

# **Week 24 is the Optimal Time Point for Predicting Outcomes at 2 Years with Telbivudine**

## **ROC Analysis**

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# **Chronic Hepatitis B (CHB)**

## **Background**

- **Effective viral suppression during treatment of CHB is the most important predictor of long-term outcomes**
- **While there are well defined responses (RVR, complete EVR, partial EVR) to HCV treatment that guide therapy, there are none for HBV**
- **Periodic monitoring of the virologic response to treatment would appear useful to identify suboptimal responses, allowing the clinician to modify treatment accordingly**

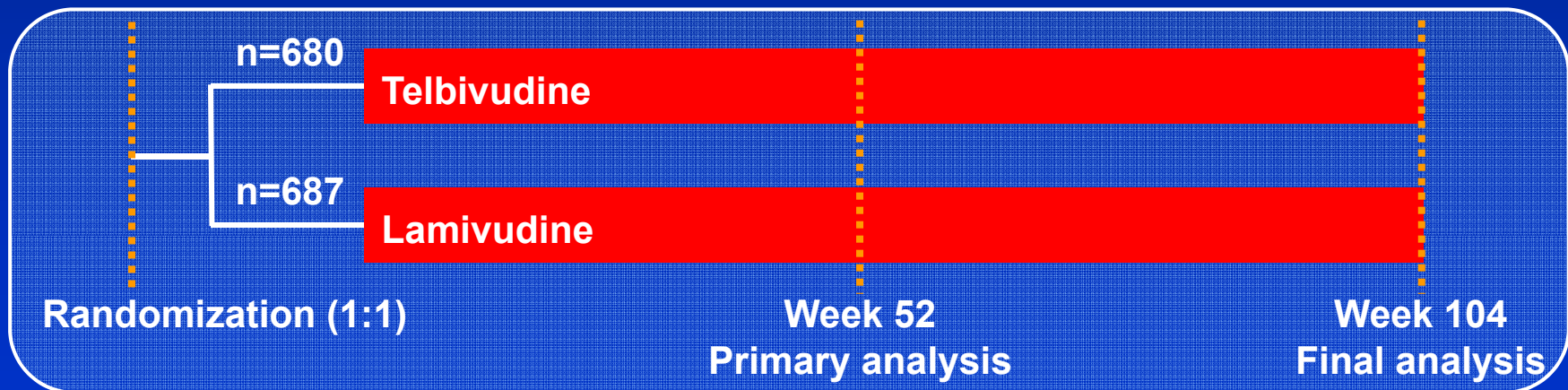
# AIMS

- To identify the best early time point for predicting long-term efficacy outcomes in patients treated with telbivudine
- To identify baseline host and viral factors that are predictive of week 24 and week 104 negative HBV DNA

# GLOBE Study (NV-02B-007)

## Entry criteria

- Nucleos(t)ide-naïve patients, aged 16–70 years, with HBeAg-positive (n=921) or HBeAg-negative (n=446) CHB and compensated liver disease
- Serum HBV DNA  $>6 \log_{10}$  copies/mL by COBAS® Amplicor polymerase chain reaction (PCR) assay
- Serum alanine aminotransferase (ALT)  $\geq 1.3$ – $10$  x upper limit of normal
- Pretreatment liver biopsy consistent with CHB



- Enrolled intent-to-treat (ITT) population: 1367 patients
- Treatment groups well matched for baseline demographics and disease characteristics

Lai C-L et al. *Hepatology*. 2006;44(suppl 1):222A (Abstract 91)

## GLOBE Study: Results at Week 104 HBeAg-Positive Patients (ITT Population)

	Telbivudine	Lamivudine	P-value
n	458	463	
Therapeutic response, (%)	63	48	<0.0001
HBV DNA reduction from baseline, log <sub>10</sub> copies/mL	-5.7	-4.4	<0.0001
PCR-negativity, (%) †	56	39	<0.0001
ALT normalization, (%)	70	62	0.014
HBeAg loss, (%)	35	29	0.056
HBeAg seroconversion, (%)	30	25	0.095
Resistance, (%) ‡	25	40	<0.0001

†Quantification limit ≤300 copies/mL by COBAS® Amplicor.

‡Cumulative resistance 1 log<sub>10</sub> copies/mL above nadir.

# GLOBE Study: Results at Week 104

## HBeAg-Negative Patients (ITT Population)

	Telbivudine	Lamivudine	P-value
n	222	224	
Therapeutic response, (%)	78	66	0.007
HBV DNA reduction from baseline, log <sub>10</sub> copies/mL	-5.0	-4.2	0.0002
PCR-negativity, (%) †	82	57	<0.0001
ALT normalization, (%)	78	70	0.073
Resistance, (%) ‡	11	26	<0.0001

†Quantification limit ≤300 copies/mL by COBAS® Amplicor.

‡Cumulative resistance 1 log<sub>10</sub> copies/mL above nadir.

# Methods

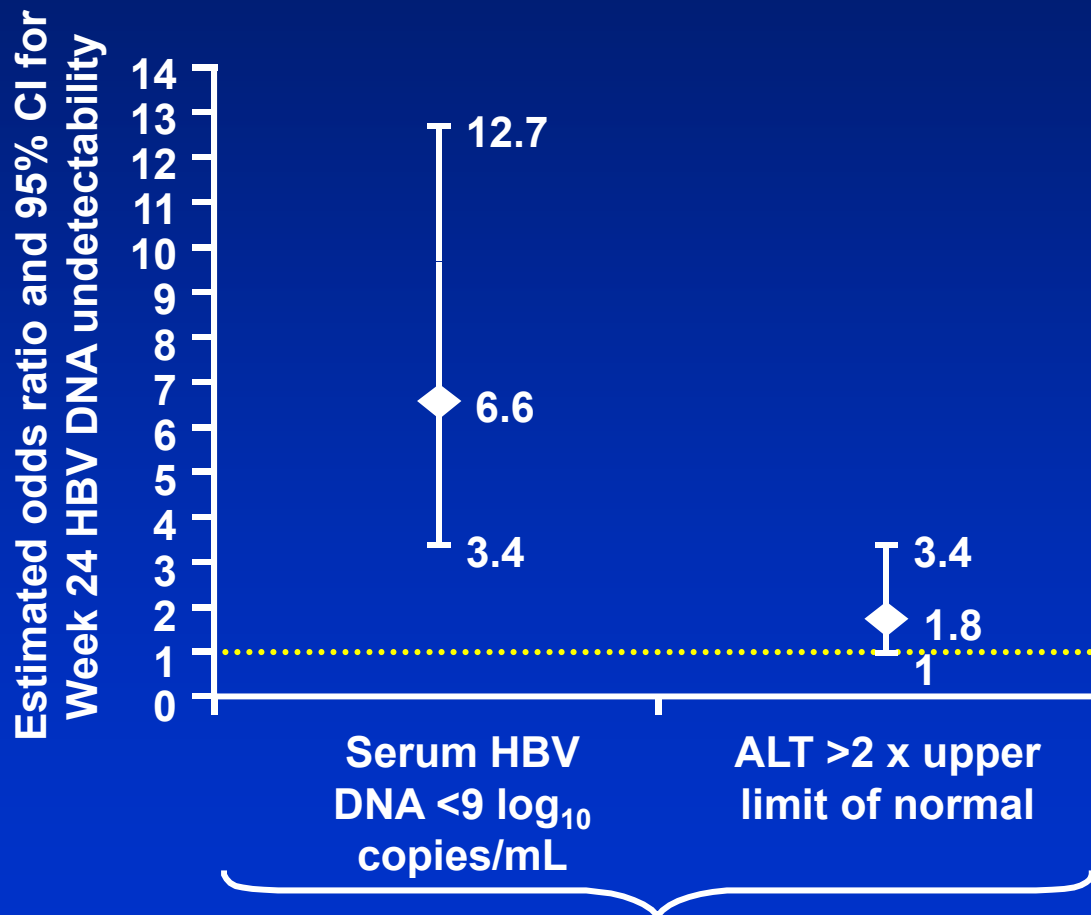
- **Study endpoints assessed included serum HBV DNA reduction, HBeAg seroconversion, and resistance**
  - serum HBV DNA was quantified by COBAS<sup>®</sup> Amplicor PCR assay (detection limit 300 copies/mL)
  - resistance was defined as viral breakthrough (increase of serum HBV DNA  $\geq 1$  log above 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 Week 24 on-treatment variables predictive of Week 104 efficacy outcomes**
  - baseline variables were age, body mass index, ALT, fibrosis Ishak score, HBV DNA, Knodell histologic activity index score, gender, and HBV genotype

# **Methods**

## **ROC Analysis**

- **ROC curves were constructed to evaluate the predictive value of HBV DNA at baseline and at 4, 8, 12, 24, and 32 weeks of therapy on each of the specified Week 104 outcomes**
- **To investigate the clinical relevance of HBV DNA levels at various time points (Weeks 8, 12, 24, and 32), we calculated positive predictive value, negative predictive value, sensitivity, and specificity at the Youden index HBV DNA threshold for the Week 104 outcomes**

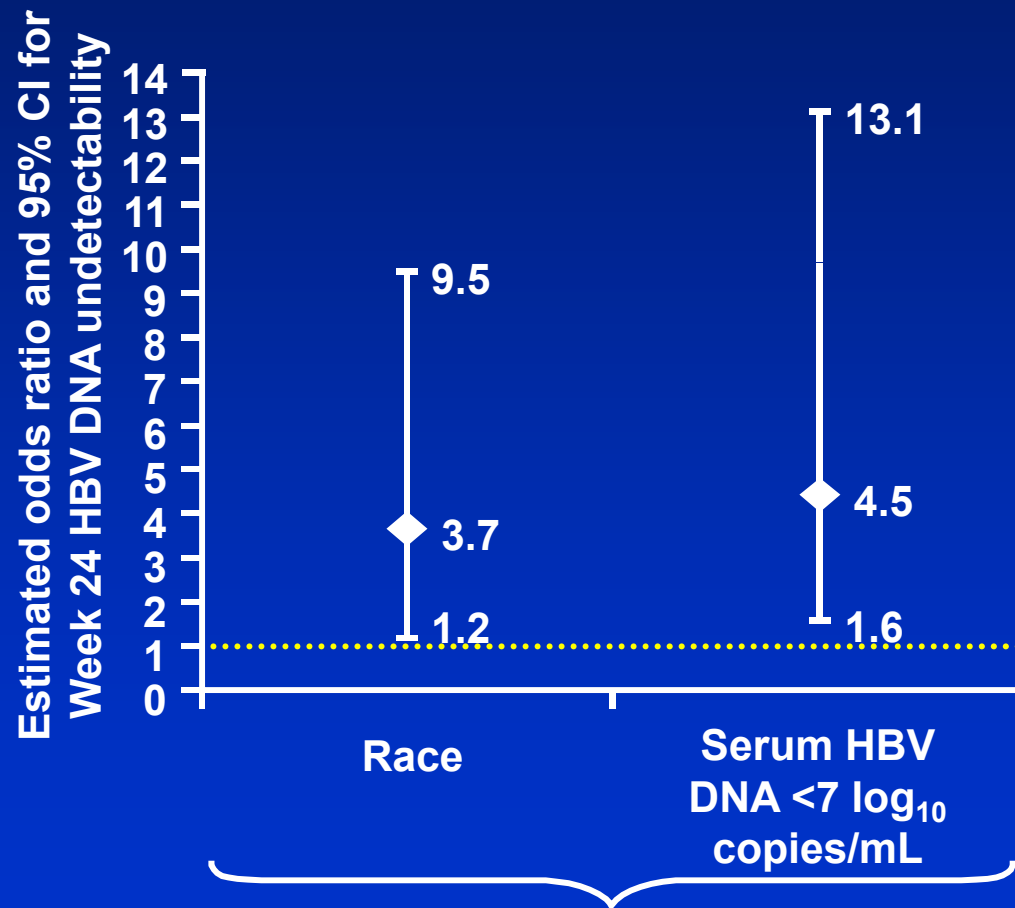
# Baseline Characteristics Associated with Week 24 Serum HBV DNA Undetectability\*



**HBeAg-positive patients**

\*MLR Analysis

# Baseline Characteristics Associated with Week 24 Serum HBV DNA Undetectability\*



**HBeAg-negative patients**

\*MLR Analysis

## Sensitivity and Specificity, Positive and Negative Predictive Values for Week 4, 8, 12, 24, and 32 Serum HBV DNA Levels as Predictor of Week 104 Outcomes

Week (n†)	4 (30)				8 (30)				12 (84)			
Week 104 outcome	Sens	Spe	PPV	NPV	Sens	Spe	PPV	NPV	Sens	Spe	PPV	NPV
Serum HBV DNA undetectable	0.64	0.70	0.73	0.60	0.62	0.78	0.78	0.61	0.70	0.77	0.79	0.66
Lack of resistance	0.57	0.76	0.87	0.38	0.56	0.77	0.88	0.37	0.60	0.8	0.9	0.41
HBeAg seroconversion	0.83	0.43	0.38	0.86	0.59	0.72	0.47	0.8	0.71	0.63	0.45	0.84

Week (n†)	24 (202)				32 (251)			
Week 104 outcome	Sens	Spe	PPV	NPV	Sens	Spe	PPV	NPV
Serum HBV DNA undetectable	0.78	0.73	0.79	0.71	0.81	0.74	0.81	0.75
Lack of resistance	0.63	0.78	0.89	0.42	0.69	0.76	0.89	0.45
HBeAg seroconversion	0.84	0.55	0.44	0.89	0.89	0.52	0.45	0.92

†Number of patients achieving serum HBV DNA <300 copies/mL at each time point.  
Sens, sensitivity; Spe, specificity

## Youden's Indices, $J$ , and Discrimination Threshold for Serum HBV DNA levels at Week 4, 8, 12, 24, and 32 as Predictors of Week 104 Outcomes

Week	4		8		12	
Week 104 outcomes	Index $J$	Threshold	Index $J$	Threshold	Index $J$	Threshold
Serum HBV DNA undetectable	0.340	5.09	0.396	4.07	0.463	3.56
Lack of resistance	0.330	5.11	0.331	4.18	0.398	3.56
HBeAg seroconversion	0.262	5.67	0.302	3.93	0.342	3.52

Week	24		32	
Week 104 outcomes	Index $J$	Threshold	Index $J$	Threshold
Serum HBV DNA undetectable	0.505	2.87	0.554	2.60
Lack of resistance	0.415	2.74	0.442	2.60
HBeAg seroconversion	0.389	3.06	0.411	2.89

The Youden's index,  $J$ , is the maximum value of (sensitivity + specificity – 1) obtained under the ROC curve, the threshold is the  $\log_{10}$  serum HBV DNA level at which this maximum  $J$  index is obtained

## Sensitivity and Specificity, Positive and Negative Predictive Values for Week 4, 8, 12, 24, and 32 Serum HBV DNA Levels as Predictor of Week 104 Outcomes

Week (n <sup>†</sup> )	4 (67)				8 (67)				12 (107)			
Week 104 outcome	Sens	Spe	PPV	NPV	Sens	Spe	PPV	NPV	Sens	Spe	PPV	NPV
Serum HBV DNA undetectable	0.83	0.45	0.87	0.37	0.69	0.6	0.89	0.3	0.69	0.65	0.9	0.31
Lack of resistance	0.82	0.58	0.94	0.29	0.7	0.75	0.96	0.23	0.68	0.79	0.96	0.23

Week (n <sup>†</sup> )	24 (177)				32 (187)			
Week 104 outcome	Sens	Spe	PPV	NPV	Sens	Spe	PPV	NPV
Serum HBV DNA undetectable	0.87	0.46	0.88	0.44	0.98	0.35	0.88	0.76
Lack of resistance	0.87	0.62	0.95	0.37	0.97	0.46	0.94	0.65

<sup>†</sup>Number of patients achieving serum HBV DNA <300 copies/mL at each time point.  
Sens, sensitivity; Spe, specificity

# Youden's Indices, $J$ , and Discrimination Threshold for Serum HBV DNA levels at Week 4, 8, 12, 24, and 32 as Predictors of Week 104 Outcomes

Week	4		8		12	
Week 104 outcomes	Index $J$	Threshold	Index $J$	Threshold	Index $J$	Threshold
Serum HBV DNA undetectable	0.280	4.93	0.292	3.42	0.335	2.79
Lack of resistance	0.407	4.93	0.452	3.50	0.467	2.79

Week	24		32	
Week 104 outcomes	Index $J$	Threshold	Index $J$	Threshold
Serum HBV DNA undetectable	0.335	2.53	0.329	3.23
Lack of resistance	0.493	2.53	0.427	3.23

The Youden's index,  $J$ , is the maximum value of (sensitivity + specificity – 1) obtained under the ROC curve, the threshold is the  $\log_{10}$  serum HBV DNA level at which this maximum  $J$  index is obtained

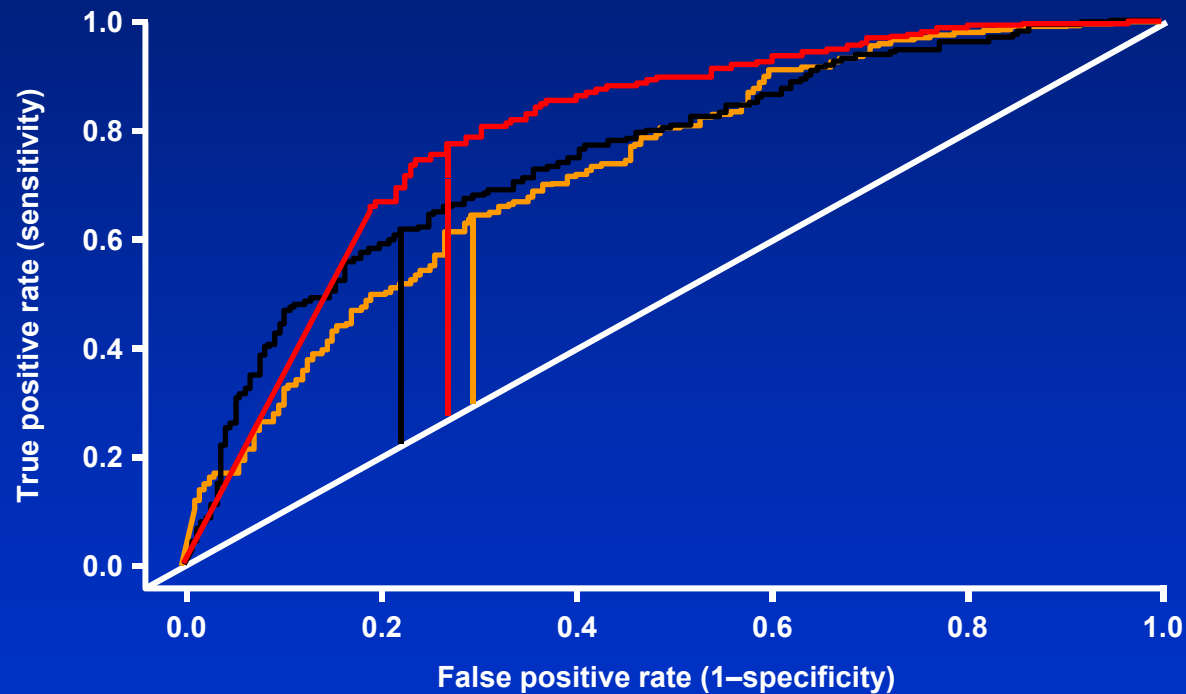
# Conclusions

- **Serum HBV DNA level at baseline is the best predictor of Week 24 response**
  - **HBeAg-positive and HBeAg-negative patients with HBV DNA prior to treatment of  $<9$  and  $<7$   $\log_{10}$  copies/mL, respectively, are more likely to achieve undetectable HBV DNA levels at Week 24**
- **Evaluation of serum HBV DNA at Week 24 is a reasonably reliable and clinically meaningful predictor of Week 104 outcomes, including serum HBV DNA undetectability ( $<300$  copies/mL), emergence of resistance, and HBeAg seroconversion (in HBeAg-positive patients)**

# Conclusions

- **Week 24 provides a favorable balance of sensitivity and specificity for identifying patients at risk of negative outcomes at 2 years**
- **Clinical decisions to either continue or modify therapy are optimally made at Week 24**
- **By combining baseline and Week 24 serum HBV DNA assessments, clinicians can maximize the benefit of telbivudine therapy**
- **Such analyses are needed for other anti-virals as well to facilitate response guided therapy**

# Comparison Between Week 24 and Weeks 8 and 12 Serum HBV DNA Youden Index to Predict Week 104 Serum HBV DNA Undetectability, HBeAg-Positive Patients



- Youden (Week 8 HBV) = 0.396 @  $\log_{10}$  HBV = 4.07: PPV = 0.78, NPV = 0.61
- Youden (Week 12 HBV) = 0.463 @  $\log_{10}$  HBV = 3.56: PPV = 0.79, NPV = 0.66
- Youden (Week 24 HBV) = 0.505 @  $\log_{10}$  HBV = 2.87: PPV = 0.79, NPV = 0.71

# ROC Curve Analysis Methods (cont'd)

- The Youden index is appropriate for analyses with immeasurable samples below the limit of detection
  - the Youden index is the maximum vertical distance from the ROC curve to the line of identity, or chance line (ie, where the curve would lie if there were no relationship between predictor and outcome), and identifies the threshold value of the test that is associated with the greatest discrimination of outcome
  - values close to one indicate that the biomarker's effectiveness is relatively large
  - values close to zero indicate limited effectiveness

## **ROC Curve Analysis: Results (cont'd) HBeAg-Positive Patients Treated with Telbivudine**

- The Youden index,  $J$ , increases consistently across all outcomes from Week 4 through Week 32, while the threshold at which the maximal distance is achieved decreases**
- Thus, Week 24 is a more reliable predictor of Week 104 outcomes than earlier time points, providing a favorable balance between sensitivity and specificity for identifying patients at risk of negative 2-year outcomes**

# **ROC Curve Analysis: Results**

## **HBeAg-Positive Patients Treated with Telbivudine**

- **At the early (Weeks 4, 8, and 12) time points, the predictive sensitivity of PCR-negativity for all outcomes is relatively low, and specificity is high**
- **At Weeks 24 and 32, sensitivity is substantially higher, consistent with the marked increase in PCR-negativity at those points, and specificity is only marginally reduced, v. Week 12**

**ROC Curve Analysis: Results (cont'd)**  
**HBeAg-Positive Patients Treated with Telbivudine**

- **Based on a logistic regression model of baseline characteristics, baseline HBV DNA level (<9 log<sub>10</sub> copies/mL) was the strongest predictor of undetectable HBV DNA by Week 24**

## **ROC Curve Analysis: Results**

### **HBeAg-Negative Patients Treated with Telbivudine**

- **Similar to the trend for HBeAg-positive patients, sensitivity increases and specificity decreases at the later time points, Weeks 24 and 32, consistent with the marked increase in PCR-negativity at those points**

## ROC Curve Analysis: Results (cont'd) HBeAg-Negative Patients Treated with Telbivudine

- Consistent with the results in HBeAg-positive patients, the Youden index,  $J$ , increases consistently across all outcomes from Week 4 through Week 24, while the threshold at which the maximal distance is achieved decreases
- Beyond Week 24, the Youden index,  $J$ , decreases for prediction of HBV DNA undetectability and lack of resistance emergence at Week 104, while the threshold at which the Youden index is calculated increases from Week 24 for both parameters

**ROC Curve Analysis: Results (cont'd)**  
**HBeAg-Negative Patients Treated with Telbivudine**

- **The only baseline characteristic associated with the probability of achieving undetectable HBV DNA by Week 24 was baseline serum DNA level (<7 log<sub>10</sub> copies/mL)**

## **Outcomes at Week 104 of Patients Reaching Serum HBV DNA Undetectable by Week 12, 24, or 32**

- **Week 24 serum HBV DNA levels ensure a higher predictability of favorable clinical outcomes than earlier time points for both HBeAg-positive and HBeAg-negative patients**
  - **although time points up to Week 12 have a high PPV (ie, patients with an early virologic response have a high probability of achieving favorable outcomes by Week 104), they also have a poor NPV (ie, patients without an early virologic response do not have a high probability of treatment failure by Week 104)**
- **Patients who do not achieve serum HBV DNA undetectable until Week 32 have outcomes less optimal than those reaching this endpoint at Week 24, and are at greater risk of developing resistance (data not shown)**

# Methods

## ROC Curves Analysis

- Two methods commonly used for establishing the “optimal” cut-point are the point on the ROC curve closest to (0,1) and the Youden index,  $J$
- Receiver Operating Characteristic (ROC) curves for HBV DNA viral load at 4, 8, 12, 24, and 32 weeks of therapy