Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES OF THE
ANTIVIRAL DRUGS ADVISORY COMMITTEE

October 19-20, 2006

Members Present (Voting)
Kenneth E. Sherman, M.D., Ph.D. *(Acting Chair)*
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.
Lynn A. Paxton, M.D. *(10/20/06 only)*
Ronald G. Washburn, M.D.

Consultants to the Antiviral Drugs Advisory Committee (Voting)
Miriam J. Alter, Ph.D.
Raymond T. Chung, M.D.
Karen F. Murray, M.D. *(10/19/06 only)*
Leonard B. Seef, M.D. *(Regular Government Employee)*
Tracy Swan *(Patient Representative)*

Consultants to the Antiviral Drugs Advisory Committee (Non-Voting)
John M. Vierling, M.D., F.A.C.P.

Antiviral Drugs Advisory Committee Industry Representative (Non-voting)
Eugene Sun. M.D.

Guest Speaker
Jules Levin

FDA Participants
Debra Birnkrant, M.D.
Katie Laessig, M.D.
William Tauber, M.D.

Designated Federal Officer
Cicely Reese, Pharm.D.

Members Not Present
John A. Bartlett, M.D.
Gail J. Demmler, M.D.
Victoria A. Johnson, M.D.
Maribel Rodriquez-Torres, M.D.

These summary minutes for the October 19-20, 2006 meeting of the Antiviral Drugs Advisory Committee were approved on January 18, 2007.

I certify that I attended the October 19-20, 2006 meeting of the Antiviral Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____/s/_____
Cicely Reese, Pharm.D.
Designated Federal Official

____/s/_____
Kenneth E. Sherman, M.D.
Acting Chair

Summary Minutes
Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Antiviral Drugs Advisory Committee

October 19-20, 2006

The following is an internal report which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at:

http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiviralDrugs

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

Prior to the meeting, the committee and the invited consultants had been provided the background material from the FDA and written statements submitted by the public. The meeting was called to order by Kenneth Sherman, M.D., F.A.C.P. (Acting Committee Chair); the conflict of interest statement was read into the record by Cicely Reese, Pharm.D. (Designated Federal Officer). There were approximately 330 in attendance.

Attendance:
Antiviral Drugs Advisory Committee Present (voting):
Kenneth E. Sherman, M.D., Ph.D. (Acting Chair), 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., Lynn A. Paxton, M.D. (10/20/06 only), Ronald G. Washburn, M.D.

Antiviral Drugs Advisory Committee Member (Industry Representative- non-voting):
Eugene Sun, M.D.

Antiviral Drugs Advisory Committee Special Government Employee (SGE) Consultants (voting):
Miriam J. Alter, Ph.D., Raymond T. Chung, M.D., Karen F. Murray, M.D. (10/19/06 only)

Antiviral Drugs Advisory Committee Regular Government Employee (SGE) Consultants (voting):
Leonard B. Seef, M.D.

Antiviral Drugs Advisory Committee Regular Government Employee (SGE) Consultants (non-voting):
John M. Vierling, M.D., F.A.C.P.

Antiviral Drugs Advisory Committee Patient Representative (voting):
Tracy Swan

Guest Speaker:
Jules Levin

FDA Participants at the Table:
Debra Birnkrant, M.D., Katie Laessig, M.D., William Tauber, M.D.

Open Public Hearing Speakers:
Janice K. Albrecht, Ph.D., David Apelian, M.D., Philip Anthony, Karen Lindsay, M.D

Topic: Presentations, discussion, and questions will focus on clinical trial design issues in the development of products for the treatment of chronic hepatitis C infection. This meeting is being convened in response to the growing number of products in development for this indication. The primary objectives for the committee deliberations are to discuss issues relating to the identification of appropriate control arms, populations for study, endpoints, and long-term follow-up.

FDA Introductory Remarks Hepatitis C: Perspective on Drug Development Issues	Debra Birnkrant, M.D. Director, Division of Antiviral Products, CDER, FDA
Hepatitis C Epidemiology, Natural History, Impact, and Viral Kinetics	Kenneth E. Sherman, M.D., Ph.D. Gould Professor of Medicine, Director, Division of Digestive Diseases University of Cincinnati Medical Center Cincinnati, Ohio
Clinical Experience: Difficulties in Trial Design for Therapeutic Products to Treat Chronic HCV Infection	John M. Vierling , M.D., F.A.C.P. Professor of Medicine and Surgery Director of Baylor Liver Health Chief of Hepatology Baylor College of Medicine Houston, Texas
Community Perspective	Jules Levin Executive Director/Founder National AIDS Treatment Advocacy Project (NATAP)
Summary of Industry Reponses and Regulatory Perspective	William Tauber, M.D. Medical Officer, Division of Antiviral Products, CDER, FDA
Questions / Clarifications	

October 20, 2006

Questions/Discussion

(see next page)

Discussion Questions

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1. Patient Populations

a. Which patient populations are strongly recommended for inclusion at the time of initial approval? In particular, comment on:

- **stage of disease (compensated and decompensated cirrhosis)**

  The committee struggled with making a "one-size fits all" statement and recommended that the compensated cirrhosis patient population should be the focus population for initial registration approval. Decompensated patients represent a high-risk population that, if an effective treatment were available, would benefit. The overall consensus was that therapeutic trials in this population should be initiated early and not at phase IV**.**

- **treatment experience (naïve and interferon+ ribavirin experienced)**

  Overall, the committee felt that naïve and treatment experienced patients should be studied separately but took no strong position.

- **genotype (1 and 4 or 2 and/or 3 or some other grouping)**

  The committee agreed that specific grouping (1/4 or 2/3) is desired for initial approval

- **co-morbidities (HIV and/or HBV co-infection)**

  Prior to initial approval, studies should be performed to evaluate safety and major drug/drug interactions (i.e. CYP-450) with antiretroviral therapy in HIV-coinfected patients. Pilot efficacy trials in HIV coinfection should be planned prior to approval. HBV studies should not be mandated

- **pre and post liver transplantation**

  The committee agreed that the pre and post transplantation groups are important but not required for initial registration. The committee felt strongly that a plan should be in place to study each of these groups prior to initial approval.

- **pediatrics**

  The committee agreed that there should be trial initiation in pediatric patients to gain necessary PK data.

- **racial and ethnic groups**

  There was overall unanimous (no vote) agreement that study designs need to be developed to include racial and ethnic groups that typically are poor responders to therapy, specifically non-Hispanic African Americans. The point was made that it is highly possible to design ways to attract this population to enroll in studies and gain measurable data, with minimal drop-out rates.

The Meeting adjourned for the day at approximately 4:15 p.m. and opened the following day at approximately 8:07 a.m.
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October 20, 2006
Before further discussion of the questions, uniform definitions were established for null, partial, and responder-elapsers:

Null Responders: < 10^1 reduction in HCV RNA at week 12
Partial Responder: 10^1 but < 2 log reduction by 12 weeks, then experience a relapse
Responder Relapser: achieve full clearance of HCV RNA by qualitative assay by week 24 EOT, then experiences a relapse after completion of therapy.

The committee agreed that the "responder relapser" represents a unique class that should be conceptually separated, but included in studies. This group could be included in nonresponder trials, but would need to be stratified. The committee agreed that it was most important to recommend that patients whose therapy histories are poorly characterized should receive a lead-in to clearly identify and stratify appropriately. Lead-in should not be a requirement for initial registration but should be used as a recruitment tool incorporated into study design.

b. For the purposes of pursuing an indication for novel agents in treatment experienced non responder patients, please comment on the following components as inclusion criteria in clinical development studies

- **Previously treated with 1 or more IFN-containing regimens that include PEG-IFN and RBV; and**

  The committee agreed that the previous definitions satisfied the above question regarding inclusion criteria.

- **Failure to achieve a ≥ 2 log reduction in HCV RNA at Week 12, or HCV detectability at Week 24 or beyond while on therapy (confirmed by a repeat test); and**

  The committee agreed that the previous definitions satisfied the above question regarding inclusion criteria.

- **Compliance documented over the first 12 weeks of previous therapy to confirm receipt of at least 80% of the prescribed RBV and PEG-IFN dose.**

  The committee agreed that the 80/80/80 rule should be used as a classification prior to enrollment. The committee also agreed that it is not appropriate to have documented adherence as a requirement.

c. Please discuss whether or not it is appropriate in a clinical trial of prior interferon treatment non-responders to study true responders, partial responders and relapsers together and why.

The committee agreed that relapsers represent a unique class that should be separated to gain further insight into viral kinetics. However, relapsers could be included in trials of nonresponders as long as they are appropriately stratified.

2. Selection of Controls

Are placebo controls or delay of initiation of therapy acceptable, and, if so, of what duration? In your answer, please consider the following patient populations:

- **treatment-naïve versus treatment-experienced**

  Having placebo controls for naïve and treatment-experienced populations is justifiable for add-on to standard of care. However, in the nonresponder population, the committee felt that the design of a

crossover component with limited placebo duration will be important to maximize recruitment and retention of subjects into trials.

- **compensated and decompensated liver disease**

  It was stated that the trial design in this population should start with safety over efficacy, which requires a placebo. Therefore, the committee agreed that placebo control is necessary and that dual stage with a cross over design is recommended.

3. Study Design-Evaluation of Efficacy
Endpoints Compensated Liver Disease

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

a. Which primary endpoint (s) should be used in clinical trials? Please discuss histologic, viral and biochemical endpoints

The division expressed further concern regarding histologic data and asked the committee to elaborate on histologic data for IFN-based therapy with a novel agent.

The committee agreed that SVR remains the standard primary endpoint to be used in clinical trials and the standard for approval using in-place definitions. However, histologic evaluation is encouraged since it may permit identification of safety issues and provide information in the path to licensure based on disease suppression strategies versus the traditional virologic clearance strategy. For non-IFN based regimens, histology may be more optimally judged at the conclusion of therapy rather than 24 weeks off therapy, when viral rebound may diminish any potential benefit of these regimens. **The division also asked the committee to discuss whether there were any endpoints acceptable for an accelerated approval?**

The committee agreed that SVR remains the only acceptable endpoint for accelerated approval.

b. When should the assessment of the primary endpoint be made? Please comment on the pros and cons of an SVR 12 (12 weeks after cessation of treatment) versus SVR 24 (24 weeks after cessation of treatment).

The committee agreed that SVR 24 is appropriate versus SVR 12 and that it is more useful to address collection of data in light of a class of new agents.

c. If a study has treatment arms of a different duration, when should assessment of SVR 24 be made? Specifically, should it be made 24 weeks after end of treatment for all arms, or 24 weeks after the end of treatment based on the arm with the longest duration of therapy?

We're not supposed to attribute comments to any one Member (though it will be in the transcript)The committee agreed that differential treatment follow-up times are appropriate as long as 24 weeks off treatment is used to define sustained virologic response. If a patient's history is used, changes/further analyses may be needed.

d. Please discuss the following study designs

- **adding the investigational agent to standard-of-care (SOC)**

  The committee agreed that this is an appropriate study design but the study should show superiority and other sub-studies based on non-inferiority (i.e., shorter treatment duration, substitution of investigational agent for ribavirin) should follow.

- **use of a dose of PEG-IFN lower than SOC or lower than SOC and of shorter duration + investigational agent**

The committee agreed that non-inferiority is not the first priority at this time and that superiority should be demonstrated for the investigational agent combined with SOC. Non-inferiority trials to test these questions should be planned to follow superiority studies.

- **ribavirin substitution**

(Ribavirin substitution was clarified by the division as removal of ribavirin).
The committee agreed that ribavirin should not be substituted in a pivotal trial. Studies could be conducted for non-inferiority once superiority trials have been completed. However, for special patient populations (such as those who are intolerant or contraindicated for ribavirin (hemodialysis patients, patients with coronary artery disease), primary studies of RBV substitution would be encouraged in phase II trials that would yield potentially important information regarding their efficacy.

- **use of two or more investigational agents**

(The division asked if there were a stage where some phase 2b trials would be beneficial.)
The committee concluded that careful small studies is agreed to be very beneficial and encourages the use of two or more investigational agents. Following phase 2b studies, safety needs to be investigated as well as viral kinetics studies that may enhance larger study designs.

- **Monotherapy**

The committee expressed concern over monotherapy with targeted antiviral agents and their potential to select for resistance. Further questioning by the division regarding induction lead the committee to agree that monotherapy is a likely option if used as short-term sequential therapy during induction to quickly lower the viral load, then add IFN.

e. What degree of change is clinically meaningful for patients with decompensated liver disease when using change in CPT or MELD score as an endpoint?

It was pointed out that MELD versus CPT should be used as an endpoint with the outcome of transplant included in the data. MELD is a more valuable endpoint since the score may be useful to predict short-term survival. It was also stated that reducing the decompensated patient from a MELD of over 15 to one of 15 or below is a useful endpoint since the benefit of transplant for persons with MELD < 15 is outweighed by the risk of transplantation itself. Hence, the clinical need for transplant is diminished with accomplishment of this endpoint.

4. Long Term Follow-Up

Beyond the assessment of the primary endpoint for registration, what is the appropriate duration of follow-up for chronic hepatitis C infection, and what kind of information should be gathered? Please discuss duration of follow-up for different patient populations (especially pediatrics), and, in particular, when an investigational agent is not added to standard-of-care.

The committee agreed that long-term follow-up is beneficial to obtain data on kinetics, especially in the pediatric population.

The Meeting adjourned for the day at approximately 12:15 p.m.