

Long-term Efficacy and Safety of Adefovir Dipivoxil for the Treatment of HBeAg-Positive Chronic Hepatitis B (CHB) Patients in Study GS-98-437

Poster Number

969

57th Annual Meeting of the American Association for the Study of Liver Diseases
October 27-31, 2006
Boston, Massachusetts, USA

P Marcellin,¹ TT Chang,² SG Lim,³ W Sievert,⁴ M Tong,⁵ S Arterburn,⁶ K Borroto-Esoda,⁶ and S Chuck⁶

¹Hopital Beaujon, Clichy, France; ²National Cheng Kung University Hospital, Tainan, Taiwan Republic of China;

³National University Hospital, Singapore, Singapore; ⁴Monash Medical Centre, Victoria, Australia;

⁵Huntington Medical Center Research Institute, Huntington, CA, USA; ⁶Gilead Sciences, Inc., Foster City, CA, USA



Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Tel: (650)574-3000
Fax: (650)578-9264

Background & Objective

- Treatment of 171 patients with HBeAg+ CHB with adefovir dipivoxil (ADV) 10 mg over 48 weeks resulted in significant histological, virological, serological, and biochemical improvement compared to placebo in the first year of this study.¹
- The long-term efficacy and safety of ADV in HBeAg+ CHB patients was investigated for up to five years.

Methods

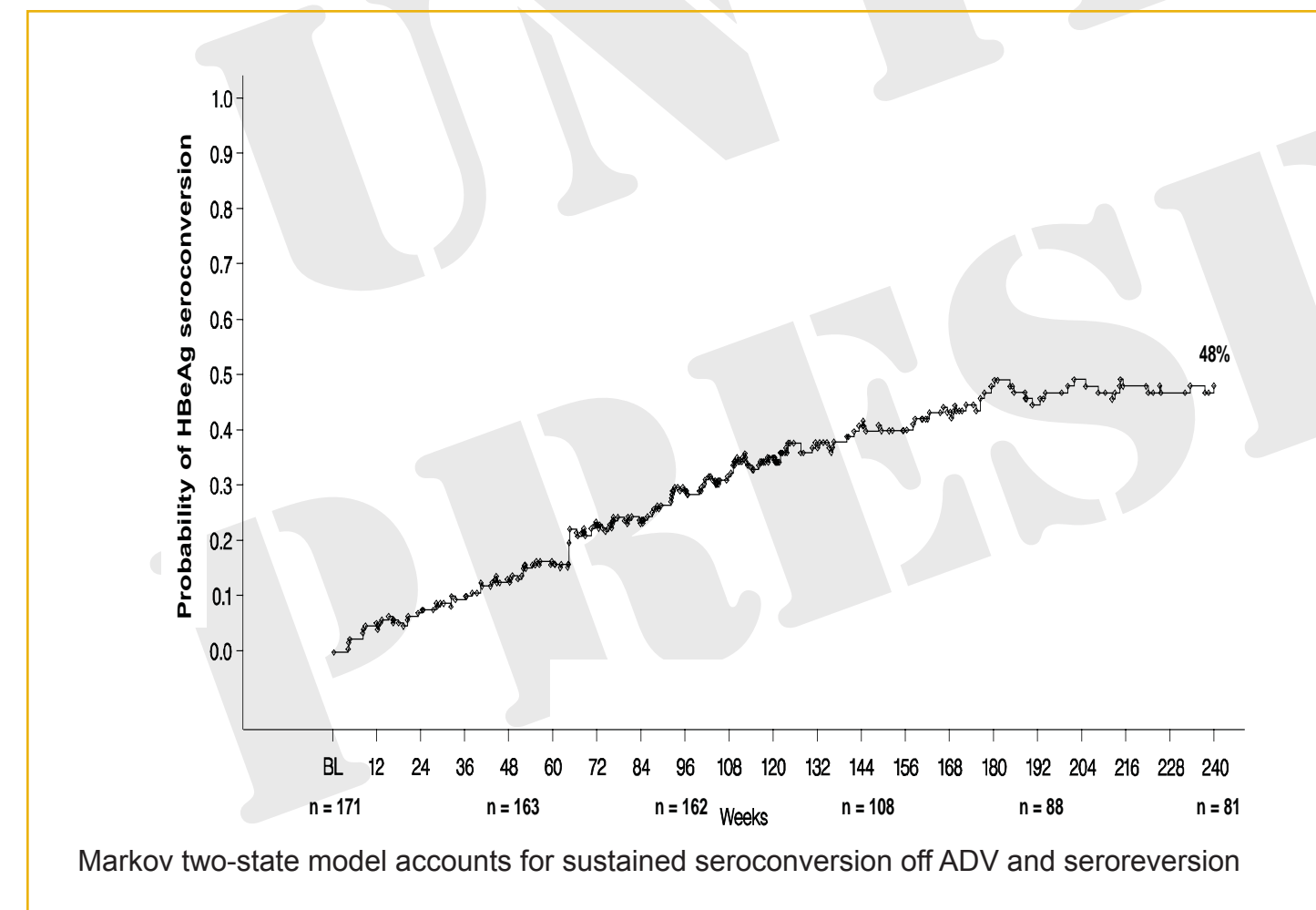
- Entry criteria were HBsAg+ ≥ 6 months, HBeAg+, serum HBV DNA ≥ 6 log₁₀ copies/mL (Roche Amplicor Monitor PCR, LLQ 1000 copies/mL), and ALT 1.2 – 10 X ULN.
- Patients were randomized to receive ADV 10 mg (n = 172), ADV 30 mg (n = 173), or placebo (n = 170) in year 1. At the beginning of year 2, patients started on ADV 10 mg (n = 224) or placebo (n = 215). However, most patients received multiple doses of both placebo and ADV in year 2.
- Patients with confirmed HBeAg loss or seroconversion discontinued from this study and were followed off treatment; thus, only non-seroconverters remained in this study.
- Patients given ADV 10 mg in year 1 who did not seroconvert in years 1 and 2 could enroll in a long-term, safety and efficacy study (LTSES; n = 65) with assessments every 3 months for 3 years. Patients with confirmed HBeAg loss or seroconversion discontinued from the LTSES and were followed off treatment.
- A two-state Markov model was used to estimate the percentage of all patients with HBeAg loss and seroconversion over time and to account for seroreversion.

Table 1. Baseline Characteristics of Patients

Characteristic	ADV 10 mg patients (n = 171)	LTSES (n = 65)
Age, median years	32	34
Male	76%	83%
Race	Asian 60%, White 35%, Black 5%	Asian 74%, White 23%, Black 3%
Serum HBV DNA, median log ₁₀ copies/mL	8.40	8.45
ALT, multiples of ULN, median	2.3 x ULN	2.0 x ULN

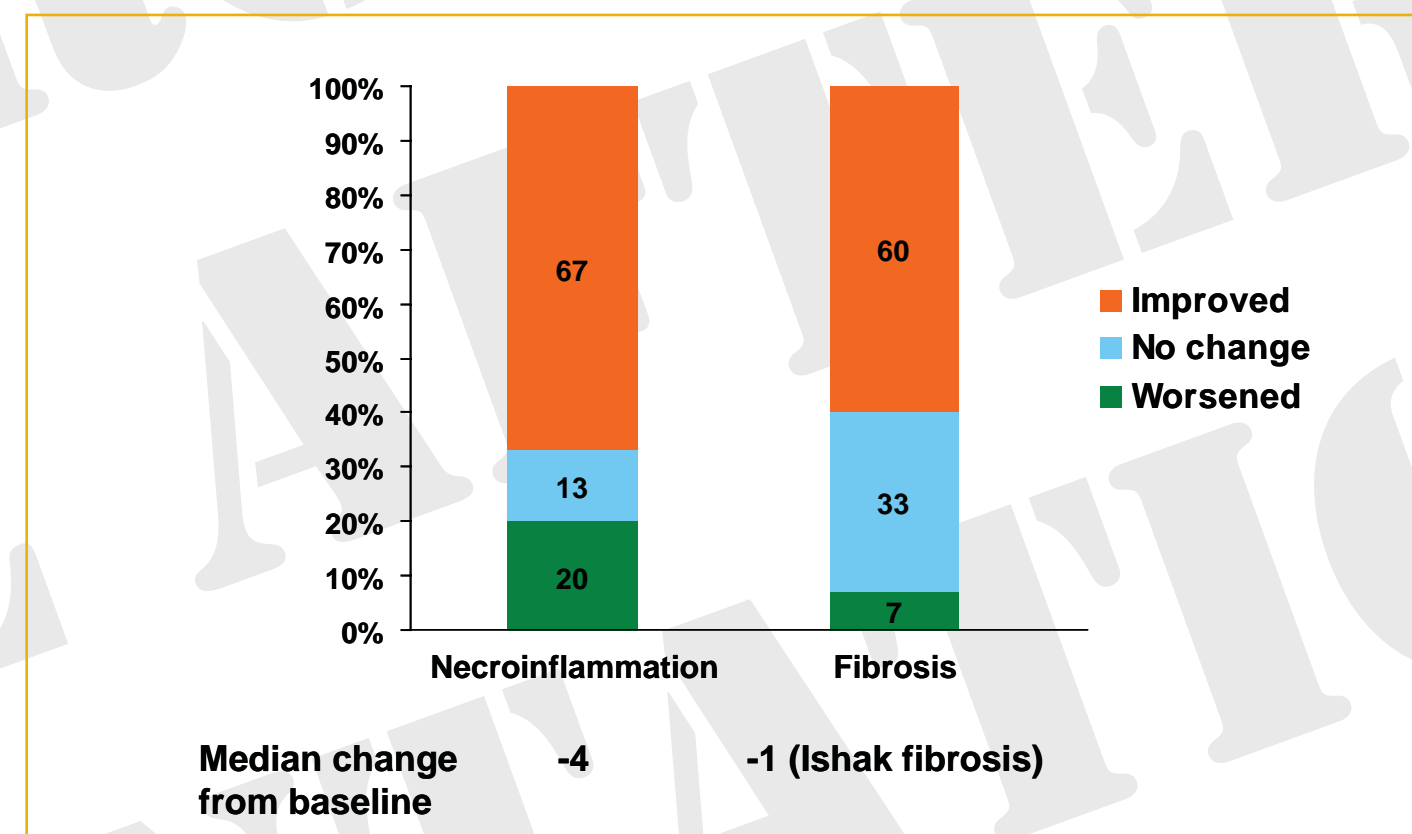
ULN = Upper Limit of normal range

Figure 1. HBeAg Seroconversion Increased to 48% at 5 Years

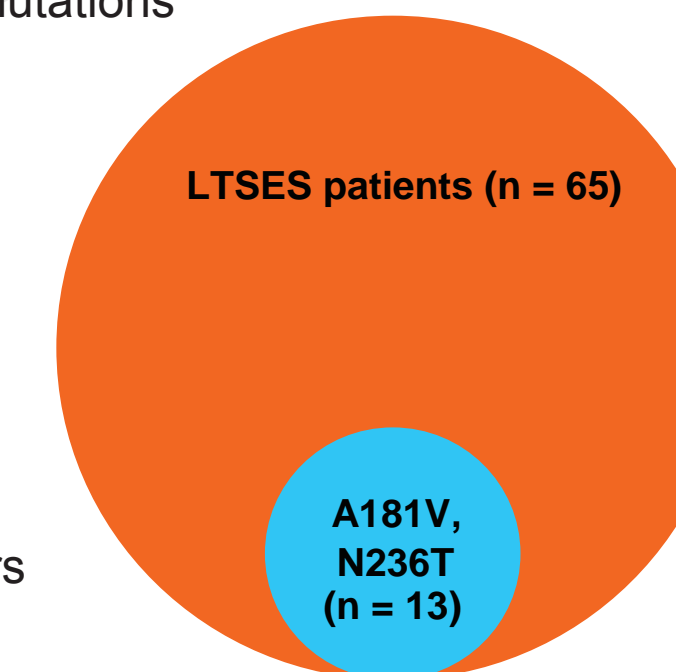


Results

Figure 2. Ranked Assessments of Baseline and LTSES Liver Biopsies (n = 15)



- In Year 1, no ADV resistance mutations were detected (0/171; 0%)
- Through Year 5, 38/65 patients had a confirmed rebound in HBV DNA or were never fully suppressed
- 13/65 (20%) LTSES patients developed ADV resistance mutations (A181V, N236T) that were first detected at 3.75 years on study
- 3 LTSES patients developed A181T; however, this mutation does not confer phenotypic resistance to ADV in vitro²



Safety

- No serious adverse events related to ADV.
- Confirmed increase of ≥ 0.5 mg/dL from baseline in serum creatinine occurred in only 6 patients treated with ADV for up to 5 years; two of these patients discontinued ADV due to increases in serum creatinine in LTSES phase of study.
- The first confirmed increase of ≥ 0.5 mg/dL in serum creatinine occurred after 3.5 years on study.

Conclusions

In this study of patients with HBeAg+ CHB:

- HBeAg seroconversion increased over time to 48% after 240 weeks on study. Seroconversion was durable in 91% of patients over a median follow up off drug of 3 years.³
- Liver biopsies at baseline and in the LTSES (n = 15) showed improvements in necroinflammation and fibrosis in the majority of patients
- Genotypic resistance occurred in 13/65 (20%) of patients treated with ADV for up to 5 years
- ADV was well tolerated

References & Disclosure

- Marcellin, et al. NEJM 348:808-816, 2003.
- Yang H, et al. AASLD, Boston, MA, 2003.
- Chang TT, et al. EASL, 2006.

DISCLOSURE: Authors have financial relationships within the last 12 months relevant to the presentation with Gilead Sciences, Inc.