let Dr. Haubrich jump in next.

DR. HAUBRICH: I agree that looking at both experienced and naive patients makes a lot of sense. Depending on the endpoint in the population, obviously, it might actually be easier to show superiority in a group where you have a very low response rate as opposed to a group where you have an expected 50 percent response rate just from simple power calculations.

I think that in looking at the different groups, particularly the null responders, we have to think very carefully. They may actually require a different endpoint because the likelihood is, as we have all suggested, that the single-agent therapy of getting them to undetectable and sustained response is probably pretty low. On the other hand, if they have a significant log reduction for some period of time, that might be meaningful. So, endpoints for certain experienced populations may need to be different.

I think we can take an analogy from HIV where there are certain drugs that took a really long time to get approved until they were paired with other drugs. I think the first ones out of the gate here are clearly not going to be paired with other novel agents. So, in the null responder, experienced-patient group we may have to think hard about having a different endpoint.

DR. SHERMAN: Dr. Andersen?

DR. ANDERSEN: Well, a different endpoint and possibly even a different design. If you have somebody who is a complete true non-responder do you really need a randomized study and, if so, randomized with what? A single-arm study may be appropriate for registration in that population and others.

DR. SHERMAN: Dr. Seef?

DR. SEEF: That was the thing that I had forgotten and it is a point that you made, that people who are true non-responders, null responders, if treated with one drug you are facing the possibility of viral resistance. Although I

know we haven=t got there, before you slap me on the wrist, Ken, I think this may be a point for perhaps combination therapy, combination molecules to do something about restricting the possibility of viral resistance. So, I do agree that this may be different from the group that are either relapsers or the naive people who have never been treated before.

DR. SHERMAN: Tracy Swan?

MS. SWAN: Without being overly specific, I think we are also really going to have to look at this question in people who are co-infected with HIV. With response rates and genotype 1 from 14-29 percent there are going to be a lot more co-infected non-responders. Also from the HIV treatment paradigm, null responders seem like the perfect population if you can=t pedigree somebody. If you do a short lead-in, if RVR gets validated, that would be great with standard of care and then add two drugs rather than just one so you are not subjecting someone to monotherapy and putting them at risk for resistance. I think it would be a lot

easier to enroll those trials as well if you have more to offer people.

DR. SHERMAN: Dr. Havens?

DR. HAVENS: This goes back to the initial discussion about what kind of study you might be suggesting in each kind of patient group. Again, in the first group we talked about the major risk of toxicity was perhaps direct drug toxicity. Here, the major risk of toxicity is development of resistance. When you look at resistance as a potential toxicity for five years from now when you can=t use these drugs when there are three small molecule drugs that could be used together, then the ethics of doing the study in a treatment-experienced patient actually are terribly problematic.

In patients with HIV we have seen that the early participants in studies can=t use later drugs and that is an issue when we learn how to use them better. So, if we are early in phases of drug developments perhaps these groups are not yet ready for inclusion at the time of initial approval but,

rather, would be best studied later after we proved in a group of standard of care plus the new molecule that the drug really worked. We need to be careful to not be driven by our own clinical desires to treat people we are faced with now and, thereby, set the bar too high so that the drugs don=t make it in a reasonable time frame to market.

DR. SHERMAN: Dr. Chung?

DR. CHUNG: I understand your point, Peter. But I think that from the standpoint of viewing this as analogous to the HIV model may be a little bit perhaps a leap of faith or too much of an assumption. I think that the exposure to a single agent and the selection of a preexisting quasispecies that might be resistant to that particular agent may or may not have deleterious consequences for that patient downstream. It is important to realize that this is a virus that can, in fact, be cleared and has, at least for many of these treatment populations, a fairly extended natural history time frame.

So, I think, you know, before we hesitate

in treating a group at need, that is, non-responders, we can plan short-term studies to look at viral kinetic responses and define our negative endpoints correspondingly. But to stage it and delay initiation of trials in that population I think might be a little--

DR. SHERMAN: I just want to remind everyone on the committee of the specific question, which is at the time of initial approval do you need to have completed data in this population? That is what we are trying to figure out, not should we do it. All of these groups are worthy of treatment and all are important. I think we all agree on that. But the question that we are facing, that the agency wants to know, is do they need to mandate trials in these and that those contribute to the registrationB-initial registration.

DR. CHUNG: I still hold my position which is, yes, we should be conducting trials in both populations.

DR. SHERMAN: Other comments from the

committee? If we have no other comments, I think that there is general agreement that naive patients should probably be part of the initial approval process. We have some concerns and controversy regarding the issue of the treatment-experienced. The question about whether we have a difficult group of patients, and concerns about long-term making these patients less viable for future treatments, which is something we don=t know the answer to yet, is an issue and I think that, again, the feeling is that it would be reasonable to have trials in both and some people feel strongly that they should be simultaneous but there are also concerns that are primarily in the experienced group and that we can=t arrive at a clear answer on this committee at this point as to do you have to have the treatment-experienced as part of initial registration. Everyone okay with that?

The next question concerns genotype. Should, again, the initial approval be genotype 1, genotype 1 and 4, genotype 1, 2, 3, 4, genotype 2, 3, any other combination that is available? So,

what constitutes requirements for initial approval? Dr. Haubrich?

DR. HAUBRICH: People will have to correct me if I am wrong, but the little I have read suggests there are some drugs that don=t have activity in genotypes 2 and 3. So, I would say definitely 1 and 4 and 2 and 3 if it is appropriate for the drug. If it is known up front that certain genotypes don=t work, then it wouldn=t make sense to require it if it works for 1 and 4, which is the major clinical problem at least in the U.S.

DR. SHERMAN: Dr. Alter?

DR. ALTER: Are we asking the impossible by requiring genotype 4 at the time of approval? Because they just may not be able to get a statistically valid number of individuals in 4. I mean, in other parts of the world, yes, but not in the U.S. If we are talking about the United States, I don=t know that you can get an adequate number of 4 to distribute between a variety of different groups. So, that may be an issue.

DR. SHERMAN: So, epidemiologic

considerations are valid in making this decision. In addition, we do have to keep in mind Dr. Sun=s question that we can=t do everything. We can=t expect every company to do everything. So, we have to arrive at what we consider is reasonable at the time of initial approval. Dr. Vierling?

DR. VIERLING: I would underscore what Dr. Alter has said, particularly since the consensus of the committee had been that you include all histologic stages. So, if you are going to stratify on that basis you have compounded the issue of identifying and enrolling adequate subgroups for genotype 4.

DR. SHERMAN: Dr. Andersen?

DR. ANDERSEN: You are also getting into potentially small groups if you are also requiring naive versus experienced because then you are looking at genotype, and I think it needs to be discussed whether you need specific information in each corner of the multiple cells that are being developed here, or at what point can data be combined as long as there is evidence of safety.

DR. SHERMAN: Dr. Chung?

DR. CHUNG: Many of the investigational agents currently in testing are actually very genotype 1 specific. So, I would even narrow it further to say genotype 1 with or without 4 and not even require 2 or 3. I would confine this to 1.

DR. SEEF: That was my initial thought as well. If, indeed, we are going to replace interferon with these new molecules that would be a different story. But since the response rate is upwards of 85 percent, I mean, by far the more important group is genotype 1. The question is, I mean, ultimately we will need to know whether this is going to bring us from 85 to 100 percent, and it would have to be done, but I would think by far the priority would be genotype 1 patients. If we are talking about this as an international drug, which presumably ultimately it is, we have to take into account that there are other parts of the world where genotype 4 is common.

DR. CHUNG: It doesn=t have to be done at the time of initial approval.

DR. SHERMAN: Just to be devil=s advocate here, if an agent has particularly good efficacy in genotype 3 because it was designed for genotype 3, would you say that that is not an approvable element?

DR. CHUNG: Is there such an agent?

DR. SEEF: You can answer your own question.

DR. SHERMAN: Well, again, that is the type of question they do need an answer to so someone doesn=t say we shouldn=t pursue that.

DR. BIRNKRANT: That is something we are actually facing, where we have someone proposing just to study their product for 2, 3 and that would be the marketing application.

DR. SHERMAN: Dr. Andersen?

DR. ANDERSEN: Specifically, and to bring up the bugaboo of non-inferiority and equivalence studies, in a population of 2, 3 that would be an entirely appropriate approach where you are not trying to show increase over 85 percent response to 100 percent response but you are trying to show

that you have a safer or easier to provide drug that is equivalent and could be, I think, registered as such.

DR. CHUNG: Or could it be recommended for inclusion as a genotype 1 drug regimen and for inclusion at the time of approval for genotype 2 or 3? In other words, separate approval processes.

DR. SHERMAN: Well, that is an interesting question, this issue of non-inferiority. Would this committee support that only in genotype 2, 3 because we have fairly good treatments, or also genotype 1 non-inferiority? Dr. Alter?

DR. ALTER: In fact, you might find that with an easier to take-Beven if the safety were the same but an easier to take drug combination your overall response rates, taking into account intention-to-treat and all that, could be higher even in the harder to treat patients because, in fact, it is an easier to comply with regimen and more patients may opt to take it who are more likely to respond because they will say, Awell, I don=t need to wait any longer; this is easy. I=ll

take this for a year,@ or whatever it is. So, in fact, it could be a benefit to have something that is equivalent from the point of view of the clinical trial but in real life, actually, it may even be better.

DR. SHERMAN: Dr. Havens?

DR. HAVENS: Can the FDA approve things by genotype?

DR. SHERMAN: Dr. Birnkrant, do you want to comment?

DR. BIRNKRANT: That would be a new area for us and we are seeking your advice on that. How do you feel about having an approval for just 2, 3 or just 1 and not encompassing all the genotypes?

DR. SHERMAN: Dr. Chung?

DR. CHUNG: It seems we have hit a new era now, right? Because the drugs are being designed specifically for those genotypes based on structure-function relationships between drugs and their targets. So, if that is the way the drug designed is being targeted, then perhaps this is the time to talk about such a thing because the

study populations are all homogeneous. They are genotype 1 for many of these agents.

DR. HAVENS: And in the same way we don=t use penicillin for E. coli, maybe we will start to get that level of understanding for how to use drugs for hepatitis C.

DR. ALTER: And we have strain-specific vaccines. Why not antivirals?

DR. SHERMAN: Dr. Andersen?

DR. ANDERSEN: Well, in HIV they are now designing drugs for specific genotypes.

DR. SHERMAN: Ray, can you comment on what you think about this issue in genotype 1 of non-inferiority? Is tolerability with equal efficacy something that you would find a viable approval?

DR. CHUNG: Boy, that is a tough issue. Depending on how you are describing tolerability, I mean, there is tolerability in terms of shortening duration, which I think would be a very easily quantifiable and I think readily accepted distinction between two sets of choices. But if it

is tolerability in terms of AEs, I think you get into a much more difficult can of worms from the standpoint of defining your endpoints. The quality of life issues and AE reports would be a much more difficult area to define superiority or non-inferiority, for that matter. So, I think that would be difficult. Absolute sort of tolerability from an AE standpoint would be a difficult area I think to be specific on. But I think if you could shorten duration, if you are talking about shortening duration of standard of care in genotype 1 by adding an agent to shorten the course from 48 weeks to 24 weeks, and showing non-inferiority, I think that is absolutely defensible.

DR. SHERMAN: So, you would not accept non-inferiority, in other words an equivalent drug for the same period of time in genotype 1 patients?

DR. CHUNG: The same drug--

DR. SHERMAN: Non-inferiority compared to standard of care for same duration, six months, one year-Bwell, one year assuming it is genotype 1, 48 weeks of therapy, and an addition of a combination

or perhaps removal of one of the agents that has the same efficacy outcome in terms of viral clearance, in terms of SVR.

DR. CHUNG: Well, I think if you can clearly subtract from the standard of care regimen, i.e., subtract ribavirin for instance, I think that is also supportable. I think that is an important study to do but I think that it is important to define the efficacy of the agent before doing substitution studies. So, I don=t think that those studies should have priority for initial approval.

DR. SHERMAN: Dr. Alter?

DR. ALTER: I wasn=t really thinking about substitution studies from that point of view. I was thinking more in terms of measuring compliance or ease of use. But if you were, let=s say, to design a regimen that did not include an injectable therapy and you found that it was non-inferior but that was the sole difference from a clinical trial point of view, would you consider that as eligible for approval?

DR. CHUNG: You are essentially describing

substituting for interferon there.

DR. ALTER: Well, let=s say that the series of therapies they design, the manufacturers design don=t happen to have interferon in them, let=s say that is the way they design those and they find in their pilot studies that that works very well so they go ahead and they do a trial with itB-do you see what I am saying?

DR. CHUNG: Absolutely. If you could obviate interferon, an injectable, that is a clear advantage.

DR. ALTER: The 80-80-80, wasn=t that shown only retrospectively? Has that been shown prospectively? You know what I am saying?

DR. VIERLING: There are studies that have taken the prospective route but they weren=t initiated with the intent of doing that.

DR. ALTER: So, after the trial was over, they went back and looked at that.

DR. VIERLING: With pegylated as well as non-pegylated-interferon combinations. So, I think it is important and your point is well taken.

DR. SHERMAN: Dr. Seef?

DR. SEEF: I agree with you that if it shortened the duration of treatment that is an advantage. But if what we are trying to say is that there is an equivalent response rate but a lower rate of AEs, that implies that either you are going to have to reduce the dose of either interferon or ribavirin in the hope of reducing AEs or substituting. Because that is the only way that I can see that there would be an equivalence and that it would be worth doing such a study. Otherwise, if you are using the same dose of interferon and ribavirin and now you are simply adding another novel drug, is there any reason to believe that the drug itself will reduce the side effects of interferon and ribavirin? It would have to be that they would have to be reduced as well, or they would have to be reduced or changed or modified.

DR. SHERMAN: But that is a viable design that the agency may see. Can we get away with 600 mg of ribavirin or two-thirds of the dose of

interferon and have similar rates of efficacy?

DR. SEEF: Again, I would agree. I think that if, in fact, you can reduce AEs by reducing dose of one or either of these drugs and come up with an equivalent response rate that is not an unreasonable approach to take.

DR. SHERMAN: Dr. Haubrich?

DR. HAUBRICH: It seems to me that the first studies that are going to be done, that were presented and referenced as what industry thought should be the first studies, are interferon and ribavirin at full dose plus/minus the new agent. In that context non-inferiority doesn=t make sense. Since we don=t know what it is about that regimen that makes it work, until we show that the new agent adds something I think the substitution studies are the next generation of studies that we will be doing, not necessarily the first.

So, I think to some extent whatever we say here will, and should, evolve with time as we learn what part of interferon and ribavirin are needed when combined with new drugs. So, anything we say

today shouldn=t be held against us or the companies at a future date. So, non-inferiority right now I think doesn=t make sense.

DR. SHERMAN: Dr. Chung?

DR. CHUNG: I agree with what Richard just said. I think that we should phase this and substitution strategies should be pursued after we demonstrate superiority.

DR. SHERMAN: To sum up the response, genotype specific approval seems reasonable to this committee because of the nature of the drugs that are, in fact, targeted and designed by genotype and that initial approval may constitute approval only within a single genotype, not necessarily across multiple genotypes.

There are other strategies that may be considered approvable as well, including some form of non-inferiority, though at this time it seems likely that those will be follow-on studies rather than primary studies with the first crop of drugs that are out there. Everyone okay with that?

I would like to take a 15-minute break.

People are squirming in their seats. We will reconvene here and address the next issue of co-morbidities including HIV.

[Brief recess]

DR. SHERMAN: What we would like to do is get through the rest of 1.a. before we break for the day. I don=t think this is going to be too bad because we have already had some discussion from a number of sources about issues of HIV, and much of the pre and post transplant is encompassed by the decompensated cirrhosis issue which we already discussed. We will clearly need to have some discussion related to pediatrics and, again, the specific question at hand, and finally the racial and ethnic groups.

So, we are going to start with co-morbidities. In particular, let=s take separately HIV and then HBV co-infection. For HIV, again the question is for initial approval what should be required at the time of registration? What should have been done? Anyone want to start?

DR. FISH: In thinking about this, I think

clearly it has been stated earlier that we know that HIV is a factor for progression so this would be a group we would want to have early treatment for. On the other hand, there is the concern that I think Miss Swan raised earlier about drug-drug interactions and cytochrome P450 interactions, and so on, so we would have to be careful and thoughtful about patients that we would want to enter into those trials.

Ideally, we would like I think to have a group that is either a concomitant therapy group that is initiated or a subgroup of a larger initial therapy, initial naive hep. C patient population treated. Of the HIV group, if we think of those as being on antiretroviral therapy versus those not, those could be enrolled if they were naive to HIV therapy and we didn=t have the concerns about the drug therapy interactions and maybe those patients could be enrolled into an early trial, a broader trial as a subgroup or as a concomitant therapy group.

I think it is harder and there are more

concerns if they are on highly active antiretorviral therapy. We would need the pharmacokinetic data to look at drug-drug interactions and make sure that the non-nucleosides and the protease inhibitors for HIV maintain adequate blood levels and that your hepatitis C therapy maintains adequate blood levels. So, those would probably, by necessity, delay a trial that I would not see necessarily as a requirement for approval. So, I think we would like to have data on HIV. I don=t know if it is realistic to expect that that information is going to be available at the time of an IND approval process.

DR. SHERMAN: Tracy Swan?

MS. SWAN: I would like to say first that drug-drug interaction studies with antiretrovirals and also other drugs commonly used by people who are living with HIV need to be done very early on in the drug development process so that it can=t be used as a rationale not to bring the drugs into co-infected people who are taking antiretroviral agents and other drugs.

I can=t stress the interaction studies= importance enough. There was a life-threatening interaction of an antiretroviral drug, Videx and ribavirin. I don=t know off the top of my head how many deaths it caused but they were all unnecessary, and if better studies had been done to characterize that interaction those lives would have been saved.

If you follow that argument, if we can bring these treatments into a population with such urgent need we are going to save more lives. So, I would say at the barest minimum what I would find the perfect amount of data would be the interaction studies and at least 12-week efficacy data in co-infected people, given that EVR is validated with the particular drug. Thanks.

DR. SHERMAN: Dr. Chung?

DR. CHUNG: I would amplify on both what Doug and Tracy said, and take it that now is the time to start those PK studies and cytochrome P450 studies so that the groundwork can be laid to do parallel trials in both mono-infection and

co-infection. One plausible scenario could be an initiation of a naive trial in HCV/HIV co-infection at the same time you are doing a naive trial in HCV mono-infection. That would be a treatment group that had a reasonable likelihood of success, of superior responsiveness to the add-on therapy to the standard of care, and could allow licensing and immediate implementation within the HIV co-infected population and likely extension into more difficult to treat populations within the HIV co-infected group.

So, I would argue for parallel trials in both mono-infection and co-infection. But that requires, as Tracy suggested, early up-front work now on the part of PhRMA to do the interaction studies.

DR. SHERMAN: Yes, Dr. Haubrich?

DR. HAUBRICH: I will take a little bit of an intermediate stance. I already stated that for this population PK and at least pilot data ought to be available at the time of registration. However, the expectation of having PK with 22 approved

antiretroviral drugs is probably not realistic. So, that clearly has to be targeted and so exactly what data is needed to have a full parallel registrational trial in HIV I think is also unrealistic and would probably slow down the process. So, I would be satisfied with pilot data over 12 weeks as one proposal. I think the details of that could be worked out. But I would want to have data in hand, not just promised.

DR. SHERMAN: Dr. Havens?

DR. HAVENS: I think a lot of these discussions depend on the foundation that we have to have adequate data in hand on the exposure-response relationships in a basic group. So, that would be, for example, the treatment naive for the initial approval. Then, using the exposure-response relationships it is probably adequate to get PK and safety data in smaller numbers of these subpopulations that we are talking about. The safety data includes not just primary drug toxicity in special populations like decompensated cirrhosis but, in this context,

safety data is safety when combined with antiretrovirals in the context of this discussion. So, as long as we have the exposure-response relationship in an easy to study population, like treatment naive, these smaller studies don=t have to go 12 weeks. It may be enough to show the lack of a pharmacokinetic interaction in a much shorter study, which would allow for a more rapid move towards approval, but it is critical to have those data available at the time of the initial marketing approval.

You had asked me that question before and I did not answer it. As I listened to this conversation that has been ongoing, I think one of the approaches to take is to say get the easiest to do, largest study that makes you believe that the drug is helpful when added to standard of care and the easiest to do group, but then, understanding that there is danger when the drug is available because people will use it in groups for whom it was not initially studied, require before approval smaller but well done studies looking for drug

interactions, kinetics and toxicity.

DR. SHERMAN: Dr. Andersen?

DR. ANDERSEN: In a way the HIV population is being pushed on to one box here. There is a large HIV-positive population that is not taking HAART. They are earlier in their disease, yet, they may well have HCV. So, the question is not to require but to accept a stratification or a stratum in the registration studiesB-I am asking whether there is a reason to restrict the initial registration study to only HIV negative.

DR. SHERMAN: So, you are suggesting--

DR. ANDERSEN: Well, I am asking. I am not a clinician so I am asking whether that is appropriate.

DR. SHERMAN: Dr. Havens?

DR. HAVENS: Well, there could be reasons. Clearly, kinetics of some drugs are different in the people with HIV compared to people without HIV and drug interactions, therefore, may be different in people with or without HIV. So, there may be reasons of biology.

DR. ANDERSEN: Well, I think what I am bringing up is with stratification if the response rate is lower but still differential between two arms, then that is important information to have and could still produce a highly positive study.

DR. SHERMAN: Tracy Swan?

MS. SWAN: From my understanding, there is a large group of co-infected people who have both advanced HIV and advanced hepatitis C. That is where I would see the greatest clinical need and the greatest urgency to move these therapies forward, although I also think stratification by HAART or no HAART or other parameters is a very, very good idea.

The other thing is that some of the new drugs in development might be good candidates for pharmacokinetic boosting with a protease inhibitor. Retanovir is given with a lot of other HIV protease inhibitors. So, it sort of begs the question if you have a t.i.d. regimen, which are notorious for poor adherence, risk of resistance, etc., wouldn=t you want to sort of cover that

waterfront anyway and make sure you are getting the data you need?

DR. SHERMAN: I would just like to make a point, and that is, remember, one of the features of the population of HCV/HIV co-infected is a tendency towards very high viral loads, which is probably one of the factors that affects efficacy but, again, may be an issue in terms of evaluation of treatment. So, I would argue that before a drug is released and might be used in that population that some understanding of resistance emergence in the setting of very high viral load be evaluated carefully. Dr. Haubrich?

DR. HAUBRICH: Getting back to the question of whether to have stratification for HIV, I think that makes a lot of sense and is efficient in terms of study design. I think that we have to make sure that studies are conducted in centers that have expertise both in HIV and hepatitis to ensure safety of those patients, particularly if the trial is designed to allow antiretroviral therapy in those patients.

DR. SHERMAN: Other comments? Yes?

DR. MUNK: Yes, I think the risk of having an HIV off-treatment stratum would be restricting the options for the HIV treatment of those patients as the HCV trial progressed.

DR. SHERMAN: If there are no other comments, I think that the summation feeling here is that prior to initial approval efforts should be made to initiate early stage studies at least in co-infected patients; that those studies should include analysis of major drug interactions and pharmacokinetics particularly related if not to all drugs, because there is a huge number of drugs out there, to some of the more common drugs that are being used in treatment and that include evaluation of cytochrome P450 effects that may provide some predictability for what is likely to happen by class in patients with HIV; that at least early efficacy trials, pilot trials, are probably indicated to give some sense that patients can be treated both safely and with some degree of efficacy, though you do not need to have definitive

efficacy criteria established at the time of initial drug approval. Everyone okay with that? Dr. Havens?

DR. HAVENS: Can I ask a question about the last part of your statement. So, if we had a big trial in a treatment-naive group that showed efficacy when added to standard of care and 100 patients with HIV were treated safely in whatever context, would you suggest that that drug be approved for use in persons with HIV?

DR. SHERMAN: No. I am suggesting that that might be sufficient to establish that some baseline of the reality of when this drug is out there and people may choose to use it, that there is at least some indication but that probably will be insufficient for that indication.

DR. HAVENS: So, you are asking the drug companies to do extra work, which is to get information in these subgroups we are all talking about, with no apparent extra benefit.

DR. SHERMAN: Well, I am not--

DR. HAVENS: Which is okay with me.

DR. SHERMAN: This is my sense of what the committee is suggesting they would like to see at that time.

DR. HAVENS: Yes, I am just trying to make it clear what it is--

DR. SHERMAN: That is correct.

DR. HAVENS: B-we are putting out.

DR. SHERMAN: This is very similar to what we agreed upon earlier for decompensated cirrhotic patients, that there should be studies initiated and under way. They don=t have to be pivotal trials taken to completion, but we shouldn=t wait till Phase IV.

DR. HAVENS: Yes, you were very clear in this one, you said Aprior to.@ And, I am very supportiveB-very supportive of that. I am just pointing out that for registration of the drug in a treatment-naive population we are suggesting that these substudies or extra studies be done in special populations that would not lead to registration or approval--

DR. SHERMAN: At the time of initial

approval. They may.

DR. HAVENS: Thank you, just a point of clarification and I thank you very much.

DR. SHERMAN: Dr. Birnkrant?

DR. BIRNKRANT: We could put that type of dataB-we would do it more as safety data so we would include it in labeling but it wouldn=t be its own indication.

DR. HAVENS: Right. Thank you.

DR. SHERMAN: Tracy Swan?

MS. SWAN: I think it is good to think about ways to incentivize more rapid full-blown safety and efficacy trials in co-infected people since we are saying that we require these things in your pre-approval package for mono-infection, but I don=t know if this is exactly the right moment to think about what that looks like.

DR. SHERMAN: Within that same area, we also have to address the issue of hepatitis B. We haven=t seen much in the way of data in the prior presentations for hep. B. The overall co-infection rates, if I can share that, are relatively low and

it is thought that in most cases one virus suppresses the other, usually the B, somehow not being as bad in most patients as the C. That should launch us into the discussion again will studies in B co-infected patients be required? Dr. Murray, you are nodding. Dr. Andersen?

DR. ANDERSEN: If you can find them.

[Laughter]

The issue right now is there are treatments out there that are working, tenofovir specifically. So, the question is to try to find naive subjects who have not seen prior treatment is really very, very difficult right now. So, I will just throw out not requiring in B.

DR. CHUNG: Janet, just for clarification, you are referring to triply infected patients, or are you talking about B and C? Because tenofovir would only be used--

DR. ANDERSEN: This is true. Adefovir then in mono-infected B. Basically, there are drugs out there that are being used by the primary care physicians, not getting into research centers until

people are pretty far along where you are now dealing with a highly experienced population.

DR. SHERMAN: So, looking around, it seems the general consensus is that studies in B should not be mandated at this time.

Pre and post liver transplantation, this category really overlaps with decompensated cirrhosis because it is patients with decompensated cirrhosis who are the ones coming to transplantation or are post transplant and we discussed that rather extensively. Does anyone on the committee have additional comments related to this population?

DR. SEEF: I guess the issue is, and maybe John can speak to this, treatment after transplantation. Is that an issue? Did we talk about that?

DR. SHERMAN: We did not. We discussed decompensated and, following transplantation presumably a healthy liver is healthy for a while. So, John, do you want to address that?

DR. VIERLING: I think there are two

issues. We talked about treating the decompensated patients, and with the issue of safety perhaps designing the studies for patients listed for transplant in transplant centers, partly as a safety net. But there is an additional issue, and that is whether if you achieve an aviremic state prior to transplant, do you then post transplant avoid recurrent disease in the allograft? I think that is a legitimate area of study. That is where Greg Everson and others have provided us the preliminary evidence, but we really do not know yet how to achieve that goal. So, that would be the first post transplant issue.

The second post transplant issue is how to abort the progressive nature, the accelerated nature of post transplant recurrent hepatitis C, which can in 20-30 percent, eventuate in cirrhosis within 5-7 years and a very large rate of decompensation within the next several years. Clearly, in the transplant community it is our greatest problem right now because we have transplanted so many of them who have had numerous

attempts, and I think it can be well summarized by saying that we are still woefully inadequate in terms of knowledge of safety and efficacy regimens. The regimens are all across the spectrum with our standard agents and they haven=t been effective, except in some very specific patients.

Intention-to-treat analysis shows very, very low response rates in these patients. So, standard of care therapy post transplant, if you use the models that are being discussed pre transplant and for the naive, addition of therapy to standard of care is of itself problematic because of the poor tolerance of standard of care therapy in these patients. That is an issue where we really almost are going to be forced into looking at either lower doses of standard of care with addition of single agents or multiple agents or substitutions, particularly for ribavirin in the circumstance. I think it is a much more difficult issue but it is an extraordinarily important one.

I think the consensus of the transplant community is that, very unfortunately, people that

end up with decompensated disease due to recurrence are increasingly ineligible for consideration for re-transplantation when we have so many people on the waiting list that have never had the opportunity for a first transplant. Thus, this is almost a worst scenario of having given these patients a liver and having an inadequate life expectancy due to recurrent disease post transplant and having consumed that organ. So, it is a societal issue when there are too few organs to be donated in the first place.

So, I think that this design post transplant deserves special consideration of the individual agents that are being proposed for study. There may be agents among multiple classes of new targets for HCV therapy that would be more appropriate to prioritize in the post transplant setting. Whatever can be done to minimize the standard of care utilization post transplant, I would advocate it would be laudatory to minimize it because it has been ineffective.

DR. SHERMAN: Similarly though, as with the

world of HIV, you are going to have to probably do drug interaction studies with a variety of other immunosuppressive agents, which almost certainly have to precede actual trials with efficacy.

DR. VIERLING: I would agree, but I think that the difference there is that we have historically, I think, contended well with just our monitoring capacities of trough and Cmax levels for calcineurin inhibition, defined drug-drug interactions and changes in metabolism to which we kind of adapt almost by reflex when patients are placed on different antimicrobials or other things on a temporary basis that change the drug levels. But I don=t think it raises the question and the level of concern that we just discussed regarding HIV drug interaction potential, say, with HAART. But it clearly has to be studied, but I think in a way we almost routinely do that in the post transplant setting. We don=t have as much ability to look at things such as mycophenolic acid as an adjunct agent. There is very little ability to rapidly turn around your trough level analysis for

sirolomus, but all of these things I think could be adapted into an appropriate study design and are probably going to be forthcoming in clinical care anyway.

DR. SHERMAN: So, you are advocating for doing these studies prior to a drug registration or simultaneously?

DR. VIERLING: Well, I think you are going to do them virtually by treating a post transplant group. You are going to I think rapidly ascertain what the impacts are of any therapeutic trial regimen for C on your levels of immunosuppression because you monitor those levels so frequently and so carefully. I don=t think it takes a lot of prior study to anticipate that you will be able to respond by dose modification of your standard immunosuppressive agents.

DR. SHERMAN: So, you would include these patients with the other decompensated patients?

DR. VIERLING: Well, again, I think there are two arms here. I think that the arm of the decompensated patient with a low MELD score--and in

different areas we can almost predict on the basis of that MELD score how much time may elapse before they would reach a score at which they would be offered an organ--is one group that I was advocating be a select population. If we then extend to the group that has a higher MELD score--in whom you may achieve only an aviremic state but have no prospect or pre-intent of acquiring an SVR in this population--and take them to transplant without viremia to see whether you can prevent recurrent infection, I think that is a separate group in terms of potential design and inclusion criteria. Anyone who recurs post transplant, again, is a third group. Could one translate to the other? Obviously, the second group, if they are viremic and they did have a recurrence of disease and might, therefore, be eligible for post transplant treatment, presumably would have the same risk of a bad adverse outcome that you would prevent with a successful therapy. So, that could be the same but I am not sure about the first group.

Again, if one looks optimistically--and the glass is half empty or half full, but if you look at it as more than half full, if we are able to take low MELD score patients and truly reverse the trajectory of their disease progression, we will have done something amazingly important for those patients and obviously for the balance between organ availability and the need for transplantation in the United States. So, maybe we will get lucky as we did with hepatitis B therapy, as we had discussed before, as a potential paradigm. For those that are going to get a transplant I would certainly advocate that we consider post transplant treatment.

But the key question you are asking here, and I would just like to give an opinion about, is that I believe this is a very difficult area, as I have already mentioned with respect to design. I do not feel that your naive or your treatment-experienced protocols are going to be adaptable to the post transplant arena. I think it has to be viewed as a separate area of study. For

that reason, as much as I advocate it be studied as quickly as possible, I do not think it is going to be appropriate to make it part of the registration trial approval process because of its uniqueness.

DR. SHERMAN: Ray Chung?

DR. CHUNG: I agree with the absolute importance of this patient population. I think it would be important to define that group of progressors post transplant, and I think you can actually do that with protocol biopsies at one year after transplant, identifying those who are at risk for that rapid fibrosis progression that you speak of, John. Perhaps those are the patients to single out for inclusion in such studies, as perfectly well stated by you, John.

Add to that the complexity of center variations in practices, immunosuppressive choices, both induction and maintenance immunosuppression, and you have a very difficult mix for doing clinical trials which are notoriously difficult to do in transplant centers. So, I agree with John that we shouldn=t impose that as a precondition of

approval.

But I would add one other potential target area, and that would be the use of these novel antiviral drugs in a manner analogous to the real advance that antiviral therapy brought for HBV in preventing graft reinfection in the first place. To use those agents, the C-specific agents in the antihepatic and early post transplant phase to try to do just what you are talking about, prevent graft reinfection in the first place, the idea being that you have the virus at a low ebb presumptively, I mean potentially at a low ebb and viral loads often can be quite low in these patients. We know kinetics of HCV RNA drop in the first four days to often aviremic. The question here is whether you can maintain that aviremic state with a short course of virus-specific therapy. So, I think that would be another important target of a clinical trial design. We don=t have immunoglobulin for C as we do for B, but there have been successful monotherapy strategies with antiviral prophylaxis for B prevention. So, I

think that is just another target.

DR. SHERMAN: Other comments from the committee? Dr. Seef?

DR. SEEF: I recognize my total naivete on this, but I would hate to hold up release of a drug that we know to be good in a naive patient because we haven=t done all the studies in the most difficult to treat patients and the reason for this is that we are worried that people are going to go out there and use it inadvertently.

First of all, the FDA is going to have to say don=t use it until we have proven it. Second of all, I will say categorically do not use it until we have done the appropriate studies. I mean, surely, what comes out of the registration is the studies that have been done. That is what you can approve and state categorically that you should not be using it in other categories that are difficult to treat until we have more information.

I mean, I absolutely agree that it has to be done. All of these have to be done. But I don=t think that registration should be held up

because these have not been completed. We need to get these drugs out if we can, if they work, and take it from there.

DR. SHERMAN: Unless there is another comment, I think the response is that while the pre and post transplant group is important and there are subgroups that are present within it, including patients with rapidly progressive or fibrosing cholestatic hepatitis, those that might benefit from post transplant prophylaxis and those that might benefit from pre transplant studies should be encouraged but not necessarily mandated at the time of initial approval. Is everyone okay with that?

DR. HAVENS: I just wanted to ask Dr. Seef a question. The question of whether or not these are required before approval or not is the key issue, and you just said not before approval. Was that just specifically for the pre and post liver transplant group we are talking about, or does that include the other special subgroups that we have been talking about?

DR. SEEF: I think it is required that we

do the pharmacokinetic and viral kinetic studies that you have been talking about. That is essential so that we have this information and don=t have to depend on post-marketing commitments to get this done. We need to have it done, I believe, before we register these drugs. But I don=t think that we need to have the final answer before approving the drug if it turns out to be effective in, for example, the naive group or people who have compensated liver disease.

DR. SHERMAN: The next area is pediatrics. I would ask that Dr. Murray perhaps give us a brief overview of disease progression particularly and severity of disease in pediatric populations.

DR. MURRAY: Thank you. I will certainly do that. My own feeling is that at the time of initial marketing it would be very useful and I would very much like to see PK/PD information on pediatric patients at the time of initial approval. That would be true of any of the newer drugs coming down the pike that seem to have some reasonable safety profile and efficacy in adults.

So, hepatitis C affects approximately 0.4 percent of children over the age of 12, a lesser percentage, approximately 0.2 in children under the age of 12 years. That having been said, if we do the math you can see that that is actually quite a few children and I, myself, follow approximately 200-250 children in the Pacific Northwest alone.

HCV is, relatively speaking compared to adults, slowly progressive in children. We and others have looked at the severity of disease over unit time and with all other factors, to the best of our ability, it is equal. Children with X number of years of infection tend to have less severe liver disease compared to adults. That has been shown over and over again, and most likely has to do with the immune response to that infection. There is also a spontaneous clearance. Its quantification is not completely understood. It is probably in the early years after infection and wanes as the individual ages.

Of the pediatric hepatitis C population, 60-plus percentage of those individuals have

acquired the virus through vertical infection, so infected mother to child. The other percentages are really the same risk factors as seen in adults.

The difference that that portends for this population is that they come generally with a family set who already is very well informed, highly motivated and may themselves already be taking part in some of what is standard of care for adults.

The other caveat to know is that for pediatric treatment of hepatitis C my standard of care is different from your standard of care. Standard of care for adults is pegylated-interferon plus ribavirin. We do not yet have pegylated-interferon approved for children so my standard is interferon. So, when we are talking about the previously treated non-responders, children who have been previously treated in this day and age, right now in 2006, that is on interferon-ribavirin treatment. Because there are a couple of large PEG-interferon trials under way in pediatrics, I would expect that in the next few

years, hopefully, PEG will be approved for usage.

DR. SHERMAN: Other comments from members of the committee? Dr. Havens?

DR. HAVENS: How long has pegylated-interferon been approved for use in adults?

DR. SHERMAN: Five years.

DR. HAVENS: And what are the requirements for approval of pegylated-interferon for use in children? Showing efficacy, safety and kinetics?

DR. SHERMAN: I would have to defer to Dr. Birnkrant.

DR. BIRNKRANT: The trials that are under way are efficacy trials.

DR. HAVENS: This is why I made a point before that if we just require some PK and safety data in smaller subgroups that don=t lead to registrational approval of the drug in those subgroups, then people won=t pay and practitioners can=t use those drugs in those subgroups. So, this is a terrible conundrum because we don=t want to delay approval of the drug for a huge population of

people who need it right now. We don=t want to make it so that the bar for drug companies to jump over to get their drug approved is too high. But we can=t have it that special subgroups can=t get care that is available for five years or more at this point when we know that interferon alone is inadequate. So, as we go through this subgroup analysis we have to figure out a way not just to say that if you want to use it off-label you can, but make it so that we can get it paid for and make it real. So far this is not real.

DR. MURRAY: I would make another reality point, as much as all of us in the room may not want to hear this it is a fact of reality in pediatrics that although those of us who are involved in studies would prefer to say a drug is not approved in my age group for instance, therefore, don=t use it unless you are part of a trial, the reality is that in pediatrics many pediatricians and sub-specialists are very used to drugs not being approved in pediatrics. Consequently, there are a lot of drugs that are

used for various things, not just in GI and hepatology, that are not approved. I think we are really in a position here to set a new model. Pediatricians want optimal care for our pediatric patients and, quite frankly, in a vertically acquired infection like hepatitis C the families do as well.

If you don=t mind, I would make one other point. The other couple of points that I think might be of concern that we might want to address are, number one, safety in pediatrics and, number two, formulation. So, for hepatitis C using the current models of interferon-ribavirin and now developing information on pegylated-interferon, the interferon backbone has the same side effect profile as it does in adults, however, it is much better tolerated in pediatrics. Children are very robust in tolerating these medications, rarely miss schoolB-the equivalent of missing work, and have minimal side effects. The hematologic side effects that we see with these drugs, similarly, are very easily tolerated, much better so than in adults.

So, at least for the interferon medications, I do not feel that is an argument not to use it in children. For new drugs we will just have to see.

The other one is formulation. For the very young children, needing a liquid if it is an oral is obviously relevant. But, quite frankly, children, easily at the age of seven, eight, nine, can swallow pills. If the pill is crushable, it can be crushed. So, that is not necessarily an obstacle and certainly we are using interferon subcutaneously and that is not an obstacle.

DR. SHERMAN: And response rates in PEG-interferon trials to date with ribavirin?

DR. MURRAY: Yes, there are at least two large studies that I am aware of, and Schering Plough currently has a study under way and the NIH/Roche is currently under way with a trial.

DR. SHERMAN: But we have no results from those yet?

DR. MURRAY: No. I am personally involved in the NIH/Roche one. All children have been enrolled. We did meet our goal for enrollment and

we should have at least end-of-treatment data on all patients within a year.

DR. SHERMAN: Other comments? Dr. Birnkrant?

DR. BIRNKRANT: Can you comment at what age you begin treatment?

DR. MURRAY: In the NIH/Roche trial that I am involved with five is our younger age limit. With interferon there are real safety concerns certainly under the age of two and most people take that to the age of three, although two to three is a grey zone. Then it has to do with what medication, as the far as the formulation of it, can be delivered if it is an oral.

DR. SHERMAN: Yes, Dr. Fish?

DR. FISH: A question for Dr. Murray, are children treated based on histology or on virology alone?

DR. MURRAY: Actually, it is a very good point. So, the earlier point I made is that children for the most part have lesser disease so the standard of care for pediatrics is still to do

a biopsy pre treatment. I and others certainly do that. That is the mandate, at least in the study that I am involved with.

That having been said, most of the patients don=t have advanced liver disease. So, we use that as a factor in discussing treatment but not as a piece of information that would talk us out of treatment necessarily. These are very highly motivated families as well as children, very well informed and generally with information about potential toxicities of the drugs, and they still want to proceed with the understanding that if the virus can be cleared when this liver is very healthy, that really positively impacts the child=s not only physical health long term but also their mental health because they are living with this virus that is a problem for them for quality of life, not to mention the decades to follow as they age.

DR. SEEF: May I ask a question of Dr. Havens? I am not sure that I understood what you said. Are you suggesting that for each of these

categories we have to have data on response rates before we consider any approval? Did I misunderstand you?

DR. HAVENS: Oh, no, I am not saying that at all. I am trying to make sure that we are clear about the difference between approval and getting a little bit extra information on these different subgroups, and that a little bit of extra information in the initial package insert or product label may not mean that the drug is immediately available for use in those subgroups. So, as we approach this topic it is tricky because the more subgroups we demand, the harder it is to get the initial approval. Then, by demanding the subgroup information we need to ask ourselves what are we really getting from it. Now, you say that you don=t use pegylated-interferon in kids.

DR. MURRAY: No, I do use pegylated-interferon in children but I am part of a treatmentB-

DR. HAVENS: Only in the context of the study or outside of the context of the study?

DR. MURRAY: I have treated a few children outside of the context of the study, but not many.

DR. HAVENS: I certainly use unapproved drugs--

[Laughter]

What? Was that the wrong thing to say on camera?! I treat many children with HIV with many drugs that are not approved for use in children by the FDA and I am proud of it!

[Laughter]

What I am saying is that the information we are asking for is important to get for the different subgroups that different ones of us have identified as our subgroup, decompensated, pediatrics, whichever, but we need to be careful to recognize that that should not stop further studies that might finally lead to real registrational type approval.

DR. SEEF: For each of these categories?

DR. HAVENS: That would be finally the goal. These are preambles to those other studies.

DR. SEEF: I am just trying to think, for

each of the companies that have a product, if they are told that before they can be approved they are going to have to study HIV, and liver transplant, and kids, etc., etc., it will take us years before we get the answer to all of this. So, I quite agree that all of these should be in process and as far along as we possibly can, but it should not stop the possibility of getting registration of the drug if, indeed, we get information from the category which is easier to treat that it has really been effective, and with the urging that people continue to do the studies that we need in order to get all of this. I just didn=t know whether what you were saying is that no approval should come out until we have done all the studies in each of the categories.

DR. HAVENS: I guess what I am talking about is Aall the studies@ is a big phrase and we need to be very careful about what we are really asking for before initial approval, and I am arguing we need very narrow requirements for PK and safety in small numbers but, because I am arguing

for a narrow requirement, I am arguing that it be done prior to initial approval so that bigger studies can happen after initial approval but without studies in special populations prior to approval, at least PK, exposure response five years down the road--

DR. SEEF: I completely agree with that. As an aside, I grew up at the time of Tom Chalmers who said that you randomize the first case. So, if you have a drug or treatment that you don=t know works, he doesn=t think that anything should be done until you do this in a randomized fashion because you literally don=t know whether this is working or not. But, I mean, if you feel convinced it works, that is fine.

DR. HAVENS: So, the initial registrational trial in the easiest to get, most homogeneous population proves that the drug works biologically in people for whom you would think it would be intended. Then, assuming that at least what we are asking for is to clear the virus, the biology is not dramatically different in some of these

subpopulations and probably not in 12-year olds compared to 25-year olds. So, assuming that the biology is not dramatically different, then the issues are PK and safety. Your point is well taken about randomized trials but I think there is a way to speed the process which does require prior activity and it is possible; it has been done.

DR. SHERMAN: I think it is an important discussion. One of the things that drove the earlier discussion about HIV in decompensated patients was the high risk of disease severity without a lot of choices. I would like to perhaps advance the argument, and it doesn=t mean I am against kids, but disease severity seems to be less of an issue in most pediatric populations and if you are willing to treat even off-label, by the time a kid is 14 or 15 they can be handled and behave biologically much like an adult. So, if the overwhelming majority do not progress by that age to advanced liver disease--again not minimizing that getting rid of it earlier is better for a variety of public health reasons as well, but this

whole issue of mandating the studies up front is an issue and I think that we do have to at some point balance the ability to do these studies and get these drugs out on the market sooner rather than later. Yes, Dr. Havens?

DR. HAVENS: You bet! And I don=t think you don=t like kids! And the issue may not be one of biology of hepatitis C but, in fact, the PK of a 70 kilo 14-year old may be dramatically different than the PK of a 70 kilo 55-year old. In fact, the 14-year old may need higher than the adult dose of drug to get the same drug exposure. So, those PK studies are crucial to do in the population in which you will be using the drug because adolescents have much higher clearance of many drugs and may need higher than the FDA approved Aadult@ maximum dose.

DR. MURRAY: I was actually going to say exactly the same thing. The jury for me is still out on whether you like kids or not!

[Laughter]

But I was actually going to make the exact

same point. I don=t think you can assume that a 14-year old is the same as a 25-year old, for the reasons he just said. In the adult population, my understanding is that a small adult is not the same as a large adult. Pediatrics is a unique population. Yes, it is true that they do not have as severe disease, hence, the urgency from a medical perspective is not there. But we have to push the companies to get the PK information or it won=t happen in a timely fashion at all.

DR. SHERMAN: Dr. Birnkrant?

DR. BIRNKRANT: How do we feel about lowering the age for entry into the clinical trials down to about 12 so they can be run simultaneously? We have had this request for HIV drug development so I was wondering what you thought about HCV drug development, if we could just lower that age, that lower end a little bit more?

DR. SHERMAN: Dr. Havens?

DR. HAVENS: Again, I would point out that I don=t necessarily think the biology of the disease is so dramatically different that that is

the issue, but it is very clear that the clearance of drugs is dramatically different. So, an adult taking unboosted adazanovir may need 400 mg to get a trough of 300, and an adolescent aged 12 or 14 may need 800-1000 mg, two and a half times as much drug, to get the same drug exposure. So, given the dramatic difference in pharmacokinetics and the recognition that adolescents may need much higher drug doses to get the same drug exposure, it worries me greatly that we would just add a few patients in the lower age range and then say go ahead and use the drug. That still doesn=t get us the information that is required on pharmacokinetics and drug exposure to know that we are doing the right thing for kids.

DR. SHERMAN: I think that we can sum up that there is strong feeling that prior to approval there should at least be initiation of studies that focus on safety and PK.

The last area, which I would like to try and get through-BI know that it is a little after four o=clockB-is the issue of racial and ethnic

groups. I think there will be some discussion though I suspect it will all be in one direction that, yes, we should be focusing on racial and ethnic groups and I would like to hear discussions. Dr. Haubrich?

DR. HAUBRICH: I will just sum up by parroting what Janet said so eloquently, that by including strata and having powered strata and requiring that the strata be filled, I think we should be able to achieve the goals, meaning that you have a certain number of people that it would take to show the effect within the strata. Then, if that strata isn=t full you close the trial to the other group and just fill that strata, as opposed to just saying we are going to have the strata but then not having it filled. I think that would achieve both the goals.

DR. SHERMAN: So, a way of paraphrasing this discussion is to say should groups, such as African Americans where response rates are lower, be (a) required and, (b) separated into separate studies or included in the main body studies so

that efficacy can be determined, and is there any reason to do such separation? Dr. Andersen?

DR. ANDERSEN: I think, as Richard brought up, the issue is interactions so if there is a treatment-race interaction, then the issue becomes delineating that as opposed to lower efficacy but still efficacy with a new regimen. That can be dealt with by stratification that does not necessarily need an increase in the sample size. That would be a focus for pathogenesis studies, genetic studies to understand the difference. But where there is an interaction where potentially new treatment does not work well in one racial group and works in another, that is where one would need to target some sample sizes.

DR. SHERMAN: Dr. Alter?

DR. ALTER: I mean, as you said it is virtually in one direction, but in my opinion we at least have to include the two major racial ethnic groups in the U.S., if not three. It should be a requirement that there be a sufficient sample size to address efficacy in the three major racial

ethnic groups in the United States, two or three. I mean, you shouldn=t be able to look at a new drug in middle to upper middle class whites with genotype 1 alone.

DR. SHERMAN: So, to be specific, you want non-Hispanic Caucasians--

DR. ALTER: Non-Hispanic blacks--

DR. SHERMAN: African Americans and Hispanics.

DR. ALTER: Well, Hispanics is a very mixed group so it could be Mexican Americans. I mean, I don=t know whether that is necessary because we really don=t know very much but at least non-Hispanic whites and non-Hispanic blacks because those are the groups we know about and they make up the majority of the population and we have no reason to believe that Hispanics respond differently, however, it would be nice if Hispanics were also addressed, or at least Mexican Americans because they represent a substantial group. It is like doing hepatitis B studies without Asians who represent the most hepatitis B in the U.S.

DR. ANDERSEN: If I could ask, are you advocating sufficient sample size to be able to detect the full efficacy in each of those groups, in other words, making the study three times as large? Is that what you are saying?

DR. ALTER: I don=t think so.

DR. ANDERSEN: Good.

[Laughter]

DR. SHERMAN: Tracy Swan, please?

DR. ALTER: I think I agree with you. I just want to make sure this wasn=t one of these, yeah, we can have some PK data when we go for approval but that you know, that there would be sufficient data for approval at the time of initiation.

DR. SHERMAN: Tracy?

MS. SWAN: What a perfect seque for me to say we also really need to look at Phase II and get population-specific PK data to see if there is any signal of difference before we move into Phase III with adequately populated studies, and also it is not a question of whether you can enroll, it is a

question of how. There are studies that have done it. Many of the sponsors of these products have done studies, say, in HIV that have enrolled people of color without a problem so it can definitely be done.

DR. SHERMAN: Dr. Seef?

DR. SEEF: Well, I expressed my view earlier. I think that, as Miriam says, there are not only whites in this country, there are whites and African Americans and maybe Hispanics as a separate group I presume, and I think that all studies should be sure to take this into account because there could be differences. Specifically for hepatitis C, I asked Miriam earlier what proportion of people in this country who have chronic hepatitis C are African American and she gave me this figure of 23 percent. So, one quarter of the people in this country who have chronic hepatitis C, most of whom happen to have genotype 1 are, therefore, more likely to have progressive disease, although there is some question about that, but they absolutely, in my viewB-I honestly

believe that I cannot believe that we are even thinking about this. This has to be a reflex I believe in doing this. We have to have whites and blacks in the study, absolutely.

DR. ALTER: You know, now that I think about it, Brian Evelyn should be hearing me when I say this, but in this instance the fact that incarcerated aren=t included in that estimate probably means that that percentage is a little higher, probably not a great deal higher but a little higher because of the disproportionate percentage of incarcerated individuals who are black.

DR. SHERMAN: Dr. Chung?

DR. CHUNG: I would fully agree with the stratification for all three of these major ethnic groups, but I would just add perhaps a word of anticipation when you are planning the studies, especially in African Americans, given what we know about their high frequency of null responses or at least non-responses from viral hep. C and other studies, that we ought to plan to look carefully,

at least in the subgroups of these folks, at biologic endpoints including resistance because of those concerns given that they are flat PEG-ribavirin responses.

DR. SHERMAN: Dr. Andersen?

DR. ANDERSEN: One thing to realize as well is that, because of the response profile, that does mean that the populations going into the experienced studies, the non-responsive studies, are going to potentially be inverted and that is going to be the way it is. The issue is making sure that within the proportions that you expect that is approximately what is happening on the studies. So, it means monitoring the studies on a continuous basis rather than finding out at the end of the study that, all of a sudden, it needs to be held open for one group. That could even be extended to gender to also consider in terms of gender in ensuring that there are sufficient women, sufficient men depending on the population so that there is good accrual.

DR. SHERMAN: I think that one of the

issues that needs to be raised is the issue of the barriers to enrollment in clinical trials. I think that is a big issue. In the major pivotal trials today African American have been exceedingly low relative to their risk and prevalence in the population. I would think that this committee should be encouraging the FDA to look at the issues related to barriers that appear in trial designs that then lead to populations that are primarily upper middle class white populations that are not representative of the disease as a whole in this country. Dr. Alter?

DR. ALTER: With that in mind, these trials take a lot of work to begin with, granted. But it takes a lot more work to get difficult to reach populations. But just because it does doesn=t mean we shouldn=t do them. It just takes more work. It doesn=t mean it can=t be done. Maybe different types of consultants need to be used, people with different types of experience, people who need to be used in order to enhance the entry of hard to reach populations, not just academic upper middle

class physicians but others as well. I think that there are a lot of people experienced in getting to hard to reach populations and there are a lot of ways to do it, and those are the things that need to be worked out.

DR. SHERMAN: I would point out that in ACTG 5071, which was a co-infected study, there are two salient points related to the trial. There was 33 percent African American enrollment and the overall dropout rate in the study was 13 percent, which was no different than what was seen in the pivotal trials in HCV mono-infection in mostly perfect populations.

DR. SEEF: And in the viral hep. C trial compliance, which is something that people have raised, was not an issue. There was no less compliance among the African Americans, at least in the viral hep. C trial, than there wsd among the whites. So, I don=t think that is an issue either.

DR. SHERMAN: Dr. Fish?

DR. FISH: There is another group I would just like to bring to the table, if I may, because

it applies and there are ethnic concerns there too, and it is patients with end-stage renal disease. These patients are all excluded from any clinical trial that has, you know, primarily been designed for these drug approvals. So, while I certainly understand that it would not be a group for an initial approval, it certainly is a plea for these patients to be studied. If you look at an HIV practice, all of the patients on dialysis are black or Hispanic and the majority of them have hepatitis C as well, usually 90 percent or more, and we really don=t have anything to offer them at this point.

DR. SHERMAN: So, I would say that the response to the agency is that there is pretty much unanimous agreement that there should be efforts to target racial and ethnic groups as much as possible in proportion to the disease prevalence in the population, and that study designs should in some way include that so that appropriate stratifications later can be done. If necessary, specific PK issues that may have a genetic basis

may need to be evaluated. And, there are other populations we shouldn=t forget about.

We are going to adjourn this meeting for the day. We will reconvene tomorrow at 8:00 a.m. Tracy, did you have an additional comment you wanted to make briefly?

MS. SWAN: Very briefly. I don=t mean to make hostages of everyone. I am just very surprised when I look at this list that I see no mention of current or former drug users or people with a history of psychiatric disorders, populations mentioned earlier by my colleagues from the community, and we really need to look at interactions between particular medications that high prevalence populations are using, and people have successfully run trials with active drug users and people with a history of psychiatric disorders. It can be done. We know how to do it and we need to do it so the results are relevant to real-live people.

DR. SHERMAN: Thank you very much. We will see you all tomorrow morning.

[Whereupon, at 4:25 p.m., the proceedings were adjourned, to reconvene on Friday, October 20, 2006 at 8:00 a.m.]

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