Clinical Trial Design Issues for Drugs to Treat CHB

FDA Advisory Committee

August 7, 2002

Why Now?

- Drug Development for CHB has increased
- Additional drug availability may change types of clinical trials that are feasible
  - Active Control Trials, Combination Therapies
- Timing with consideration of new drug product, adefovir
- Lessons learned from first two drug development programs

Meeting Focus

- Antiviral Drugs Primarily
- Phase 3 and Postmarketing Studies
- Both Compensated and Decompenated Liver Disease
- Aid in planning of future clinical studies

Key Issues

- Essential Patient Populations
- Selection of Controls
- Choice of Primary Endpoint
- Long-term follow-up/Data collection

Agenda: Aug. 7, 2002

- 8:30 Natural History and Clinical Virology of Hepatitis B,
  - *Jay Hoofnagle MD, NIH*
- 9:15 Treatment Outcomes,
  - *Anna Lok MD, University of Michigan*
- 10:00 Break
- 10:30 An industry perspective,
  - *Nat Brown MD, Idenix*
- 11:00 FDA Perspective/Analysis,
  - *Jeff Murray M.D. and Greg Soon PhD, DAVDP*
- 12:00 Lunch
- 1:00 Open Public Hearing
- 2:00 Questions, and discussion

Clinical Trial Design Issues in CHB Drug Development

Jeff Murray

FDA

Key Issues

Compensated and Decompensated CHB

- Essential Patient Populations
- Selection of Controls
- Choice of Primary Endpoint
- Long-term follow-up/Data collection

Patient Populations
Essential for Marketing Applications

- **Patient Demographics**
  - **Although CHB is a global problem, regulatory guidance recommends submission of data that reasonably represents patients in the U.S.**
- **Disease Characteristics**
  - **HBeAg negative/positive**
  - **Patients with drug resistant HBV**
  - **Compensated and Decompensated**
  - **Co-infection**

Patient Populations Study Inclusion Criteria

- Value of lumping or splitting populations in the same study
  - by presence/absence of HBeAg
  - by presence/absence of other viral infections (e.g., HIV, HCV)
  - previous treatments

Selection of Controls

- Are placebo-controlled trials still feasible?
  - For phase 3? For trials of shorter duration?
- Use of Placebo: Considerations
  - Drug availability
  - Risks of Deferring Treatment
  - Strength of recommendations on when to start treatment and what therapy is the best initial therapy
- Active Controls: Lamivudine monotherapy?

Choice of Primary Endpoint Compensated CHB

- Clinical (HCC, death, cirrhosis complications)
- Histology (Knodell, Ishak, Metavir)
- Virologic: HBV DNA
- Serologic: HBeAg loss, eAg seroconversion, sAg seroconversion
- Biochemical: ALT, AST
- Combinations:
  - HBV DNA suppression + ALT normalization

Choice of Primary Endpoint Decompensated

- Child-Pugh Score
- MELD score
- Mortality
- Transplantation
- Complications
- Virologic/Serologic/Biochemical

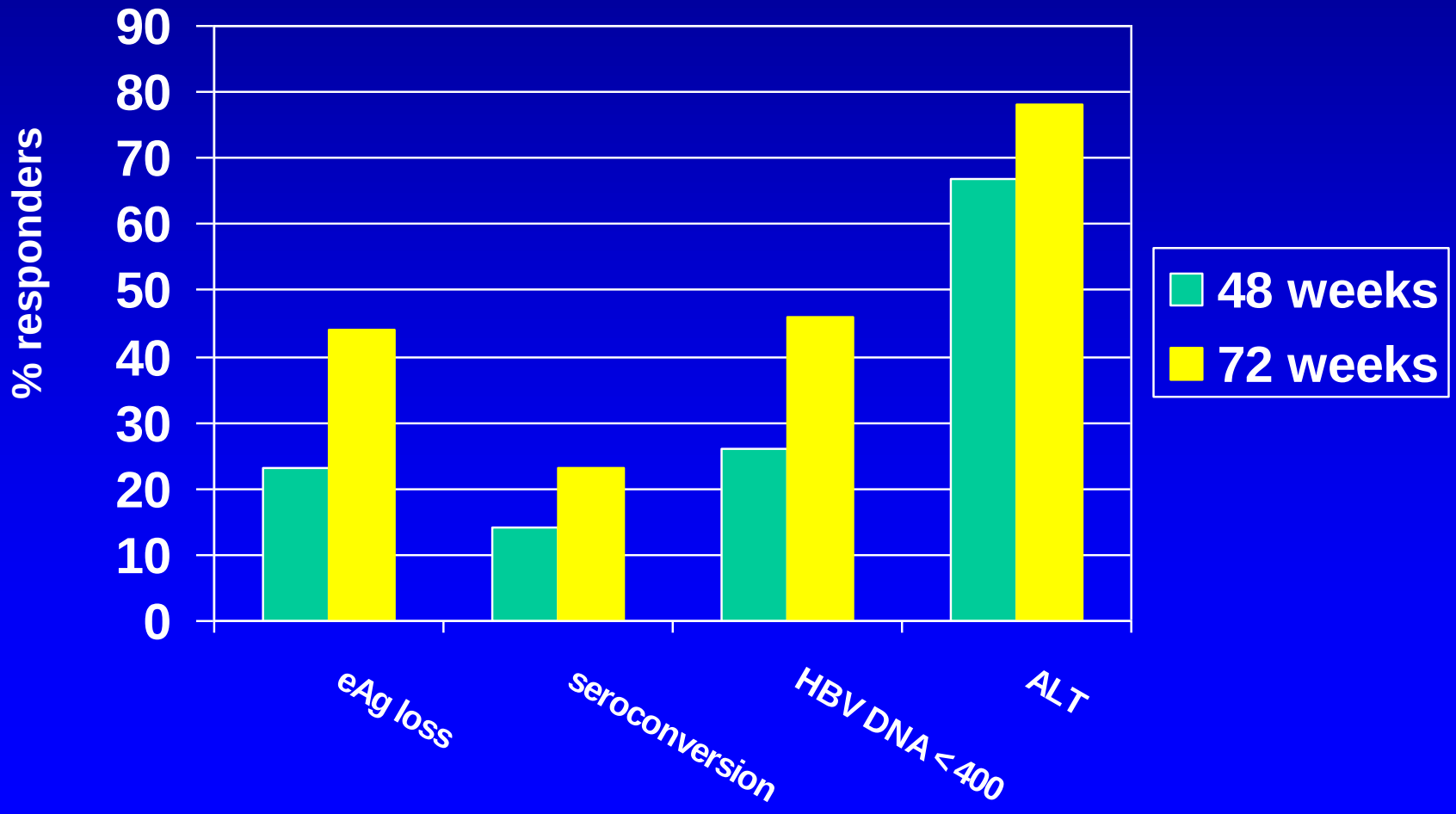
Endpoints

- From a regulatory standpoint: Clinically meaningful
- For CHB drugs, histology has been the "default" endpoint (compensated)
  - direct visualization of end organ
  - treatment induced changes in necro-inflammatory score predictive of progression to cirrhosis complications?
  - Sensitive indicator of drug activity
- In Clinical Practice, serologic endpoints often guide decisions to stop therapy, but are lower frequency events

Endpoint Considerations
In addition to endpoint choice...

- Magnitude of change that is clinically relevant
  - Knodell: 2 point change?
  - Suppression of HBV DNA: to what level?
  - Change in HBV DNA (continuous)
- Duration: Timing of Measurement
  - on/off treatment
  - 48 weeks or longer?
  - Different endpoints may require different duration, seroconversion occurs later

Outcomes at 48 and 72 wks Adefovir Study 437



Endpoint Validation against histology

- Correlations between other endpoints and histologic outcome
- Lamivudine, adefovir data sets
- An endpoint “validation” is strengthened by consistency across multiple studies and drugs
- Metanalysis-Literature

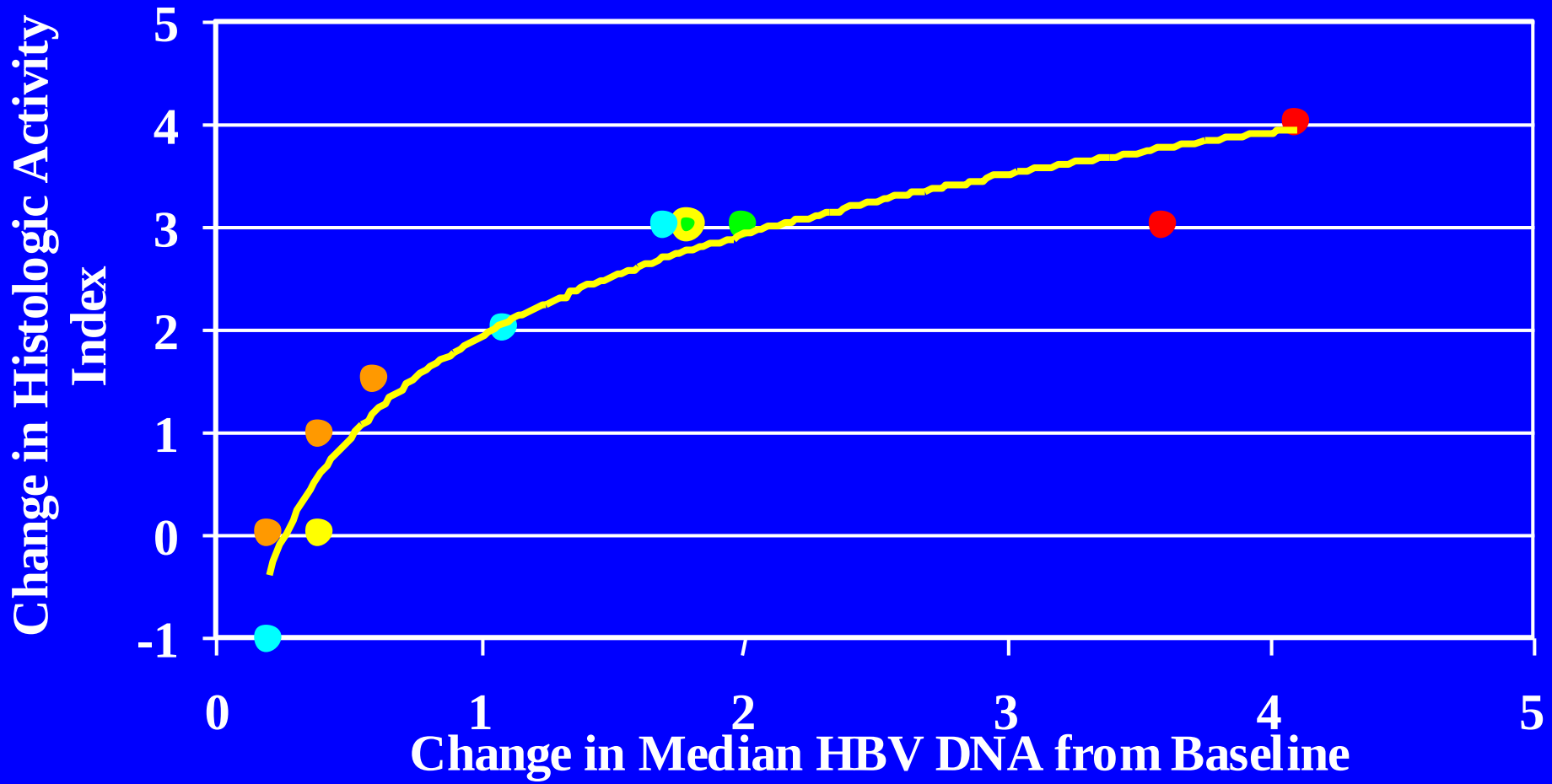
Endpoint Validation

- **Mommeja-Marin H, Mondou E, Blum R. Rousseau F. Serum HBV DNA as a Marker of Efficacy during Antiviral Therapy for Chronic Hepatitis B Virus Infection: Analysis and Review of literature. *Submitted for publication***
- **One Analysis evaluated association between HBV DNA and histologic outcome.**

HBV DNA change and Histology
Studies Analyzed

- Lai et al. *NEJM* 1998
  - Placebo, lamivudine 25mg, lamivudine 100mg QD
- De man et al. *Hepatology* 2000
  - Placebo, famciclovir 1.5g QD and 0.5g tid.
- Dienstag et al. *NEJM* 1999
  - Placebo and lamivudine 100mg QD.
- Barbaro et al. *J. Hepatol* 2001
  - Lamivudine and lamivudine + interferon
- Lau et al. *Hepatology* 2000
  - Lamivudine HBeAg - and + groups

Correlation between Changes in HBV DNA and Histologic Grading (r=0.97, p<0.000001)



Endpoint Validation FDA Analyses

- Lamivudine and Adefovir data-sets
- Correlations between endpoints and histologic outcome (improvement in Knodell score)
  - Year 1 HBV DNA (log10)
  - Change in ALT (log10)
- Strength of correlation method dependent
- Association weaker for HBeAg negative
- Consistency of association important for validating predictive value of a surrogate

Long-term follow-up

- 48 week histologic assessment
  - provides snapshot of drug efficacy
  - not helpful for addressing clinical question relating to duration of therapy, assessing relapse
- In addition to evaluation of a primary endpoint for registration, longer term data collection for CHB is crucial

Questions To The Committee

Patient Population

1. Please identify patient populations that are appropriate targets for treatment studies (consider attributes such as stage of disease,viral genotype, co-morbidities, lamivudine resistance, IFN-experience, pediatrics,HBeAg-/HBV DNA+)? Please Include demographics in your discussion, ie.race and ethnicity.

Cont. Patient Population

2. Which of the aforementioned patient subgroups is essential in a marketing application? In particular, comment on race and ethnicity, disease stage and comorbidities.

Control Arms

3a. Discuss the role of the following controls in the compensated liver disease group:

- Placebo controls/delay of initiation of treatment; and of what duration?

-Lamivudine (or other antiviral drug) monotherapy

-Interferon

Cont. Control Arms

3b. Please also discuss controls for patients with decompensated liver disease or who have failed previous regimens.

Study Endpoints and Timing of Evaluation

4. Consider the patient populations identified in question #1, the information presented today, and the necessity that endpoints for registration be clinically meaningful, please answer the following:

Cont. Endpoints...

Cont. Question #4

a. Which endpoint (or combination or endpoints) should be the primary in clinical trials? Please discuss histologic, serologic (HBeAg loss vs seroconversion; HbsAg loss vs. seroconversion), biochemical, and virologic endpoints.

Cont. Endpoints...

b. When should the assessment of the primary endpoint be made?

c. List the most appropriate secondary endpoints and rank them in order of importance.

Cont. Endpoints...

5. For histologic endpoints, what is the preferred method of histologic scoring? What degree of change in histologic score is clinically meaningful?
6. For virologic endpoints, which assay is best suited for clinical trials? What is the appropriate cutoff point for HBV DNA (eg < 10^5, <10^4, etc)? Should viral genotyping be done and why?

Cont. Endpoints...

7. For Patients with decompensated liver disease, please discuss the feasibility/validity of the following alternative endpoints:

   - mortality

   - change in Child Pugh or MELD score (or its components)

   - transplant/no transplant

   - occurrence of liver disease assciated illness (variceal bleed, SBP, etc)

Long Term Follow-Up

8. Beyond the assessment of the primary endpoint for registration, what is the appropriate duration of studies for treatment of chronic hepatitis B infection, and what kind of information should be gathered?