CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-449

STATISTICAL REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Medical Division: **Division of Antiviral Drug Products (HFD-530)**

Biometrics Division: **Division of Biometrics III (HFD-725)**

NEW DRUG APPLICATION (NDA):	21-449
SERIAL NUMBER:	000
NAME OF DRUG:	HEPSERA™ (adefovir dipivoxil; ADV)
DOSAGE:	10 mg tablets once daily
INDICATION(S):	Treatment of Chronic Hepatitis B infection
APPLICANT:	Gilead Sciences
SUBMISSION DATE:	March 20, 2002
PRESCRIPTION DRUG USER FEE ACT (PDUFA) DATE:	September 20, 2002
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1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

Gilead Sciences filed a New Drug Application (NDA 21-449) on March 20, 2002 seeking approval for HEPSERA™ (adefovir dipivoxil; ADV) 10 mg once daily for the treatment of chronic hepatitis B. Adefovir dipivoxil is an oral prodrug of adefovir which is a nucelotide analog. Due to limited treatment options for treatment of chronic hepatitis B and the seriousness of this disease, the Division of Antiviral Drug Products, Office of Drug Evaluation IV at the FDA granted this NDA a priority review status.

We reviewed the efficacy data on adefovir (ADV) submitted in this NDA on the following patient groups:

- Chronic hepatitis B virus (HBV) infection with compensated liver disease
  - HBeAg+ (wild-type chronic hepatitis B) (Studies 437)
  - HBeAg-/anti-HBe+/HBV DNA+ (presumed pre-core mutant chronic hepatitis B) (Studies 438)
- Lamivudine-resistant Chronic HBV
  - Post-liver transplantation or waiting liver transplantation (Study 435)
  - Patients with compensated liver disease (Study 461)

Study Designs

Studies 437 and 438 were both double-blind, placebo-controlled studies to evaluate the safety and efficacy of ADV 10 mg; Study 435 was an open-label single-arm with ADV 10 mg once daily dosing; and Study 461 was an active-control study designed to evaluate the safety and efficacy of monotherapy with adefovir 10 mg versus dual therapy in combination with lamivudine 100 mg versus lamivudine 100 mg monotherapy.

Efficacy of adefovir 30 mg once daily and adefovir 10 mg once daily—both with respect to Placebo—was evaluated at Week 48 in Studies 437 and 438 through histologic response (primary endpoint), virologic response (serum HBV DNA), biochemical response (serum alanine aminotransferase [ALT]) and serologic response (HBeAg serconversion in Study 437 only). The primary efficacy endpoint in Studies 437 and 438 was histologic improvement at Week 48 defined as a 2 point or more reduction from baseline in Knodell necroinflammatory score with no concurrent worsening in fibrosis. In Studies 435 and 461 (lamivudine-resistant HBV), the primary efficacy endpoint was time-weighted average change from baseline in serum HBV DNA at Week 24 and Week 16 respectively ($DAVG_{24}$ for Study 435 and $DAVG_{16}$ for Study 461).

Demographics and Baseline Characteristics

Studies 437 and 438 which were double-blind, placebo-controlled, multicenter studies were conducted multinationally in the United States, Canada, Australia, France, Germany, Italy, Spain, United Kingdom, Taiwan, Thailand, Malaysia, Singapore, and the Phillipines. Study

437 enrolled 515 patients who were tested positive for the Hepatitis B e Antigen at baseline (HBeAg+) and in Study 438, 185 patients tested HBeAg-negative were enrolled. Study 435 was an open-label single arm study to evaluate safety and effectiveness of adefovir 10 mg once daily conducted in chronic hepatitis B patients who either received a liver-transplant (n=196) or were waitlisted for liver transplant (n=128). Study 461 is an ongoing active-control study (n=59 enrolled) to evaluate effectiveness of monotherapy vs. dual therapy. Both, Studies 435 and 461 enrolled patients with lamivudine-resistant HBV.

In all studies, patients were predominantly male (approximately 75% or more). Also, patients in all studies were primarily of White or Asian ethnic origin. In Study 437 (HBeAg+) approximately 2/3rds of the patients were Asian while in Studies 438 (HBeAg-) and 435, approximately 2/3rds of the patients were White. Note that these studies were multinational studies with patients of different races enrolled in different countries.

The median baseline serum HBV DNA level in Study 437 was higher (8.36 log10 copies/mL) than that in Study 438 (7.08 log10 copies/mL). However, the median ALT at baseline in both studies were similar and so were the mean Knodell necroinflammatory and fibrosis scores.

Conclusions

Based on all the available data through Week 48 and beyond, in Studies 437, 438, and 435 as well as data through 16 weeks in Study 461 we reached the following conclusions.

1. Based on the epidemiology of chronic hepatitis B, the prevalence of hepatitis B virus infection in the United States is higher among African-Americans and Hispanics than in patients of White origin. As such, these patient populations were significantly under-represented in the Applicant's drug development program.

2. In Study 437, a statistically significantly greater proportion of patients receiving adefovir (ADV) 30 mg or 10 mg once daily showed histologic improvement (as defined by the primary efficacy endpoint of 2 point or more reduction in Knodell necroinflammatory score with no concurrent worsening of fibrosis) as compared with Placebo at Week 48. A similar result was observed for the ADV 10 mg daily dose in Study 438.

   At Week 48, the observed treatment difference in Study 437 for ADV 30 mg vs. Placebo was 34.5% with a 95% confidence interval of (24%, 44%), while the observed treatment difference for ADV 10 mg versus Placebo was 27.5% with a 95% confidence interval of (17%, 37%). In Study 438, the observed treatment effect was 29.4% for ADV 10 mg vs. Placebo with a 95% confidence interval of (14%, 44%).

3. Additional analyses based on the Ishak scoring system were done to evaluate the treatment effect on fibrosis at Week 48 because of two reasons: a) changes in fibrosis were considered to be clinically relevant in evaluating the treatment of chronic hepatitis B (which is a liver disease) and b) the Ishak scoring system is a more detailed and precise scoring system than the Knodell scoring system used in the primary efficacy

endpoint.

In both studies, 437 and 438, based on the Ishak scores, a statistically significantly greater proportion of patients treated in the adefovir groups (30 mg or 10 mg) showed improvement in fibrosis relative to Placebo at Week 48.

4. With respect to the virologic response based on *change from baseline in serum HBV DNA* (Roche Amplicor PCR assay), the mean reduction in serum HBV DNA in the ADV 10 mg group (-3.52 log10 copies/mL in Study 437 and –3.54 log10 copies/mL in Study 438) was significantly greater than the mean reduction in the Placebo group (-0.99 log10 copies/mL in Study 437 and –1.23 log10 copies/mL in Study 438).

   Also, the mean reduction in serum HBV DNA in the ADV 30 mg (-4.38 $\log_{10}$ copies/mL in Study 437) was significantly greater than that in the ADV 10 mg group.

5. Upon continued treatment with ADV 10 mg up to 72 weeks, the viral suppression that was observed at Week 48 was maintained in both studies. However, when treatment was discontinued at Week 48, the HBV DNA levels in patients returned to levels closer to baseline.

6. Among the patients with lamivudine-resistant HBV in Studies 435 and 461, significant reduction in the serum HBV DNA was also seen upon treatment with ADV 10 mg. In Study 435, a mean reduction in serum HBV DNA of approximately 4 log10 copies/mL was observed at Week 48 while in Study 461 a mean reduction of approximately 2.9 log10 copies/mL was observed at Week 16 when treated with ADV 10 mg once daily. Study 461 is an ongoing study, in which the monotherapy arm (ADV 10 mg) and the dual therapy arm (ADV 10 mg + LAM 100 mg) provided similar viral suppression and both had statistically significantly greater reduction in HBV DNA relative the monotherapy with LAM 100 mg at Week 16.

7. With respect to the biochemical response: The proportion of patients with *normalization of ALT* in Studies 437 and 438 were significantly greater in the adefovir groups (30 mg or 10 mg) than the Placebo group. Mean reductions in ALT levels were significantly lower in the ADV 10 mg group relative to Placebo through 48 Weeks. However, when adefovir treatment was discontinued after Week 48, ALT levels peaked within 12 weeks and returned to baseline levels. This phenomenon may result in exacerbation of hepatitis B in patients.

   Among the patients who did not have ALT normalization by Week 48, the additional rates of ALT normalization were evaluated in Year 2 for Studies 437 and 438. In Study 437, among these patients, the proportion of patients with ALT normalization in Year 2 was significantly higher when patients continued treatment with adefovir 10 mg up to 72 weeks (38%; 95% CI [20.7%, 55.9%]) relative to Placebo (9%; 95% CI [0%, 20.3%]).

   However, these differences were not statistically significant for Study 438 (22%; 95% CI [2.9%, 41.1%] patients with ALT normalization in ADV 10 mg group continued up to 72 weeks and 0% in the patients who switched to Placebo group up to 72 weeks.).

The number of patients followed through Week 72 was only 8 patients in the ADV 10 mg group and 7 patients in the Placebo group, which is too small to detect any significant differences.

8. With respect to the serologic response: The proportion of patients who had *HBeAg seroconversion* in Study 437 based on Kaplan-Meier analysis was estimated to be 17% in ADV 30 mg group, 14% in the ADV 10 mg group and 9% in the Placebo group at Week 48. These differences in the estimated rates for ADV groups relative to Placebo were only marginally statistically significant.

   Among patients who did not seroconvert (HBeAg) in Year 1, there were numerically greater proportion of patients who seroconverted at Week 72 in those who discontinued adefovir, i.e., switched to Placebo (20%; 95% CI [5.6%, 34.2%]) as compared with those who continued treatment with adefovir 10 mg (7%; 95% CI [0.1%, 13.7%]) through Week 72. This difference was not statistically significant.

   We also analyzed data on patients who experienced loss of HBeAg in Year 2, but not in Year 1. At Week 72, the additional proportion of patients who had HBeAg loss was 22% (95% CI [9.2%, 34.4%]; n=10) in patients continuing adefovir 10 mg versus 15% (95% CI [1.0%, 28.2%]; n=11) in those who discontinued (i.e., switched to Placebo after Week 48). This difference was also not statistically significant.

9. Histologic response as measured by proportion of patients with improvement in fibrosis based on Ishak scores was evaluated in various subgroups of patients by gender, race and age.

   Based on Study 437, approximately 20% additional men are estimated to have improvement in fibrosis when treated with ADV 10 mg as compared with Placebo. However, in Study 437, similar proportion of women had improvement in fibrosis whether they received ADV 10 mg or Placebo. Therefore, among HBeAg+ patients, men had greater therapeutic benefit in terms of improvement in fibrosis with adefovir 10 mg treatment (relative to Placebo) than women. In Study 438, the subgroup of women patients was small in order to make any statistical conclusions about the differences in therapeutic benefit in men versus women.

   Among HBeAg+ patients, White and Asian patients showed similar rates of improvement in fibrosis in Study 438. In Study 438, among HBeAg- patients, White patients had a greater rate of improvement in fibrosis with ADV 10 mg (relative to Placebo) as compared with Asian patients.

   In both studies, the additional therapeutic benefit due to ADV 10 mg in terms of improvement in fibrosis was similar among younger or older patients (based on median age of enrolled patients).

10. A quantitative assessment of nephrotoxicity due to adefovir as characterized by increase in serum creatinine and hypophosphatemia was also made. This was done by performing time-to-event analyses using the Kaplan-Meier method for estimating the cumulative incidence of patients who met the criteria of increase in serum creatinine ≥0.3 mg/dL from baseline and decrease in serum phosphorus <2.0 mg/dL.

    When adefovir 10 mg once daily was given to patients with normal renal functions (Studies 437 and 438), the overall risk of nephrotoxicity was found to be low. However, patients with end-stage liver disease in Study 435 were found to be at high risk of nephrotoxicity when administered adefovir 10 mg once daily. Since these patients had compromised renal function, took concomitant nephrotoxic drugs and adefovir is excreted renally, these patients had significantly higher exposures of the drug when given the 10 mg daily dose. Nevertheless, a substantial proportion of these patients were found to have experienced treatment-emergent nephrotoxicity as mentioned below.

    - By Week 96, 36% of the post-liver transplant patients (cohort A) had a confirmed increase from baseline in serum creatinine ≥0.3 mg/dL with a 95% confidence interval of (30.3%, 41.8%).
    - By Week 48, 30% of the waitlisted for liver transplant patients (cohort B) had a confirmed increase from baseline in serum creatinine ≥0.3 mg/dL with a 95% confidence interval of (22.2%, 40.5%).
    - By Week 96, 6% of the post-liver transplant patients (cohort A) had a confirmed hypophosphatemia <2.0 mg/dL with a 95% confidence interval of (3.5%, 11.6%).
    - By Week 48, 5% of the waitlisted for liver transplant patients (cohort B) had a confirmed hypophosphatemia <2.0 mg/dL with a 95% confidence interval of (2.2%, 12.5%).

11. In summary, the ADV 10 mg once daily dose for which the Applicant seeks approval showed statistically significant benefit relative to Placebo as measured by the histologic responses, virologic response (serum HBV DNA) and biochemical response (ALT) through 48 weeks of treatment. Serologic response as measured by HBeAg seroconversion at Week 48 was only marginally significant in the ADV 10 mg treated group relative to Placebo.

    The duration of therapy in treating chronic hepatitis B patients has not yet been established. Upon discontinuation of treatment with adefovir 10 mg once daily, patients had elevations in both serum HBV DNA levels and ALT levels which may not beneficial to patients. Continued treatment beyond 48 weeks was beneficial with respect to maintaining the viral suppression and normalization of ALT levels. The effect of continued treatment with adefovir beyond 48 weeks on the loss of HBeAg and HBeAg seroconversion was statistically inconclusive.

    The overall risk of nephrotoxicity was low in patients with normal renal functions. However, patients with underlying abnormal renal function were found to be at high risk for developing nephrotoxicity.

2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

This is a priority review of the New Drug Application (NDA 21-449) which seeks approval for HEPSERA™ (adefovir dipivoxil) 10 mg tablets for the treatment of chronic hepatitis B.

Despite the availability of licensed vaccines (Recombivax™ and Engerix-B™) to prevent Hepatitis B, new hepatitis B infections are still common. In the United States, currently there are two treatments for chronic hepatitis B that are approved by the FDA: the *immune modulator* interferon alfa-2b (Intron™ A; IFN-α) in *an injection form*, and the *oral nucleoside analogue*, lamivudine (Epivir-HBV™; 3TC). Adefovir dipivoxil is an oral prodrug of adefovir, a phosphonate nucleotide analog of adenosine monophosphate. The applicant, Gilead Sciences, seeks the following indication for Hepsera™ (adefovir dipivoxil):

> Hepsera™ is indicated for the treatment of chronic hepatitis B infection in adults with evidence of hepatitis B viral replication and active liver inflammation

2.1.1 Chronic Hepatitis B

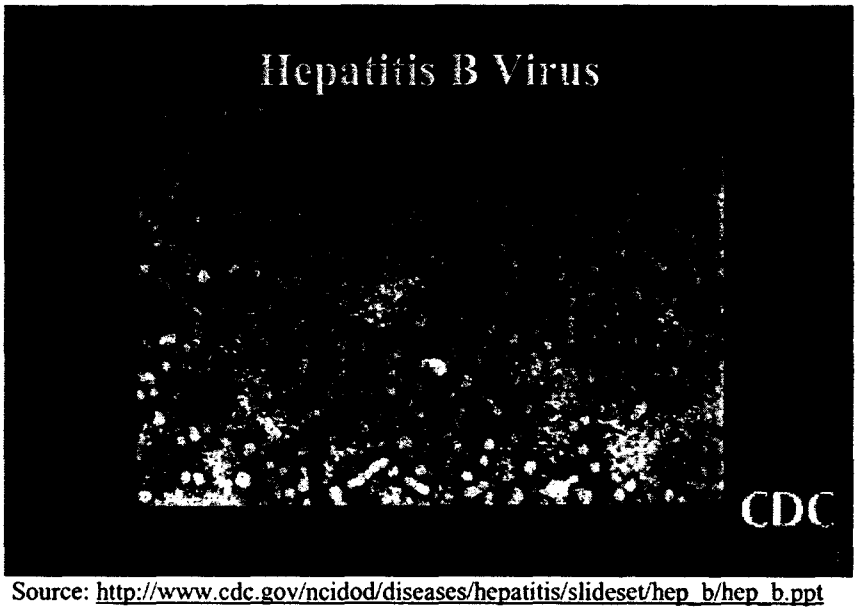
Hepatitis B can be either an *acute* or a *chronic* disease, which is caused by infection due to the Hepatitis B virus (HBV) that attacks the liver.

The estimated incidence of HBV infection worldwide is 2 billion, out of which 400 million people have developed chronic hepatitis B (WHO 2000; NDA 21-449, Vol. 1, Page 19). According to the U.S. Centers for Disease Control and Prevention (CDC), the geographic distribution of Chronic Hepatitis B infection is divided into regions with high endemicity (>8% prevalence; Africa, Asia, and the Western Pacific), intermediate endemicity (2-7% prevalence; Southern and Eastern Europe), and low endemicity (<2% prevalence; Western Europe, North America, and Australia). The United States is considered as an area of low endemicity of Hepatitis B (<2% prevalence). In the United States, an estimated 1.25 million people are infected with chronic hepatitis B.

Most of the persons with acute HBV infections result in complete recovery with clearance of the HBV from the blood and the production of antibodies designating immunity from future infection. However, approximately 30-90% of young children and 2-10% of adults infected with HBV develop chronic HBV infection. Persons with chronic HBV infection are often symptomatic, but are at high risk for developing *chronic hepatitis B* which can lead to progressive liver disease including cirrhosis (scarring of liver), liver failure and hepatocellular carcinoma. Approximately, 15-25% of these persons may die prematurely due to either cirrhosis or liver cancer. (Source: Centers for Disease Control and Prevention.)

2.1.2 Hepatitis B Virus (HBsAg, HBcAg, HBeAg, HBV DNA)

In order to understand the efficacy and safety parameters associated with *chronic Hepatitis B* as well as understand the patient population studied in the clinical trials for HEPSERA™ (adefovir dipivoxil), it is important to understand the Hepatitis B virus. The source of this information is http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep_b/slide_1.htm .



Source: http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep_b/hep_b.ppt

Figure 1: Hepatitis B Virus

Hepatitis B virus (HBV) is a 42-nm double-shelled deoxyribonucleic acid (DNA) virus of the class Hepadnaviridae. The outer surface membrane contains Hepatitis B surface Antigen (HBsAg), which also circulates in the blood as 22-nm spherical and tubular particles. The inner core of the virus contains the Hepatitis B core Antigen (HBcAg), Hepatitis B e Antigen (HBeAg), a single molecule of partially double-stranded DNA, and DNA-dependent DNA polymerase. Each of the antigens induces corresponding protective, neutralizing antibodies that are supposed to provide protection against HBV infection.

The antigens and antibodies are *serologic markers* of HBV infection and vary depending on whether the infection is acute or chronic.

In patients with *acute HBV infection*, the first serologic marker that appears, is the *HBsAg*, which becomes no longer detectable after an average period of about 3 months. *Anti-HBs* (antibodies to Hepatitis B surface antigen) becomes detectable upon convalescence, in patients who do not progress to chronic infection.

In patients with *chronic HBV infection*, both HBsAg and IgG anti-HBc (Immune globulin [Ig]G class antibody to HBc antigen) remain persistently detectable, generally for life. HBeAg may or may not be detectable in these patients. The presence of HBsAg for 6 months ~~or~~ more is generally indicative of chronic infection.

2.2 Overview of the Clinical Program and Studies Reviewed

Clinical studies with *adefovir dipivoxil* at a range of doses (5 mg to 125 mg per day) were conducted in chronic hepatitis B patients, non-HBV infected patients and healthy volunteers. Table 1 summarizes the Clinical Program for adefovir.

As shown in Table 1, adefovir dipivoxil was studied in the following patient groups:

- Chronic hepatitis B virus (HBV) infection with compensated liver disease
  - HBeAg+ (wild-type chronic hepatitis B) (Studies 437, 404, 412)
  - HBeAg-/anti-HBe+/HBV DNA+ (presumed pre-core mutant chronic hepatitis B) (Studies 438, 412, and 413)
- Lamivudine-resistant Chronic HBV
  - Post-liver transplantation or waiting liver transplantation (Study 435)
  - Patients with compensated liver disease (Study 461)
  - Patients with decompensated liver disease (Study 465)
  - Patients co-infected with HBV and HIV (human immunodeficiency virus) (Study 460i).

Statistical Reviewer's Comments:

The studies that will be reviewed thoroughly in this Statistical Review and Evaluation of NDA 21-449 for adefovir for the indication of *treatment of Chronic HBV infection* are Studies 437, 438, 435 and 461. Study 461 is an ongoing randomized, three arm, active-controlled study evaluating the safety and efficacy of adefovir 10mg once daily with or without lamivudine in patients with chronic hepatitis B who have developed lamivudine-resistant HBV (YMDD mutant). In Study 461, 59 patients were enrolled, out of which 58 patients have completed 16 weeks of treatment. Since the 48-week endpoint is not yet reached, the efficacy data from Study 416 is evaluated only until the 16 week time point.

Studies 404, 412, and 413 are the Phase 1 and Phase 2 dose finding studies, which will not be reviewed here in detail. Study 465 was a collaborative study between the Applicant, Gilead Sciences, and GlaxoSmithKline Company. Data was not submitted for Study 465 in this NDA. Finally, study 460i, which is a smaller study in co-infected HIV/HBV patients will not be reviewed for the indication of the treatment of chronic HBV infection.

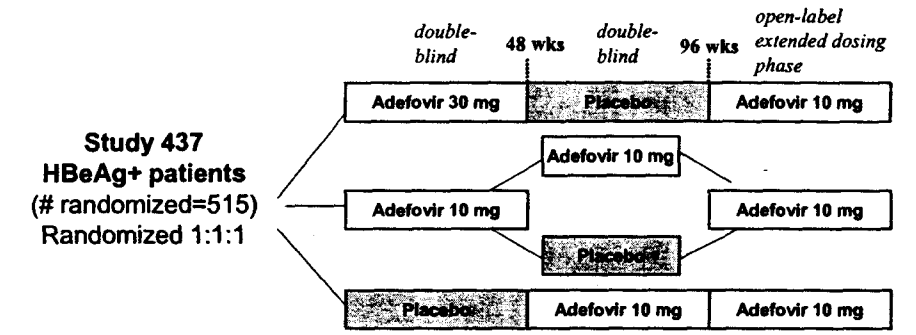
Table 1: Clinical Development Program for adefovir dipivoxil

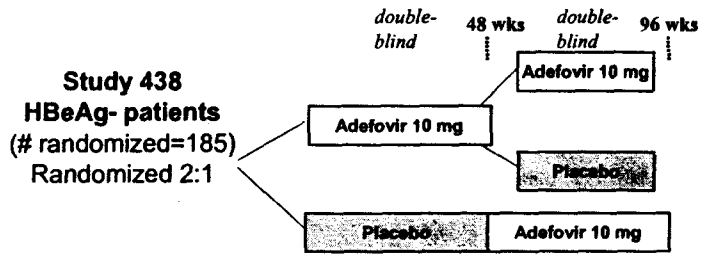
Study	Development Phase	Design and Treatment Duration (Follow-up)	Treatment Arms	Patient Population	Number Enrolled	Primary and Secondary End points.
GS-98-437	Phase 3	Double-blind, randomized, Placebo-controlled, multi-center Year 1=48 weeks Year 2 = 48 weeks (16-24 weeks)	ADV 10 mg, ADV 30 mg, or Placebo (1:1:1)	**HBeAg+**	515	*Primary:* **Liver histology** *Secondary:* Anti-HBe seroconversion; HBV DNA suppression; decreases in ALT levels, safety; and emergence of resistance
GS-98-438	Phase 3	Double-blind, randomized, Placebo-controlled, multi-center Year 1=48 weeks Year 2 = 48 weeks (16-24 weeks)	ADV 10 mg or Placebo (2:1)	**HBeAg-/anti-HBe+/HBV DNA+**	185	*Primary:* **Liver histology** *Secondary:* Anti-HBs seroconversion, HBV DNA suppression, decreases in ALT levels, safety; and emergence of resistance
GS-98-435	Phase 3	Open-label Indefinite	ADV 10 mg	**Liver transplant or waitlisted for liver transplant patients who are lamivudine-resistant**	370	*Primary:* **Time-weighted average change from baseline in serum HBV DNA up to Week 24 ($DAVG_{24}$)** *Secondary:* HBeAg loss, changes in Child-Pugh-Turcotte Score, seroconversion, normalization of ALT, safety
GS-00-461	Phase 3	Double-blind, randomized Year 1=48 weeks (24 weeks)	ADV 10mg + lamivudine 100 mg, ADV 10 mg, lamivudine 100 mg	**HBeAg+ with lamivudine-resistant HBV**	59	*Primary:* **Time-weighted average change from baseline in serum HBV DNA up to Week 16 ($DAVG_{16}$),** *Secondary:* HBV DNA $DAVG_{48}$, virologic response, safety

Study	Development Phase	Design and Treatment Duration (Follow-up)	Treatment Arms	Patient Population	Number Enrolled	Primary and Secondary End points.
GS-99-**465** **(GSK Study NUC20904 ; following completion of NUC20904 , rollover to NUC20917)**	Phase 3	Double-blind, randomized, stratified by liver disease (Stratum A: Compensated liver disease)	ADV 10 mg QD+ lamivudine 100mg QD vs lamivudine 100 mg QD	**HBeAg+ and HBeAg- with compensated**	135 (95 compensated and	*Primary:* **HBV DNA at Week 48 and 52** *Secondary*: ALT response at Week 48 and 52; HBeAg and HBsAg seroconversion; and safety
		Open-label (Stratum B: Decompensated liver disease) 96 weeks (16 weeks)	ADV 10 mg QD + lamivudine 100 mg QD	**Or decompensated liver disease and lamivudine-resistant HBV**	40 decompensated)	
GS-94-**404**	Phase 1 / 2	Double-blind, randomized, Placebo-controlled, Dose Escalation 4 weeks (12 weeks)	ADV 60 mg,. 120 mg, 125 mg	**HBeAg+**	20	*Primary:* **HBV DNA suppression** *Secondary:* HBV DNA, HBV serologic markers, and safety
GS-96-**412**	Phase 2	Double-blind, randomized, Placebo-controlled, Dose Escalation Initial Phase: 12 weeks (24 weeks) Extension Phase: 52 weeks (24 weeks)	ADV 5 mg, 30 mg, 60 mg	**HBeAg+ and HBeAg-/anti-HBe+/HBV DNA +**	53 + 10	*Primary:* **Safety and tolerability** *Secondary:* HBV DNA suppression, HBV DNA, HBV serologic markers
GS-96-**413**	Phase 2	Double-blind, randomized, Placebo-controlled, Dose Escalation 12 weeks (24 weeks)	ADV 30 mg	**HBV DNA+**	14	*Primary:* **Safety and tolerability** *Secondary:* HBV DNA suppression, HBV DNA, HBV serologic markers
GS-99-**460i**	Investigator-IND	Open-label, single center 48 weeks (24 weeks)	ADV 10mg QD + lamivudine 150 mg BID	**HIV/HBV co-infected/lamivudine resistant patients**	35	*Primary:* **Liver histology, HBV DNA change from baseline at Week 24 and 48** *Secondary:* normalization of ALT, safety

Source: Integrated Summary of Efficacy, Vol. 193 of NDA 21-449, SN000.

2.3 Study Designs and Data Analyzed





2.3.1 Study GS-98-437 (HBeAg+ patients)

Title: "A Double-Blind, Randomized, Placebo-Controlled Study of Adefovir Dipivoxil for the Treatment of Patients with HBeAg$^+$ Chronic Hepatitis B Virus Infection." [Study Period: March 16, 1999 (first patient randomized) through current. Database lock for interim analysis was May 31, 2001. Data from central laboratory included through November 15, 2001 is included.]

GS-98-437 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study. The study was designed to evaluate the efficacy of adefovir 30 mg once daily and adefovir 10 mg once daily compared with placebo in treatment of patients with HBeAg+ chronic hepatitis B virus infection.

Population

The study was conducted at 78 centers in the United States, Canada, Australia, France, Germany, Italy, Spain, United Kingdom, Taiwan, Thailand, Malaysia, Singapore, and the Philippines.

The patient population chosen for this study were to be male or female patients aged 16-65 years with chronic hepatitis B, HBeAg+, HBsAg+, positive serum HBV DNA $\geq 10^6$ copies/mL (Roche Amplicor PCR assay), serum ALT value 1.2 to 10 times the upper

limit (ULN). In addition, patients had to have compensated liver disease, be HIV, HCV, and HDV seronegative, along with adequate renal function (serum creatinine ≤1.5 mg/dL) and adequate hematological function. Patients should have been willing to and able to undergo at least two liver biopsies (prior to dosing, and after 12 months of therapy). Prior therapy with interferon-α or anti-HBV treatment (e.g., lamivudine famciclovir, lobucavir, ganciclovir, etc.) was permitted as long as the last dose was administered ≥6 months prior to screening or prior to baseline liver biopsy, and patients should not have received such therapies for more than 12 weeks in duration in the past. Patients with active liver disease due to other causes (e.g., Wilson's disease, hemochromatosis, autoimmune hepatitis, hepatitis C or hepatitis D co-infection) were to be excluded. Also, patients receiving within 2 months prior to screening or expecting to receive hepatotoxic (anabolic steroids, ketaconazole, itraconazole, isoniazid, rifampin, rifabutin) or nephrotoxic drugs (aminoglycosides, amphotericin B, vancomycin, cidofovir, foscarnet, cis-platinum, pentamidine) or competitors of renal excretion (probenecid, sulfinpyrazone) were to be excluded.

Sample Size

A total of 513 patients (171 per arm) were planned to detect a pairwise treatment difference between one or both of adefovir (30 mg or 10 mg) groups versus placebo with respect to the primary histologic endpoint with a statistical power of 90%. It was assumed that 8% of patients will have missing baseline biopsies, the histologic response in adefovir arm will be 66.7% and 40% in placebo group, and a two-sided significance level of α=0.025. A conservative α adjustment was assumed in computing the sample size so as to account for multiple comparisons using the Benjamini-Hochberg procedure.

Randomization

During the first 48 weeks, a total of 515 patients were randomized in a blinded fashion (1:1:1) to one of the following three treatment groups

Group 1: Adefovir 30 mg once daily (n=173)

Group 2: Adefovir 10 mg once daily (n=172)

Group 3: Placebo once daily (n=170)

Since adefovir (ADV) treatment may result in a decrease of serum carnitine, all patients in the ADV 30 mg group received daily administration of 250 mg of L-carnitine. Patients in the ADV 10 mg group or placebo group were randomized to receive either 250 mg of L-carnitine or L-carnitine placebo.

During the second 48 weeks patients were to be re-randomized as follows: patients who received ADV 30mg will receive Placebo, patients who received ADV 10mg will receive either ADV 10 mg or Placebo (in a 1:1 ratio), and patients who received Placebo will receive ADV 10 mg. Therefore, all patients would receive at least one year of active treatment.

The study was amended in June 2001 to change the primary objective to include only ADV 10 mg treatment group analysis due to the emergence of laboratory abnormalities consistent with nephrotoxicity seen in some patients in the ADV 30 mg treatment group. Additionally, on or after September 2000, misallocation of study medication resulted in 416 of the 459 patients who entered the second 48 weeks of the study receiving at least one incorrect bottle of drug. Gilead became aware of the error on July 12, 2001. A decision was made with DAVDP concurrence to terminate the blinded phase of the study on July 19, 2001, and the study protocol was amended to offer all patients open-label treatment with ADV 10 mg. Data collected during the first 48 weeks were unaffected by the error. Gilead planned to performed safety and effectiveness analyses on the second 48 weeks of the study up until the first incorrect treatment assignment.

Efficacy Analyses

The primary efficacy endpoint was *improvement in liver biopsy* (i.e., *histologic improvement*) which was based on liver biopsies done at Baseline and at Week 48. Baseline liver biopsies were pretreatment biopsies that were done either

- within 6 months of randomization (if a recent biopsy did not exist), or
- within 6 months of randomization and ≥6 months after completion of any anti-HBV therapy (if a recent biopsy existed).

Week 48 biopsies were post-treatment biopsies to be performed at or after Week 48, or performed at the termination visit in the event of early termination. Patients were to remain on the Year 1 study drug until the biopsy was performed.

Baseline and Week 48 liver biopsies were evaluated for necrosis, inflammation, and fibrosis by the same central pathologist who was blinded to both the treatment assignment and sequence of each patient's biopsies. The extent and severity of liver damage on each biopsy was assessed using the Knodell Histology Activity Index (HAI) scoring system. Another scoring system called the Ishak scoring system as well as ranked assessment system was also used.

The primary efficacy endpoint of *histologic improvement* was defined by the Applicant as a reduction from baseline of ≥2 points in the Knodell necroinflammatory score with not concurrent worsening in the Knodell fibrosis score.

The Knodell histological activity index (HAI) is a grading and staging system to assess the histopathology of liver biopsies (Source: Medical Officer's Review of NDA 21-449, by Dr. Tan Nguyen). It contains the following four components with higher score indicating more severe abnormalities.

1. Periportal injury (scored 0 to 10):

   0=none; 1=mild; 3=moderate; 4=marked; 5=moderate bridging necrosis; 6=marked bridging necrosis; 10=multiacinar necrosis

2. Parenchymal injury (scored 0 to 4):

   0=none; 1=mild; 3=moderate; 4=marked

3. Portal inflammation (scored 0 to 4):

   0=none; 1=mild; 3=moderate; 4=marked

4. Fibrosis (scored 0 to 4)

   0=none; 1=portal; 3=bridging; 4=cirrhosis

Statistical Reviewer's Comments:

Note that the scores of all components jump from 1 to 3 (score of 2 does not exist). Additionally, for periportal injury, the score jumps from 6 to 10.

The necroinflammatory score is the sum of the first 3 components (periportal injury, parenchymal injury, and portal inflammation) and thus ranges from 0 to 18. The fibrosis score of 0 indicates absence of fibrosis (i.e., normal connective tissue); score of 1, fibrosis is restricted to the portal area; score of 2, fibrosis involves periportal or rare portal-portal septa; score of 3, fibrosis involves many septa leading to subjective architectural distortion; and score of 4, the presence of cirrhosis.

The population for the primary efficacy analysis will be the intent-to-treat (ITT) population (all randomized patients who received at least one dose of study drug) who have adequate baseline liver biopsy. Patients for whom Week 48 histology results are missing or unassessable will be analyzed as failures (non-responders). The proportion of responders will be compared between each adefovir (30 mg and 10 mg) and placebo groups using the Cochran-Mantel-Haenszel test at a two-sided significance level of 0.05.

Secondary efficacy endpoints included the following: 1) change from baseline in total Knodell score, necroinflammatory score, and fibrosis score; 2) proportion of patients with HBeAg seroconversion (loss of HBeAg and acquired antibody to HBeAg [anti-HBe+]); 3) time-weighted average change from baseline in serum HBV DNA at Week 48 ($DAVG_{48}$ log_{10} copies/mL) ; 4) proportion of patients with serum HBV DNA <400 copies/mL at Week 48 (Roche Amplicor PCR assay); and 5) proportion of patients with normalization of ALT levels.

2.3.2 Study GS-98-438 (HBeAg-/anti-HBe+/HBV DNA+ patients)

Title: "A Phase 3 Double-Blind, Randomized, Placebo-Controlled Study of Adefovir Dipivoxil for the Treatment of Patients with Presumed Precore Mutant ($HBeAg^-$/$Anti\text{-}HBe^+$/$HBV\ DNA^+$) Chronic Hepatitis B Virus Infection."

GS-98-438 was also a randomized, double-blind, placebo-controlled, multicenter study. This study was designed to confirm the efficacy of adefovir 10 mg once daily compared with placebo in treatment of patients with HBeAg-negative chronic hepatitis B virus

infection. Study GS-98-438 was similar in design as Study GS-98-437, with the exception that there was no adefovir 30 mg treatment group in Study 438 and the two patient populations differed in their baseline status of HBe antigen (HBeAg+ patients in Study 437 while HBeAg– patients in Study 438).

Population

The patient population chosen for this study had chronic hepatitis B, HBeAg-negative, HBsAg-positive, positive anti-HBe antibody, serum HBV DNA $\geq 10^5$ copies/mL and ALT values 1.5xULN to 15xULN. In addition, patients had to have compensated liver disease and adequate renal function (serum creatinine ≤1.5 mg/dL), HIV, HCV, and HDV seronegative. Patients should have been willing to and able to undergo at least two liver biopsies. Prior therapy with interferon-α, lamivudine, or famciclovir was permitted provided that the last dose was administered 6 months or more prior to screening or before liver biopsy was performed. Treatment with hepatotoxic, nephrotoxic drugs, or competitors of renal excretion was prohibited within 2 months prior to screening and during the study.

Randomization

During the first 48 weeks, a total of 185 patients were randomized in a blinded fashion (2:1) to one of the following two treatment groups

Group 1: Adefovir 10 mg once daily (n=123)

Group 2: Placebo once daily (n=62)

During the second 48 weeks patients were to be re-randomized in a blinded fashion as follows: patients who received ADV 10 mg will receive either ADV 10 mg or Placebo (in a 2:1 ratio), and patients who received Placebo will receive ADV 10 mg. Therefore, all patients would receive at least one year of active treatment.

Efficacy Analyses

The primary efficacy endpoint in Study 438 was similar to that for Study 437, which was *improvement in liver biopsy* (i.e., *histologic improvement)* at Week 48 compared with baseline. The details of this endpoint are discussed under the description of Study 437 above.

Secondary efficacy endpoints included the following: 1) change from baseline in total Knodell score, necroinflammatory score, and fibrosis score; 2) proportion of patients with HBsAg seroconversion (loss of HBsAg and acquired antibody to HBsAg [anti-HBs+]); 3) time-weighted average change from baseline in serum HBV DNA at Week 48 ($DAVG_{48}$ $\log_{10}$ copies/mL); 4) proportion of patients with serum HBV DNA <400 copies/mL at Week 48; and 5) proportion of patients with normalization of ALT levels.

The primary population for efficacy analyses was the intent-to-treat (ITT) population defined as all randomized patients who received at least one dose of study drug. For the primary efficacy analysis, the ITT population with adequate baseline liver biopsy was used.

2.3.3 Study GS-98-435 (lamivudine-resistant HBV, Pre/Post Liver Transplant patients)

Title: "An Open-Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B Virus (HBV) in Liver Transplant Patients."

Study 435 is an open-label, uncontrolled, single-arm, study to evaluate the safety and efficacy of adefovir 10 mg in patients who either received liver transplant or were waitlisted for liver transplant and had lamivudine-resistant hepatitis B virus infection.

Patients who received liver transplant were referred to as Cohort A and those who were waitlisted were referred to as Cohort B. Within Cohorts A and B, patients were classified as belonging to Cohort 1, 2 or 3 based on their renal, hepatic and hematologic function at baseline and whether they had previously received open-label adefovir through a compassionate program (study GS-99-451i). Cohort 1 included patients with adequate renal, hepatic, and hematologic function and no prior adefovir use. Cohort 2 included patients who previously received adefovir and were enrolled in Study GS-99-451i which is an ongoing open-label study to evaluate adefovir 5 mg to 10 mg daily in pre- or post-liver transplant patients with chronic hepatitis B and failing anti-HBV therapies. Cohort 3 included patients with significant renal, hepatic and/or hematologic dysfunction or other significant disease that precluded eligibility into cohort 1. The primary efficacy endpoint in Study 435 was the time-weighted average change in serum HBV DNA (log_{10} copies/mL) at Week 24 ($DAVG_{24}$).

2.3.4 Study GS-00-461 (lamivudine-resistant HBV, HBeAg+ chronic HBV infected patients)

Title: "A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Adefovir Dipivoxil (ADV) Alone and in Combination with Lamivudine (LAM) for Patients with Lamivudine Resistant Hepatitis B Virus (HBV)"

Study 461 is an ongoing double-blind, active-controlled study to evaluate the safety and activity of adefovir 10 mg daily as either monotherapy or as dual therapy in combination with lamivudine 100 mg (the control being lamivudine 100 mg alone) in chronic hepatitis B patients with lamivudine-resistant hepatitis B virus (YMDD mutant). Patients with baseline ALT levels of 2 times upper limit normal were enrolled (n=59) and randomized in a 1:1:1 ration to receive either ADV 10 mg, LAM 100 mg or ADV 10 mg + LAM 100 mg. The primary endpoint of this study was the time-weighted average change from baseline in serum HBV DNA at Week 16 ($DAVG_{16}$). The study duration is 48 weeks.

2.4 Statistical Evaluation of Evidence on Efficacy and Safety

2.4.1 Applicant's Results

2.4.1.1 Demographics and Baseline Characteristics

In this section we compare the demographics and baseline characteristics of patients across Studies 437, 438, 435 and 461. These are shown for the intent-to-treat population in Table 2.

Since the demographics and baseline characteristics were balanced across the treatment groups within each study, comparisons between treatment groups are not shown.

All of these studies were conducted in patients with chronic hepatitis B. However, the studies differed with respect to the type of patient population enrolled.

- Study 437 was conducted in HBeAg+ patients.
- Study 438 was conducted in HBeAg- patients.
- Study 435 was conducted in patients with lamivudine-resistant HBV and were either waitlisted for liver transplant or received a liver transplant.
- Study 461 was conducted in HBeAg+ patients with lamivudine-resistant HBV.

Some key highlights of the demographics and baseline characteristics of Studies 437, 438, 435, and 461 are discussed below.

- The median age of patients in Study 437 was younger (33 years) as compared to Studies 438 (46 years) , 461 (45 years) and 435 (55 years).
- Majority of the patients in all studies were male (approximately 75% or more).
- In Study 437 (HBeAg+), majority of the patients were Asian (approximately less than 2/3rds) while in Study 438 (HBeAg-) and Study 435, majority of the patients were Caucasian (approximately 2/3rds or more). Note that these studies were multinational studies with patients of different races from different countries.
- Patients in studies 435 were more advanced (i.e., had decompensated liver disease) than those in studies 437, 438 and 461 (i.e., had compensated liver disease [defined as prothrombin time $\leq$1 second above normal range, albumin $\geq$3 g/dL, total bilirubin $\leq$2.5 mg/dL, no history of variceal bleeding, no history of encephalopathy]).
- Also, all patients in studies 435 and 461 had previously received at least one HBV medication and all patients had developed lamivudine-resistant HBV as compared with studies 437 and 438.
- In Study 437, 97% of the intent-to-treat patients were tested positive for the HB e Antigen with Diasorin assay and majority of the patients in Study 438 were tested

negative for HB e Antigen at baseline, as expected based on the entry criteria.

- The median baseline serum HBV DNA level in Study 437 was higher (8.36 $\log_{10}$ copies/mL) than that in Study 438 (7.08 $\log_{10}$ copies/mL).

- However, the median ALT at baseline in both Studies 437 and 438 were similar. Also, the mean Knodell necroinflammatory and fibrosis scores at baseline were similar in these two studies.

Statistical Reviewer's Comment:

Based on serologic data of chronic hepatitis B from the National Health and Nutritional Examination Survey 3, McQuillan, et al., at the National Center for Health Statistics, the prevalence of hepatitis B virus infection in the U.S. was significantly higher among African-Americans and Hispanics than in Caucasians. The 28 U.S. sites in Study 437 enrolled 15 African-Americans or 10 percent of patients, and those in Study 435 enrolled only 2 African-Americans. A total of 5 patients in these two studies were classified as "Other." It is unclear as to what this meant. It appears, therefore, that the African-Americans, Hispanic-Americans, American Indians, and Alaska Natives were significantly underrepresented in the applicant's drug development program.

Table 2:
Patient Demographics and Baseline Characteristics by Study (Intent-to-Treat Population)

Characteristic		Study Number (Patient Population)			
		437 HBeAg+ N=511	438 HBeAg-/ anti-HBe+/ HBV DNA+ N=184	435 Post-OLT, lamivudine-resistant HBV N=131	461 HBeAg+, lamivudine-resistant HBV N=58
Age (years)	Median (Range)	33 (16 to 68)	46 (18 to 65)	55 (12 to 70)	45 (26 to 69)
Weight (kg)	Median (Range)	70 (40 to 134)	75 (46 to 135)	NA	76 (45 to 118)
Gender	Male	378 (74%)	152 (83%)	113 (86%)	46 (79%)
	Female	133 (26%)	32 (17%)	18 (14%)	12 (21%)
Race	White	184 (36%)	122 (66%)	105 (80%)	35 (60%)
	Black	16 (3%)	6 (3%)	1 (1%)	1 (2%)
	Asian	304 (59%)	56 (30%)	25 (19%)	21 (36%)
	Other	7 (1%)	0 (0%)	0 (0%)	1 (2%)

Characteristic		Study Number (Patient Population) 437 HBeAg+ N=511	438 HBeAg-/ anti-HBe+/ HBV DNA+ N=184	435 Post-OLT, lamivudine-resistant HBV N=131	461 HBeAg+, lamivudine-resistant HBV N=58
Prior HBV Therapy §	Any HBV med	135 (26%)	81 (44%)	131 (100%)	58 (100%)
	Interferon-α	123 (24%)	76 (41%)	17 (13%)	21 (36%)
	Lamivudine	10 (2%)	14 (8%)	131 (100%)	58 (100%)
	Other	27 (5%)	19 (10%)	110 (84%)	12 (21%)
Baseline HBeAg positive (Diasorin) ‡	n (%)	497 (97%)	3 (2%)	58 (62%)	56 (97%)
Baseline HBV-DNA (log_{10} copies/mL)	Mean ± SD	8.20 ± 0.88	6.93 ± 0.89	7.7 ± 1.7	8.1 ± 0.7
	Median	8.36	7.08	8.2	8.1
	Q1, Q3	7.61, 8.82	6.33, 7.55	7.5, 8.8	
	Range		[redacted]		
Baseline ALT (IU/L)	Mean ± SD	133.77 ± 129	145.6 ± 151.5	122.7 ± 143.2	104.1 ± 81.1
	Median	94	98	83	79
	Q1, Q3	65, 158	69, 165	50, 124	60, 109
	Range		[redacted]		
ALT-multiples of the upper limit of normal (ULN)	≤ ULN	10 (2%)	9 (5%)	21 (20%)	1 (2%)
	> ULN	501 (98%)	175 (95%)	85 (80%)	57 (98%)
Baseline Knodell HAI Scores †					
Total	Mean ± SD	9.40 ± 3.37	9.38 ± 3.33	NA	NA
	Median	10	10		
	Q1, Q3	8, 12	8, 12		
	Range		[redacted]		
	n (%)	494 (97%)	178 (97%)		
Necroinflammatory	Mean ± SD	7.67 ± 2.82	7.52 ± 2.74	NA	NA
	Median	8	7		
	Q1, Q3	7, 10	5, 10		
	Range		[redacted]		
	n (%)	494 (97%)	178 (97%)		
Fibrosis	Mean ± SD	1.72 ± 1.09	1.86 ± 1.16	NA	NA
	Median	1	1		
	Q1, Q3	1, 3	1, 3		
	Range		[redacted]		
	n (%)	494 (97%)	178 (97%)		

Characteristic		Study Number (Patient Population)			
		437 HBeAg+ N=511	438 HBeAg-/ anti-HBe+/ HBV DNA+ N=184	435 Post-OLT, lamivudine-resistant HBV N=131	461 HBeAg+, lamivudine-resistant HBV N=58
Child-Pugh Total Score	Mean ± SD	NA	NA	6.2 ± 1.5	5.0 ± 0.2
	Median			6	5
	n			79	57
	Missing			52	1
Weeks from Liver Transplant until First Dose Date	Median (weeks)	NA	NA	209.3	NA

NA = Not available or not applicable.

OLT = Orthotopic liver transplantation

Q1 = 1st quartile or 25th percentile; Q3 = 3rd quartile or 75th percentile.

HAI = Histologic Activity Index

Note: For Study 435, data represents *all enrolled* patients in Cohorts 1A, 2A, and 3A (i.e., post-OLT patients). Insufficient data were available on patients in Cohort B (pre-OLT patients) to provide complete demographic data as of the interim study report. This study was open-label.

† Knodell HAI scores are given for patients in ITT population who had baseline liver biopsy. The number "n" shows the number of patients who had non-missing scores.

‡ Diasorin assay was used to test for Hepatitis B e Antigen positivity.

§ Patients may have had more than one prior Hepatitis B medication. Therefore, percentages may not add up to 100%.

Sources: Tables 6, 7, 20A, 21A, 22A, supporting table for Figure 12C1, of 437 CSR. Tables 6, 8, 20A, 21A, supporting table for Figure 12C2, of 438 CSR. Tables 5, 9, 11 of 435 CSR. Table 2.1, 2.5, 5.2.8.3 of 461 CSR.

2.4.1.2 Patient Disposition

Table 3 summarizes the disposition of patients during the first 48 weeks of Studies 437 and 438. A total of 515 patients were enrolled in Study 437 and 185 patients were enrolled in Study 438.

Table 3: Patient Disposition in First 48 Weeks—Studies 437 and 438

Number of Subjects	Study 437 N=515				Study 438 N=185		
	Adefovir		Placebo	Total	Placebo	Adefovir 10 mg	Total
	30 mg	10 mg					
Total Randomized	173	172	170	515	62	123	185
Randomized but not treated †	0	1	3	4	1	0	1
Treated (ITT) ‡	**173**	**171**	**167**	**511**	**61**	**123**	**184**
Completed study through Week 48	**159 (92%)**	**159 (93%)**	**154 (92%)**	**472 (92%)**	**60 (98%)**	**120 (97%)**	**180 (98%)**
Discontinued study prior to Week 48	**14 (8%)**	**12 (7%)**	**13 (8%)**	**39 (8%)**	**1 (2%)**	**3 (2%)**	**4 (2%)**
Reason discontinued							
Adverse event	5 (3%)	4 (2%)	1 (<1%)	10 (2%)	0 (0%)	1 (<1%)	1 (<1%)
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Disease progression	1 (<1%)	0 (0%)	1 (<1%)	2 (<1%)	0 (0%)	0 (0%)	0 (0%)
Lost to follow-up	1 (<1%)	2 (1%)	1 (<1%)	4 (<1%)	0 (0%)	1 (<1%)	1 (<1%)
Non-compliance	2 (1%)	2 (1%)	2 (1%)	6 (1%)	0 (0%)	0 (0%)	0 (0%)
Withdrew consent	3 (2%)	3 (2%)	7 (4%)	13 (3%)	1 (2%)	1 (<1%)	2 (1%)
Other §	2 (1%)	1 (<1%)	1 (<1%)	4 (<1%)	0 (0%)	0 (0%)	0 (0%)

Percentages in the table are calculated based on the total number of treated subjects in each group.

NOTE:

1) In Study 437, patients were enrolled in the following countries: Australia (12%), Canada (8%), Europe (26%), Taiwan (12%), Thailand (3%), USA (29%), and Other Asian countries (9%).

2) In Study 438, patients were enrolled in the following countries: Australia (11%), Canada (14%), France and Italy (24%), Greece and Israel (39%), and Taiwan and Singapore (12%)

† Randomized-but-not-treated patients were randomized but did not receive any study medication.

‡ Treated patients were randomized and received at least one dose of study medication. This is also the intent-to-treat (ITT) population.

§ Other category includes protocol violation and other reasons

Source: Tables 12 and 1 of 437 Clinical Study Report. Table 12 of Year 1, and Table 1 from Study 438 Clinical Study Report.

The number of enrolled patients who did not receive the study medication was only 4 in Study 437 and 1 in Study 438. Also, among the enrolled patients who received at least one dose of study medication (i.e., ITT), the proportion of patients who completed the study through Week 48 in both studies was quite high (92% in Study 437 and 98% in Study 438). As such, the rates of discontinuations through Week 48 were low.

2.4.2 Statistical Reviewer's Findings on Efficacy

2.4.2.1 Histologic Response in Studies 437 and 438—Efficacy

In Studies 437 (HBeAg+ patients) and 438 (HBeAg- patients), the primary efficacy endpoint was based on histologic response, while in Study 435—which was conducted in patients who either were waitlisted or received a liver transplant—the primary efficacy endpoint was based on the virologic response.

This section will present the primary efficacy results based on histologic response for Studies 437 and 438. Efficacy results for Study 435 will be discussed in Section 2.4.2.2 that follows.

Liver biopsies were conducted on patients at Baseline (prior to receiving the study medication) and at Week 48 (post-treatment) in Studies 437 and 438. The adequacy of the liver biopsies at Baseline and Week 48 in Studies 437 and 438 are shown in Table 4.

Table 4:
Adequacy of Liver Biopsies in Studies 437 and 438

	Study 437 (HBeAg+) N=515				Study 438 (HBeAg-) N=185		
	Adefovir		Placebo	Total	Adefovir	Placebo	Total
Number of Patients	30 mg	10 mg			10 mg		
Total Randomized	173	172	170	515	123	62	185
Randomized but not treated †	0	1	3	4	0	1	1
Treated (ITT) ‡	**173**	**171**	**167**	**511**	**123**	**61**	**184**
Baseline biopsies							
Adequate	**165 (95%)**	**168 (98%)**	**161 (95%)**	**494 (96%)**	**121 (98%)**	**57 (92%)**	**178 (96%)**
Inadequate	5 (3%)	3 (2%)	4 (2%)	12 (2%)	2 (2%)	4 (6%)	6 (3%)
Missing	3 (2%)	1 (<1%)	5 (3%)	9 (2%)	0 (0%)	1 (2%)	1 (<1%)
Week 48 biopsies							
Adequate	**152 (89%)**	**155 (90%)**	**153 (90%)**	**460 (89%)**	**115 (94%)**	**59 (95%)**	**174 (94%)**
Inadequate	4 (2%)	2 (1%)	1 (<1%)	7 (1%)	3 (2%)	0 (0%)	3 (2%)
Missing	17 (10%)	15 (9%)	16 (9%)	48 (9%)	5 (4%)	3 (5%)	8 (4%)
Adequate biopsy pairs §	**147 (85%)**	**152 (89%)**	**149 (89%)**	**448 (88%)**	**113 (92%)**	**56 (92%)**	**169 (92%)**

Percentages in the table are calculated based on the total randomized subjects in each group.

† Randomized-but-not-treated patients were randomized but did not receive any study medication.

‡ Treated patients were randomized and received at least one dose of study medication. This is also the intent-to-treat (ITT) population. Primary efficacy analysis population is the ITT population with adequate baseline liver biopsy.

§ Patients had adequate biopsies at both Baseline (pre-treatment) and Week 48 (post-treatment).

Source: FDA Statistical Reviewer's Analyses.

In Study 437, 88% (448/511) of all the ITT patients had adequate liver biopsies at baseline and Week 48, while in Study 438, 92% had adequate pairs of biopsies. The proportion of missing and inadequate biopsies at baseline as well as at Week 48 were comparable across the treatment groups in each study.

As mentioned earlier, the primary efficacy endpoint in both Studies 437 and 438 was *histologic improvement* at Week 48 based on the Knodell scoring system. Histologic improvement was defined as ≥2 point decrease from baseline in the Knodell necroinflammatory score with no concurrent worsening in the Knodell fibrosis score at Week 48.

The Knodell histological activity index (HAI) is a scoring system that contains four components (1: Periportal injury, 2: Parenchymal injury, 3: Portal inflammation, and 4: Fibrosis). (See Section 2.3.1 for details.) The sum of the first three components gives the necroinflammatory score and the fourth component is the fibrosis score. These scores were evaluated by a central pathologist who evaluate pairs of biopsies for each patient and was blinded to both the treatment group and the sequence of the biopsy (i.e., baseline or Week 48).

Table 5 shows the primary efficacy results on histologic improvement for Studies 437 and 438 which was based on data for only those patients who had adequate baseline biopsies. Missing or inadequate biopsies at Week 48 were considered as failures in these analyses.

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Table 5:
Histologic Response at Week 48 (Missing/Inadequate Biopsies = Failures)
—Studies 437 and 438

	Study 437 (HBeAg+)			Study 438 (HBeAg-)	
Number of Patients	Adefovir 30 mg	Adefovir 10 mg	Placebo	Adefovir 10 mg	Placebo
ITT	173	171	167	123	61
Adequate baseline biopsy	**165 (100%)**	**168 (100%)**	**161 (100%)**	**121 (100%)**	**57 (100%)**
Adequate biopsy pairs	147 (85%)	152 (89%)	149 (89%)	113 (93%)	56 (98%)
Improvement †	**99 (60%)**	**89 (53%)**	**41 (25%)**	**78 (64%)**	**20 (35%)**
No improvement ‡	48 (29%)	63 (37%)	108 (67%)	35 (29%)	36 (63%)
Both necroinflammation and fibrosis worse	4 (2%)	9 (5%)	15 (9%)	1 (1%)	8 (14%)
Only necroinflammation worse	43 (26%)	52 (31%)	92 (57%)	33 (27%)	28 (49%)
Only fibrosis worse	1 (<1%)	2 (1%)	1 (<1%)	1 (1%)	0 (0%)
Missing/Inadequate Week 48 biopsy	18 (11%)	16 (9%)	12 (7%)	8 (7%)	1 (2%)
Missing Week 48 biopsy	14 (9%)	14 (8%)	11 (7%)	5 (4%)	1 (2%)
Inadequate Week 48 biopsy	4 (2%)	2 (1%)	1 (<1%)	3 (3%)	0 (0%)
Difference in proportions (Adefovir – Placebo) (95% CI)	**34.5% (24%, 44%)**	**27.5% (17%, 37%)**		**29.4% (14%, 44%)**	
p-value	< 0.001	< 0.001		< 0.001	

Percentages calculated are based on the number of patients with adequate baseline biopsy

p-values are based on the Cochran Mantel-Haenszel chi-square test.

† Histological improvement was defined as ≥2 point decrease in the Knodell necroinflammatory score from baseline to Week 48 with no concurrent worsening in Knodell fibrosis score.

‡ No histological improvement could be due to following reasons: (a) either due to the Knodell necroinflammatory score being worse (change from baseline is < 2 points), but fibrosis is same or better, or (b) due to the Knodell fibrosis score being worse (change from baseline is < 0), but necroinflammation is better, or (c) both necroinflammation and fibrosis are worse at Week 48 compared with baseline

Source: FDA Statistical Reviewer's analysis

In Study 437, a statistically significant proportion of patients receiving adefovir 30 mg or 10 mg daily doses showed histologic improvement at Week 48 relative to those patients receiving placebo. Also, the observed proportion of patients with histologic improvement was greater in the adefovir 30 mg group than that in the adefovir 10 mg group, both relative to placebo. The observed treatment difference for ADV 30 mg vs

Placebo was 34.5% with a 95% confidence interval of (24%, 44%), while the observed treatment difference for ADV 10 mg vs Placebo was 27.5% with a 95% confidence interval of (17%, 37%). A similar result was observed in the Study 438. The observed treatment effect was 29.4% for ADV 10 mg vs Placebo with a 95% confidence interval of (14%, 44%).

Statistical Reviewer's Comments:

Since a liver biopsy is a surgical procedure whereby a small piece of tissue from the liver is obtained at a given time point, there will be inherent measurement error in evaluation of biopsy taken at Baseline (or Week 48) for a given patient. Therefore there is within-subject variability as well as between-subject variability. As a result, comparison of one sample for a given patient, taken at Baseline and one sample taken at Week 48 does not take into account the measurement error when evaluating histologic improvement in the treated population based on patient-level data using the predefined primary endpoint of ≥2 point decrease in necroinflammation and no worsening of fibrosis.

We, therefore, evaluated the robustness of evidence in histologic improvement due to adefovir by comparing the Knodell necroinflammatory scores and Knodell fibrosis scores for the entire patient population as cohorts in each treatment groups. This was done through graphical analyses using boxplots that show the entire distribution of the Knodell scores in each treatment group at Baseline and at Week 48. (See Figure 2 and Figure 3.)

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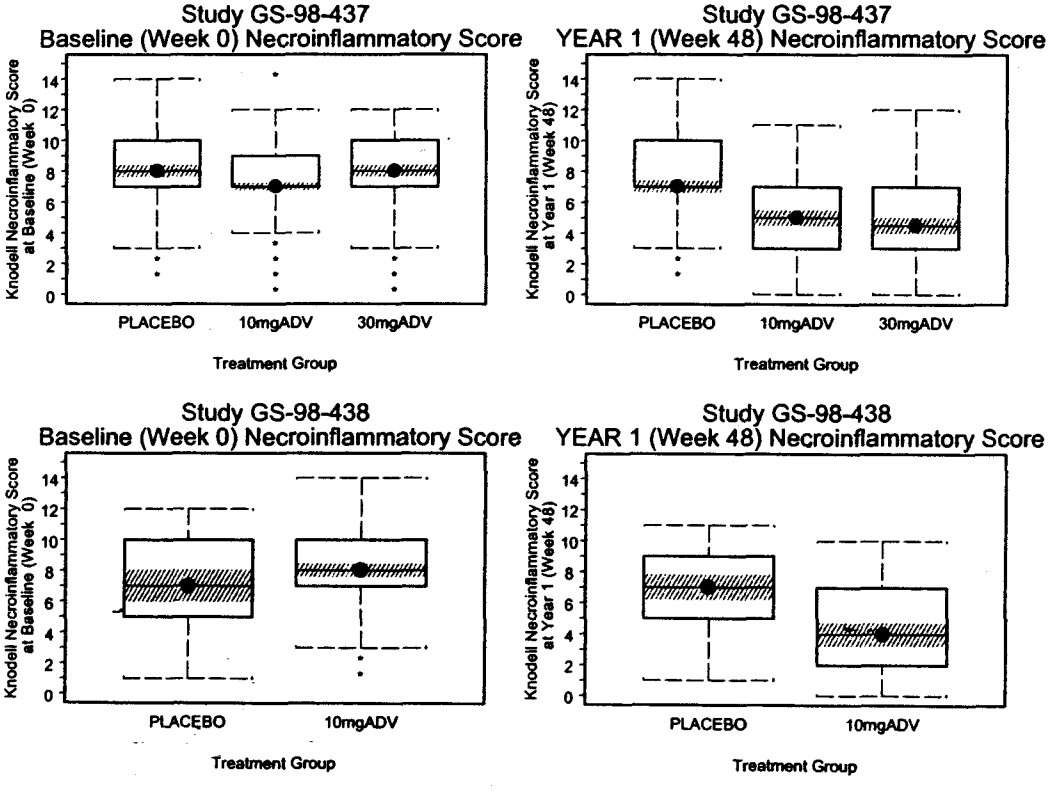
Figure 2 shows the distribution of Knodell necroinflammatory scores for each treatment group in Studies 437 and 438 at Baseline and at Week 48, based on data for the entire patient population. Similarly, Figure 3 shows the distribution of Knodell fibrosis scores.

The first row in each figure shows the scores for Study 437 and the second row is for Study 438. The left set of boxplots shows Baseline scores for each treatment group (Placebo, ADV 10 mg and ADV 30mg in Study 437, and Placebo and ADV 10 mg in Study 438). The right set shows Week 48 scores for each treatment group (Placebo, ADV 10 mg and ADV 30 mg in Study 437, and Placebo and ADV 10 mg in Study 438). In each boxplot, the median score is represented by a dot and a 95% confidence interval around the median is represented by the shaded area around the dot.

Figure 2:
Distribution of Knodell Necroinflammatory Scores at Baseline and Week 48
by Treatment Group
—Studies 437 and 438



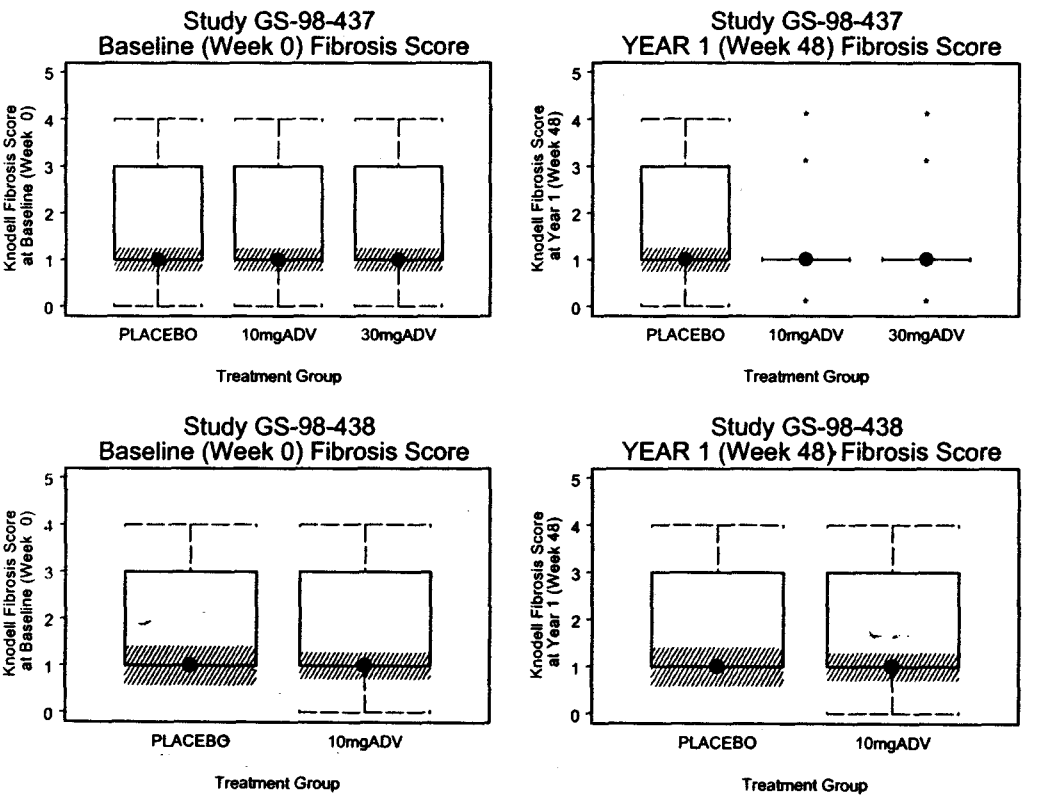
As seen here, in Study 437, the distribution of Knodell necroinflammatory scores for the ADV 10 mg treatment group has shifted downward from Baseline to Week 48, and the same is true for the ADV 30 mg treated group. The median scores for both the ADV 10 mg and 30 mg group are statistically significantly lower at Week 48 when compared with

the respective baseline median scores (since the 95% CIs do not overlap). The Placebo group however does not have a notable shift in the Knodell necroinflammatory scores at Week 48.

Similarly, in Study 438, the distribution of the necroinflammatory scores have shifted lower in the ADV 10 mg treated group at Week 48 compared to Baseline.

In summary, analysis of the entire patient population data on Knodell necroinflammatory scores showed a significant reduction in necroinflammation when treated with either ADV 10 mg or ADV 30 mg daily doses. Also, note that greater improvement was observed in the ADV 30 mg group compared with ADV 10 mg.

Figure 3:
Distribution of Knodell Fibrosis Scores at Baseline and Week 48
by Treatment Group
—Studies 437 and 438



With respect to the Knodell fibrosis scores, when the data for the entire patient population were analyzed for Study 437, there was no significant change from baseline in the median scores for any treatment group. However, there were fewer patients in ADV 10mg and 30mg groups that had a score >=1 point at Week 48 compared with placebo,

implying that fewer patients had worsening of fibrosis, relative to placebo. Similar conclusion is made regarding Study 438 with respect to the Knodell Fibrosis scores.

The above conclusions are also reached by analyzing the individual patient level data on change from baseline in the Knodell necroinflammatory and fibrosis scores as shown in Table 6 below.

Table 6:

Change from Baseline in Knodell Scores at Week 48—Studies 437 and 438

		Study 437			Study 438	
Knodell HAI Scores †		Adefovir 30 mg	Adefovir 10 mg	Placebo	Adefovir 10 mg	Placebo
Necroinflammatory						
Change from baseline	Mean ± SD	-3.18 ± 3.28	-2.52 ± 3.24	-0.11 ± 3.07	-3.42 ± 2.86	0.27 ± 3.19
	Median	-3	-2	0	-3	0
	Q1, Q3	-5, 0	-5, 0	-2, 1	-6, -1	-2, 3
	Range					
	n (# with adequate biopsy pairs)	147	152	149	113	56
Fibrosis						
Change from baseline	Mean ± SD	-0.31 ± 0.80	-0.18 ± 0.83	-0.01 ± 0.85	-0.29 ± 0.74	0.12 ± 0.93
	Median	0	0	0	0	0
	Q1, Q3	0, 0	0, 0	0, 0	0, 0	0, 0
	Range					
	n (# with adequate biopsy pairs)	147	152	149	113	56

† HAI = Histologic Activity Index

Q1 = 1st quartile or 25th percentile; Q3 = 3rd quartile or 75th percentile.

Sources: FDA Statistical Reviewer's Analyses

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Statistical Reviewer's Comments:

As noted before, the Knodell scoring system has "jumps" on the scoring scale for each component. For example, the fibrosis component which reflects the degree of fibrosis or "stage" of chronic hepatitis can be scored as 0, 1, 3, or 4 using the Knodell scoring system. Hence there is a jump from score 1 to 3.

In comparison, the Ishak scoring system has no such jumps and is more precise in scoring. With the Ishak scoring system, fibrosis can be scored from 0 to 6 as follows: 0=no fibrosis; 1=fibrosis expansion of some portal areas; 2=fibrosis expansion of most portal areas; 3=fibrosis expansion of most portal areas with occasional portal-to-portal bridging; 4=fibrosis expansion of portal areas with marked bridging; 5=marked bridging with occasional nodules (incomplete cirrhosis); and 6=cirrhosis, probable or definite.

Therefore, based on the suggestion of the Medical Reviewer, Dr. Tan Nguyen, we evaluated the patient-level data on fibrosis by computing the change from baseline in fibrosis score at Week 48 for each patient based on the Ishak scoring system. We assumed that a decrease of 1 point or lower in fibrosis score indicates improvement, a change of 0 point indicates fibrosis stage is same, and an increase of 1 point or higher indicates worsening of fibrosis. We conducted analyses for Studies 437 and 438 to see whether the proportion of patients with improvement, same or worsening of fibrosis differed across the adefovir 30 mg, 10mg and placebo groups. This would tell us whether or not adefovir had any positive treatment effect in prevention of fibrosis in patients with chronic hepatitis B.

Table 7 shows the proportion of patients with changes in fibrosis (improvement, no change, or worsening) at Week 48 in Studies 437 and 438 based on the Ishak scoring system. For the purpose of comparison, same results based on the Knodell scoring system are also presented.

There was a statistically significant difference in the pattern of changes in fibrosis across the adefovir and placebo groups in both Studies 437 and 438. Based on the Ishak fibrosis scores, a statistically significantly greater proportion of patients treated in the adefovir (30 mg or 10mg) groups showed improvement in fibrosis relative to those treated with placebo in both studies.

Table 7:

Changes in Fibrosis based on Knodell and Ishak Scores at Week 48
—Studies 437 and 438

	Study 437 (HBeAg+)			Study 438 (HBeAg-)	
Number of Patients	Adefovir 30 mg	Adefovir 10 mg	Placebo	Adefovir 10 mg	Placebo
ITT	173	171	167	123	61
Adequate baseline biopsy	165	168	161	121	57
Adequate biopsy pairs	**147 (100%)**	**152 (100%)**	**149 (100%)**	**113 (100%)**	**56 (100%)**
Ishak fibrosis scores					
Improved	61 (41%)	52 (34%)	28 (19%)	38 (34%)	8 (14%)
Same	71 (48%)	83 (55%)	89 (60%)	70 (62%)	28 (50%)
Worsened	15 (10%)	17 (11%)	32 (21%)	5 (4%)	20 (36%)
p-value for test of treatment mean scores differing	< 0.001*			< 0.001*	
p-value for Adefovir 30mg vs 10mg	0.3747				
p-value for Adefovir vs Placebo	< 0.001*	< 0.001*			
Knodell fibrosis scores					
Improved	30 (20%)	26 (17%)	15 (10%)	19 (17%)	5 (9%)
Same	112 (76%)	115 (76%)	118 (79%)	92 (81%)	43 (77%)
Worsened	5 (3%)	11 (7%)	16 (11%)	2 (2%)	8 (14%)
p-value for test of treatment mean scores differing	0.0013*			0.0047*	
p-value for Adefovir 30mg vs 10mg	0.2920				
p-value for Adefovir vs Placebo	< 0.001*	0.0011			

Percentages calculated are based on the number of ITT patients with adequate biopsy pairs.

NOTE: A decrease of 1 point or more in fibrosis score from baseline is considered improvement. If the fibrosis scores are same at baseline and at Week 48, then they are same or unchanged. An increase of 1 point or greater in fibrosis score at Week 48 from baseline is considered as worsening of fibrosis.

p-values are based on the Cochran Mantel-Haenszel chi-square test on whether the "row" mean scores differ.

* p-values are statistically significant.

Source: FDA Statistical Reviewer's analysis