

Telbivudine Research Compendium

TELBIVUDINE RESEARCH COMPENDIUM

- 1. Identification of Baseline Clinical Characteristics and Early On-treatment Parameters Predicting Long-Term Outcomes for Telbivudine-Treated Patients with Chronic Hepatitis B (the GLOBE Study)**
Authors: Zeuzem S, Buti M, Gane E, Liaw Y-F, Di Bisceglie A, Heathcote EJ, Rasenack J, Lim S-G, Hou J-L, Qiao X, Galil K, Naoumov NV
Presented at AASLD 2007
- 2. Baseline Characteristics and Early Virologic Response to Telbivudine Predict 2-Year Outcomes for Patients with HBeAg-Negative Chronic Hepatitis B (the GLOBE Study)**
Authors: Poynard T, Papatheodoridis GV, Tong M, Tsai N, Buti M
Presented at HEPDART 2007
- 3. Telbivudine GLOBE Trial at Year Two: Efficacy, Safety, and Predictors of Outcome in Patients with Chronic Hepatitis B**
Authors: Han SH, Lai CL, Gane E, Liaw YF, Thongsawat S, Wang Y, Chen Y, Heathcote J, Rasenack J, Bzowej N, Naoumov N, Brown N, and the GLOBE Study Group
Presented at DDW 2007
- 4. Efficacy of Telbivudine vs. Lamivudine at 2 Years in Patients With HBeAg-Positive Chronic Hepatitis B Who Are Eligible for Treatment Based on Guidelines**
Authors: Rasenack J, Poynard T, Lai CL, Gane E, Brown N, Heathcote EJ
Presented at EASL 2007
- 5. Adefovir Salvage Therapy for Virologic Breakthrough in Telbivudine-Treated Patients from the GLOBE Study**
Authors: Gane E, Lai CL, Min A, Heathcote J, Poynard T, Kurdas OO, Grange J-D, Brown NA
Presented at EASL 2007
- 6. Two-Year Results of a Phase III Comparative Trial of Telbivudine vs. Lamivudine in Chinese Patients**
Authors: Jia J-D, Hou J-L, Yin Y-K, Xu D-Z, Tan D, Niu J, Zhou X-Q, Wang Y, Zhu L, Brown N
Presented at EASL 2007
- 7. Cost-Effectiveness of Telbivudine vs. Lamivudine for Chronic Hepatitis B**
Authors: Wong JB, Pauker SG, on behalf of the GLOBE Investigators
Presented at EASL 2007

Identification of Baseline Clinical Characteristics and Early On-treatment Parameters Predicting Long-Term Outcomes for Telbivudine-Treated Patients with Chronic Hepatitis B (the GLOBE Study)

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AASLD 2007

Key conclusions

- Baseline clinical characteristics can predict which patients will have better treatment outcome after 104 weeks of treatment with telbivudine. In HBeAg-positive patients, baseline serum ALT levels correlate significantly with treatment outcomes at 104 weeks.
- Baseline viremia is also an important predictor as serum HBV DNA $<9 \log_{10}$ copies/mL (HBeAg-positive patients), or serum HBV DNA levels $<7 \log_{10}$ copies/mL (HBeAg-negative patients) are associated with greater efficacy and less resistance, after 104 weeks of treatment with telbivudine.
- Undetectable serum HBV DNA (by PCR) after 24 weeks of treatment with telbivudine is the strongest on-treatment predictor of week 104 outcomes, both for HBeAg-positive and for HBeAg-negative CHB. In contrast, serum ALT level at week 24 was not a significant predictor of any week 104 outcome.
- By combining the baseline and on-treatment predictors it is possible to identify telbivudine-treated patients that achieve the highest rates of efficacy and lowest resistance after 104 weeks of treatment.

IDENTIFICATION OF BASELINE CLINICAL CHARACTERISTICS AND EARLY ON-TREATMENT PARAMETERS PREDICTING LONG-TERM OUTCOMES FOR TELBIVUDINE-TREATED PATIENTS WITH CHRONIC HEPATITIS B (THE GLOBE STUDY)

Stefan Zeuzem,¹ Maria Buti,² Edward Gane,³ Yun-Fan Liaw,⁴ Adrian Di Bisceglie,⁵ E. Jenny Heathcote,⁶ Jens Rasenack,⁷ Seng-Gee Lim,⁸ Jin-Lin Hou,⁹ Xinjian Qiao,¹⁰ Karin Galil,¹⁰ Nikolai V. Naoumov,¹¹

¹JW Goethe University Hospital, Frankfurt, Germany; ²Hospital General Universitario Vall d'Hebron, Barcelona, Spain; ³Middlemore Hospital, Otahuhu, Auckland, New Zealand; ⁴Chang Gung Memorial Hospital, Taipei, Taiwan; ⁵St. Louis University, St. Louis, MO, USA; ⁶University of Toronto, Toronto, ON, Canada; ⁷Albert Ludwigs University, Freiburg, Germany; ⁸National University of Singapore, Singapore; ⁹Nanfeng Hospital, Guangzhou, China; ¹⁰Idenix Pharmaceuticals Inc., Cambridge, MA, USA; ¹¹Novartis Pharma AG, Basel, Switzerland

Background

- Treatment of chronic hepatitis B (CHB) is evolving with an increasing range of treatment options. Clinical practice guidelines in the USA, Europe, and Asia provide separate algorithms for the management of patients with HBeAg-positive and HBeAg-negative CHB.¹⁻³ In HBeAg-positive CHB antiviral treatment is recommended for patients with serum ALT levels ≥ 2 times the upper limit of normal (ULN), while in HBeAg-negative CHB treatment initiation depends mainly on viremia levels ($>10^5$ or 10^6 copies/mL).
- Therapeutic outcomes may be improved firstly through informed selection of initial therapy, and secondly by early evaluation of treatment response, which allows confirmation of the efficacy of the initial therapy or the opportunity to adjust therapy for patients with suboptimal responses.
- Analyses of clinical characteristics of patients treated with interferon demonstrated that high serum ALT and low HBV DNA levels before treatment are associated with higher rates of HBeAg loss.⁴ Similarly, elevated ALT levels and/or active histologic disease were noted to be the most important predictors of lamivudine-induced HBeAg loss.⁵ However, the existing trials with interferon or oral antiviral agents have provided limited information to evaluate the relative importance of pretreatment characteristics vs. evaluation of early on-treatment responses in predicting long-term treatment outcomes.
- The GLOBE study, which compared the efficacy and safety of telbivudine 600 mg/day and lamivudine 100 mg/day over 2 years in 1367 adult patients with CHB, provides an excellent resource for assessing factors that may contribute to therapeutic outcomes for both HBeAg-positive and HBeAg-negative patients.^{6,7}
- The aim of this analysis is to identify baseline patient characteristics that predict optimal responses to telbivudine after 2 years of treatment in the GLOBE study, and to compare these with the early on-treatment response parameters that may contribute to effective management of patients receiving telbivudine therapy.

Methods

- The GLOBE study enrolled nucleos(t)ide-naïve patients aged 16–70 years with HBeAg-positive (n=921) or HBeAg-negative (n=446) compensated CHB. Treatment groups were well matched for baseline demographic and disease characteristics.
- Study endpoints assessed in this analysis include serum HBV DNA reduction, ALT normalization, HBeAg seroconversion and resistance. Serum HBV DNA was quantified by COBAS[®] Amplicor polymerase chain reaction (PCR) assay (detection limit 300 copies/mL). Resistance was defined as viral breakthrough (increase of serum HBV DNA ≥ 1 log above nadir) with confirmed genotypic resistance, based on the full length DNA sequencing of the reverse transcriptase domain of HBV polymerase.
- Multivariate regression analyses were used to identify and assess baseline and early on-treatment (Weeks 12 and 24) variables predictive of Week 104 efficacy outcomes. The population for these analyses comprised telbivudine recipients with available Week 104 data.
- Baseline variables included in the model were age, body mass index (BMI), serum ALT, Ishak fibrosis score, serum HBV DNA level, Knodell histologic activity index (HAI) score, gender, and HBV genotype. Since 96% of patients harboring HBV genotype C were Asian, genotype and race were not considered simultaneously. Continuous variables were dichotomized along the median of HBeAg-positive and -negative groups. P-values <0.15 were required for model entry and >0.25 for model exit.
- For analysis of on-treatment predictive factors, patients were categorized according to serum HBV DNA level at Weeks 12 and 24: PCR-negative; <3 log₁₀ copies/mL; 3–4 log₁₀ copies/mL; and ≥ 4 log₁₀ copies/mL and by baseline ALT level <2 x ULN, 2–5 x ULN and >5 x ULN. For stepwise multiple regression analyses, patients were categorized as HBV DNA PCR-negative or not PCR-negative at Weeks 12 and 24.

Results

Outcomes at Week 104

- At Week 104, significantly more telbivudine recipients (vs. lamivudine) achieved therapeutic response, i.e. the primary efficacy endpoint. Telbivudine demonstrated superiority on all direct measures of antiviral efficacy in both HBeAg-positive and HBeAg-negative patients (Table 1).

Baseline variables associated with Week 104 outcomes for telbivudine

- In HBeAg-positive patients, baseline serum HBV DNA levels <9 log₁₀ copies/mL were strong predictors of PCR-negativity, HBeAg seroconversion and low resistance at Week 104 (Figure 1). BMI <22.5 kg/m² and age <30 years were significant predictors of ALT normalization.

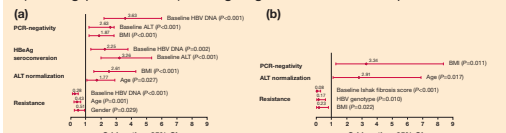
Table 1. GLOBE study results at 104 weeks

	HBeAg-positive patients			HBeAg-negative patients		
	Telbivudine	Lamivudine	P	Telbivudine	Lamivudine	P
N	458	463	–	222	224	–
Therapeutic response ¹ , %	63	48	<0.0001	78	66	0.007
Mean HBV DNA reduction from baseline, log ₁₀ copies/mL	-5.7	-4.4	<0.0001	-5.0	-4.2	0.0002
HBV DNA PCR-negative, %	56	39	<0.0001	82	57	<0.0001
ALT normalization, %	70	62	0.014	78	70	0.073
HBeAg loss, %	35	29	0.056	–	–	–
HBeAg seroconversion, %	30	25	0.095	–	–	–
Resistance ² , %	25	40	<0.0001	11	26	<0.0001

¹Serum HBV DNA <5 log₁₀ copies/mL coupled with ALT normalization or HBeAg loss.
²Viral breakthrough at Week 104 (persistent increase of HBV DNA of 1 log $>$ nadir value) with confirmed resistance mutations. Resistance rates at Week 104, calculated using protocol definition of viral breakthrough (persistent increase of HBV DNA to above 5 log₁₀ copies/mL after suppression to below that level), were 22% and 8% for telbivudine in HBeAg-positive and HBeAg-negative patients, respectively, compared with 34% and 20% for lamivudine.

- In HBeAg-positive patients, the rates of PCR-negativity, HBeAg loss and HBeAg seroconversion at Week 104 showed positive correlation with baseline ALT levels (<2 x ULN, 2–5 x ULN or >5 x ULN), while the resistance rates were inversely correlated. Importantly, within each baseline ALT category, the rates of PCR-negativity at Week 104 were significantly higher with telbivudine, compared with lamivudine, and the resistance rates were significantly lower with telbivudine for patients with baseline ALT levels <2 x ULN or 2–5 x ULN (Table 2).
- In HBeAg-negative patients, BMI was the only significant predictor of PCR-negativity at Week 104, and age was the only significant predictor of ALT normalization (Figure 1). BMI, baseline Ishak fibrosis score <3 , and genotype C were predictors of Week 104 resistance. Although baseline HBV DNA level was not a significant predictor in HBeAg-negative patients, there was a trend suggesting better outcomes for patients with baseline HBV DNA <7 log₁₀ copies/mL.

Figure 1. Significant baseline predictors of Week 104 outcomes in a) HBeAg-positive and b) HBeAg-negative telbivudine recipients



Baseline variables that were identified by multivariate analysis as significant predictors of outcomes at Week 104 are shown. Data indicate odds ratios \pm 95% confidence intervals (CIs). Odds ratios >1 indicate direct relationships; odds ratios <1 indicate inverse relationships. Selection criteria: serum HBV DNA at Week 24 PCR-negative (<300 copies/mL) vs. not PCR-negative; baseline HBV DNA <9 vs. ≥ 9 log₁₀ copies/mL (HBeAg-positive patients) or <7 vs. ≥ 7 log₁₀ copies/mL (HBeAg-negative patients); BMI <22.5 vs. ≥ 22.5 ; Age <30 vs. ≥ 30 ; gender female vs. male.

- In HBeAg-negative patients, the rates of PCR-negativity at Week 104 correlated positively with baseline ALT levels (<2 x ULN, 2–5 x ULN, or >5 x ULN), while the rates of resistance were inversely correlated with baseline ALT levels. The rates of PCR-negativity at Week 104 were significantly higher and the resistance rates were significantly lower with telbivudine, compared with lamivudine, for patients with baseline ALT levels <2 x ULN or 2–5 x ULN (Table 2).
- Compared with the overall population of HBeAg-positive telbivudine recipients, higher rates of efficacy responses at Week 104, and less resistance, were seen in patients eligible for treatment (baseline ALT levels ≥ 2 x ULN) if the baseline HBV DNA levels were <9 log₁₀ copies/mL. In the HBeAg-negative population, telbivudine-treated patients with baseline HBV DNA levels <7 log₁₀ copies/mL experienced higher rates of efficacy responses and less resistance at Week 104 (Table 3).

Table 2. Week 104 outcomes based on ALT at baseline

	ALT at baseline					
	Lamivudine n/N (%)			Telbivudine n/N (%)		
HBeAg-positive						
Week 104 outcomes	<2 x ULN	2–5 x ULN	>5 x ULN	<2 x ULN	2–5 x ULN	>5 x ULN
Seroconversion	32/159 (20.0)	50/197 (25.4)	27/86 (31.2)	26/150 (17.8)	67/207 (32.3)	35/75 (46.3)
E antigen loss	39/159 (24.3)	59/197 (29.9)	31/86 (35.8)	36/150 (24.4)	79/207 (38.2)	37/75 (48.8)
PCR-negative	52/170 (30.4)	78/205 (37.7)	48/88 (54.3)	74/163 (45.7)*	125/219 (57.0)*	56/76 (73.3)*
Cumulative 1 log above nadir resistance, %	46.1	40.8	22/88 (25.3)	47/163 (28.6)*	54/219 (24.5)*	14/76 (18.7)

	ALT at baseline					
	Lamivudine n/N (%)			Telbivudine n/N (%)		
HBeAg-negative						
Week 104 outcomes	<2 x ULN	2–5 x ULN	>5 x ULN	<2 x ULN	2–5 x ULN	>5 x ULN
PCR-negative	51/99 (50.9)	53/90 (58.9)	23/35 (67.2)	75/92 (82.4)*	81/99 (81.8)*	26/31 (82.8)
Cumulative 1 log above nadir resistance, %	30/99 (30.7)	22/90 (24.2)	6/35 (15.6)	10/92 (10.4)*	11/99 (11.1)*	3/31 (9.4)

*P <0.05 , telbivudine vs. lamivudine.

Table 3. Week 104 outcomes with telbivudine according to baseline HBV DNA level

	HBeAg-positive ¹		HBeAg-negative ¹	
	Telbivudine n=80	Lamivudine n=78	Telbivudine n=91	Lamivudine n=103
PCR negativity, %	77.3	55.2	89.2	66.4
HBeAg seroconversion, %	47.1	40.7	–	–
ALT normalization, %	75.0	71.5	82.0	78.1
Cumulative 1 log above nadir resistance, %	11.3	19.0	3.1	20.7

¹HBeAg-positive patients: baseline ALT ≥ 2 x ULN and HBV DNA <9 log₁₀ copies/mL; HBeAg-negative patients: baseline HBV DNA <7 log₁₀ copies/mL.

Early on-treatment variables associated with Week 104 outcomes

- The degree of early viral suppression (HBV DNA reduction) increased from Week 12 to Week 24 of telbivudine treatment in both HBeAg-positive and negative patients (Figure 2).
- Since elevated baseline ALT was established as a predictor of response in HBeAg-positive patients, we first analyzed the predictability of response in these patients with ALT ≥ 2 x ULN at baseline. Since no baseline characteristic was a significant predictor across outcomes in the HBeAg-positive cohort, we analyzed this relationship in the overall HBeAg-negative population.

Figure 2. Serum HBV DNA levels at Weeks 12 and 24 in telbivudine recipients

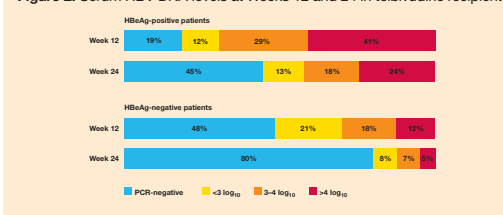
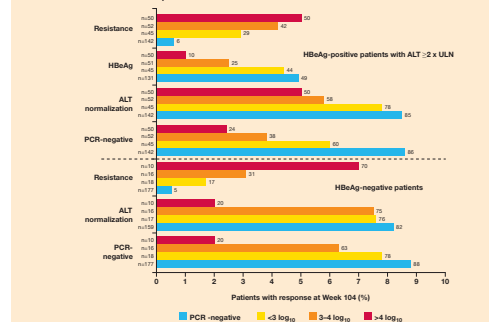


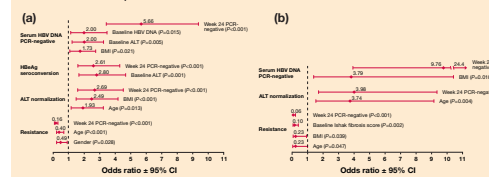
Figure 3. Effect of early virologic response to telbivudine on outcomes at Week 104 in CHB patients considered for antiviral treatment



Viral breakthrough at Week 104 (persistent increase of HBV DNA of 1 log $>$ nadir value) with confirmed resistance mutations. Resistance rates at Week 104, calculated using protocol definition of viral breakthrough (persistent increase of HBV DNA to above 5 log₁₀ copies/mL after suppression to below that level), were 4% and 3% for telbivudine-treated HBeAg-positive with ALT ≥ 2 x ULN and HBeAg-negative patients, respectively, who were PCR-negative at Week 24.

- Undetectable serum HBV DNA (by PCR) at Week 24 emerged as a significant, and the strongest predictor of Week 104 outcomes (Figure 3). When this parameter was added to the multiple regression model; the predictive value of baseline parameters became weaker or insignificant. In contrast, serum ALT level at Week 24 was not a significant predictor of any Week 104 outcome in the multiple regression model (Figure 4).

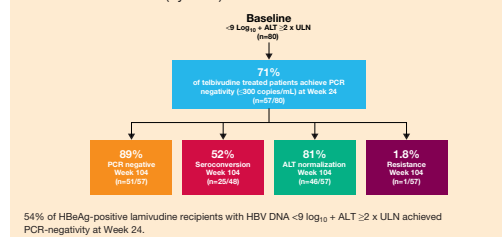
Figure 4. Significant baseline and on-treatment (Week 24) predictors of outcomes at Week 104 in a) HBeAg-positive and b) HBeAg-negative telbivudine recipients



Baseline and on-treatment variables that were identified by multivariate analysis as significant predictors of outcomes at Week 104 are shown, with PCR-negativity at Week 24 included in the statistical model. Data indicate odds ratios \pm 95% CIs. Odds ratios >1 indicate direct relationships; odds ratios <1 indicate inverse relationships. Selection criteria: serum HBV DNA at Week 24 PCR-negative (<300 copies/mL) vs. not PCR-negative; baseline HBV DNA <9 vs. ≥ 9 log₁₀ copies/mL (HBeAg-positive patients) or <7 vs. ≥ 7 log₁₀ copies/mL (HBeAg-negative patients); baseline ALT ≥ 2.5 x ULN vs. <2.5 x ULN; BMI <22.5 vs. ≥ 22.5 ; Age <30 vs. ≥ 30 ; gender female vs. male.

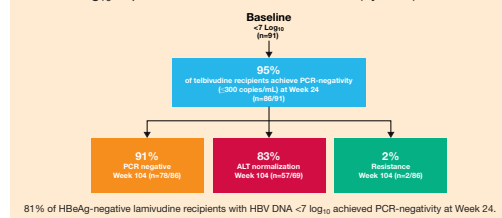
- Undetectable serum HBV DNA (by PCR) at Week 12 was also a significant predictor of most Week 104 outcomes, however the odds ratios were generally lower, with reduced statistical significance, compared with the odds ratios for PCR-negativity at Week 24 (data not shown).
- HBeAg-positive patients eligible for guideline-recommended treatment (baseline ALT levels ≥ 2 x ULN with baseline HBV DNA levels <9 log₁₀ copies/mL) achieved higher rates of PCR-negativity at Week 24 than the overall HBeAg-positive patients in the study (71% vs. 44%). Those patients who were PCR-negative at Week 24 experienced high rates of efficacy responses and a low rate of resistance at Week 104 (Figure 5).

Figure 5. Outcomes at Week 104 for HBeAg-positive patients eligible for treatment (ALT ≥ 2 x ULN) with HBV DNA <9 log₁₀ copies/mL and undetectable viremia (by PCR) at Week 24



54% of HBeAg-positive lamivudine recipients with HBV DNA <9 log₁₀ + ALT ≥ 2 x ULN achieved PCR-negativity at Week 24.

Figure 6. Outcomes at Week 104 for HBeAg-negative patients with HBV DNA <7 log₁₀ copies/mL and undetectable viremia (by PCR) at Week 24



81% of HBeAg-negative lamivudine recipients with HBV DNA <7 log₁₀ achieved PCR-negativity at Week 24.

Conclusions:

- Baseline clinical characteristics can predict which patients will have better treatment outcome after 104 weeks of treatment with telbivudine. In HBeAg-positive patients, baseline serum ALT levels correlate significantly with treatment outcomes at 104 weeks. Baseline viremia is also an important predictor as serum HBV DNA <9 log₁₀ copies/mL (HBeAg-positive patients), or serum HBV DNA levels <7 log₁₀ copies/mL (HBeAg-negative patients) are associated with greater efficacy and less resistance, after 104 weeks of treatment with telbivudine.
- Undetectable serum HBV DNA (by PCR) after 24 weeks of treatment with telbivudine is the strongest on-treatment predictor of Week 104 outcomes, both for HBeAg-positive and for HBeAg-negative CHB. In contrast, serum ALT level at Week 24 was not a significant predictor of any Week 104 outcome.
- Comparison of baseline and early on-treatment parameters showed that HBV DNA level after 24 weeks of telbivudine treatment is overall the strongest predictor of outcomes at Week 104, and is therefore a very relevant parameter for evaluation of therapeutic response. Patients with a viral load that remains high at Week 24 have poorer long-term outcomes, suggesting that modification of the therapeutic regimen should be considered.
- By combining the baseline and on-treatment predictors it is possible to identify telbivudine treated patients that achieve the highest rates of efficacy and lowest resistance after 104 weeks of treatment.

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NOVARTIS Disclosures

Dr. Zeuzem has received consulting fees from BMS, Gilead, GSK, Idenix, Novartis, Roche, and Schering-Plough and lecture fees from Idenix and Novartis.
 Dr. Buti has served as a scientific advisor for Novartis, Idenix, and Gilead and has received lecture fees from Schering-Plough, GSK, Gilead, and Novartis.
 Dr. Gane received consulting fees from Gilead, GSK, and Novartis and honoraria from GSK, Idenix, Novartis, Roche, and GSK.

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 Prof. Di Bisceglie has received research grants and/or consultancy fees/honoraria and/or has served on advisory boards for Abbott, Analysis, BMS, F. Hoffmann-La Roche, Gilead, GlaxoSmithKline, Idenix, Metabasis Therapeutics, Novartis, Pharmasset, Schering-Plough, SciClone, and Vertex.
 Dr. Heathcote has received consulting fees from Idenix and Novartis and grant support from Idenix.
 Dr. Rasenack has no disclosures.
 Dr. Lim has acted as a scientific advisor to Novartis, Idenix, and BMS, and is on the Speaker's Bureau for GSK and Schering-Plough.
 Dr. Hou has provided scientific advice to Novartis, GSK and BMS.

Dr. Qiao is a former employee of Idenix Pharmaceuticals Inc.
 Dr. Galil is an employee of Idenix Pharmaceuticals Inc.
 Dr. Naoumov is an employee of Novartis Pharma AG.

Baseline Characteristics and Early Virologic Response to Telbivudine Predict 2-Year Outcomes for Patients with HBeAg-Negative Chronic Hepatitis B (the GLOBE Study)

Poynard T, Papatheodoridis GV, Tong M, Tsai N, Buti M

HEPDART 2007

Key conclusions

- Therapeutic outcomes may be optimized in HBeAg-negative patients through informed selection of initial therapy and by early evaluation of treatment response.
- In the GLOBE study, telbivudine demonstrated more profound early (week 24) viral suppression and superiority on all direct measures of antiviral efficacy at week 104 of treatment among HBeAg-negative patients, compared with lamivudine.
- Among HBeAg-negative patients with baseline HBV DNA level $<7 \log_{10}$ copies/mL, telbivudine demonstrated higher rates of PCR negativity at week 24 and higher rates of efficacy responses and less resistance at week 104, compared with lamivudine.
- HBeAg-negative patients with baseline HBV DNA levels $<7 \log_{10}$ copies/mL who were PCR-negative at week 24 showed the highest rates of efficacy responses and the least resistance at week 104 in both treatment arms, although predictability of long-term response was greater for telbivudine than for lamivudine.

BASELINE CHARACTERISTICS AND EARLY VIROLOGIC RESPONSE TO TELBIVUDINE PREDICT 2-YEAR OUTCOMES FOR PATIENTS WITH HBeAg-NEGATIVE CHRONIC HEPATITIS B (THE GLOBE STUDY)

Thierry Poinard,¹ George V. Papatheodoridis,² Myron Tong,³ Naoky Tsai,⁴ Maria Buti⁵

¹Groupe Hospitalier Pitié-Salpêtrière, Paris, France; ²Athens University Medical School, Athens, Greece; ³Huntington Medical Research Institutes, Pasadena, CA, USA; ⁴John A. Burns School of Medicine, Honolulu, HI, USA; ⁵Hospital Valle de Hebrón, Barcelona, Spain

Background

- The major treatment objective in chronic hepatitis B is to achieve sustained suppression of hepatitis B virus (HBV) replication, and long-term therapy is often required to maintain response.^{1,2}
- There are few data available to guide clinical decision-making regarding individual patient management and early evaluation of treatment response. The ability to predict long-term treatment response based on baseline demographics and early responses to therapy may help physicians individualize patient management and optimize outcomes in hepatitis B e-antigen (HBeAg)-negative chronic hepatitis B.
- The large phase III GLOBE study compared the efficacy and safety of telbivudine 600 mg/day and lamivudine 100 mg/day in 1367 adult patients (including 446 HBeAg-negative patients) with compensated chronic hepatitis B.³ Due to its size, the GLOBE study provides an excellent resource for assessing factors that may contribute to therapeutic outcomes.
- The aim of this analysis is to assess baseline characteristics and HBV DNA levels at Week 24 as predictors of outcomes among patients with HBeAg-negative chronic hepatitis B following 2 years of treatment with telbivudine, and to compare long-term outcomes achieved with telbivudine and lamivudine.

Methods

- The GLOBE study enrolled 1367 nucleos(t)ide-naïve patients aged 16–70 years, including 446 HBeAg-negative patients, with compensated CHB.
- Study endpoints assessed in this analysis include serum HBV DNA negativity (≤ 300 copies/mL), alanine aminotransferase (ALT) normalization, and resistance at Week 104 (2 years). Serum HBV DNA was quantified by COBAS® Amplicor polymerase chain reaction (PCR) assay (detection limit 300 copies/mL). Resistance was defined as viral breakthrough (increase of serum HBV DNA ≥ 1 log above nadir) with confirmed genotypic resistance, based on the full length DNA sequencing of the reverse transcriptase domain of HBV polymerase.
- Multivariate regression analyses were used to identify and assess baseline and early on-treatment (Week 24) variables predictive of Week 104 efficacy outcomes. The population for these analyses comprised HBeAg-negative telbivudine recipients with available Week 104 data.
- Baseline variables included in the model were age, body mass index (BMI), serum ALT, Ishak fibrosis score, serum HBV DNA level, Knodell histologic activity index (HAI) score, gender, and HBV genotype. Continuous variables were dichotomized along the median of HBeAg-negative groups. *P*-values < 0.15 were required for model entry and > 0.25 for model exit.
- For analysis of on-treatment predictive factors, patients were categorized according to serum HBV DNA level at Week 24: PCR-negative; $< 3 \log_{10}$ copies/mL; 3–4 \log_{10} copies/mL; and $\geq 4 \log_{10}$ copies/mL.

Results

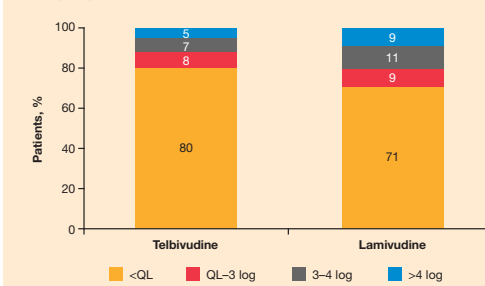
HBeAg-Negative Patient Population

- The intent-to-treat population of the GLOBE study comprised 446 HBeAg-negative patients treated with telbivudine (*n*=222) or lamivudine (*n*=224).

Outcomes in HBeAg-Negative Patients, Telbivudine vs. Lamivudine

- Telbivudine was associated with early, profound viral suppression by 24 weeks of treatment. A greater percentage of HBeAg-negative patients receiving telbivudine were serum HBV DNA PCR-negative, compared with lamivudine (*P*<0.05) (Figure 1).
- At Week 104, telbivudine demonstrated superiority on all direct measures of antiviral efficacy among HBeAg-negative patients (Table 1).

Figure 1. Viral load achieved by Week 24, telbivudine vs. lamivudine, HBeAg-negative patients.



QL, quantitation limit; PCR nondetectable at < 300 copies/mL by COBAS® Amplicor. **P*<0.05, telbivudine vs. lamivudine.

Table 1. GLOBE study results at 104 weeks among HBeAg-negative patients

	HBeAg-negative patients		
	Telbivudine	Lamivudine	<i>P</i>
N	222	224	—
Therapeutic response ¹ , %	78	66	0.007
Mean HBV DNA reduction from baseline, \log_{10} copies/mL	-5.0	-4.2	0.0002
HBV DNA PCR-negative, %	82	57	<0.0001
ALT normalization, %	78	70	0.073
Resistance ² , %	11	26	<0.0001

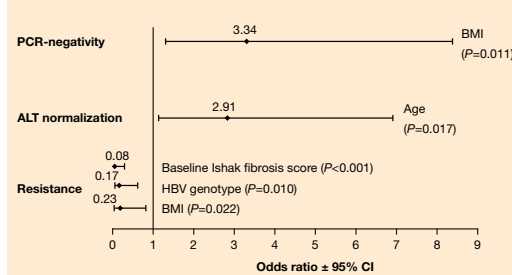
¹Serum HBV DNA $< 5 \log_{10}$ copies/mL coupled with ALT normalization.

²Viral breakthrough at Week 104 (persistent increase of HBV DNA of 1 log $>$ nadir value) with confirmed resistance mutations. Resistance rates at Week 104, calculated using protocol definition of viral breakthrough (persistent increase of HBV DNA to above $5 \log_{10}$ copies/mL after suppression to below that level), were 8% and 20% for telbivudine and lamivudine, respectively, in HBeAg-negative patients.

Baseline Variables Associated with Week 104 Outcomes, HBeAg-Negative Patients

- In HBeAg-negative telbivudine recipients, BMI was the only significant predictor of PCR-negativity at Week 104 (*P*=0.011), and age was the only significant predictor of ALT normalization (*P*=0.017) (Figure 2). BMI (*P*=0.022), Ishak fibrosis score < 3 (*P*<0.001), and genotype C (*P*=0.010) were predictors of Week 104 resistance.
- Because of a trend suggesting better Week 104 outcomes for HBeAg-negative patients with baseline HBV DNA $< 7 \log_{10}$ copies/mL, data from these patients were analyzed separately. A total of 194 HBeAg-negative patients with HBV DNA $< 7 \log_{10}$ copies/mL were randomized to telbivudine (*n*=91) or lamivudine (*n*=103). The groups were well-matched at baseline.
- Significantly more HBeAg-negative telbivudine recipients with baseline HBV DNA $< 7 \log_{10}$ copies/mL were HBV DNA PCR-negative at Week 24, compared with lamivudine (95% vs. 81%, *P*=0.0039) (Figure 3).
- At Weeks 52 and 104, telbivudine demonstrated higher rates of efficacy responses and less resistance among HBeAg-negative patients with HBV DNA $< 7 \log_{10}$ copies/mL, compared with lamivudine (Table 2).

Figure 2. Baseline variables associated with Week 104 outcomes in HBeAg-negative telbivudine recipients.



Baseline variables that were identified by multivariate analysis as significant predictors of outcomes at Week 104 are shown. Data indicate odds ratios \pm 95% confidence intervals (CIs). Odds ratios > 1 indicate direct relationships; odds ratios < 1 indicate inverse relationships. Selection criteria: serum HBV DNA at Week 24 PCR-negative (< 300 copies/mL) vs. not PCR-negative; baseline HBV DNA < 7 vs. $> 7 \log_{10}$ copies/mL; BMI < 22.5 vs. ≥ 22.5 ; Age < 30 vs. ≥ 30 ; gender female vs. male.

Figure 3. Week 24 PCR-negativity in HBeAg-negative patients with baseline HBV DNA $< 7 \log_{10}$ copies/mL.

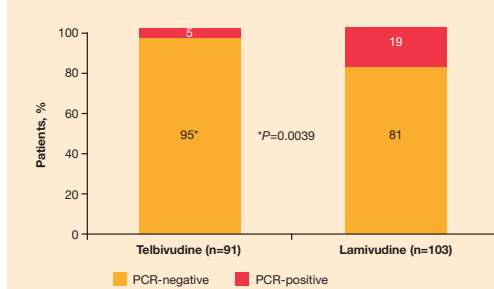


Table 2. GLOBE study results HBeAg-negative patients with baseline serum HBV DNA levels $< 7 \log_{10}$ copies/mL

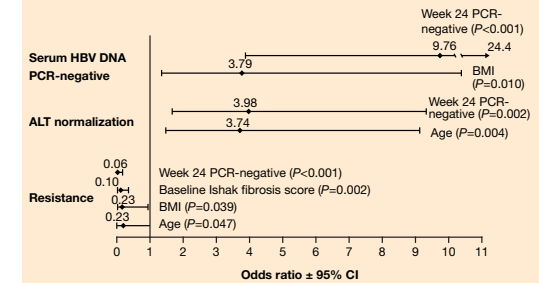
	HBeAg-negative patients with pretreatment serum HBV DNA levels $< 7 \log_{10}$ copies/mL					
	Week 52	Week 104				
	Telbivudine	Lamivudine	<i>P</i>	Telbivudine	Lamivudine	<i>P</i>
HBV DNA PCR-negative, n/N (%)	87/91 (96)	84/101 (83)	0.0094	81/91 (89)	69/101 (68)	0.0005
ALT normalization, n/N (%)	53/73 (73)	68/96 (79)	0.3407	60/73 (82)	69/96 (80)	0.7530
Resistance ¹ , n/N (%)	1/91 (1)	6/101 (6)	0.1217	3/91 (3)	21/101 (21)	0.0003

¹Viral breakthrough at Week 104 (persistent increase of HBV DNA of 1 log $>$ nadir value) with confirmed resistance mutations.

Early On-Treatment Variables Associated with Week 104 Outcomes, HBeAg-Negative Patients

- Viral load at Week 24 was the strongest predictor of Week 104 outcomes among HBeAg-negative patients. When Week 24 PCR-negativity was added to the multiple regression model, the predictive value of baseline parameters became weaker or insignificant, and Week 24 PCR-negativity remained the strongest predictor for PCR-negativity (*P*<0.001), ALT normalization (*P*=0.002), and resistance (*P*<0.001) at Week 104 (Figure 4).

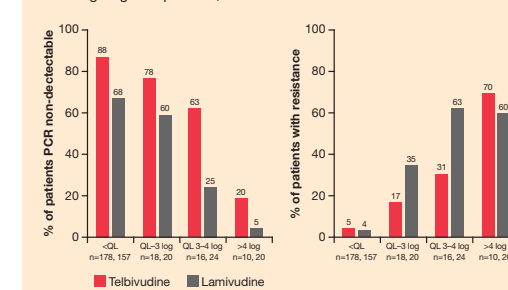
Figure 4. Significant baseline and on-treatment (Week 24) predictors of outcomes at Week 104 in HBeAg-negative telbivudine recipients.



Baseline and on-treatment variables that were identified by multivariate analysis as significant predictors of outcomes at Week 104 are shown, with PCR-negativity at Week 24 included in the statistical model. Data indicate odds ratios \pm 95% CIs. Odds ratios > 1 indicate direct relationships; odds ratios < 1 indicate inverse relationships. Selection criteria: serum HBV DNA at Week 24 PCR-negative (< 300 copies/mL) vs. not PCR-negative; baseline HBV DNA < 7 vs. $> 7 \log_{10}$ copies/mL; baseline ALT ≥ 2.5 x ULN vs. < 2.5 x ULN; BMI < 22.5 vs. ≥ 22.5 ; Age < 30 vs. ≥ 30 ; gender female vs. male.

- Patients who achieved PCR-negativity at Week 24 had higher rates of efficacy responses and less resistance at Week 104 in both treatment groups. Moreover, telbivudine demonstrated better outcomes than lamivudine at Week 104 within each Week 24 viral load subgroup (Figure 5).

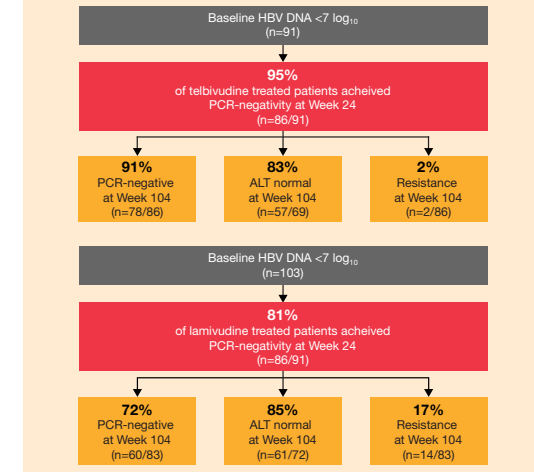
Figure 5. Effect of early (Week 24) viral response on Week 104 outcomes in HBeAg-negative patients, telbivudine vs. lamivudine.



¹Viral breakthrough at Weeks 52 and 104 (persistent increase of HBV DNA of 1 log $>$ nadir value) with confirmed resistance mutations.

- HBeAg-negative patients with baseline HBV DNA levels $< 7 \log_{10}$ copies/mL who were PCR-negative at Week 24 showed the highest rates of efficacy responses and the least resistance at Week 104. Predictability of long-term response was greater for telbivudine (91% PCR-negativity and 2% resistance at Week 104) than for lamivudine (72% PCR-negativity and 17% resistance at Week 104) (Figure 6).

Figure 6. Durability of outcomes at Week 104 among HBeAg-negative patients with baseline HBV DNA $< 7 \log_{10}$ copies/mL and PCR-negativity at Week 24, telbivudine (a) vs. lamivudine (b).



Conclusions

- In the GLOBE study, telbivudine demonstrated more profound early (Week 24) viral suppression and superiority on all direct measures of antiviral efficacy at Week 104 of treatment among HBeAg-negative patients, compared with lamivudine.
- Among HBeAg-negative patients with baseline HBV DNA level $< 7 \log_{10}$ copies/mL, telbivudine demonstrated higher rates of PCR-negativity at Week 24 and higher rates of efficacy responses and less resistance at Week 104, compared with lamivudine.
- Combining both baseline viremia and early on-treatment PCR-negativity at Week 24 can help identify HBeAg-negative chronic hepatitis B patients who can achieve optimal outcomes after 2 years of treatment.
- HBeAg-negative patients with baseline HBV DNA levels $< 7 \log_{10}$ copies/mL who were PCR-negative at Week 24 showed the highest rates of efficacy responses and the least resistance at Week 104 in both treatment arms, although predictability of long-term response was greater for telbivudine than for lamivudine.
- These results suggest that therapeutic outcomes may be optimized in HBeAg-negative patients through informed selection of initial therapy and by early evaluation of treatment response.

References

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- EASL Jury. J Hepatol. 2003;39(suppl 1):S3-S25.
- Lai CL et al. Hepatology. 2006;44(suppl 1):222A (Abstract 91).

Disclosures

Prof. Poinard is on the Speaker's Bureau for Novartis and Schering-Plough, and has acted as an investigator for GSK, Roche and Vertex. He is also an investor in BioPredictive. Dr. Papatheodoridis has served on the advisory boards for Bristol-Myers Squibb, Gilead, Idenix-Novartis, Roche and Wyeth Research. He has received research grants from Gilead, Idenix-Novartis and Roche, and honoraria from Bristol-Myers Squibb, Gilead, Idenix-Novartis and Roche.

Dr. Tong has received consulting fees from Gilead. Dr. Tsai has served on the advisory boards for BMS, Gilead and Novartis, and has received research support, honoraria, and lecture fees from BMS, Gilead, Novartis and Roche. Dr. Buti has served as a scientific advisor for Gilead, Idenix and Novartis, and has received lecture fees from Gilead, GSK, Novartis and Schering-Plough.



Telbivudine GLOBE Trial at Year Two: Efficacy, Safety, and Predictors of Outcome in Patients with Chronic Hepatitis B

Han SH, Lai CL, Gane E, Liaw YF, Thongsawat S, Wang Y, Chen Y, Heathcote J, Rasenack J, Bzowej N, Naoumov N, Brown N, and the GLOBE Study Group

DDW 2007

Key conclusions

- Telbivudine exhibited significantly greater antiviral and clinical efficacy, with less resistance, than lamivudine after 2 years of treatment.
- The post-treatment durability of HBeAg loss or seroconversion was >80% with telbivudine and lamivudine.
- In HBeAg-positive patients with baseline ALT >2 x ULN, generally considered the best treatment candidates, a significantly higher rate of seroconversion was observed with telbivudine than with lamivudine.

Telbivudine GLOBE Trial at Year Two: Efficacy, Safety, and Predictors of Outcome in Patients with Chronic Hepatitis B

S.H. Han¹; C.L. Lai²; E. Gane³; Y.F. Liaw⁴; S. Thongsawat⁵; Y. Wang⁶; Y. Chen⁷; J. Heathcote⁸; J. Rasenack⁹; N. Bzowej¹⁰; N. Naoumov¹¹; N. Brown¹²; and the GLOBE Study Group
¹UCLA School of Medicine, Los Angeles, CA, USA; ²University of Hong Kong, Hong Kong, China; ³Middlemore Hospital, Auckland, NZ; ⁴Chang Gung University and Memorial Hospital, Taipei, Taiwan; ⁵Chiang Mai University, Chiang Mai, Thailand; ⁶Southwest Hospital, Chongqing, China; ⁷Zhejiang University College of Medicine, Hangzhou, China; ⁸Toronto Western Hospital, Toronto, ON, Canada; ⁹Albert Ludwigs Universität, Freiburg, Germany; ¹⁰Sutter Health, San Francisco, CA, USA; ¹¹University College, London, UK; ¹²Idenix Pharmaceuticals, Cambridge, MA, USA.

Background

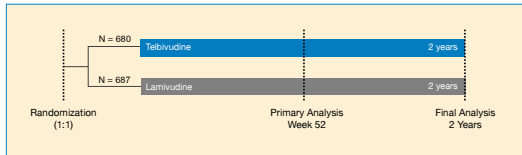
Telbivudine, an L-nucleoside with potent and specific activity against the hepatitis B virus (HBV), is widely approved for the treatment of compensated chronic hepatitis B (CHB).¹ A large, 2-year, international randomized clinical trial (GLOBE) compared the safety and efficacy of telbivudine and lamivudine in 1367 nucleoside-naïve patients with hepatitis B e antigen (HBeAg)-positive or HBeAg-negative CHB. The GLOBE trial is the largest hepatitis B drug registration trial to date. After 1 year, telbivudine showed significantly greater efficacy vs lamivudine on all direct measures of antiviral efficacy in both HBeAg-positive and HBeAg-negative patients.² A quantitative association between serum HBV DNA reduction in the first 6 months of treatment and subsequent efficacy outcomes was also established.³ Here we report preliminary efficacy results from GLOBE after 2 years of treatment, including an analysis of relationships between serum HBV DNA levels at week 24 and efficacy outcomes at week 104.

Experimental Design and Methods

Study Design

Eligible male and female patients were aged 16 to 70 years and had serum HBV DNA $\geq 6 \log_{10}$ copies/mL, serum alanine aminotransferase (ALT) 1.3-10 times the upper limit of normal (ULN), positive serum HBeAg, and compensated liver disease. Patients were randomized 1:1 to treatment with telbivudine (600 mg/day PO) or lamivudine (100 mg/day PO) (Figure 1). Treatment assignments were stratified by baseline HBeAg status (positive or negative) and baseline ALT levels ($\geq 2.5 \times$ ULN).

Figure 1. GLOBE Design



- Safety assessments and serum samples for analysis of laboratory parameters were obtained at screening, baseline, and weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 52, 60, 68, 76, 84, 92, 100, and 104.
- Serum HBV DNA was quantified by COBAS[®] AmpliCor HBV Monitor assay (Roche Molecular Systems, Branchburg, NJ; lower limit of detection 300 copies/mL).

Study Endpoints

Efficacy

- Therapeutic Response (primary efficacy endpoint):
 - Serum HBV DNA $\leq 10^3$ copies/mL, and either ALT normalization or HBeAg loss
- HBV DNA response:
 - Mean/median reduction from baseline
 - Clearance of PCR-detectable HBV DNA (<300 copies/mL)
- ALT normalization
- HBeAg loss and seroconversion (HBeAg-positive patients only)
- Liver histology (evaluated only at week 52)

Safety

- Study discontinuations for any reason, and discontinuations for clinical or laboratory-determined adverse events.
- Analysis of adverse events, serious adverse events, and graded laboratory abnormalities at each study visit up to week 104.

Resistance

- Confirmed rebound of serum HBV DNA by $\geq 1 \log_{10}$ copies/mL above nadir, after initial reduction of $\geq 1 \log_{10}$.
- Return of HBV DNA to $>5 \log_{10}$ or within 1 log of baseline (per protocol).
- Resistance at week 92:
 - Viral breakthrough with documented treatment-emergent resistance mutations, identified by PCR amplification of serum HBV DNA from patients with viral breakthrough, followed by automated DNA sequencing of the entire 344-codon reverse transcriptase domain of the HBV polymerase. Here we report a preliminary analysis of resistance at week 92.

Predictors of response

- Efficacy and resistance outcomes after 2 years were assessed according to serum HBV DNA levels at 24 weeks: PCR-negative (<300 copies/mL); PCR-detectable but $<3 \log_{10}$ copies/mL; $3-4 \log_{10}$ copies/mL; and $>4 \log_{10}$ copies/mL.
- Stepwise logistic regression analyses were performed to identify baseline and on-treatment parameters influencing outcomes at 2 years.
- On-treatment factors included serum HBV DNA and ALT levels at week 24.
- Baseline factors included age, ethnicity, geographic region, HBV genotype, HBV DNA level, ALT level, Knodell HAI score, cirrhosis, BMI, weight, years since diagnosis, probable source of infection, previous interferon use, and treatment group.

Statistical Analysis

- All 1367 patients who started the GLOBE study and received ≥ 1 dose of drug were included in intent-to-treat (ITT) analyses of efficacy and safety at 2 years, including patients who discontinued for any reason.
- Missing data = failure for categorical endpoints.
- Categorical endpoint responses are reported only if maintained through week 104.⁴ Patients must have at least two consecutive qualifying values, and value at last visit must qualify.
- A prospectively defined analysis identified a statistical interaction between HBeAg status and treatment effect for the primary and key secondary endpoints at 1 year. Therefore, results were analyzed separately for the HBeAg-positive and HBeAg-negative populations.

Results

Patients

The randomized ITT population included 1367 patients; 921 HBeAg-positive and 446 HBeAg-negative. Treatment groups were well matched with respect to demographic and disease parameters at baseline (Table 1).

Table 1. Baseline Demographics and Disease Characteristics[†]

	HBeAg-Positive (n = 921)		HBeAg-Negative (n = 446)	
	Telbivudine	Lamivudine	Telbivudine	Lamivudine
n	458	463	222	224
Age, mean years (range)	32 (16-63)	33 (16-67)	43 (17-68)	43 (16-68)
Gender, male (%)	73	76	78	80
Weight, mean kg (range)	66 (38-126)	68 (38-150)	72 (42-123)	71 (45-148)
Race (%)				
Asian (Chinese)	83 (58)	80 (57)	65 (52)	64 (66)
Caucasian	11	12	21	25
African/African American	1	2	1	1
Latino	<1	1	1	2
Middle Eastern/Indian	2	2	3	2
Other	3	4	9	6
HBV DNA				
Log ₁₀ mean (±SE)	9.5 (0.1)	9.5 (0.1)	7.7 (0.1)	7.4 (0.1)
Log ₁₀ median (range)	9.6 (4-16)	9.6 (4-16)	7.2 (3-13)	7.1 (4-12)
ALT				
ULN, mean (±SE)	146 (5.4)	159 (6.3)	137 (7.0)	144 (8.8)
ULN, median (range)	111 (19-1137)	111 (25-1133)	99 (31-569)	99 (12-982)

Efficacy Results in HBeAg-positive Patients

- At year 2, significantly more HBeAg-positive telbivudine recipients achieved Therapeutic Response and ALT normalization, and had PCR-negative HBV DNA, compared to lamivudine recipients. Telbivudine recipients also demonstrated significantly greater log₁₀ reduction of serum HBV DNA levels (Table 2).
- Higher rates of HBeAg loss and seroconversion were also observed with telbivudine vs lamivudine, however these differences did not reach statistical significance in the overall HBeAg-positive population. From year 1 to year 2, rates of HBeAg loss for telbivudine increased from 26% to 35%, respectively, while rates of HBeAg seroconversion increased from 23% to 30%.
- Among the 64% of HBeAg-positive patients with baseline ALT $\geq 2 \times$ ULN, generally considered the best treatment candidates, telbivudine recipients demonstrated significantly higher rates of HBeAg loss and seroconversion after 2 years compared with lamivudine recipients (Table 2).^{††} Telbivudine also demonstrated significantly greater responses vs lamivudine for all other key efficacy endpoints in this subgroup.

Table 2. Efficacy at Week 104 in HBeAg-positive Patients^{††}

	ITT Population		Baseline ALT $\geq 2 \times$ ULN [†]	
	Telbivudine	Lamivudine	Telbivudine	Lamivudine
n	458	463	295	293
Therapeutic Response (%)	64	48	68	52
HBV DNA \downarrow from baseline (mean log ₁₀)	-6.7	-4.4	-6.05	-5.04
PCR-negative HBV DNA* (%)	56	39	61	43
ALT normalization, $\leq 1 \times$ ULN (%)	70	62	72	63
HBeAg loss (%)	35	29	41	32
HBeAg seroconversion (%)	30	25	36	27

[†] PCR assay limit of detection = 300 copies/mL.

^{††} Includes 64% of the HBeAg-positive ITT population.

- HBeAg-positive patients were eligible for treatment discontinuation for efficacy provided they had (1) received ≥ 1 year of treatment; (2) serum HBV DNA $<5 \log_{10}$ copies/mL; and (3) received ≥ 24 weeks of further treatment after initial detection of HBeAg loss. Discontinued patients received post-treatment follow-up with normal per protocol scheduled study visits.¹²
- Treatment was restarted upon posttreatment disease relapse (increase of serum HBV DNA to levels $\geq 6 \log_{10}$ copies/mL on ≥ 2 consecutive visits AND ALT levels $\geq 2 \times$ ULN).
- Among HBeAg-positive patients discontinued for efficacy, HBeAg responses were sustained in $\geq 80\%$ of patients in both treatment groups, following a median 31 weeks off-treatment (Table 3).

Table 3. Post-treatment Durability of HBeAg Responses in HBeAg-positive Patients Who Discontinued Therapy for Efficacy^{††}

	Telbivudine	Lamivudine
Patients discontinued therapy for efficacy, n [†]	39/458	20/463
Weeks off treatment, median (range)	29.1 (4-59)	32.6 (0-53)
Sustained HBeAg loss, n (%) [‡]	31/38 (82%)	17/19 (89%)
Sustained HBeAg seroconversion, n (%) [‡]	28/35 (80%)	15/17 (88%)

[†] 134/458 (29%) of patients receiving telbivudine, and 123/463 (27%) of patients receiving lamivudine, were eligible for treatment discontinuation; 59/257 (23%) patients were discontinued at the discretion of the investigator.

[‡] Includes patients with at least one post-treatment follow-up visit.

Efficacy results in HBeAg-negative patients

- HBeAg-negative telbivudine recipients demonstrated significantly greater log₁₀ reduction of serum HBV DNA, and significantly greater rates of Therapeutic Response and PCR-negative HBV DNA at week 104 compared with lamivudine recipients (Table 4). ALT normalization was more frequent with telbivudine vs lamivudine; however, this difference was not statistically significant.[‡]

Table 4. Efficacy at Week 104 in HBeAg-negative Patients

	Telbivudine	Lamivudine	P Value
ITT population, n	222	224	
Therapeutic Response (%)	78	69	0.007
HBV DNA \downarrow from baseline (mean log ₁₀)	-6.0	-4.2	0.0002
PCR-negative HBV DNA* (%)	82	57	<0.0001
ALT normalization, $\leq 1 \times$ ULN (%)	78	70	0.07

ITT = intent-to-treat.

Colored text indicates P < 0.05, telbivudine vs lamivudine at year 2.

* PCR assay limit of detection = 300 copies/mL; COBAS[®] AmpliCor.

Resistance and Treatment Failure

- In a preliminary analysis of M204 codon changes at week 92, cumulative resistance rates were significantly lower with telbivudine vs lamivudine, in HBeAg-positive and in HBeAg-negative patients (Table 5).

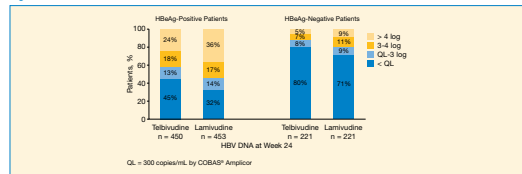
Table 5. Preliminary Cumulative Resistance Analysis at Year 2 (92 weeks)

	HBeAg-Positive		HBeAg-Negative	
	Telbivudine	Lamivudine	Telbivudine	Lamivudine
Per protocol	17.8	30.1	7.3	16.6
1 log above nadir	21.6	35.0	8.6	21.9

Association Between Early Viral Suppression and Outcomes at 2 Years

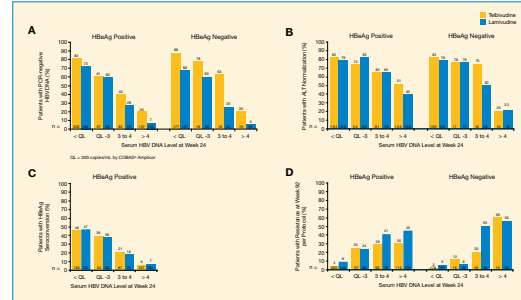
- At week 24, a greater proportion of telbivudine recipients were serum HBV DNA PCR-negative, compared with lamivudine (Figure 2).

Figure 2. Serum HBV DNA Levels at Week 24



- Patients who achieved the best early viral suppression (PCR-negative HBV DNA at week 24) had the highest rates of efficacy response and the lowest rates of resistance at year 2 (92 weeks).
- Serum HBV DNA levels at week 24 were inversely correlated with efficacy outcomes at week 104, extending results reported previously at week 52.³ These relationships were evident for all efficacy responses evaluated at week 104, including HBeAg loss, ALT normalization, and PCR-negative HBV DNA (Figure 3a-c).¹¹
- A direct relationship was observed between HBV DNA levels at week 24 and subsequent resistance (based upon a per protocol preliminary resistance analysis at week 92) (Figure 3d). Of telbivudine recipients who had PCR-negative HBV DNA at week 24, only 4% of HBeAg-positive patients and 2% of HBeAg-negative patients developed resistance at week 92.
- Similar relationships between week 24 HBV DNA levels and outcomes at 2 years were observed for telbivudine and lamivudine; however, HBV DNA was PCR-negative in a significantly greater proportion of telbivudine recipients at week 24 (Figure 2). This suggests that the overall higher rates of efficacy response and lower resistance seen with telbivudine at 2 years (Table 2 and Table 4) are associated with the greater early viral suppression achieved with telbivudine.

Figure 3. Relationship Between Serum HBV DNA Levels at Week 24 and Outcomes at 2 Years



- The probability of achieving efficacy outcomes at 2 years, and of minimizing resistance, was high for telbivudine recipients who had PCR-negative HBV DNA at week 24 (Table 6).¹¹

Table 6. Percentage of Telbivudine Recipients With PCR-Negative HBV DNA at Week 24 Who Achieved Outcome at Year 2

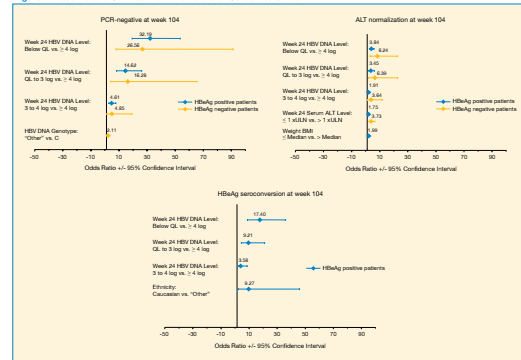
HBeAg status	Year 2 Outcome	Probability (%)	
		Year 2 Outcome	Probability (%)
HBeAg-positive	HBeAg seroconversion	46	
	ALT normalization	82	
	PCR-negative HBV DNA	82	
HBeAg-negative	No resistance at week 92	96	
	ALT normalization	82	
	PCR-negative HBV DNA	88	
	No resistance at week 92	98	

ALT = alanine aminotransferase.

Predictors of Response

- Stepwise linear regression analyses were undertaken to identify baseline and on-treatment parameters that influence treatment outcomes. Results indicate that serum HBV DNA level at week 24 was the strongest predictor of HBeAg seroconversion, PCR nondetectability, and ALT normalization at 2 years. Factors with statistically significant odds ratios are shown in Figure 4.

Figure 4. Baseline and On-Treatment Predictors of Outcomes at Year 2



Safety Through Week 104

- Most adverse events were classified as mild or moderate in severity and not attributed to telbivudine.
- 56 (8.2%) telbivudine recipients and 88 (12.8%) lamivudine recipients discontinued. Discontinuations for adverse events, clinical disease progression or lack of efficacy were 11 (1.6%) for telbivudine and 28 (4.1%) for lamivudine.
- Grade 3-4 creatine kinase (CK) elevations were more frequent among telbivudine recipients (12.9%) vs. lamivudine (4.1%). Most CK elevations were asymptomatic, but the mean recovery time was longer for subjects on telbivudine vs. lamivudine.
- On-treatment ALT flares using AASLD criteria ($> 10.0 \times$ ULN and $2.0 \times$ baseline) were more frequent with lamivudine (7.4%) vs. telbivudine (4.1%).
- Cases of myopathy were reported with telbivudine use several weeks to months after starting therapy.

Table 7. Clinical Adverse Events, Baseline to Week 104

Body System/Adverse Event	Telbivudine (n = 680) % of patients	Lamivudine (n = 687) % of patients
Patients reporting adverse events (%)	81.0	77.0
Upper respiratory tract infection	17.5	16.2
Nasopharyngitis	15.0	13.1
Fatigue	13.4	12.1
Headache	11.6	13.4
Blood creatine kinase increased	12.4	7.4
Influenza	6.8	8.3
Post-procedural pain	7.2	6.6
Abdominal pain upper	6.3	7.0
Cough	6.8	5.8
Diarrhea	6.6	5.7
Nausea	6.0	5.4
Dizziness	4.7	5.7
Arthralgia	5.0	4.9
Pharyngolaryngeal pain	5.1	4.2
Dyspepsia	3.5	5.4

Table 8. Grade 3-4 laboratory abnormalities, baseline to week 104.

Test	Telbivudine 600mg (n = 680) % of patients	Lamivudine 100mg (n = 687) % of patients
Creatine kinase (CK) $\geq 7.0 \times$ ULN	12.94.1	7.4
ALT (BGP) [†] $> 3.0 \times$ baseline	6.3	11.6
AST (BGP) [†] $> 3.0 \times$ baseline	6.0	8.9
Lipase $> 2.5 \times$ ULN	2.5	4.7
Neutropenia (ANC $<500/mm^3$)	2.1	2.0

[†] ALT = alanine aminotransferase.

Conclusions

- Telbivudine exhibited significantly greater antiviral and clinical efficacy, with less resistance, than lamivudine after 2 years of treatment.
- In HBeAg-positive patients with baseline ALT $> 2 \times$ ULN, generally considered the best treatment candidates, a significantly higher rate of seroconversion was observed with telbivudine than with lamivudine.
- The post-treatment durability of HBeAg loss or seroconversion was $\geq 80\%$ with telbivudine and lamivudine.
- Patients achieving the best early viral suppression, assessed as serum HBV DNA levels at week 24, had the highest rates of efficacy response and the least resistance at week 104.
- Any persistent, unexplained muscle-related symptoms with telbivudine should be evaluated promptly. Patients with myopathy (confirmed muscle weakness) should have telbivudine discontinued permanently.

Disclosures

C.L. Lai and E. Gane have acted as consultants to Idenix Pharmaceuticals and Novartis Pharmaceuticals, Inc. N. Brown is a former employee of Idenix Pharmaceuticals.

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Efficacy of Telbivudine vs. Lamivudine at 2 Years in Patients With HBeAg-Positive Chronic Hepatitis B Who Are Eligible for Treatment Based on Guidelines

Rasenack J, Poynard T, Lai CL, Gane E, Brown N, Heathcote EJ

EASL 2007

Key conclusions

- At 2 years, telbivudine produced significantly greater responses, compared with lamivudine, for all key efficacy endpoints in this analysis.
- Maximal reduction of serum HBV DNA levels at week 24 was correlated with improved outcomes at week 104.
- Significantly less primary treatment failure was observed with telbivudine vs. lamivudine.

Efficacy of Telbivudine vs Lamivudine at 2 Years in Patients With HBeAg-Positive Chronic Hepatitis B Who Are Eligible for Treatment Based on Guidelines

J. Rassenack¹; T. Poyrnard²; C.L. Lafé; E. Gané⁴; N. Brown⁵; E.J. Heathcote⁶
¹Albert Ludwigs University, Freiburg, Germany; ²Gruppe Hospitalier Pitié-Salpêtrière, Paris, France; ³University of Hong Kong, Hong Kong, China; ⁴Middlemore Hospital, Auckland, New Zealand; ⁵Idenix Pharmaceuticals, Cambridge, Massachusetts, USA; ⁶Toronto Western Hospital, Toronto, Ontario, Canada.

Background

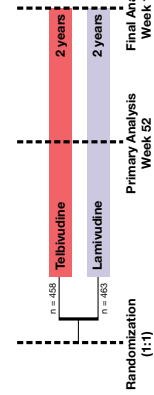
According to international guidelines, antiviral treatment is generally recommended for hepatitis B e antigen-positive chronic hepatitis B (CHB) patients with elevated HBV DNA and pretreatment alanine aminotransferase (ALT) ≥ 2 times the upper limit of normal (ULN). The Asia-Pacific Association for the Study of the Liver (APASL) consensus statement indicates that treatment should be considered if serum ALT is persistently elevated to ≥ 2 x ULN (at least 1 month between observations).¹ The European Association for the Study of the Liver (EASL) consensus statement recommends treatment for patients with HBV DNA levels above 10^7 copies/mL and persistent elevation of aminotransferases after 3–6 months of observation.² Because patients meeting these criteria are often considered for antiviral therapy, it is useful to assess the efficacy and safety of antiviral agents in this subpopulation. We report the 2-year results of a preliminary analysis from the large international GLOBE trial, comparing telbivudine vs lamivudine treatment for HBeAg-positive patients with serum ALT levels ≥ 2 x ULN.

Methods

Study Design

The GLOBE trial is a phase III, randomized, double-blind, controlled trial, conducted at 112 centers in 20 countries, which compared two treatment regimens for CHB over 2 years (104 weeks). The study enrolled 1,367 treatment-naïve adult patients with CHB, baseline HBV DNA $> 6 \log_{10}$ copies/mL, ALT 1.3–10 x ULN, and compensated liver disease. Patients were randomized (1:1) to receive telbivudine 600 mg/day PO or lamivudine 100 mg/day PO (Figure 1). This analysis includes HBeAg-positive patients with pretreatment ALT ≥ 2 x ULN (ULN = 48 IU/L for males, 37 IU/L for females). The study was sponsored by Idenix Pharmaceuticals and Novartis Pharmaceuticals.

Figure 1. Trial design for evaluating HBeAg-positive patients.



Serum samples for analysis were obtained at screening, baseline, and weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 52, 60, 68, 76, 84, 92, 100, 104, premature study discontinuation, and at all follow-up visits. Serum HBV DNA was assayed by COBAS® Amplicor™ HBV Monitor (Roche Molecular Systems, Branchburg, NJ, USA, with a lower limit of detection of 300 copies/mL). Histologic scoring of liver biopsy specimens was performed by independent expert hepatopathologists under blinded conditions.

Key Efficacy Endpoints

- Therapeutic Response (primary efficacy endpoint)
 - HBV DNA $< 5 \log_{10}$ copies/mL AND ALT normalization or HBeAg loss
- Antiviral response
 - \log_{10} HBV DNA reduction from baseline
 - Clearance of HBV DNA to polymerase chain reaction (PCR)-nondetectable levels (< 300 copies/mL)
- ALT normalization
- HBeAg loss and seroconversion

Treatment Failure

- Primary treatment failure
 - Serum HBV DNA levels never suppressed to $< 5 \log_{10}$ copies/mL

Predictability

- Efficacy outcomes at week 104 were assessed according to week-24 viral load categories
- We report the 2-year results of a preliminary analysis of a locked database from the GLOBE trial.

Results

The GLOBE trial enrolled 1,367 patients (921 HBeAg-positive) with baseline HBV DNA $> 6 \log_{10}$ copies/mL and ALT 1.3–10 x ULN. Among these HBeAg-positive patients, serum ALT at baseline was ≥ 2 x ULN in 588/921 (64%). Baseline demographic and disease characteristics for the 588 HBeAg-positive patients with baseline ALT ≥ 2 x ULN enrolled in the GLOBE trial are shown in Table 1. Treatment groups were well matched and similar to the overall population for parameters other than ALT.

Table 1. Baseline Demographic and Disease Characteristics in HBeAg-Positive Patients With Baseline ALT ≥ 2 x ULN

	Telbivudine	Lamivudine
n	295	293
Age, mean years (SE)	31.7 (0.59)	32.2 (0.64)
Gender, male (%)	71.2	75.8
Weight, mean kg (SE)	65.3 (0.78)	68.1 (0.87)
Race (%)		
Asian (Chinese)	86.8 (59.3)	80.5 (57.7)
Caucasian	9.2	11.6
African/African American	0.3	1.7
Latino	0	1.0
Other	3.7	5.1
HBV DNA (\log_{10})		
Mean (SE)	9.66 (0.030)	9.77 (0.107)
Median	9.60	9.68
ALT (IU/L)		
Mean (SE)	191.2 (7.04)	213.0 (8.44)
Median	154	166

SE = standard error; ALT = alanine aminotransferase.

Efficacy

After 2 years, telbivudine demonstrated a significantly greater response for the primary efficacy endpoint of Therapeutic Response compared with lamivudine (66% vs 52%, respectively, $P < 0.001$). Telbivudine also demonstrated significantly greater responses, compared with lamivudine, for all key secondary efficacy endpoints reported at 2 years, including \log_{10} HBV DNA reduction, HBV DNA PCR negative, primary treatment failure, HBeAg loss, HBeAg seroconversion, and ALT normalization (all $P < 0.05$ [Table 2 and Figure 2]).

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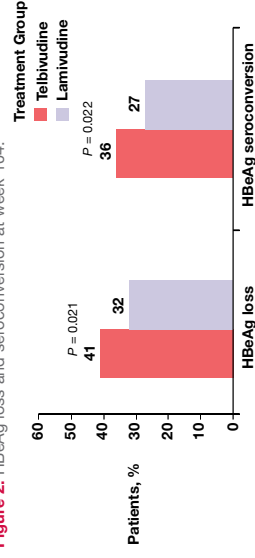
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Table 2. Efficacy Outcomes at Week 104 in HBeAg-Positive Patients With Baseline ALT ≥ 2 x ULN

	Telbivudine	Lamivudine	P Value
n	295	293	
Therapeutic Response (%)	66	52	< 0.001
HBV DNA decrease from baseline (mean \log_{10})	- 6.05	- 5.04	< 0.001
HBV DNA nondetectable by PCR (%)	61	43	< 0.001
ALT normalization (≤ 1 x ULN) (%)	72	63	0.024
HBeAg loss (%)	41	32	0.021
HBeAg seroconversion (%)	36	27	0.022
Primary treatment failure (%)	2	8	< 0.001

PCR = polymerase chain reaction; ALT = alanine aminotransferase; ULN = upper limit of normal; HBeAg = hepatitis B e antigen.

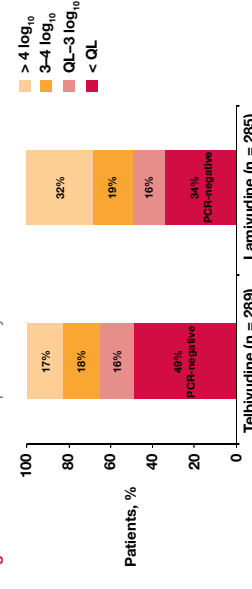
Figure 2. HBeAg loss and seroconversion at week 104.



Association of HBV DNA Levels at Week 24 With Outcomes at Week 104

For this analysis, patients were categorized according to serum HBV DNA levels at week 24. HBV DNA was nondetectable by PCR assay at week 24 in a significantly greater proportion of telbivudine recipients compared with lamivudine recipients (49% vs 34%, $P < 0.05$) (Figure 3).

Figure 3. Distribution of patients by serum HBV DNA levels at week 24.

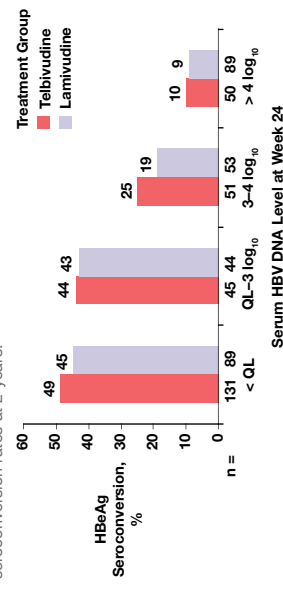


QL = quantitative limit of 300 copies/mL by COBAS® Amplicor™ assay. Includes only patients with observed serum HBV DNA at week 24.

Predictors of Outcomes at Week 104

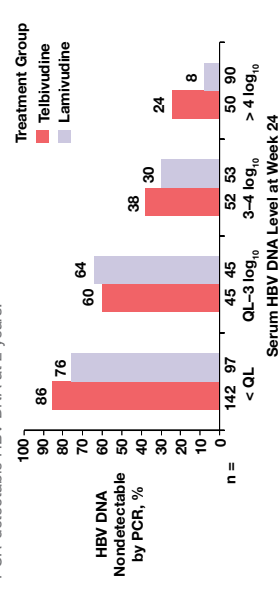
Serum HBV DNA levels at week 24 were associated with outcomes at week 104, similar to results reported for the full GLOBE population of HBeAg-positive and HBeAg-negative patients.³ PCR-nondetectable HBV DNA levels at week 24 were associated with the highest frequencies of HBeAg seroconversion (Figure 4) and loss of PCR-detectable HBV DNA (Figure 5) at 2 years.

Figure 4. Relationship between serum HBV DNA levels at week 24 and HBeAg seroconversion rates at 2 years.



QL = quantitative limit of 300 copies/mL by COBAS® Amplicor™ assay. Includes only patients with observed serum HBV DNA at week 24.

Figure 5. Relationship between serum HBV DNA levels at week 24 and loss of PCR-detectable HBV DNA at 2 years.



QL = quantitative limit of 300 copies/mL by COBAS® Amplicor™ assay. Includes only patients with observed serum HBV DNA at week 24.

In telbivudine recipients with PCR-nondetectable serum HBV DNA at week 24, there was a high probability of achieving HBeAg seroconversion (49%), ALT normalization (85%), and HBV DNA nondetectability (86%) at 2 years (Table 3). Conversely, patients who did not achieve HBV DNA levels below $3 \log_{10}$ by week 24 were less likely to achieve a positive outcome at 2 years.

Table 3. Probabilities of Achieving Outcomes at 2 Years for Telbivudine-Treated Patients With PCR-Nondetectable HBV DNA at Week 24

Year 2 Outcome	Telbivudine	Probability
HBeAg seroconversion	49%	45%
ALT normalization	85%	85%
HBV DNA nondetectable by PCR	86%	76%

* Preliminary data. HBeAg = hepatitis B e antigen; ALT = alanine aminotransferase; HBV = hepatitis B virus; PCR = polymerase chain reaction.

Safety

Both treatments were well tolerated. Reported adverse events were generally mild and transient, with similar rates in both treatment groups. The most frequently reported adverse events in all HBeAg-positive patients were upper respiratory tract infection, fatigue, nasopharyngitis, and headache (all ranging from 10%–20%) (Table 4).

Table 4. Most Frequent Adverse Events in HBeAg-Positive Patients Through Week 104 Regardless of Attributability to Study Drug in HBeAg-Positive Patients With Baseline ALT ≥ 2 x ULN

	Telbivudine (n = 288)	Lamivudine (n = 290)
Total patients with adverse events (%)*	81.6	77.9
Upper respiratory tract infection	20.8	18.3
Fatigue	17.0	15.5
Nasopharyngitis	16.3	14.5
Headache	9.7	14.8
Blood CK increased	12.2	7.2
Influenza	7.3	8.6
Postprocedural pain	6.3	8.3
Upper abdominal pain	6.3	7.6
Diarrhea	7.3	6.6
Nausea	6.9	6.6
Cough	6.3	6.6
Pharyngolaryngeal pain	6.6	5.9
ALT increased	5.6	5.9
Dizziness	6.9	4.5
Dyspepsia	3.5	7.2
Pyrexia	5.9	4.1
Arthralgia	3.5	5.5

* Adverse events occurring in $\geq 2.4\%$ of patients in either treatment group. CK = creatine kinase; ALT = alanine aminotransferase.

Grade 3/4 elevations in ALT, AST, and absolute neutrophil count were more frequent in patients treated with lamivudine than those treated with telbivudine (Table 5). Transient creatine kinase elevations, not requiring treatment modification, were more common with telbivudine than with lamivudine.

Table 5. New Onset Grade 3/4 Laboratory Abnormalities On-Treatment in HBeAg-Positive Patients With Baseline ALT ≥ 2 x ULN

	Telbivudine (%) (n = 288)	Lamivudine (%) (n = 290)
ALT > 3.0 x baseline (%)	6.3	11.7
AST > 3.0 x baseline (%)	5.9	10.0
Creatine kinase ≥ 7.0 x ULN (%)	11.8	3.1
Hemoglobin < 8 g/dL (%)	0	0.3
Lipase > 2.5 x ULN (%)	1.7	2.8
Absolute neutrophils $\leq 500/\text{mm}^3$ (%)	1.4	1.4
Platelet count $\geq 20,000/\text{mm}^3$ (%)	0.3	1.4
Prothrombin time > 1.5 x ULN (%)	0.7	0.3
Total bilirubin > 5.0 x ULN (%)	0.3	0.7

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Conclusions

- The efficacy and safety of telbivudine and lamivudine were compared in HBeAg-positive patients from the GLOBE trial with baseline ALT ≥ 2 x ULN, a patient population recommended for treatment by international guidelines
- At 2 years, telbivudine produced significantly greater responses, compared with lamivudine, for all key efficacy endpoints in this analysis
 - Therapeutic Response
 - \log_{10} HBV DNA reduction
 - HBV DNA nondetectable by PCR
 - HBeAg loss and HBeAg seroconversion
 - ALT normalization
- Significantly less primary treatment failure was observed with telbivudine, vs lamivudine
- Maximal reduction of serum HBV DNA levels at week 24 was correlated with improved outcomes at week 104
 - HBeAg seroconversion
 - ALT normalization
 - HBV DNA nondetectability

Disclosures

C.L. Lai and E. Gané have acted as consultants for Idenix Pharmaceuticals, Inc., and/or Novartis Pharmaceuticals, Inc. N. Brown is a former employee of Idenix Pharmaceuticals, Inc.

Adefovir Salvage Therapy for Virologic Breakthrough in Telbivudine-Treated Patients from the GLOBE Study

Gane E, Lai CL, Min A, Heathcote J, Poynard T, Kuras OO, Grange J-D, Brown NA

EASL 2007

Key conclusions

- Adefovir may be a salvage treatment option for patients experiencing viral breakthrough during telbivudine treatment
 - Adefovir restored suppression of serum HBV DNA
 - Adefovir reduced serum ALT during 16 weeks of adefovir salvage therapy, 2/15 HBeAg-positive patients lost detectable HBeAg
- Adefovir and the adefovir plus telbivudine combination were well tolerated during the period of this analysis.
- Limitations of these data:
 - Non-randomized, observational, *post hoc* study of a small patient cohort not powered to compare monotherapy vs. combination
 - More extended follow-up needed to assess durability of response.

Adefovir Salvage Therapy for Virologic Breakthrough in Telbivudine-Treated Patients From the GLOBE Study

¹Middlemore Hospital, Auckland, NZ; ²University of Hong Kong, Hong Kong, China; ³Beth Israel Medical Center, New York, NY, USA; ⁴Toronto Western Hospital, Toronto, ON, Canada; ⁵Groupes Hospitalier Pitié-Salpêtrière, Paris, France; ⁶Haydarpaşa Numune Hospital, Istanbul, Turkey; ⁷Hopital Tenon, Paris, France; ⁸Idemix Pharmaceuticals, Cambridge, MA, USA

Background

Telbivudine (β-L-2'-deoxythymidine) is an orally bioavailable L-nucleoside with potent and specific anti-HBV activity.¹ After 2 years of treatment in the phase III GLOBE trial, telbivudine produced significantly greater reductions of serum hepatitis B virus (HBV) DNA compared with lamivudine, with significantly less resistance, in hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients with chronic hepatitis B (CHB).²

The M204I mutation was identified as the primary mutation associated with telbivudine resistance.³ In vitro studies demonstrated that HBV with the M204I substitution remains susceptible to adefovir.³

Adefovir has been shown to restore adequate viral suppression in patients with lamivudine resistance, which is associated with selection of M204I and M204V HBV polymerase mutations.^{4,5} The preliminary analysis of an ongoing study presented here evaluates the effectiveness and safety of adefovir as salvage therapy for telbivudine recipients with viral breakthrough in the GLOBE trial.

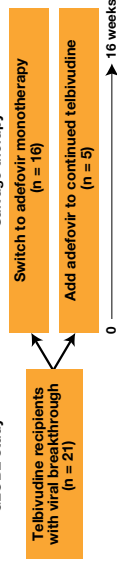
Methods

Study Design

The GLOBE trial is a phase III, randomized, double-blind, controlled trial, conducted at 112 centers in 20 countries, which compared telbivudine (600 mg/day PO) with lamivudine (100 mg/day PO) for HBeAg-positive and HBeAg-negative patients with CHB over 2 years (104 weeks). Eligible patients had baseline HBV DNA $\geq 6 \log_{10}$ copies/mL, alanine aminotransferase (ALT) 1.3–10 × ULN, and compensated liver disease.

The objective of this preliminary analysis was to evaluate adefovir for restoration of viral suppression and ALT response in a case series of telbivudine recipients with viral breakthrough (HBV DNA $> 1 \log_{10}$ copies/mL from nadir). Twenty-one telbivudine recipients with viral breakthrough during the GLOBE study received adefovir, either as follow-on monotherapy or in combination with continued telbivudine at the discretion of the investigator.

GLOBE study



Evaluations

- Serum HBV markers
 - Serum HBV DNA assessed by Roche COBAS® Amplicor™ polymerase chain reaction (PCR) assay
- Serum ALT
- Clinical and laboratory safety parameters

Results

Results are reported for 21 telbivudine-treated patients with viral breakthrough who have received ≥ 16 weeks of adefovir salvage treatment in the GLOBE trial, initiated either as follow-on monotherapy (n = 16) or in combination with telbivudine (n = 5).

Patient characteristics

- Fifteen patients were HBeAg-positive at baseline
- Six patients were HBeAg-negative at baseline
- Median time to viral breakthrough on telbivudine was 60 weeks (range, 36–111 weeks)
- The M204I telbivudine resistance mutation was detected in all 21 patients prior to adefovir treatment
- The A181T adefovir resistance mutation was not detected in any patient at the start of adefovir treatment

Serum HBV DNA and ALT Responses

After 16 weeks of adefovir salvage treatment, patients overall experienced a mean 3.8 \log_{10} copies/mL reduction in serum HBV DNA levels and a mean 92.5 IU/L reduction in serum ALT activity (Table 1). Patients who switched to adefovir monotherapy (n = 16) experienced a mean 3.7 \log_{10} copies/mL reduction in HBV DNA levels and a mean 94.8 IU/L reduction in ALT activity after 16 weeks (Table 1 and Figure 1).

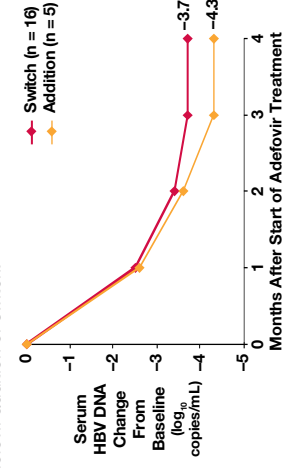
Patients who added adefovir to continued telbivudine (n = 5) experienced a mean 4.3 \log_{10} copies/mL reduction in serum HBV DNA levels and a mean 87.2 IU/L reduction in ALT activity.

Table 1. Serum HBV DNA and ALT Levels

Measurement Point	HBV DNA (Mean \log_{10} copies/mL \pm SD)	ALT (Mean IU/L \pm SD)
Baseline	10.0 \pm 2.5	107.8 \pm 36.1
Nadir value on telbivudine	3.5 \pm 1.0	52.4 \pm 26.9
Initiation of adefovir treatment	8.9 \pm 2.1	151.0 \pm 179.2
Change after 16 weeks of adefovir	–3.8 \pm 1.8*	–92.5 \pm 181.2
All 21 patients	–4.3 \pm 1.7*	–87.2 \pm 91.2
Five adefovir + telbivudine combination recipients	–3.7 \pm 1.9*	–94.8 \pm 203.8
Sixteen patients switched to adefovir monotherapy	–3.7 \pm 1.9*	–94.8 \pm 203.8

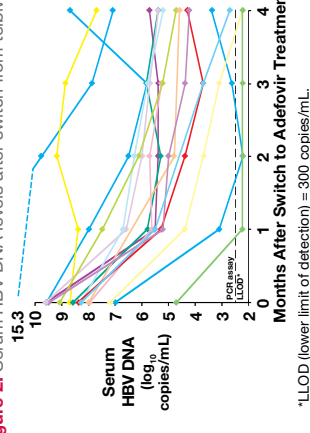
*P<0.01 for HBV DNA reduction at 16 weeks vs start of adefovir. SD = standard deviation; ALT = alanine aminotransferase.

Figure 1. Mean serum HBV DNA change from baseline: comparison of adefovir addition or switch.



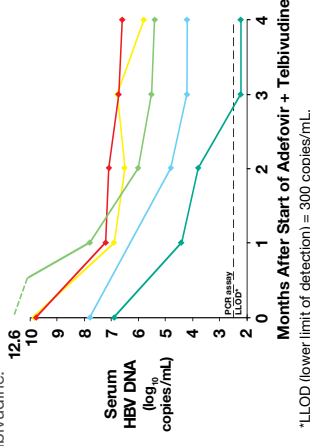
Among the 16 patients who switched to adefovir monotherapy, there was an initial general downward trend in serum HBV DNA levels (Figure 2). After 16 weeks of adefovir monotherapy, serum HBV DNA levels were below 5 \log_{10} copies/mL in 8/16 patients, and a reduction of HBV DNA levels $< 3 \log_{10}$ copies/mL was observed in 4/16 patients. At the last visit (week 16) reported here, there was evidence of possible loss of initial response to adefovir in at least one patient. Further follow-up and genotypic analyses will be undertaken to assess possible causes for this outcome.

Figure 2. Serum HBV DNA levels after switch from telbivudine to adefovir.



A relatively consistent initial reduction in serum HBV DNA levels was observed in the five patients who received combination therapy with adefovir and telbivudine. After 16 weeks of treatment, serum HBV DNA levels were $< 3 \log_{10}$ copies/mL in all five patients. HBV DNA was nondetectable by PCR assay in one patient after 16 weeks (Figure 3).

Figure 3. Serum HBV DNA levels after addition of adefovir to continued telbivudine.



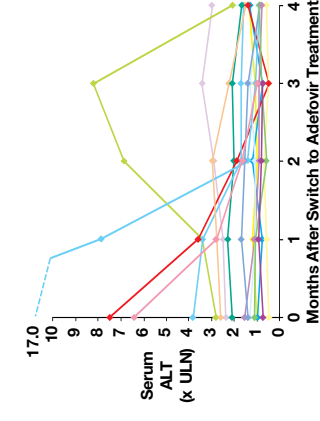
Biochemical Response

Among the 16 patients who switched to adefovir monotherapy, those with ALT levels $> 3 \times$ ULN at the start of adefovir treatment showed rapid improvement that persisted through the 16 week follow-up (Figure 4). Those with less pronounced ALT elevations, or normal ALT levels, at the start of adefovir treatment generally showed stable ALT levels or

modest improvements. One patient experienced an increase in serum ALT to $\sim 8 \times$ ULN at 3 months, which mostly resolved by the next visit. Another patient exhibited an ALT elevation that reached 21 \times ULN 2 weeks prior to the start of adefovir salvage therapy; this declined to 17 \times ULN at the start of adefovir salvage therapy and improved subsequently, becoming normal after 4 months.

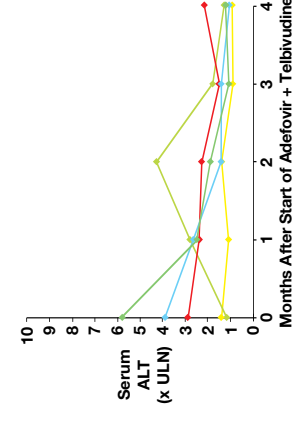
For the 15 patients with a recorded measurement at 16 weeks, 13 had ALT $< 2 \times$ ULN and 6 had ALT $< 1 \times$ ULN after 16 weeks of adefovir monotherapy. For the 11 patients with ALT $> 1 \times$ ULN at the start of adefovir treatment, 9/11 had ALT $< 2 \times$ ULN and 5/11 had ALT $< 1 \times$ ULN after 16 weeks of adefovir monotherapy.

Figure 4. Serum ALT levels after switch from telbivudine to adefovir.



Among the five patients who continued telbivudine after starting adefovir, serum ALT levels were generally improved after 16 weeks of follow-up (Figure 5). One patient experienced an elevation of $\sim 4.5 \times$ ULN at month 2, but improved subsequently. All five patients had ALT $> 1 \times$ ULN at the start of adefovir treatment; 4/5 had ALT $< 2 \times$ ULN and 1/5 had ALT $< 1 \times$ ULN after 16 weeks of treatment.

Figure 5. Serum ALT levels after addition of adefovir to telbivudine.



Serologic Response

None of the 15 HBeAg-positive patients lost HBeAg during telbivudine monotherapy in the GLOBE trial. Two patients lost HBeAg during adefovir salvage treatment: one adefovir monotherapy recipient and one telbivudine/adefovir combination recipient. Both patients subsequently lost PCR-detectable serum HBV DNA.

Safety

To date, during the period of this analysis, no serious adverse events have been reported in the 21 telbivudine-treated patients with viral breakthrough who have received ≥ 16 weeks of adefovir salvage treatment in the GLOBE trial, initiated either as follow-on monotherapy (n = 16) or in combination with telbivudine (n = 5).

Conclusions

- Adefovir may be a salvage treatment option for patients experiencing viral breakthrough during telbivudine treatment
 - Adefovir restored suppression of serum HBV DNA
 - Adefovir reduced serum ALT
 - During 16 weeks of adefovir salvage therapy, 2/15 HBeAg-positive patients lost detectable HBeAg
- Adefovir and the adefovir + telbivudine combination were well tolerated during the period of this analysis
- Limitations of these data:
 - Nonrandomized, observational, post hoc study of a small patient cohort not powered to compare monotherapy vs combination
 - More extended follow-up needed to assess durability of response

Disclosures

C.L. Lai and E. Gane have acted as consultants for Idenix and/or Novartis. N. Brown is a former employee of Idenix Pharmaceuticals, Inc.

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Two-Year Results of a Phase III Comparative Trial of Telbivudine vs. Lamivudine in Chinese Patients

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Key conclusions

Efficacy at 2 years

- Telbivudine demonstrated significantly greater responses vs. lamivudine for key efficacy endpoints:
 - Log₁₀ HBV DNA reduction and PCR negativity
 - ALT normalization
 - HBeAg loss in HBeAg-positive patients
 - Therapeutic response
- There was significantly less primary treatment failure in patients treated with telbivudine compared with lamivudine.

Impact of early viral suppression on treatment outcomes

- Rates of efficacy outcomes after 2 years of therapy were highest in patients with the greatest degree of early viral suppression (PCR-negative at week 24).
 - Log₁₀ HBV DNA reduction and PCR negativity
 - ALT normalization
 - HBeAg loss in HBeAg-positive patients
 - Therapeutic response
- The same relationship was observed with telbivudine and lamivudine, but greater viral reduction at week 24 was observed with telbivudine, consistent with the generally higher rates of efficacy responses associated with telbivudine at 2 years.

Two-Year Results of a Phase III Comparative Trial of Telbivudine vs Lamivudine in Chinese Patients

J.-D. Jia¹; J.-L. Hou²; Y.-K. Yin³; D.-Z. Xu⁴; D. Tan⁵; J. Niu⁶; X.-Q. Zhou⁷; Y. Wang⁸; L. Zhu⁹; N. Brown¹⁰

¹Beijing Friendship Hospital, Beijing, China; ²Nantang Hospital, Guangzhou, China; ³Shanghai Hua Shan Hospital, Shanghai, China; ⁴Beijing Ditan Hospital, Beijing, China; ⁵Xiang Ya Hospital, Changsha, China; ⁶No. 1 Hospital, Changchun, China; ⁷Ruijin Hospital, Shanghai, China; ⁸Xi Nan Hospital, Chongqing, China; ⁹Tianjin Infectious Diseases Hospital, Tianjin, China; ¹⁰Genex Pharmaceuticals, Cambridge, Massachusetts, USA.

Background

In a large international phase III trial (GLOBE), telbivudine showed significantly greater efficacy vs lamivudine on all direct measures of antiviral efficacy and on several key clinical measures, with significantly less resistance compared with lamivudine through year 2 in adults with chronic hepatitis B.¹⁻³ Chronic hepatitis B remains a significant healthcare concern in many Asian countries, particularly in China. Therefore, the present study was designed to confirm the findings of the GLOBE trial in a large population of Chinese patients with chronic hepatitis B. Results of a preliminary analysis of a locked database at 2 years from the intent-to-treat (ITT) population of this phase III study are presented here.

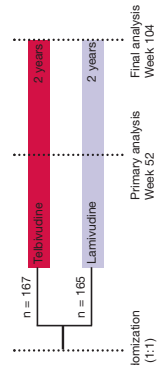
Maximizing and maintaining hepatitis B virus (HBV) suppression is emerging as a key milestone correlating with clinical improvement in chronic hepatitis B. Better early viral suppression has been linked to improved therapeutic outcomes in several reports. This report therefore includes an analysis of quantitative relationships between early viral suppression (serum HBV DNA levels after 24 weeks of treatment) and subsequent therapeutic responses.

Methods

Study Design

This randomized, double-blind trial compared 2 years of treatment with telbivudine 600 mg/day with lamivudine 100 mg/day in Chinese adults with hepatitis B e antigen (HBeAg)-positive or HBeAg-negative chronic hepatitis B (Figure 1). Key entry criteria included baseline HBV DNA $\geq 6 \log_{10}$ copies/mL, alanine aminotransferase (ALT) between 1.3 and 10 times the upper limit of normal (ULN), and compensated liver disease.

Figure 1. Trial design.



Key Efficacy Measures and Endpoints

- Primary efficacy endpoint
 - Serum HBV DNA reduction from baseline by Roche COBAS[®] Amplicor[™] assay
- Key secondary endpoints
 - Clearance of HBV DNA to nondetectability by polymerase chain reaction (PCR) assay
 - ALT normalization
 - HBeAg loss and seroconversion
 - Therapeutic Response: HBV DNA $\leq 5 \log_{10}$ AND ALT normalization or HBeAg loss
 - Treatment failure
 - Primary treatment failure: serum HBV DNA never $\leq 5 \log_{10}$
- Efficacy outcomes at 2 years were assessed according to serum HBV DNA levels at week 24.
 - HBV DNA nondetectability by PCR assay
 - Serum ALT normalization
 - HBeAg seroconversion

Results

The study enrolled an ITT population of 332 patients in 18 centers in China (290 HBeAg positive, 42 HBeAg negative). Baseline demographic and disease characteristics of the ITT population are shown in Table 1. Treatment groups were well matched at baseline for demographic and disease parameters.

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	HBeAg Positive		HBeAg Negative	
	Telbivudine	Lamivudine	Telbivudine	Lamivudine
n	147	143	20	22
Age, mean years (range)	28 (16-64)	29 (15-63)	38 (20-56)	36 (19-59)
Gender, male (%)	80	75	85	86
Weight, mean kg (range)	62 (43-93)	62 (42-94)	64 (52-99)	65 (49-93)
HBV DNA, median \log_{10}	9.7	9.7	7.3	7.2
ALT, mean IU/L	156	157	162	177

Efficacy

At 2 years, telbivudine was superior ($P < 0.05$) to lamivudine for the primary/efficacy endpoint of HBV DNA suppression, with mean \log_{10} HBV DNA reductions of -5.48 vs -4.00 (Table 2). Telbivudine also provided significantly greater response rates for serum HBV DNA nondetectability by PCR assay, ALT normalization, therapeutic response, and HBeAg loss (for HBeAg-positive patients), compared with lamivudine (all $P < 0.05$) (Table 2).

Significantly fewer patients receiving telbivudine exhibited primary treatment failure, defined as serum HBV DNA levels that remained above $5 \log_{10}$ copies/mL (3% vs 15% for lamivudine, $P < 0.001$).

Table 2. Efficacy Outcomes at 2 Years – All Patients

	Telbivudine	Lamivudine
n	167	165
HBV DNA decrease from baseline (mean \log_{10})	-5.48*	-4.00
HBV DNA PCR-nondetectable (%)	63*	39
Therapeutic Response [†] (%)	70*	44
ALT normalization (%)	76*	61
HBeAg loss (HBeAg+ only) (%)	40*	28
HBeAg seroconversion (HBeAg+ only) (%)	29	20
Primary treatment failure [‡] (%)	3*	15

* $P < 0.05$ for telbivudine vs lamivudine.
[†]HBV DNA suppressed to $\leq 5 \log_{10}$ with ALT normalization or HBeAg loss.
[‡]Serum HBV DNA levels never $\leq 5 \log_{10}$.

In HBeAg-positive patients with baseline ALT $\geq 2 \times$ ULN, the population recommended for treatment in European Association for the Study of the Liver (EASL) and Asia-Pacific Association for the Study of the Liver (APASL) guidelines,^{4,5} telbivudine demonstrated a significantly greater reduction of serum HBV DNA from baseline, compared with lamivudine. Telbivudine also provided significantly greater rates of Therapeutic Response and nondetectability of serum HBV DNA by PCR, compared with lamivudine (Table 3).

Table 3. Efficacy Outcomes at 2 Years in HBeAg-Positive Patients With Baseline ALT $\geq 2 \times$ ULN

	Telbivudine	Lamivudine
n	95	86
HBV DNA decrease from baseline (mean \log_{10})	-5.86*	-4.64
HBV DNA PCR-nondetectable (%)	60*	43
Therapeutic Response [†] (%)	69*	50
ALT normalization (%)	74	62
HBeAg loss (HBeAg+ only) (%)	46	36
HBeAg seroconversion (HBeAg+ only) (%)	36	24
Primary treatment failure [‡] (%)	3	8

* $P < 0.05$ for telbivudine vs lamivudine.
[†]HBV DNA suppressed to $\leq 5 \log_{10}$ with ALT normalization or HBeAg loss.
[‡]Serum HBV DNA levels never $\leq 5 \log_{10}$.

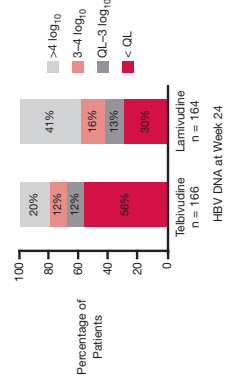
Relationship of Early Virologic Response to Outcomes at 2 Years

To assess the potential relationship between early antiviral response and outcomes at 2 years, patients were categorized into four groups according to serum HBV DNA levels at week 24:

- PCR nondetectable (< 300 copies/mL)
- Quantitation limit to 10^3 copies/mL
- $\geq 10^3$ to 10^4 copies/mL
- $\geq 10^4$ copies/mL

HBV DNA was below the limit of detection at week 24 in a greater proportion of patients (combined HBeAg-positive and HBeAg-negative subpopulations) receiving telbivudine, compared with lamivudine (66% vs 30%) (Figure 2).

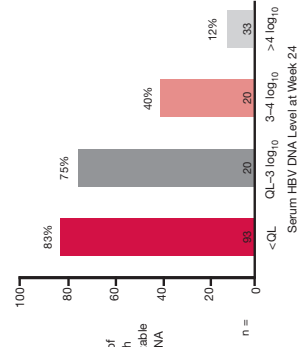
Figure 2. Serum HBV DNA levels at week 24.



* $P < 0.001$ for telbivudine vs lamivudine.
[†]CL = quantitation limit of 300 copies/mL by Roche COBAS[®] Amplicor[™] assay.

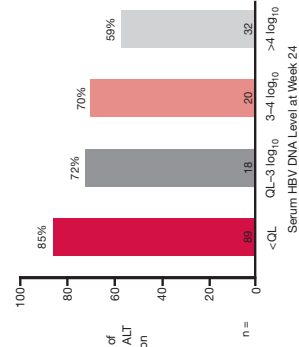
Serum HBV DNA levels at week 24 were associated with treatment outcomes at 2 years. Telbivudine-treated patients with minimal or nondetectable serum HBV DNA at week 24 had a high rate of HBV DNA nondetectability at 2 years (Figure 3). Rates of ALT normalization at 2 years were similarly high for telbivudine-treated patients who achieved maximal viral suppression at week 24 (Figure 4).

Figure 3. Relationship between the degree of week 24 viral suppression and rates of serum HBV DNA nondetectability by PCR at 2 years in all telbivudine-treated patients.



* $P < 0.001$ for telbivudine vs lamivudine.
[†]CL = quantitation limit of 300 copies/mL by Roche COBAS[®] Amplicor[™] assay.

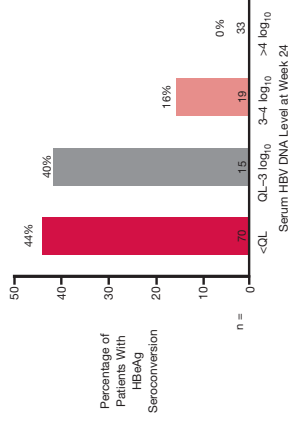
Figure 4. Relationship between the degree of week 24 viral suppression and rates of ALT normalization at 2 years in telbivudine-treated patients.



* $P < 0.001$ for telbivudine vs lamivudine.
[†]CL = quantitation limit of 300 copies/mL by Roche COBAS[®] Amplicor[™] assay.

For HBeAg-positive patients treated with telbivudine who had HBV DNA levels ≤ 300 copies/mL at week 24, the rate of seroconversion at 2 years was 44% (Figure 5).

Figure 5. Degree of week 24 viral suppression affects rate of HBeAg seroconversion at 2 years in HBeAg-positive patients treated with telbivudine.



* $P < 0.001$ for telbivudine vs lamivudine.
[†]CL = quantitation limit of 300 copies/mL by Roche COBAS[®] Amplicor[™] assay.

Safety

Both treatments were generally well tolerated. Reported adverse events were generally mild and transient, occurring at similar rates in both treatment groups (Table 4). The most frequently reported adverse events included nasopharyngitis, fatigue, and upper respiratory tract infection. One patient in the lamivudine group developed a polymyositis that was not attributed to the study drug; the event abated over approximately 4 months, with continued treatment.

Table 4. Frequently Occurring On-Treatment Adverse Events Regardless of Attributability to Telbivudine or Lamivudine Through 2 Years

	Telbivudine (n = 167)	Lamivudine (n = 165)
Total patients with adverse events (%)	64.7	60.6
Nasopharyngitis	35.9	27.9
Fatigue	9.0	6.7
Upper respiratory tract infection	5.4	6.1
Hepatitis B (flare/worsening/exacerbation)	3.0	7.3
Diarrhea	3.6	4.2
Abdominal distention	4.2	3.0
Upper abdominal pain	3.0	3.0
Pharyngitis	1.8	4.2
Cough	3.0	2.4
Abdominal discomfort	1.2	3.6
Headache	2.4	1.8
Toothache	2.4	0.6
Pyrexia	1.8	2.4
Increased blood creatine kinase	3.0	0.6
Gastritis	0.6	3.0

Grade 3 or 4 elevations of ALT and aspartate aminotransferase (AST) were more frequent in lamivudine recipients than in telbivudine recipients (Table 5). Grade 3 or 4 creatine kinase (CK) elevations, not requiring treatment modification, were more common with telbivudine than with lamivudine (Table 5).

Table 5. New Onset Grade 3/4 Laboratory Abnormalities During the On-Treatment Period[†]

Grade 3/4 Laboratory Abnormalities (%)	Telbivudine (n = 167)	Lamivudine (n = 165)
ALT $> 3.0 \times$ baseline	8.4	18.8
Amylase $> 3.0 \times$ ULN	0.6	0
AST $\geq 3 \times$ baseline	7.2	13.9
Creatine kinase $\geq 7.0 \times$ ULN	11.4	3.6
Lipase $> 2.5 \times$ ULN	1.8	1.8
Neutrophils (absolute) $< 750/\text{mm}^3$	0	0.6
Platelet count $< 50,000/\text{mm}^3$	0	1.8
Prothrombin time $> 1.5 \times$ ULN	1.2	0.6
Total bilirubin $> 5.0 \times$ ULN	0	2.4

[†]On-treatment value increased from baseline to grade 3 or grade 4 during therapy.
 ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Conclusions

Efficacy at 2 Years

- Telbivudine demonstrated significantly greater responses vs lamivudine for key efficacy endpoints:
 - \log_{10} HBV DNA reduction and PCR nondetectability
 - ALT normalization
 - HBeAg loss in HBeAg-positive patients
 - Therapeutic Response
- There was significantly less primary treatment failure in patients treated with telbivudine compared with lamivudine.
- Response rates were generally higher in the subset of HBeAg-positive patients considered the best candidates for treatment by association guidelines (baseline ALT $\geq 2 \times$ ULN), compared with the overall population.
- Both treatments were generally well tolerated. Most frequently reported adverse events included nasopharyngitis, fatigue, and upper respiratory tract infection.

Impact of Early Viral Suppression on Treatment Outcomes

- Rates of efficacy outcomes after 2 years of therapy were highest in patients with the greatest degree of early viral suppression (PCR negative at week 24).
 - HBeAg seroconversion
 - HBV DNA nondetectability
 - ALT normalization
- The same relationship was observed with telbivudine and lamivudine, but greater viral reduction at week 24 was observed with telbivudine, consistent with the generally higher rates of efficacy responses associated with telbivudine at 2 years.

Disclosures

J.-D. Jia has acted as a consultant for Novartis Pharmaceuticals, Inc. N. Brown is a former employee of Idenix Pharmaceuticals, Inc.

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Cost-Effectiveness of Telbivudine vs. Lamivudine for Chronic Hepatitis B

Wong JB, Pauker SG, on behalf of the GLOBE Investigators

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Key conclusions

- Telbivudine should be a cost-effective alternative to lamivudine, with an incremental cost-utility ratio falling within the range of other accepted medical interventions.
- Computer simulation model results extrapolating the 104-week GLOBE trial results for patients with chronic hepatitis B suggest that telbivudine may provide a greater reduction in the projected future incidence of cirrhosis than lamivudine.



Cost-Effectiveness of Telbivudine versus Lamivudine for Chronic Hepatitis B

John B. Wong and Stephen G. Pauker on behalf of the GLOBE Investigators
Tufts-New England Medical Center, Tufts University School of Medicine, Boston, MA, USA



ABSTRACT

Aim: To estimate the cost-effectiveness of telbivudine versus lamivudine for HBeAg-positive or negative chronic hepatitis B.

Methods: Individual patient data (age, gender, virological, serological and biochemical response and resistance to telbivudine versus lamivudine) after 104 weeks from the multinational GLOBE registration trial (n=1367) were applied to a Markov cohort simulation to project lifelong clinical and economic outcomes using US data for life expectancy, quality of life, liver transplant survival, drug costs (2007 WAC telbivudine \$16.23 and lamivudine \$7.61 per pill) with a 3% annual discount rate. Because of differences in demographic characteristics and response, separate analyses were performed for HBeAg-positive and negative patients.

Results: At week 104, non-detectable HBV DNA responses occurred in 56% with telbivudine and 38% with lamivudine of HBeAg-positive patients (p<0.0001), and in 82% with telbivudine and 57% with lamivudine of HBeAg-negative patients (p<0.0001).

For HBeAg-positive patients, telbivudine reduced the 10-year relative risk of cirrhosis by 33% (from 13.4% to 9.0%) and extended life by 4.6 years (4.9 quality-adjusted life years) in the model. Telbivudine had an incremental cost-effectiveness ratio of \$12,900 per discounted quality-adjusted life year (DQALY) gained. Because disease progression is more rapid in older patients and in men, incremental cost-effectiveness ratios for telbivudine were \$14,800 at age 20, \$13,100 at age 30, \$12,300 at age 40 and \$12,100 at age 50 (baseline 74.3% men) and were \$11,900 for men and \$16,500 for women (baseline mean age 32.4).

For HBeAg-negative patients, telbivudine reduced the 10-year relative risk of cirrhosis by 43% (from 12.9% to 7.3%) and extended life by 4.1 years (4.1 quality-adjusted life years). Telbivudine had an incremental cost-effectiveness ratio of \$24,500 per DQALY. In sensitivity analysis, incremental cost-effectiveness ratios for telbivudine were \$31,200 at age 20, \$27,700 at age 30, \$25,100 at age 40, \$23,500 at age 50 (baseline 78.9% men) and were \$22,500 for men and \$35,100 for women (baseline mean age 42.9).

Conclusion: Based on the 104-week GLOBE trial results for patients with chronic hepatitis B, telbivudine may prolong life and should be a cost-effective alternative to lamivudine with an incremental cost-utility ratio falling within the range of other accepted medical interventions.

INTRODUCTION

- Chronic hepatitis B virus infection:
 - Affects more than 5% of the world population (350 million people)
 - Can lead to cirrhosis and hepatocellular carcinoma
 - May induce substantial direct and indirect costs
- Telbivudine recently approved based on 52-week GLOBE trial for treatment of chronic hepatitis B in treatment-naïve patients with non-detectable HBV DNA responses.
 - HBeAg-positive: 56% with telbivudine versus 38% with lamivudine (P < 0.0001)
 - HBeAg-negative: 82% with telbivudine versus 57% with lamivudine (P < 0.0001)
- Lamivudine, a currently available standard antiviral therapy, has previously been found to be cost-effective for CHB, raising questions about whether telbivudine provides sufficient clinical benefit or value for its cost.

PURPOSE OF STUDY

- To estimate the cost-effectiveness of telbivudine versus lamivudine for HBeAg-positive or -negative chronic hepatitis B.

METHODS

- After 104 weeks, individual patient data from the multinational GLOBE registration trial (n = 1367) were extrapolated to potentially lifelong therapy:
 - Age, gender, initial viral load
 - Virological, serological and biochemical responses
 - Development of drug resistance
- A Markov model of the natural history of hepatitis B was used to project lifelong clinical and economic outcomes:
 - HBeAg, HBsAg serological status and HBV DNA viral levels
 - Chronic hepatitis and compensated cirrhosis
 - Decompensated cirrhosis, hepatocellular carcinoma, liver transplantation
 - Drug resistance
- US data for life expectancy, quality of life, liver transplant survival, drug costs (2007 WAC telbivudine \$16.23 and lamivudine \$7.61 per pill) with a 3% annual discount rate.
- Because of differences in demographic characteristics and responses to therapy, separate analyses were performed for HBeAg-positive and -negative patients and for alternative ages and gender.

RESULTS

HBeAg-Positive

	10-year Risk of Cirrhosis	Life Expectancy	Quality-adjusted Life Expectancy
Lamivudine	13.4%	28.4	25.2
Telbivudine	9.0%	33.0	30.1

- Telbivudine decreased the 10-year likelihood of developing cirrhosis by 33%, and extended life by 4.6 years and by 4.9 quality-adjusted life years.
- By comparison, eliminating coronary artery disease in 35-year-olds would increase life expectancy by 3 years.

	Discounted Lifetime Cost	Discounted Quality-adjusted Life Expectancy	Incremental Cost-effectiveness
Lamivudine	\$ 78,820	16.4	
Telbivudine	\$104,265	18.4	\$12,900

Sensitivity Analysis	↑ Quality-adjusted Life Expectancy	Incremental Cost-effectiveness
Age (74.3% men)		
20-year-olds	+5.7	\$14,800
30-year-olds	+5.0	\$13,100
40-year-olds	+4.2	\$12,300
50-year-olds	+3.3	\$12,100
60-year-olds	+2.4	\$12,600
Gender (age = 32.4 years)		
Women	+4.7	\$16,500
Men	+4.8	\$11,900

- By comparison, antiretroviral therapy for HIV costs \$23,000 per DQALY gained.

HBeAg-Negative

	10-year Risk of Cirrhosis	Life Expectancy	Quality-adjusted Life Expectancy
Lamivudine	12.9%	24.2	21.7
Telbivudine	7.3%	28.3	25.8

- Telbivudine decreased the 10-year likelihood of developing cirrhosis by 43%, and extended life by 4.1 years and by 4.1 quality-adjusted life years.
- By comparison, treating hepatitis C in 43-year-olds would increase life expectancy by 3.6-4.0 years.

	Discounted Lifetime Cost	Discounted Quality-adjusted Life Expectancy	Incremental Cost-effectiveness
Lamivudine	\$ 66,257	15.1	
Telbivudine	\$112,291	17.0	\$24,500

Sensitivity Analysis	↑ Quality-adjusted Life Expectancy	Incremental Cost-effectiveness
Age (78.9% men)		
20-year-olds	+5.4	\$31,200
30-year-olds	+5.0	\$27,700
40-year-olds	+4.3	\$25,100
50-year-olds	+3.4	\$23,500
60-year-olds	+2.5	\$23,000
Gender (age = 42.9 years)		
Women	+3.5	\$35,100
Men	+4.2	\$22,500

- By comparison, hemodialysis costs \$55,000-\$80,000 per DQALY gained.

CONCLUSION

- Computer simulation model results extrapolating the 104-week GLOBE trial results for patients with chronic hepatitis B suggest that telbivudine may provide a greater reduction in the projected future incidence of cirrhosis than lamivudine.
- Telbivudine should be a cost-effective alternative to lamivudine, with an incremental cost-utility ratio falling within the range of other accepted medical interventions.

