

To: Members and Guests of the Antiviral Drugs Advisory Committee

From: The Division of Antiviral Drug Products

Re: August 7th Advisory Committee Meeting to discuss clinical trial design issues in the development of drugs to treat chronic hepatitis B

Date: July 10, 2002

The purpose of this document is to provide background information for the Aug. 7th advisory committee meeting, which is being convened to discuss issues in clinical trial design for the development of drugs to treat chronic hepatitis B disease. As you are aware there are two therapeutic agents approved for the treatment of chronic hepatitis B (CHB), interferon alpha and the antiviral drug, lamivudine. In addition, on Aug. 6th, the committee will be asked to provide comments on the safety and efficacy of a second antiviral drug, adefovir, to treat CHB (please refer to the separate adefovir background document). Also, several other anti-HBV drugs are currently in phase 2 and 3 development. Given recent advances in the field, the Division believes this is an opportune time to discuss clinical trial design issues in hepatitis B drug development. Although therapeutics for CHB includes both antiviral drugs and immune modulators, we would like the discussion on Aug. 7 to focus primarily on antiviral drugs, and on the design of the principal phase 3 studies intended to support registration.

The attached references and information/analyses included in this document are intended to aid the committee as they address these issues. In the initial planning for this advisory committee meeting, the Division asked pharmaceutical sponsors to submit written opinions on clinical trial design issues. They were asked to support any conclusions with references or data from their own drug development. This background document was written taking into consideration information from these submissions.

Please see attachment A for the discussion points/questions that the advisory committee will be asked to address. In brief, the discussion points focus on the following issues: the appropriate and essential patient groups that should be studied in CHB drug development, selection of control arms for phase 3 studies, the most appropriate endpoint or combination of endpoints to evaluate efficacy, and the type of information that should be collected during longer-term follow-up in phase 3 studies. Background information pertinent to each of these issues is presented in the following sections along with the corresponding questions/discussion points (in boxes at the beginning of each section below) that the committee will be asked to address.

1.0 Patient Populations

Advisory Committee Discussion Points

- 1. 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, i.e. race and ethnicity.*
- 2. Which of the aforementioned patient subgroups are essential in a marketing application? In particular, comment on race and ethnicity, disease stage and co-morbidities.*

Hepatitis B drugs are developed globally. While an estimated 1.25 million individuals in the United States are chronically infected with HBV (surface antigen positive for at least 6 months), approximately 350 million persons are chronically infected worldwide [1]. Therefore it is reasonable that a development program would study patients with CHB throughout the world. However, from a regulatory standpoint, a marketing application should also contain safety and efficacy data that includes a fair representation of CHB patients from the U.S. In the U.S. CHB is more common among African Americans than Caucasians but rates are highest among Asian Americans, especially immigrants. [2]

We would like the committee to focus on both demographics (race/ethnicity) and disease characteristics when considering patient groups that are most appropriate for establishing safety and efficacy in principal phase 3 studies. We would also like the committee's opinion regarding the essential patient groups to support a marketing application considering that certain demographic and disease characteristics may be correlated, such as race/ethnicity and frequency of CHB with precore mutant.

After discussing the important subgroups that should be studied and included in a marketing application, the Division would like the committee to comment on the types of studies that should be conducted to obtain data in various subgroups. The committee should comment on whether it is advisable or necessary to conduct separate studies for certain disease characteristics or whether larger studies should be conducted that stratify randomization based on baseline characteristics. Information on the response rates in various patient subgroups will help to address this question. For example, response rates appear to be fairly similar for HBeAg negative or positive CHB among patients treated with antivirals such as lamivudine; however response rates differed for these two groups in studies of interferon (patients with HBeAg negative disease showed a lower response than those with HBeAg positive disease)[3].

A high level of morbidity or other factors may make it difficult to conduct a randomized controlled study in certain patient groups. Patients at imminent risk of complications may be better suited to enroll in open-label expanded access safety studies. For subgroups with certain demographics or disease characteristics, such as co-infection with HCV or HIV, we would like the committee to comment on whether it is essential that adequately-powered, randomized controlled studies be completed for all subgroups, or whether it would be more appropriate to include these patients in larger pivotal studies or in studies with alternative designs. Another issue to consider is whether all current drug candidates should be studied for activity against lamivudine resistant populations.

2.0. Selection of Controls

Advisory Committee Discussion Points

- 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?*
 - *Active controls: Lamivudine (or other antiviral drug) monotherapy or Interferon*
- 3b. *Please also discuss controls for patients with decompensated liver disease or those who have failed previous regimens*

We would like the committee to comment on selection of control groups for studies evaluating drugs in both compensated and decompensated liver disease due to CHB. Most experts appear to agree that placebo controlled trials in patients with decompensated liver disease would not be acceptable. In addition, many investigators contend that placebo-controlled phase 3 studies in patients with compensated liver disease are also no longer acceptable because several approved therapies for CHB are available. However, factors other than drug availability may be important when considering the feasibility of placebo controlled studies. These factors may include the rate of disease progression without treatment (risk to the study participant) and the certainty in which the optimal choice and timing of an initial regimen is known (clinical equipoise). Although rapid progression to cirrhosis has been documented among some individuals, CHB is generally considered to be slowly progressive for most individuals. Among patients with CHB referred to clinical centers, the incidence of cirrhosis is estimated to be up to 2-3% per year [1]. For patients with compensated cirrhosis the 5 year survival rate is 84% [1]. Thus, most patients would not be expected to have substantial morbidity if left untreated for a period of time (perhaps up to one year). In addition, in one of the pivotal studies for

lamivudine, 2 point worsening in the HAI occurred in 24% of patients on placebo compared to 11% on lamivudine [4,5] (an absolute difference of 13%).

The optimal timing and choice of initial therapy for hepatitis B does not appear to be definitively established. As stated in a summary of a workshop sponsored by the National Institute of Diabetes and Digestive Kidney Diseases (NIDDK) and the American Gastroenterological Association [2] regarding recommendations for starting therapy,

“Currently, therapy of hepatitis B is difficult and limited in long-term efficacy. Therefore the decision to initiate therapy should not be taken lightly and should be based on a combination of serum liver tests (ALT elevations), virologic assays (presence of HbeAg and/or HBV DNA at levels $> 10^5$ copies /mL), liver histology (presence of moderate disease activity and fibrosis), and virologic testing to exclude concurrent hepatitis C or D and HIV infection. **In patients with mild disease, it is appropriate to monitor ALT levels and defer therapy until advances have been made that allow for sustained benefit in most patients. At issue is what criteria should be used to define moderate-to-severe disease and to recommend therapy [emphasis added].**”

Therefore, it appears that there may be equipoise, at least for some patient groups, to consider deferred therapy, pending future clinical studies. If placebo controlled studies (or “treatment-deferred studies”) are not acceptable for 48-week phase 3 studies, we will ask you to comment on whether they are still feasible for shorter-term (< 6 months) dose-ranging studies or other phase 2 studies.

The alternative to placebo-controlled studies is active-controlled studies comparing a new drug with interferon, lamivudine, or subsequently approved agents. It must be recognized that active controlled studies will require larger sample sizes to assess non-inferiority. Sample size will also depend on the endpoint chosen. If lower frequency events are chosen for an endpoint (such as seroconversion), then a smaller delta will be needed, this will in turn require a much larger sample size.

Another issue regarding active controlled studies with lamivudine is the known risk of emergence of resistance to lamivudine. In addition because of interferon’s route of administration and tolerability profile, blinding active controlled studies with interferon will not be feasible.

For decompensated disease active controlled studies with lamivudine could be used, whereas interferon is not recommended for decompensated patients. However, one must consider that many patients with decompensated liver disease may have already developed resistance to lamivudine and may not be willing to participate in a controlled study with lamivudine. The other issue is

whether the treatment effect of an active control in decompensated hepatitis is adequately known relative to placebo in order to choose an appropriate delta for a noninferiority study.

3.0 Evaluation of Efficacy: Endpoints

3.1 Compensated Liver Disease

Advisory Committee Discussion Points

4. *Considering the patient populations identified in question #1, the information presented, and the necessity that endpoints for registration be clinically meaningful, please answer the following:*
 - *Which endpoint (or combination of endpoints) should be the primary in clinical trials? Please discuss histologic, serologic, biochemical, and virologic endpoints.*
 - *When should the assessment of the primary endpoint be made?*
 - *List the most appropriate secondary endpoints and rank them in order of importance.*
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?*

Probably the most pressing issue confronting clinical studies evaluating drugs to treat CHB is the choice of primary endpoint. Choice of endpoint may depend on the population studied such as, compensated vs. decompensated liver disease, and presence or absence of e antigen. From a regulatory standpoint, primary endpoints that assess differences in clinically meaningful outcomes are generally required. For CHB, the ultimate goal of treatment is to prevent clinical sequelae such as cirrhosis complications, hepatocellular carcinoma, or death. However, given the amount of time required to detect treatment arm differences for such outcomes in patients with compensated liver disease, studies employing these endpoints would not be logistically feasible. Thus to support the approval of lamivudine a histologic endpoint was considered to be a stringent primary endpoint in that the disease in the end organ could be directly visualized. Changes in histology have been the recommended primary endpoint for subsequent phase 3 drug studies. However, it must be recognized that even liver histology is a surrogate for the desired clinical endpoints. In CHB drug development, multiple secondary endpoints have been evaluated to support efficacy including biochemical, serologic and virologic parameters.

When selecting an endpoint, one must consider the choice of measurement (e.g., histologic, HBV DNA), the timing of the measurement (e.g., 1 year on treatment), and the magnitude of change in measurement deemed to be clinically meaningful (e.g., suppression of HBV DNA below a threshold, loss of e antigen, or changes or improvement in histologic scores). One may also consider using a composite endpoint consisting of two or more measurements (ALT + HBV DNA).

The following sections review some of the advantages and disadvantages of several possible endpoints for evaluating CHB drugs. In addition, data showing correlations between the endpoint and clinical outcome or with histologic outcome are presented when available.

3.1.1 Histologic Endpoint

To date, histologic improvement has been the recommended primary endpoint for regulatory purposes in studies of antiviral drugs to treat CHB. For lamivudine and adefovir, histologic changes served as the primary endpoint in pivotal registrational studies. For lamivudine studies the proportion of participants with a 2 point improvement in the total Histologic Activity Index (Knodell score)[4] was used. For adefovir the definition of improvement was slightly modified to include a 2 point reduction in the Knodell score with no worsening of the fibrosis score.

Some contend that there will be a lot of missing data for histologic endpoints because of patient refusal to undergo a second biopsy or because of specimen mishandling. But the lamivudine and adefovir phase 3 trials do not support this opinion. There was lack of paired biopsy specimens in approximately 15-21% of patients participating in lamivudine studies and in only 5-9% in adefovir phase 3 studies.

Advantages:

- direct visualization of inflammation and changes in structure of the liver;
- histologic treatment difference between active drug and placebo is sufficiently large (approx. 30% difference in 2-point improvement) to allow for “reasonably sized” studies

Disadvantages:

- invasive procedure
- multiple assessments (more than two) not feasible on a large scale
- variability in measurement owing to small sample or subjectivity of reading
- because of limited sampling cannot provide information regarding the time course of the response; unlikely to provide guidance on the duration of therapy

Correlation with clinical outcomes:

- no analyses correlating treatment induced changes in the Knodell score and ultimate clinical outcome, such as the development of cirrhosis related complications, hepatocellular carcinoma, or death

3.1.2 Serologic Endpoints

Serologic endpoints include clearance of e antigen, e antigen seroconversion (defined as e-antigen loss, e-antibody gain and suppression of HBV DNA < 10⁵ copies), or clearance of surface antigen with acquisition of surface antibody. These were important secondary endpoints in previous drug development programs. In clinical practice e antigen seroconversion is often the “endpoint” used for deciding when to stop therapy [1].

Advantages:

- noninvasive
- can obtain measurements at multiple time points, can measure onset and duration of efficacy.
- HBeAg seroconversion often used in the decision to stop treatment in clinical practice
- loss of surface antigen considered as resolution of CHB

Disadvantages:

- Can't use e antigen seroconversion in studies of e-antigen negative CHB (precore mutant).
- Loss of e-antigen may not be stable
- May have histologic improvement even in the continued presence of e-antigen
- Surface antigen loss is a low frequency event
- Treatment differences in e-antigen seroconversion between active drugs and placebo is approximately 10% at 1 year. For noninferiority studies this would require a delta of < 10 %. This would necessitate large sample sizes or longer studies. Larger treatment differences between active drugs and placebo would be expected for clearance of e antigen (without acquisition of Ab).

Correlation with clinical outcomes:

Loss of e-antigen and seroconversion have been shown to be associated with a reduction in the risk of clinical complications of CHB. In follow-up studies, interferon responders (loss of e-antigen and sustained suppression of HBV DNA) had lower rates of liver related complications and mortality [6].

3.1.3 Virologic Endpoint

Reduction in HBV DNA is the preferred endpoint in phase 1 and 2 dose-ranging studies.

Advantages:

- dynamic endpoint with rapid reduction/rebound with start or cessation of antivirals
- quantitative, can measure at multiple time points
- well suited to evaluate inhibition of viral replication by antiviral agents

Disadvantages:

- different assays with different range of sensitivity
- does not measure liver inflammation

Correlation with clinical outcomes

No analyses showing direct correlations with clinical outcomes. However as discussed below, there is some information correlating changes in HBV DNA with other outcomes (histologic, serologic) and there is indirect evidence that lowering HBV DNA leads to clinical improvement in patients with decompensated liver disease.

- One small study suggested that patients maintaining HBV DNA levels $< 10^4$ genomes/mL are more likely to have HBeAg seroconversion (4/12 patients) than patients with HBV DNA levels $> 10^4$ genomes/mL (0/11 patients) [7].
- In studies of decompensated liver disease, patients receiving lamivudine demonstrated concomitant suppression of HBV DNA and improvement in Child-Pugh-Turcotte scores [8,9]. The authors state that previous studies have shown that spontaneous improvement in liver function is unusual in CHB patients with established cirrhosis and hepatic decompensation. Consequently, the improved liver function in these studies was unlikely to be due to factors other than the antiviral effect (i.e., HBV-DNA suppression) of lamivudine. This indirectly supports the notion that HBV DNA suppression is the mechanism through which the treatment effect is mediated for antivirals.
- FDA conducted several analyses using data sets from the lamivudine and adefovir development programs evaluating correlations between changes in HBV DNA and improvements in histologic outcome (the currently recommended primary endpoint for registrational trials). These are shown in detail in section 5.0 below. In brief, for both drugs there was a weak correlation between year 1 HBV DNA levels and changes in histology scores when evaluating associations at the individual or trial level. However, such analyses may have been limited by substantial variability in histologic measurements, in which the intrasubject variability (standard deviation) for sequential biopsies is substantial. When evaluating the proportion of the histologic treatment effect explained by HBV DNA some lamivudine and adefovir studies, it appears that HBV DNA measurements were predictive of histologic outcome. The disparity in these results may be explained by the fact that analyses evaluating “proportion of treatment effect explained” are less influenced by the variability of the histologic measurements.

3.1.4 Biochemical Endpoints

Biochemical endpoints typically include transaminases, AST and ALT. Although a single measurement is not a good indicator of hepatic damage, measurements over time particularly when combined with other parameters may be an indicator of changes in histology.

Advantages:

- easy, inexpensive, can measure at multiple time points
- with repeated measurements, elevated transaminases may correlate with liver inflammation

Disadvantages

- an elevated ALT does not necessarily signal worsening disease but may herald clinical improvement

Correlation with clinical outcomes:

- FDA analyses using data sets from the lamivudine and adefovir development program show a modest correlation between reductions in transaminases and changes in HAI. The correlation between changes in transaminases and histology was greater than that found for HBV DNA and histology. These are shown in section 5.0 below.

3.2 Endpoints: Decompensated Liver Disease*Advisory Committee Discussion Points*

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

- *mortality*
- *change in Child-Pugh score (or its components)*
- *transplant/no transplant*
- *occurrence of liver disease associated illness (variceal bleed, SBP, etc)*

Several uncontrolled studies have been conducted using antivirals to treat patients with decompensated liver disease secondary to CHB. In studies, decompensated liver disease generally includes patients with Child-Pugh (CP) scores of B and C (appendix C). In studies of both lamivudine [8,9] and adefovir (see Aug. 6 background documents), patients experienced improvements in CP score concomitant with reductions in HBV-DNA. Some patients were removed from wait lists for transplantation. In addition comparisons of mortality rates with historical controls (realizing the caveats of historical controls) appeared to show improvement. From what is known regarding the natural history of decompensated liver disease, spontaneous improvements without intervention would be highly unlikely.

4.0 Long Term Follow-up

Advisory Committee Discussion Points

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

Since many patients with CHB require prolonged treatment with antivirals to maintain a treatment response, there will be value in collecting long-term data. Although studies of 1 year duration (or less) have been used to approve previous therapeutic agents for hepatitis B, a longer duration of follow-up may show further improvements in markers of CHB. Based on the adefovir data, mean changes in HBV DNA appear to slowly decrease over time (even after one year) and additional people show loss of e antigen or seroconversion.

In addition, longer-term studies should be conducted to assess the occurrence of any late-occurring toxicities or maintenance of treatment response of patients who have discontinued therapy

5.0 FDA Exploratory Analyses of Clinical Trial Data

This section describes the outcomes of exploratory analyses correlating measurements such as ALT and HBV DNA with histologic outcomes at 48 weeks. Additional data may be presented to the committee on August. 7th.

5.1 Description of Data Sources

The following analyses were conducted using data from NDA reviews of lamivudine and adefovir. The tables below list the studies included in the exploratory analyses. Treatment groups, respective sample sizes, and the frequency of missing biopsies are shown. Only subjects who had a baseline and follow-up biopsy were included in these exploratory analyses. The total number of patients from the two NDAs is 1573, of whom 1372 had biopsies at one year. Among 1372 subjects evaluable for biopsy, 17 subjects had missing ALT or HBV DNA at the end of one year.

Table 5a: Lamivudine Studies Included in Exploratory Analyses

Lamivudine (N=901)							
Study	Protocol	PBO	LAM 100	LAM 25	LAM +IFN	IFN	Missing Biopsy
US	NUCA3010	63	62				17%
IFN Nonresponder	NUCAB3011	54	110		59		21%
Asian	NUCB3009	68	131	134			10%
Active-control	NUCB3010		81		72	67	21%
Total		185	384	134	131	67	16%

Table 5b: Adefovir Studies Included in Exploratory Analyses

Adefovir (N=672)					
Study	Protocol	PBO	ADV10	ADV30	Missing Biopsy
HbeAg+	GS-98-437	161	168	165	9%
HbeAg-	GS-98-438	57	121		5%
Total		218	289	165	8%

Patients randomized to interferon-containing regimens were treated for 24 weeks followed by an off-treatment period, all other patients were treated for one year. Biopsies were done after one year.

HBV DNA and ALT levels were typically measured every 4 weeks. For lamivudine studies, the HBV DNA was measured by Abbott hybridization assay, which has a very high lower limit (around 500,000 copies/mL by some conversion method). Adefovir trials used PCR assay, which has a lower limit of 400 copies/mL. The high lower limit for the assay used to measure HBV DNA in lamivudine studies may impose limitations on the interpretability of the correlation analyses of HBV DNA and histology.

5.2 Procedures

Analyses exploring the relationship between average year 1 HBV DNA (\log_{10}) levels or changes in ALT and histologic outcomes were conducted using four methods.

- The first method examined individual patient level correlations
- The second method simply involved plotting average Year 1 absolute HBV DNA level vs. change in histology for each treatment arm in several studies. Studies were subdivided into smaller “trials” determined by region and race to increase the number of data points.
- The third method examined trial level correlations, i.e., the correlation of treatment effects (treatment differences between drug and placebo) for change in ALT or year 1 absolute HBV DNA vs. treatment effects on biopsy

score. As in method 2, studies were divided into smaller “trials” determined by region and race to increase the number of data points for trial level correlation.

- The fourth method evaluated the proportion of treatment effect (change in Knodell score) explained by changes in ALT or year 1 HBV DNA.

Both ALT and HBV DNA was converted to a \log_{10} scale. In all analyses, patients with missing values were excluded.

For analyses examining individual correlations, coefficients were computed for each study and each treatment arm. Within studies, consistency in how certain parameters (i.e., ALT or HBV DNA) predict histologic outcome were explored by fitting a linear model and examining the treatment by surrogate endpoint interaction. An overall correlation for each study was computed after adjustment for treatment effect. Similarly, consistency in the relationship between change in ALT or year 1 HBV DNA vs. histologic outcome was examined.

Trial level correlation examines how treatment responses in potential surrogate endpoints relate to treatment effects on biopsy across many different trials in order to evaluate how well the potential surrogate markers could predict the biopsy outcome in a future trial. It should be noted that some of the trials used in these analyses had more than two treatment arms. To generate independent data for studies with more than two treatment arms, the control was re-randomized into several subgroups to be combined with the treatment groups. This was done for Asian lamivudine study and adefovir study 437. For example, for study 437 the placebo arm was re-randomized equally into two arms to form two new two-arm studies. This was not done for IFN-containing regimens.

5.3 Results of Exploratory Analyses

5.3.1 HBV DNA vs Histology

Individual-Level Correlation (method 1)

Table 5c shows correlation coefficients for year 1 \log_{10} HBV DNA level vs. changes in Knodell score at one year in lamivudine studies. Table 5 d shows the same for adefovir studies. Note that the assay used in the lamivudine studies had an insensitive lower limit. Many patients achieved suppression below this assay limit, therefore the assay could not differentiate among these subjects. The correlation between year 1 HBV DNA and changes in Knodell score is relatively weak. For adefovir studies, the correlation for the HBeAg negative group (study 437) was weaker than that of the HBeAg positive group (study 438)

Although the correlations would be considered to be weak, they were statistically significant when combining studies (overall) for each drug. Note that all

correlations were adjusted for study and randomized treatment (* = significantly different from 0 at level 0.05, ** = significance level at 0.0001).

**Table 5c: Individual Correlation Analyses for Lamivudine Studies
Year 1 HBV DNA vs. Change in Knodell Score**

Lamivudine						
Study	PBO	LAM 100	LAM25	LAM+ IFN	IFN	Overall
US	0.19	0.41*				0.30*
IFN Nonresponder	0.27	0.34*		0.62**		0.40**
Asian	0.23	0.16	0.29*			0.22**
Active-control		0.28*		0.31	0.34*	0.31**
Overall	0.23*	0.28**	0.29*	0.46**	0.34*	0.30**

LAM: lamivudine. PBO=Placebo. IFN=interferon

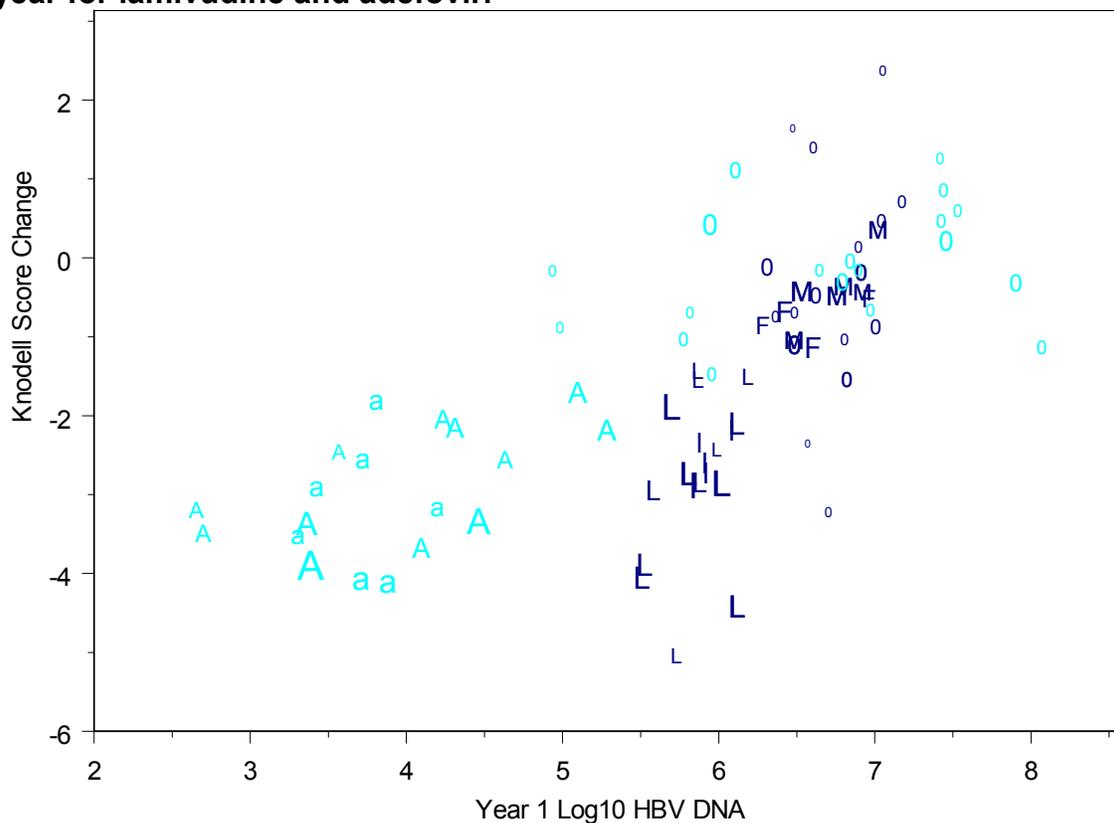
**Table 5d: Individual Correlation Analyses for Adefovir Studies
Year 1 HBV DNA vs. Change in Knodell Score**

Adefovir				
Study	PBO	ADV10	ADV30	Overall
Study HbeAg+ 437	0.33**	0.35**	0.36**	0.34**
Study HbeAg- 438	0.13	0.05		0.09
Overall	0.28**	0.26**	0.36**	0.29**

Plot of HBV vs. Histology (method 2):

Figure 5a is a plot of year 1 \log_{10} HBV DNA vs. change in Knodell score at 1 year for treatment groups in adefovir and lamivudine studies. The plot shows a clear separation of data points for the lamivudine vs. adefovir studies that is probably a reflection of the different assay limits for the assays used for the two NDAs. For this reason, analyses of trial level associations were conducted for each drug separately.

Figure 5a: HBV DNA (\log_{10}) level at year 1 vs Change in Knodell Score at 1 year for lamivudine and adefovir.



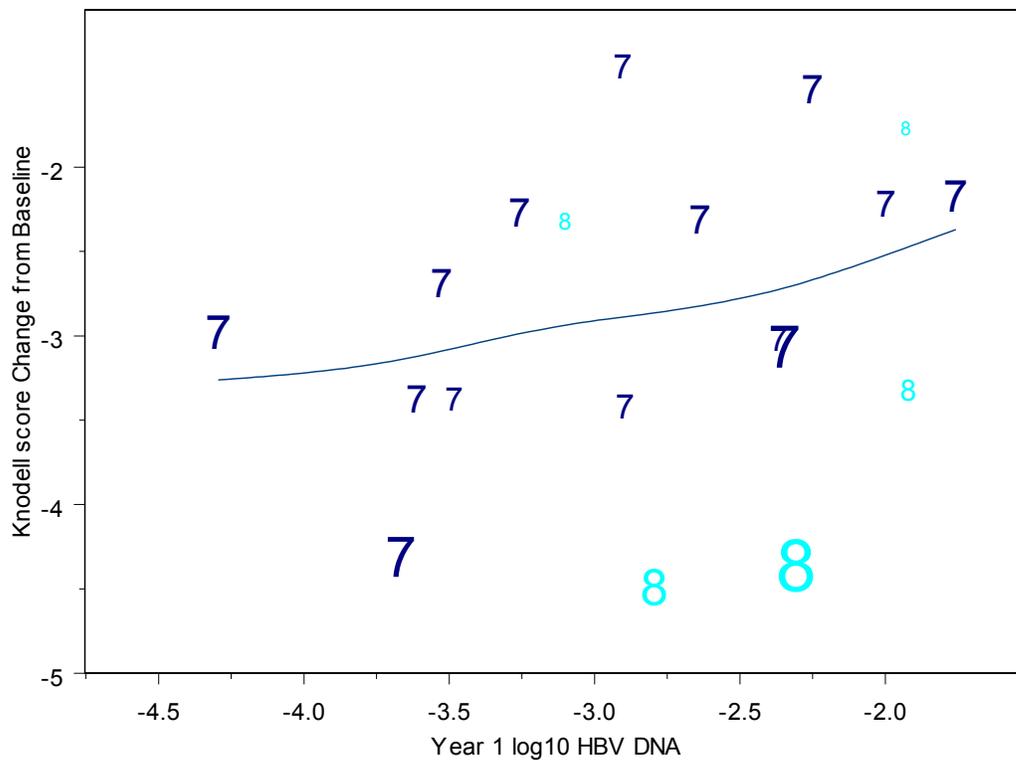
L=Lamivudine 100mg, I=lamivudine 25mg, O=Placebo, M=LAM+IFN, F=IFN alone, A=adefovir 10 mg, a=adefovir 30 mg. Size of characters is proportional to sample size.

Trial Level Correlations: HBV vs. Histology (method 3)

The trial level correlations examine treatment differences in \log_{10} HBV DNA (at 1 year) between treatment arms vs. treatment differences in Knodell score change across studies.

Figure 5b shows the associations for adefovir trials. At trial level, treatment differences for \log_{10} HBV DNA at year 1 of therapy correlate with treatment differences in the change in Knodell score with a correlation coefficient of 0.41 ($R^2 = 17\%$, confidence limits, 0% to 49%).

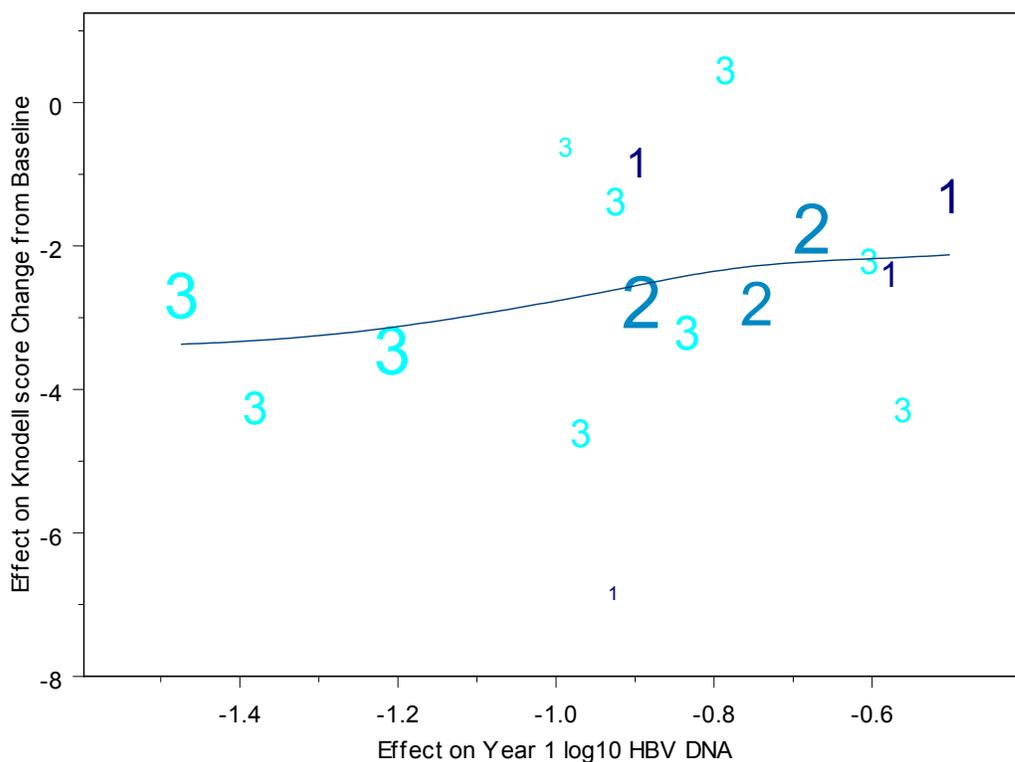
**Figure 5b: Year 1 HBV DNA (\log_{10}) vs Change in Knodell Score at 1 year.
Trial level correlations for adefovir studies.**



*7's represent data points from adefovir study 437 and 8's represent data points from 438.
Size of characters is proportional to sample size.

Figure 5 C shows the correlation for lamivudine studies, excluding IFN-containing arms. The R^2 value was only 5%, worse than that observed for the adefovir trial level correlations.

Figure 5c: Year 1 HBV DNA (\log_{10}) vs Change in Knodell Score.
Trial level correlations for lamivudine studies



1=US Study, 2=IFN-non-responder Study, 3=Asian Study
 Size of characters is proportional to sample size.

5.3.2 Results: ALT vs Histology

Individual Level Correlation (method 1)

Tables 5 e and f show the correlation between the change from baseline in \log_{10} ALT with the total change in necro-inflammatory scores from baseline at one year, for lamivudine and adefovir studies, respectively. Note that all correlations were adjusted for study and randomized treatment (* = significantly different from 0 at level 0.05, ** = significance level at 0.0001).

Overall the correlation between change in ALT and histology was greater than that observed for HBV DNA and histology.

**Table 5e: Individual Correlation Analyses for Lamivudine Studies
Change in ALT vs. Change in Knodell Score**

Lamivudine							
Study	PBO	LAM 100	LAM25	LAM+ IFN	IFN	Overall	Homogeneity
US	0.56**	0.59**				0.57**	0.38
IFN Nonresponder	0.31*	0.25*		0.74**		0.39**	0.001
Asian	0.37*	0.53**	0.64**			0.54**	0.21
Active-control		0.26*		0.26*	0.26	0.26**	0.98
Overall	0.40**	0.37**	0.64**	0.50**	0.26	0.43**	0.02
Homogeneity	0.54	0.55		<0.0001		<0.0001	0.013

LAM: lamivudine. PBO=Placebo. IFN=interferon

**Table 5f: Individual Correlation Analyses for Adefovir Studies
Change in ALT vs. Change in Knodell Score**

Adefovir					
Study	PBO	ADV10	ADV30	Overall	Homogeneity
HbeAg+	0.47**	0.50**	0.57**	0.52**	0.30
HbeAg-	0.23	0.32*		0.29**	0.59
Overall	0.41**	0.44**	0.57**	0.46**	0.37
Homogeneity	0.12	0.12		0.03	0.85

ADV10 = adefovir 10 mg; ADV30 = ADV 30

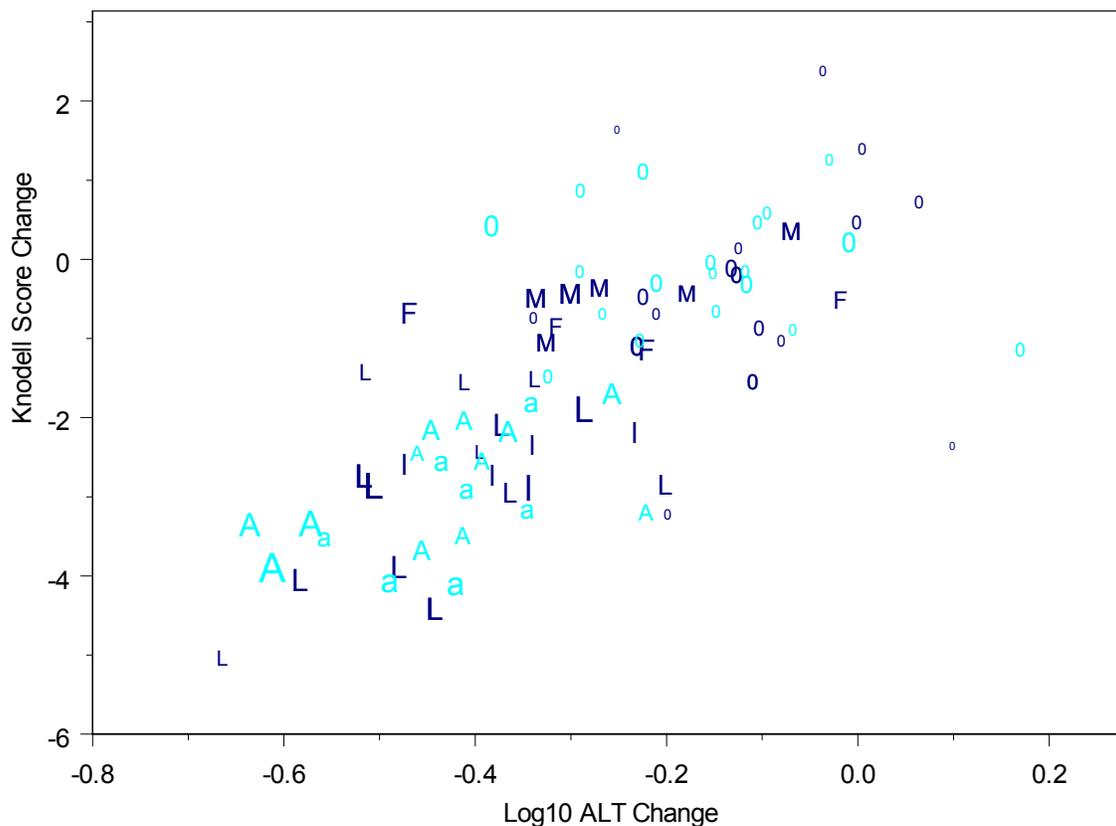
Homogeneity: p-value for testing if unit change in log₁₀ ALT has the same impact on the Knodell score across the row or column.

There is considerable variation in the correlation coefficients across studies. For adefovir, within study variation between treatment groups are small. For lamivudine, the within study variation arises from the larger correlation in the LAM+IFN arm of the IFN-Nonresponders study, and the smaller correlation in the placebo arm of the Asian study.

Plot of ALT vs Histology:

Fig. 5d shows the correlation between change in log₁₀ ALT and change in Knodell score at 1 year for all the treatment arms.

Figure 5d. Change from Baseline in ALT (\log_{10}) vs Change in Knodell Score at 1 year for lamivudine and adefovir studies.



L=Lamivudine 100mg, I=lamivudine 25mg, O=Placebo, M=LAM+IFN, F=IFN alone, A=adefovir 10 mg, a=adefovir 30 mg.

Size of characters is proportional to sample size.

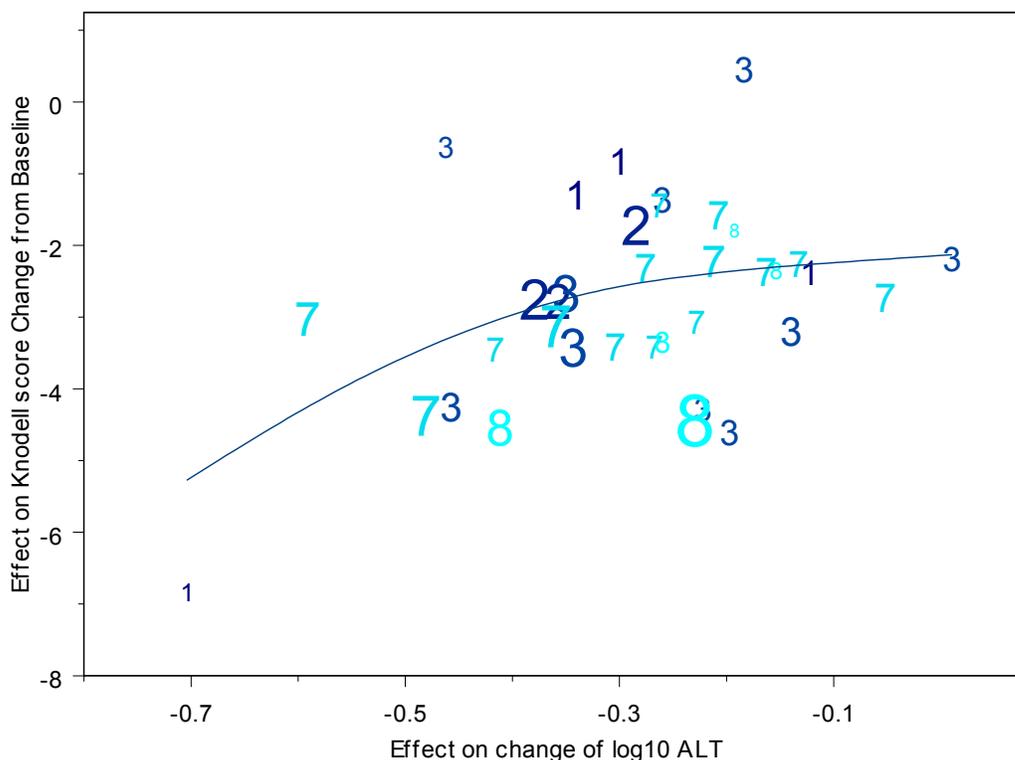
Note that the responses were separated into several groups according to treatment. In the lower left corner of Figure 5d the data points are mostly from lamivudine or adefovir arms, in the upper right corner the data points are mostly from placebo arms, and in between the data points are mostly from IFN-containing regimens or placebo arms.

Trial Level Correlations: ALT vs Histology

The trial level correlations examine treatment differences in \log_{10} ALT change between treatment arms vs. treatment differences in Knodell score change across studies.

The trial-level correlation shown in Fig. 5e included placebo, lamivudine and adefovir arms, but excluded IFN-containing arms. Each study was divided into smaller “substudies” according to region and race. A scatter plot of the relationship for treatment effects on log₁₀ ALT change vs. biopsy change is given below.

Fig. 5e. Trial Level Correlations for Change in ALT vs. Change in Histology, for adefovir and lamivudine studies.



1=US Study, 2=IFN-non-responder Study, 3=Asian Study, 4=Active Control Study, 7=HbeAg+ Study, 8=HbeAg- Study, size of symbol is proportional to the sample size of each sub-study.

From the graph we see there is a trend that the larger the treatment difference between either lamivudine or adefovir arm compared to the placebo arm, the larger the treatment effects on Knodell score change. However, there is also considerable noise in this prediction. In fact, the estimated R^2 value is 17% (95% C.I. 0% to 40%), indicating a limited predictive value of treatment effect on log₁₀ ALT change.

Note in the graph above there is one sub-study in the US study at the lower left corner, that deviates significantly from other points. Removing this sub-study decreased the trial level association considerably, $R^2= 4\%$.

When restricted to adefovir alone, trial level $R^2 = 25\%$ (95% C.I., 0% to 61%). When restricted to lamivudine vs. placebo comparisons the $R^2 = 17\%$ (95% C.I. 0% to 50%) when the influential point at the lower left corner is not removed, or 4% (95% CI 0% to 18%) when the influential point is removed.

5.3.3 Proportion of Treatment Effect Explained (method 4)

The approaches discussed in the sections above, based on individual and trial level-correlations, attempt to address the surrogacy issue directly with empirical evidence. Using these methods, the underlying association of the potential surrogate endpoint with the biopsy (i.e., HBV DNA or ALT with histology) is potentially affected by the following factors:

- Sampling variation and reading error for biopsy will weaken both the individual and trial-level correlation. If biopsy assessment has considerable variation, this will reduce the strength of the correlation.
- Variation in trial results is desirable. Two studies with different effect sizes will be more useful than two studies with similar results.
- The correlations may be influenced by how the sub-studies are constructed. There may be many plausible ways of forming sub-studies for meta-analysis, different constructions could yield somewhat different results.

Another concept for validation is the proportion of “treatment effect explained” by a surrogate endpoint (PTE). In this case PTE modeling attempts to determine how much of the overall effect on histologic outcome is mediated through HBV DNA or ALT. Measurement errors in biopsy and surrogate endpoints affect the estimation of PTE less than that of the methods described previously. However, its use has been widely debated. The results on the proportion of treatment effect (histologic outcome) explained are summarized below in Tables 5g and 5h for year 1 \log_{10} HBV DNA and change in \log_{10} ALT, respectively. More detailed results will be presented in the meeting.

Table 5g: PTE by HBV DNA as measured using Year 1 log₁₀ HBV DNA

Study Drug	Study	Treatments	PTE	95% CI
Adefovir	HBeAg+ (437)	ADV10 vs PLA	65%	41%, 104%
		ADV30 vs PLA	78%	49%, 110%
	HBeAg- (438)	ADV10 vs PLA	15%	-8%, 39%
Lamivudine	US Study	LAM100 vs PLA	33%	10%, 87%
	IFN-Non-resp	LAM100 vs PLA	37%	22%, 63%
		LAM+IFN vs PLA	23%	-241%, 312%
	Asian	LAM100 vs PLA	40%	6%, 79%
		LAM25 vs PLA	48%	18%, 104%
	Active-Control	LAM100 vs IFN	75%	-525%, 950%
		LAM+IFN vs IFN	19%	-205%, 276%

Table 5h: PTE by ALT as measured using change in log₁₀ALT at 1 year

Study Drug	Study	Treatments	PTE	95% CI
Adefovir	ADV HbeAg+	ADV10 vs PLA	46%	31%, 68%
		ADV30 vs PLA	40%	28%, 55%
	ADV HbeAg-	ADV10 vs PLA	17%	7%, 31%
Lamivudine	US Study	LAM100 vs PLA	65%	30%, 129%
	IFN-Non-resp	LAM100 vs PLA	27%	13%, 47%
		LAM+IFN vs PLA	-24%	-469%, 466%
	Asian	LAM100 vs PLA	42%	21%, 72%
		LAM25 vs PLA	49%	26%, 91%
	Active-Control	LAM100 vs IFN	63%	-352%, 479%
		LAM+IFN vs IFN	-37%	-344%, 321%

6.0 Conclusions

Given recent advances in the treatment of CHB and the increased interest in drug development for the treatment of CHB, this is an opportune time to discuss clinical trial design issues facing future drug development in this field. We have provided you with a list of what we believe are the most crucial issues in the design of phase 3 studies evaluating drugs to treat CHB. We have also presented advantages and disadvantages of some of the options one might consider when selecting controls, study designs, endpoints, and patient populations.

As stated previously, choice of endpoint may be one of the most pressing issues facing current drug development. Presently, the recommended primary endpoint for registrational studies is changes in histologic scores. The Division utilized clinical trial data sets to explore associations between treatment effects on other less invasive measurements (HBV DNA, ALT) and histologic outcome. Associations between HBV DNA and histologic outcome were weak on the individual level; associations were better for ALT and histology but still modest. However, the weakness of the associations may have been a result of a large degree of variability in histologic measurements. Analyses exploring the proportion of treatment effect explained by the surrogate showed that some associations between HBV DNA or ALT and histologic outcome were fairly strong, specifically for adefovir study 437 in HBeAg-positive patients. The correlations were weaker for adefovir study 438. Similar analyses using lamivudine studies were generally supportive of a correlation and were consistent with the adefovir studies; however, lamivudine studies containing interferon treatment arms were not supportive of a positive correlation between HBV or ALT and histologic outcome.

We realize that there is a large amount of information to consider, but hope that this document and the attached references will help the committee to have a productive discussion on August 7th. We look forward to your feedback.

Attachment A: Discussion Points/Questions for Antiviral Advisory Committee

Patient Populations

1. Please identify patient populations that are appropriate targets for treatment studies (consider attributes such as stage of disease, viral genotype, comorbidities, lamivudine resistance, IFN-experience, pediatrics, HBeAg-/HBV DNA+)? Please include demographics in your discussion, i.e. race and ethnicity.
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
- 3b. Please also discuss controls for patients with decompensated liver disease or who have failed previous regimens

Study Endpoints and Timing of Evaluations

4. Considering 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:
 - Which endpoint (or combination of endpoints) should be the primary in clinical trials? Please discuss histologic, serologic, biochemical, and virologic endpoints.
 - When should the assessment of the primary endpoint be made?
 - List the most appropriate secondary endpoints and rank them in order of importance.
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?
7. For patients with decompensated liver disease, please discuss the feasibility/validity of the following alternative endpoints:
 - mortality
 - change in Child- Pugh-Turcotte score (or its components)
 - transplant/no transplant
 - occurrence of liver disease associated 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 CHB infection, and what kind of information should be gathered?

Attachment B: Bibliography

- 1 Lok AS, McMahon BJ. Chronic Hepatitis B, AASLD Practice Guidelines. *Hepatology* 2001; 34:1225-41.
- 2 Lok AS, Heathcote J, Hoofnagle JH. Management of Hepatitis B: 2000-Summary of a Workshop. *Gastroenterology* 2001; 120: 1828-1853.
- 3 Rizzetto M. Efficacy of lamivudine in HBeAg-negative chronic hepatitis B. *J Med Vir* 2002; 66:435-451.
- 4 Knodell RG, Ishak KG, Black WC, et al. Formulation and Application of a Numerical Scoring System for Assessing Histologic Activity in Asymptomatic Chronic Active Hepatitis. *Hepatology* 1981; 5: 431-435.
- 5 Dienstag JL, Schiff ER, Wright TL et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. *NEJM* 1999; 341:1256-1263.
- 6 Lau DT, Everhart J, Kleiner DE, et al. Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. *Gastroenterology* 1997; 113; 1660-1667.
- 7 Gauthier J, Bourne EJ, Lutz MW et al. Quantitation of Hepatitis B viremia and emergence of YMDD variants in patients with chronic hepatitis B treated with lamivudine. *J Infect Dis* 1999; 180:1757-1762.
- 8 Yao FY, Bass NM. Lamivudine treatment in patients with severely decompensated cirrhosis due to replicating hepatitis B infection. *J Hepatol* 2000; 33:301-307.
- 9 Kapoor D, Guptan RC, Wakil AM. Beneficial effects of lamivudine in hepatitis B virus-related decompensated cirrhosis. *J Hepatol* 2000; 33: 308-312.
- 10 Jonas MM, Kelley DA, Mizerski J et al. Clinical trial of lamivudine in children with chronic hepatitis B. *NEJM* 2002; 346: 1706-1710.
- 11 Zavaglia C, Mondazzi L, Maggi G et al. Are alanine aminotransferase, hepatitis B virus DNA or IgM antibody to hepatitis B core antigen serum levels predictors of histological grading in chronic hepatitis B. *Liver* 1997; 17: 83-87.
- 12 Pawlotsky JM, Bastie A, Hezode C et al. Routine detection and quantification of hepatitis B virus DNA in clinical laboratories: performance of three commercial assays. *J Virol Meth* 2000; 85:11-21.

Attachment C: Child-Pugh Score**Scoring System**

- A. Total Serum Bilirubin
 - 1. Bilirubin <2 mg/dl: 1 point
 - 2. Bilirubin 2-3 mg/dl: 2 points
 - 3. Bilirubin >3 mg/dl: 3 points
- B. Serum Albumin
 - 1. Albumin >3.5 g/dl: 1 point
 - 2. Albumin 2.8 to 3.5 g/dl: 2 point
 - 3. Albumin <2.8 g/dl: 3 point
- C. INR
 - 1. INR <1.70: 1 point
 - 2. INR 1.71 to 2.20: 2 point
 - 3. INR >2.20: 3 point
- D. Ascites
 - 1. No ascites: 1 point
 - 2. Ascites controlled medically: 2 point
 - 3. Ascites poorly controlled: 3 point
- E. Encephalopathy
 - 1. No Encephalopathy: 1 point
 - 2. Encephalopathy controlled medically: 2 point
 - 3. Encephalopathy poorly controlled: 3 point

Classification/Interpretation

Child Class A: 5 to 6 points

Child Class B: 7 to 9 points

Child Class C: 10 to 15 points