

HEP DART 2005

frontiers in drug development for viral hepatitis

A Phase III comparative trial of telbivudine (LdT) vs. lamivudine for chronic hepatitis B: first-year results from the large international GLOBE trial

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**A Phase III Comparative Trial of
Telbivudine (LdT) vs. Lamivudine
for Chronic Hepatitis B:
First-year Results from the Large
International GLOBE Trial**

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N Naoumov, G Chao, B Fielman, N Brown
and the GLOBE Study Group**

**HepDart
Kohala Coast, Hawaii
15 December 2005**

Telbivudine (LdT)

- **Specific inhibitor of HBV polymerase**
 - Not active against HIV or other viruses
- **Favorable toxicology for long-term treatment:**
 - Non-mutagenic, non-carcinogenic, non-teratogenic, no mitochondrial toxicity
- **Once daily oral dosing indicated by PK**
 - Consistent absorption, no food effect
- **Phase IIb comparative trial¹**
 - Greater viral suppression & ALT normalization compared to lamivudine
- **Well tolerated in all clinical trials to date**



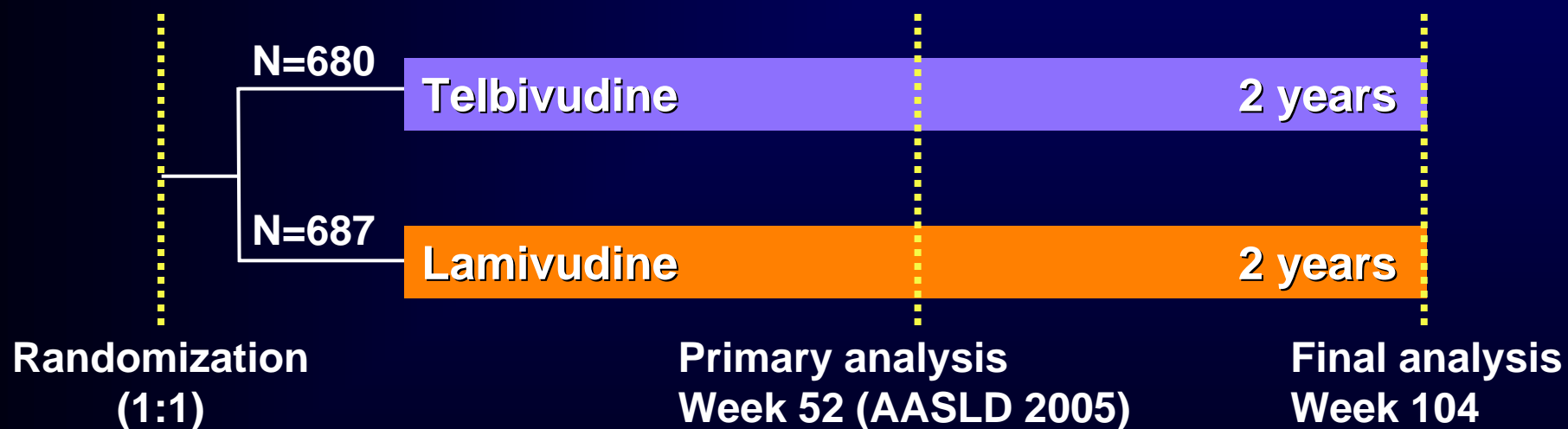
**β -L-2'-deoxythymidine
(LdT, telbivudine)**

¹ Lai *et al.*, *Gastroenterology* 2005; 129:528-536

The GLOBE Study Design

Entry criteria:

- Chronic hepatitis B with compensated liver disease
- Serum HBV DNA $> 10^6$ by COBAS PCR assay
- ALT ≥ 1.3 xULN and < 10 xULN
- Clinical history and baseline biopsy consistent with chronic hepatitis B



Enrolled ITT population: 1367 patients

- 921 HBeAg-positive
- 446 HBeAg-negative



GLOBE Efficacy Endpoints

Primary endpoint:

- Therapeutic Response
 - HBV DNA suppressed to $\leq 5 \log_{10}$, with ALT normalized OR HBeAg loss

Key secondary endpoints:

- Histologic Response
 - ≥ 2 point improvement in Knodell necroinflammatory score with no worsening of fibrosis
- Antiviral efficacy
 - \log_{10} HBV DNA reduction from baseline
 - Clearance of HBV DNA to PCR-nondetectable
- ALT normalization
- HBeAg loss and seroconversion



Viral Breakthrough

- HBV DNA increasing to $>5 \log_{10}$ copies / mL after decreasing to $\leq 5 \log_{10}$ copies / mL
- For patients whose HBV DNA never $<5 \log_{10}$ copies / mL, increase of HBV DNA to within $1 \log_{10}$ copies / mL of baseline after decreasing by $>2 \log_{10}$ copies / mL

Viral Resistance & Treatment Failure

- **Viral resistance**

- Viral breakthrough (rebound) with resistance mutations that emerged during treatment

- **Primary treatment failure**

- Serum HBV DNA levels never below 5 logs (AASLD recommended response threshold)

Baseline Demographics

1,367 patients (ITT Population)

	HBeAg-Positive (N=921)		HBeAg-Negative (N=446)	
	Telbivudine	Lamivudine	Telbivudine	Lamivudine
n	458	463	222	224
Mean years (range)	32 (16-63)	33 (16-67)	43 (17-68)	43 (18-68)
Percent Male	73	76	78	80
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 (46)
Caucasian	11	12	21	25
Other	6	8	14	11



Baseline Disease Characteristics

1,367 patients (ITT Population)

	HBeAg-Positive (n=921)		HBeAg-Negative (n=446)	
	Telbivudine	Lamivudine	Telbivudine	Lamivudine
n	458	463	222	224
Mean HBV DNA (log ₁₀)	9.5	9.5	7.7	7.4
ALT				
Mean IU/L	146	159	137	144
Median IU/L	111	111	99	99
Histology scores				
Knodell necroinflammatory	7.4	7.3	7.3	7.6
Ishak fibrosis	2.1	2.2	2.3	2.5



Efficacy at Week 52

ITT Population, HBeAg-Positive Patients

	Telbivudine	Lamivudine
	Wk 52	Wk 52
n	458	463
Therapeutic response (%)	75	67
Histologic response (%)	64.7	56.3
HBV DNA ↓ from baseline (mean log ₁₀)	- 6.5	- 5.5
HBV DNA non-detectable by PCR (%)	60	40
ALT normalization [$\leq 1 \times$ ULN] (%)	77	75
HBeAg loss (%)	26	23
HBeAg seroconversion (%)	22	21

Color designates $P < 0.05$, telbivudine vs lamivudine at Week 52



Efficacy at Week 52 and Week 76

ITT Population, 328 HBeAg+ Patients at Week 76 in Primary Database

	Telbivudine		Lamivudine	
	Wk 52	Wk 76	Wk 52	Wk 76
n	458	163	463	165
Therapeutic response (%)	75	75	67	58
Histologic response (%)	64.7		56.3	
HBV DNA ↓ from baseline (mean log ₁₀)	-6.5	-6.6	-5.5	-5.2
HBV DNA non-detectable by PCR (%)	60	69	40	41
ALT normalization [$\leq 1 \times$ ULN] (%)	77	78	75	68
HBeAg loss (%)	26	40	23	26
HBeAg seroconversion (%)	22	33	21	24

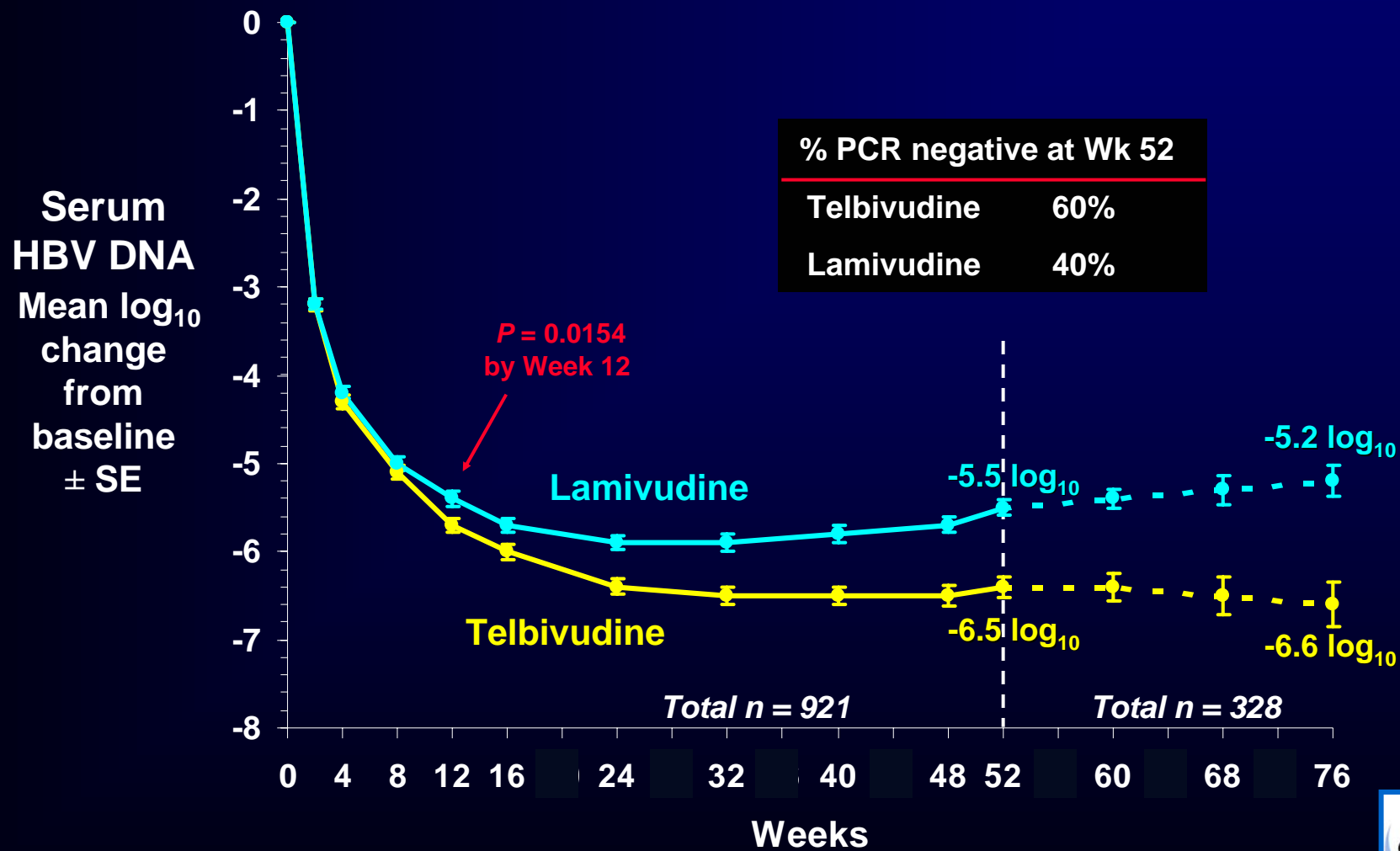
Color designates $P < 0.05$, telbivudine vs lamivudine at Week 52

Color designates $P < 0.05$, telbivudine vs lamivudine at Week 76

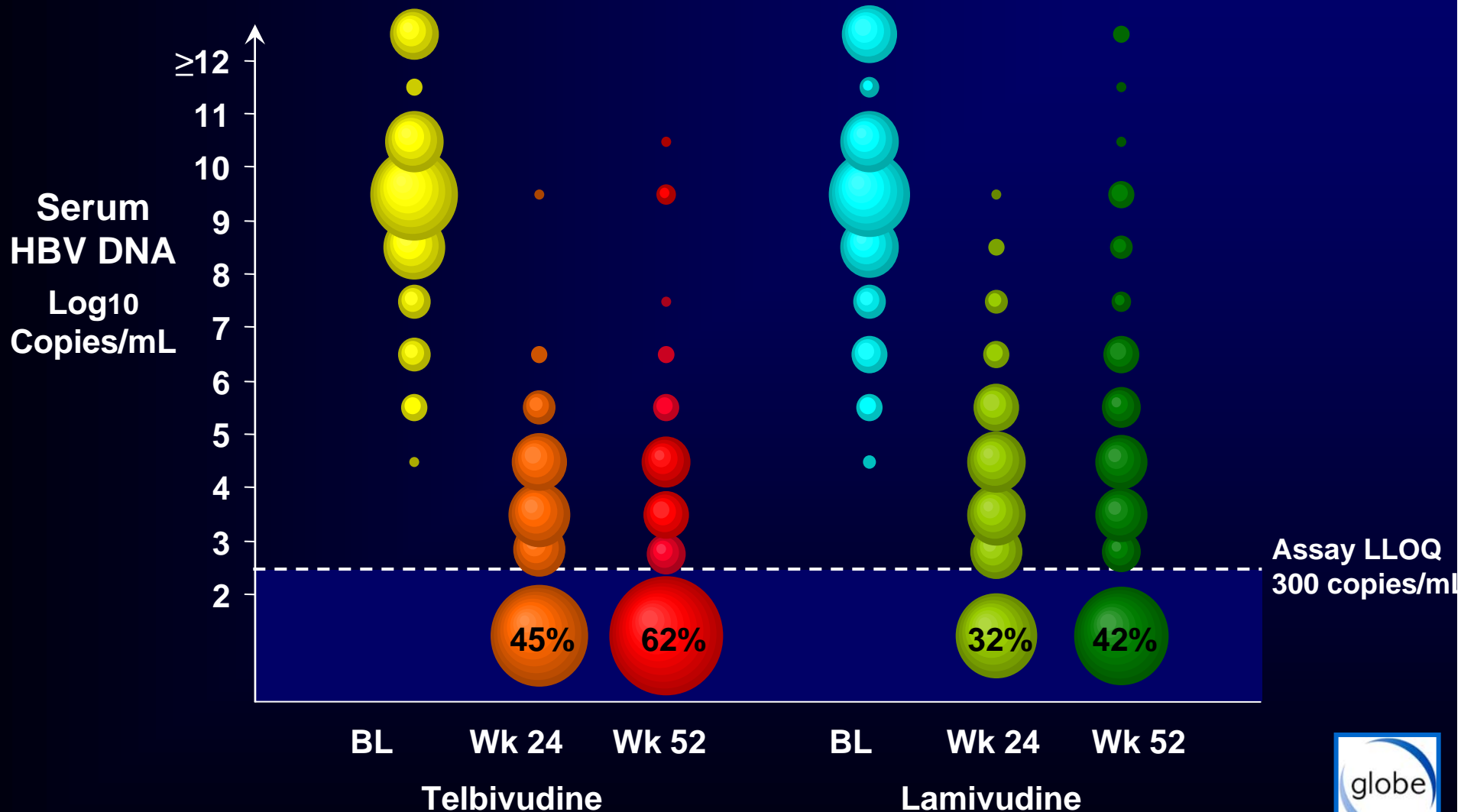


Mean Change in HBV DNA from Baseline

HBeAg-Positive Patients

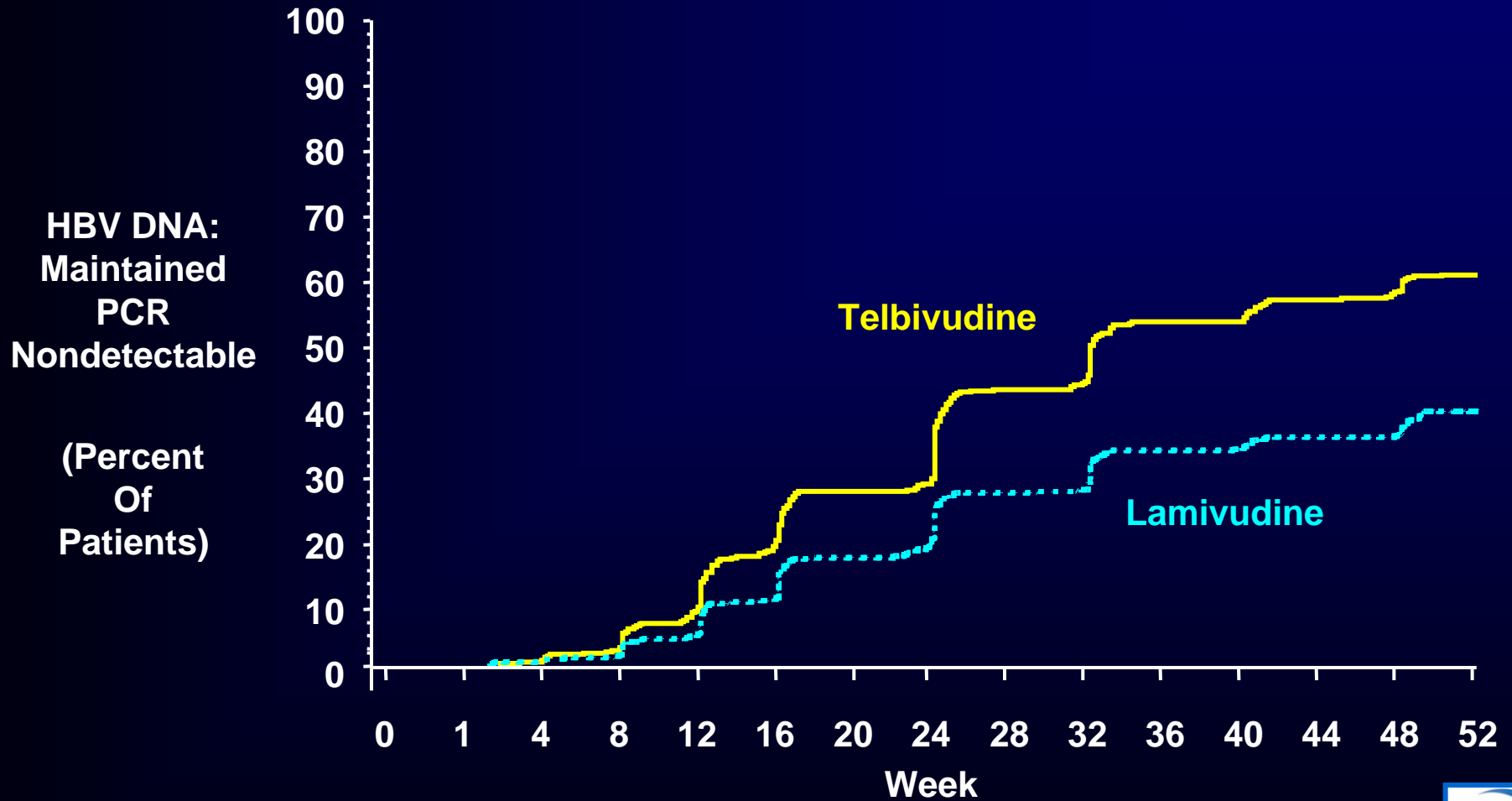


Distribution of Patients by Viral Load at Baseline, Week 24 and Week 52: HBeAg positive patients

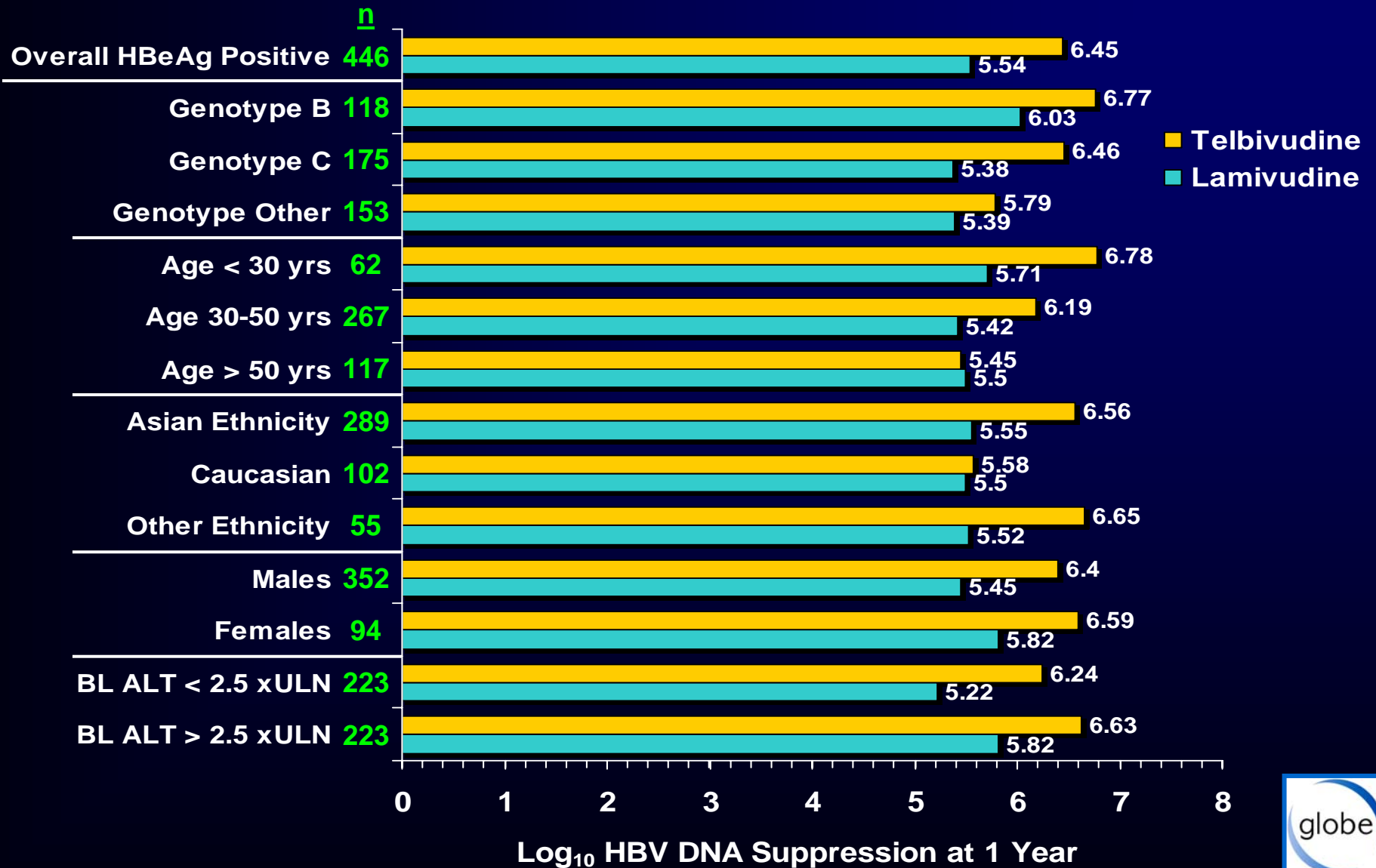


Serum HBV DNA: Time to PCR-Negativity

HBeAg positive patients



Consistently Greater Viral Suppression with Telbivudine in Key Patient Subgroups: HBeAg Positive Patients



HBeAg Responses at Week 52 and Week 76

HBeAg Positive Patients, Baseline ALT ≥ 2 xULN

Population recommended for treatment in AASLD and APASL guidelines

	Telbivudine		Lamivudine	
	Week 52	Week 76	Week 52	Week 76
n	320	100	317	93
HBeAg loss (%)	32	49	27	29
HBeAg seroconversion (%)	28	41	24	26

Color designates $P < 0.05$, telbivudine vs lamivudine, Week 76



Efficacy at Week 52

ITT Population, HBeAg Negative Patients

	Telbivudine	Lamivudine
	Wk 52	Wk 52
n	222	224
Therapeutic response (%)	75	77
Histologic response (%)	66.6	66.0
HBV DNA ↓ from baseline (mean log ₁₀)	-5.2	-4.4
HBV DNA non-detectable by PCR (%)	88	71
ALT normalization [$\leq 1 \times$ ULN] (%)	74	79

Color designates $P < 0.05$, telbivudine vs lamivudine at Week 52



Efficacy at Week 52 and Week 76

ITT Population, 135 HBeAg- Patients at Week 76 in Primary Database

	Telbivudine		Lamivudine	
	Wk 52	Wk 76	Wk 52	Wk 76
n	222	68	224	67
Therapeutic response (%)	75	75	77	70
Histologic response (%)	66.6		66.0	
HBV DNA ↓ from baseline (mean log ₁₀)	-5.2	-5.3	-4.4	-4.7
HBV DNA non-detectable by PCR (%)	88	84	71	67
ALT normalization [$\leq 1 \times$ ULN] (%)	74	76	79	64

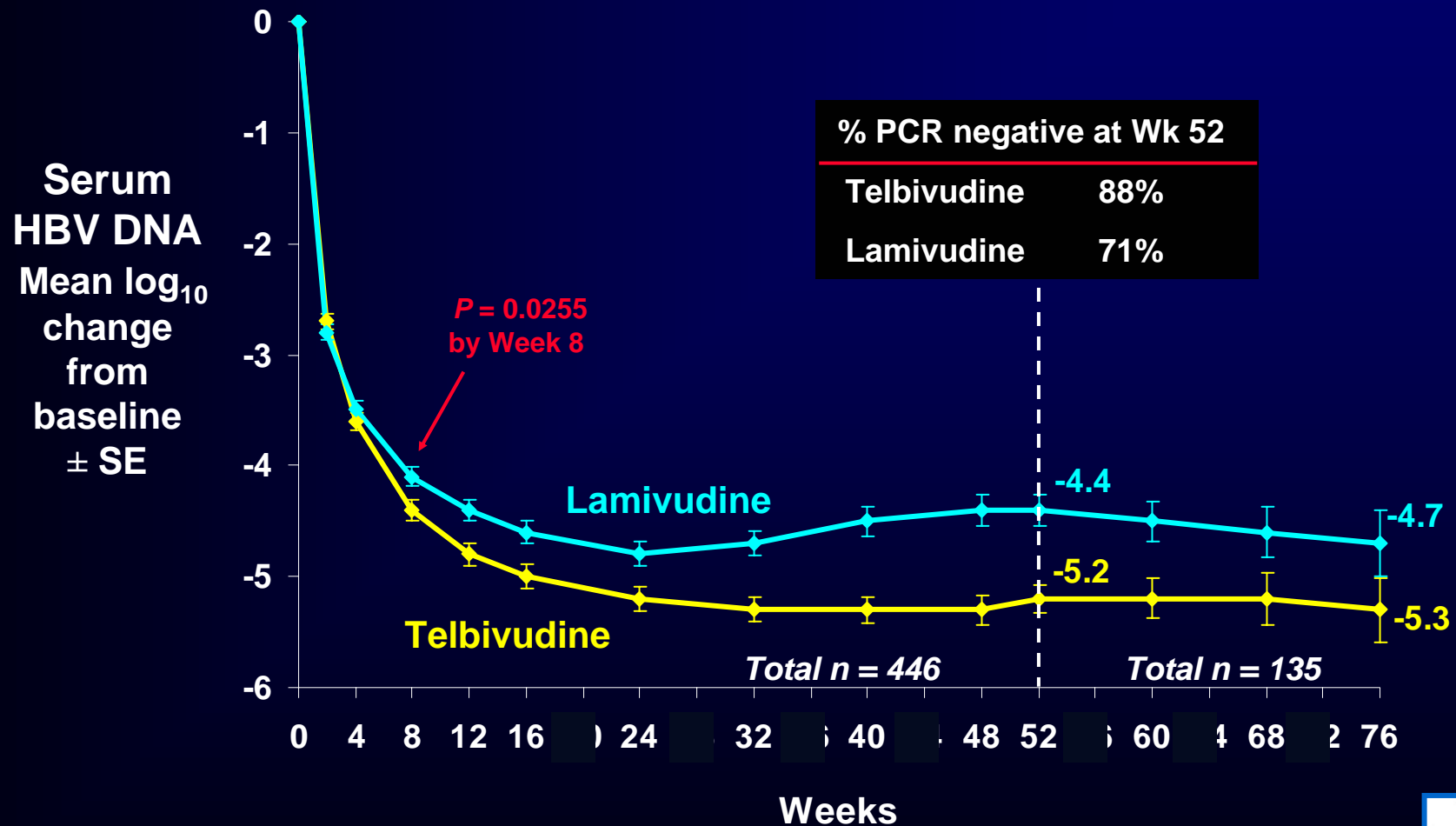
Color designates $P < 0.05$, telbivudine vs lamivudine, Week 52

Color designates $P < 0.05$, telbivudine vs lamivudine, Week 76



Mean Change in HBV DNA from Baseline

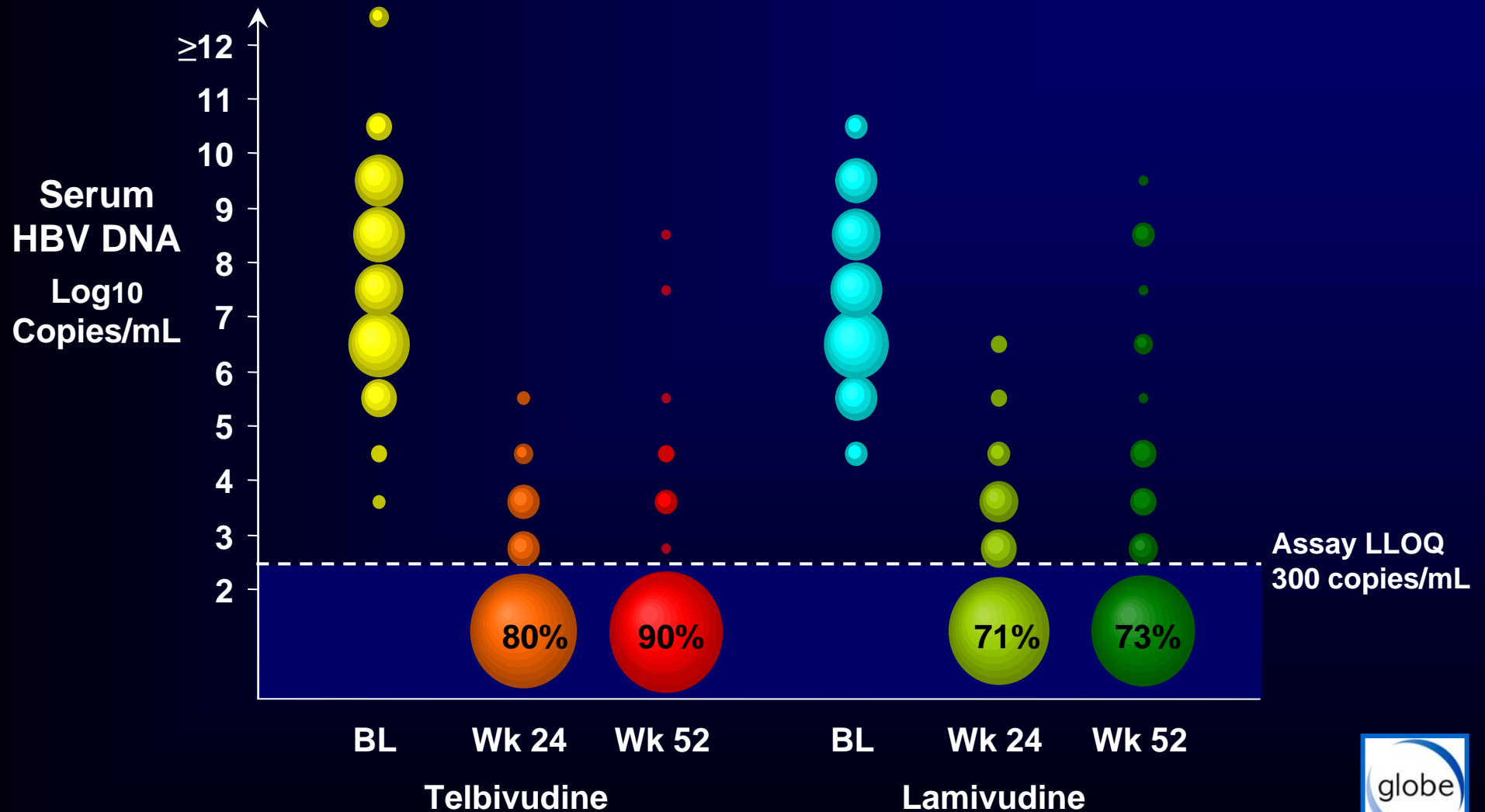
HBeAg-Negative Patients



% PCR negative at Wk 52	
Telbivudine	88%
Lamivudine	71%

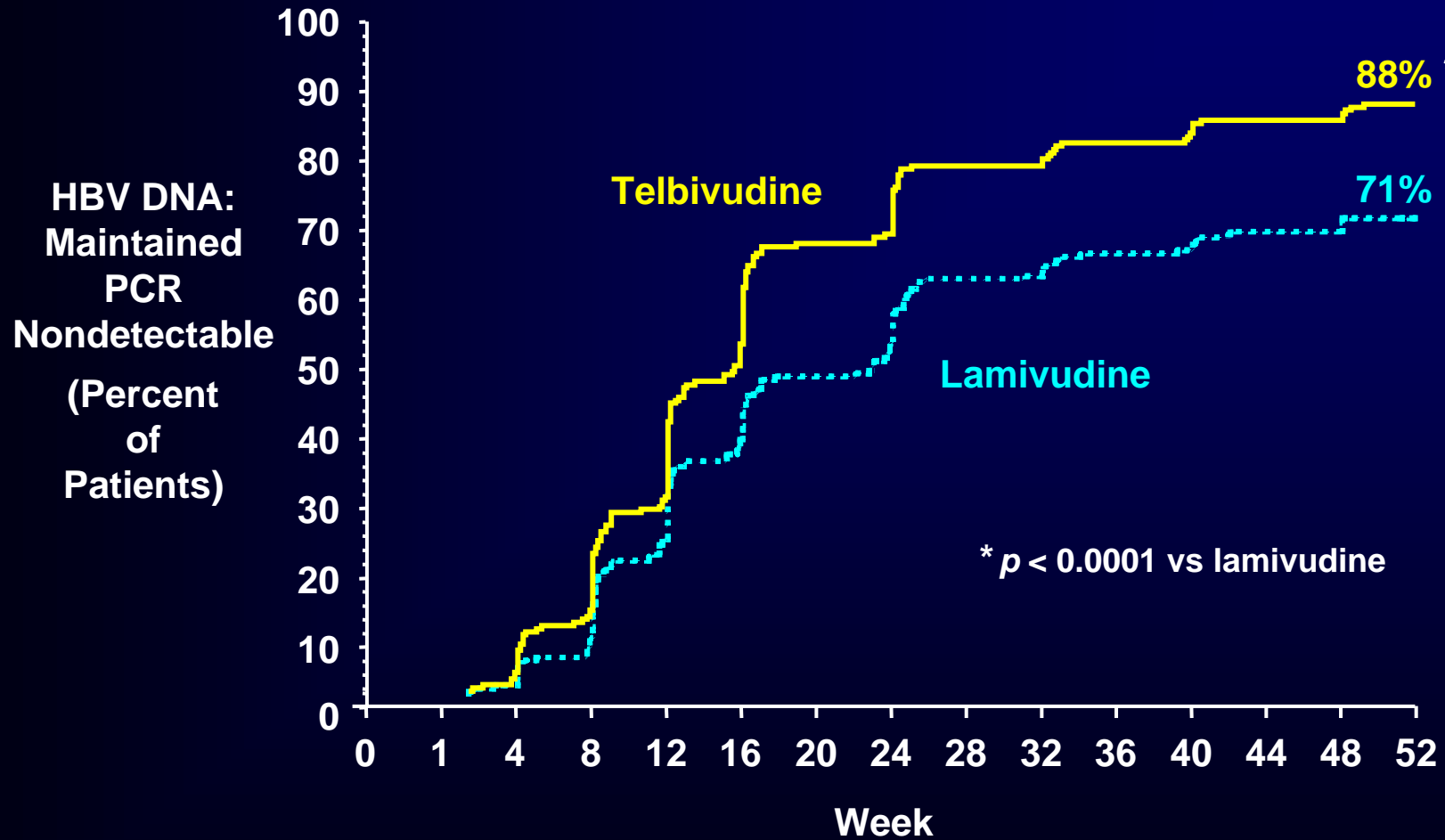


Distribution of Patients by Viral Load at Baseline, Week 24 and Week 52: HBeAg negative patients

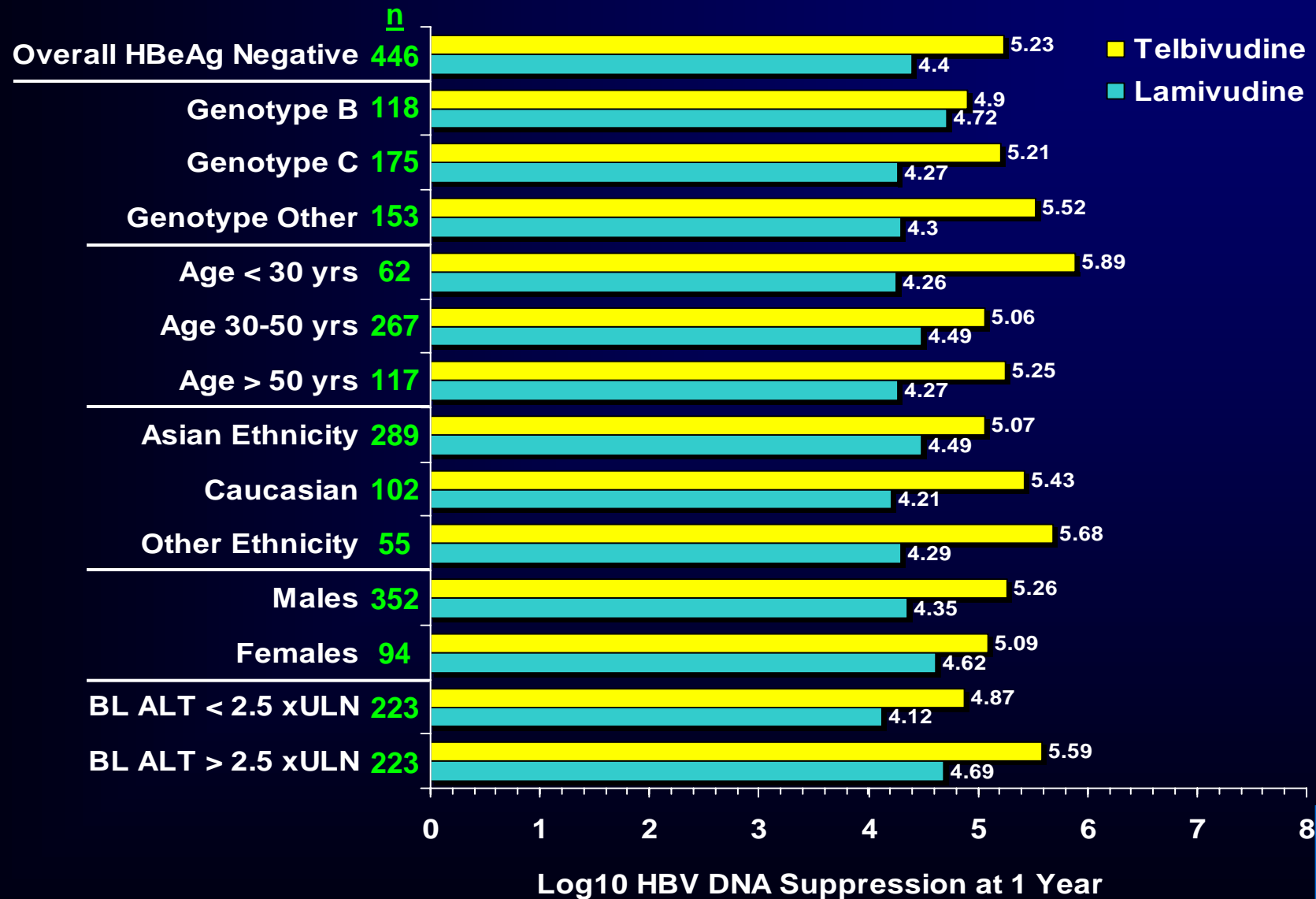


Serum HBV DNA: Time to PCR-Negativity

HBeAg negative patients



Consistently Greater Viral Suppression with Telbivudine in Key Patient Subgroups: HBeAg Negative Patients



Histology Populations for Analysis

	HBeAg +ve	HBeAg -ve	Overall
ITT	921	446	1367
mITT	872 (5.3% missing)	430 (3.6% missing)	1302 (4.8% missing)
mITT with paired biopsies	753 (86% of mITT)	394 (92% of mITT)	1147 (88% of mITT)

- Modified (mITT) population for histology = all ITT patients with evaluable baseline biopsy
- Efficacy Evaluable population for histology = pts in histologic mITT who:
 - Meet the Efficacy Evaluable population criteria and
 - Have a baseline Knodell HAI score > 3
- Where Week 52 biopsy is not available, analyses utilise two conventions:
 - Missing = failure (primary mITT analysis in SAP)
 - Missing = missing



Histologic Response

	Missing =	N	Telbivudine	Lamivudine	Diff.	p-value
HBeAg Positive	Failure	872	64.7%	56.3%	8.3%	0.011
	Excluded	753	73.9%	66.2%	7.7%	0.018
HBeAg Negative	Failure	430	66.6%	66.0%	0.6%	ns
	Excluded	394	72.8%	71.9%	0.9%	ns



Bridging Fibrosis and Cirrhosis: Progression and Regression During Year 1 of GLOBE

- Progression to bridging fibrosis or cirrhosis:
 - Ishak fibrosis score of 0-3 at Baseline increasing to 4-6 at Week 52
- Regression from bridging fibrosis or cirrhosis:
 - Ishak fibrosis score of 4-6 at Baseline decreasing to 0-3 at Week 52

		Telbivudine	Lamivudine
HBeAg Positive	Progression (n, %)	5/353 (1%)	2/328 (1%)
	Regression (n, %)	21/31 (68%)	25/41 (61%)
HBeAg Negative	Progression (n, %)	1/167 (1%)	1/174 (1%)
	Regression (n, %)	16/27 (59%)	12/26 (46%)

Breakthrough / Treatment Failure

ITT Population

		Telbivudine (n=458)	Lamivudine (n=463)	P-value
HBeAg Positive	Viral breakthrough at Week 48 (%)	3	10	0.001
	HBV resistance (%)	3 *	8 †	0.001
	Primary treatment failure (%)	5	13	0.001
HBeAg Negative	Viral breakthrough at Week 48 (%)	2	9	0.005
	HBV resistance (%)	2 *	9 †	0.005
	Primary treatment failure (%)	<1	3	0.056

* Telbivudine-associated resistance mutations were all M204I

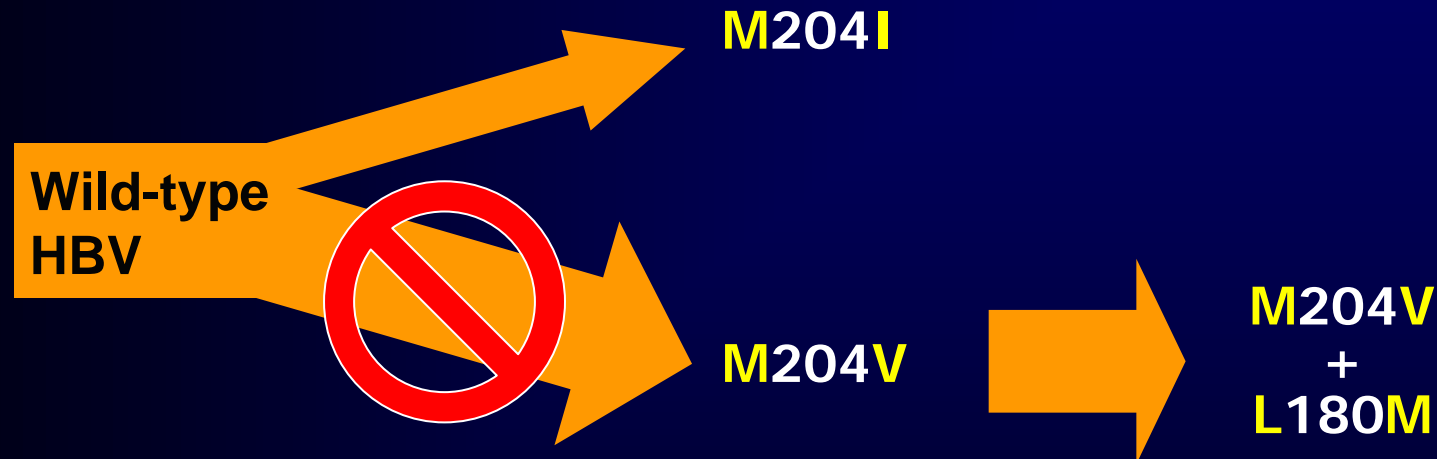
† Lamivudine-associated resistance mutations were a mixture of M204V, M204I, and M204V + L180M double mutants



Pathways for YMDD-Mediated HBV Resistance

In vitro findings:

- Lamivudine activity reduced against M204V and M204I mutants
- Telbivudine active against M204V; activity reduced only vs M204I



Less clinical resistance with telbivudine for 2 reasons:

- Greater antiviral effect reduces mutation frequency
- Telbivudine blocks M204V pathway to YMDD-mediated resistance

Most Frequent Adverse Events Through Week 52

% of Patients With Event, Regardless of Attributability to Study Drug

	Telbivudine (n=680)	Lamivudine (n=687)	Total
Total patients with AE (%)	75	71	73
URI	14	13	14
Headache	11	13	12
Fatigue	12	10	11
Nasopharyngitis	11	10	11
Blood CPK increased	9	7	8
Post procedural pain	7	6	6
Upper abdominal pain	5	7	6
Cough	6	6	6
Influenza	5	7	6
Diarrhea	5	4	5
Nausea	5	4	5
Pharyngolaryngeal pain	5	4	5
Dizziness	4	5	4

Includes adverse events occurring in at least 5% of patients in either treatment group



Grade 3-4 Lab Abnormalities Through Week 52

Percent of Patients With Event

	Telbivudine (n=680)	Lamivudine (n=687)	Total
ALT	4	8	6
Amylase	0.1	0.3	0.2
AST	3	6	5
Creatine kinase (CK)	7.5	3	6
Lipase	2	4	3
Abs. neutrophils	2	2	2
Platelet count	0.7	0.6	0.7
Protein	0.7	0.3	0.5
Total bilirubin	0	0.3	0.1

Color designates $P < 0.05$, telbivudine vs lamivudine



ALT Flares by HBeAg Stratum: Weeks 24 to 52

Late ALT Flares 5-10x more common with Lamivudine

ALT Flare Category	HBeAg-Positive		HBeAg-Negative	
	Telbivudine	Lamivudine	Telbivudine	Lamivudine
% \geq 2 x Baseline	0.4	1.3	0.5	1.3
% \geq 3 x Baseline	0	1.1	0	3.6
% \geq 500 IU/L AND \geq 2 x Baseline	0.4	1.5	0	0.4
% \geq 2x Baseline with bilirubin \geq 2 x ULN	0	0.6 [†]	0	0
TOTAL (%)	0.9*	4.5	0.5*	5.4

* $P < 0.001$, Telbivudine vs Lamivudine.

[†]4 severe ALT flares with Lamivudine, 0 with Telbivudine.



ALT Flares

Grade 3-4 ALT Flares

- Early flares (1st 24 weeks) associated with large HBV DNA drops ($> 4 \log_{10}$) early in treatment
 - Some patients with transient ALTs > 500 , none with liver failure
 - All early flares resolved with continued study drug treatment
- Later ALT flares (after Week 24) mostly associated with resistance
- Regression modeling performed for ALT flares (preliminary results):
 - Significant risk factors for grade 3-4 ALT flare: viral breakthrough ($p=0.001$), high Baseline HBV DNA ($p=0.001$), low Baseline ALT ($p=0.01$), lamivudine treatment ($p=0.02$)
- Four severe ALT flares (ALT \uparrow with bilirubin \uparrow), all on lamivudine:
 - 1 was intercurrent HEV infection, other 3 with viral breakthrough
 - 1 patient with severe lamivudine breakthrough required liver transplant



CK Elevations

- Seen in lamivudine, adefovir, and placebo recipients in previous trials
- CK elevations in ~ 20% of pts at Screen/Baseline visits
- Most affected patients with just one grade 3-4 episode
- > 80% of CK elevations resolved by next visit, 100% resolved by 2nd-3rd visit, with continued treatment
- No consistent association between CK elevations and specific clinical AE's for either drug



Summary: Efficacy and Safety of Telbivudine

- High degree of efficacy on all virologic and clinical endpoints
- Significantly greater responses vs. lamivudine on all direct measures of antiviral efficacy, in HBeAg+ and HBeAg- patients
 - Superior HBV DNA reduction & PCR non-detectable
 - Significantly faster viral clearance to PCR-nondetectable
 - Significantly reduced viral breakthrough & resistance
 - Significantly reduced treatment failure (primary, secondary)
- Significantly greater Therapeutic Response and Histologic Response vs. lamivudine in HBeAg+ patients; non-inferiority in HBeAg- patients



Summary: Efficacy and Safety of Telbivudine (2)

- > 50% of patients with baseline Ishak fibrosis > 3 showed regression of pre-existing bridging fibrosis/cirrhosis
- Progression of fibrosis rare in pts with Ishak ≤ 3 (1%)
- Well-tolerated, clinical side-effect profile similar to lamivudine
- Partial Year 2 (Week 76) data encouraging with regard to cumulative HBeAg loss/seroconversion, ALT normalization, and other efficacy parameters
 - Final 2-year data in second half of 2006



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