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Baseline Genotype And HBsAg Were Found To Have Significant Association With HBeAg Seroconversion Following Up To 4 Years Of Tenofovir Disoproxil Fumarate Treatment

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Background

- Tenofovir disoproxil fumarate (TDF) was approved for chronic hepatitis B (CHB) in 2008
- TDF patients treated for 192 weeks maintained undetectable HBV DNA, normal ALT levels and experienced increasing HBeAg and HBsAg loss
  - 68% (TDF-TDF) and 72% (ADV-TDF) of HBeAg (+) patients with HBV DNA <400 copies/mL (ITT analysis)
  - ~80% of all patients with normal ALT
  - 41% of HBeAg (+) patients on TDF with HBeAg loss and 29% with HBeAg seroconversion
  - 10.8% HBeAg (+) patients on TDF with HBsAg loss

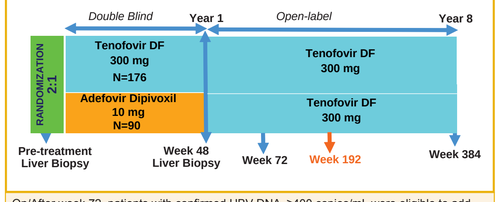
Objective

- To identify the baseline characteristics associated with HBeAg seroconversion for HBeAg (+) patients who have been treated with TDF for up to 4 years

Methods

- Patients with HBeAg (+) CHB were randomized to double-blind, once daily TDF 300 mg or adefovir dipivoxil 10 mg (ADV). After Week 48, eligible patients initiated open-label TDF for 7 additional years
- Based on the study protocol, patients with HBeAg seroconversion continued on treatment unless reaching either HBsAg loss or HBsAg seroconversion
- A multivariate stepwise logistic regression analysis was performed to screen for baseline factors associated with HBeAg seroconversion
  - A p-value of 0.1 was used for entry and remaining in the screening model
  - Significance level of 0.05 was used for the final model
- The Markov 2-State Model (considering a stochastic process as opposed to one time event) reflects HBeAg seroconversion as a non-permanent event allowing the estimate to account for obseved reversibility of HBeAg status

Figure 1. Study Design of Phase 3 Pivotal Study 103 HBeAg+



On/After week 72, patients with confirmed HBV DNA ≥400 copies/mL were eligible to add emtricitabine (FTC) in a fixed dose combination tablet (FTC/TDF)

Results

Table 1. Baseline Characteristics

	HBeAg seroconversion (N=104)	No HBeAg seroconversion (N=155)
Race – n (%) Asian Non-Asian	 28 (27%) 76 (73%)	 62 (40%) 93 (60%)
Gender (M) – n (%)	73 (70%)	108 (70%)
HBsAg – mean (SD) (log_{10} IU/mL)	4.38 (0.766)	4.54 (0.572)
HBV DNA –mean (SD) (log_{10} copies/mL)	8.59 (1.059)	8.87 (0.935)
Viral Genotype – n (%) A B C D	 38 (37%) 8 (8%) 22 (21%) 28 (27%)	 20 (13%) 24 (15%) 44 (28%) 57 (37%)
Mean ALT U/L (SD)	159.5 (112..2)	138.2 (108.8)
ALT≥ 1ULN and ≤ 2xULN - n (%) ALT>2xULN and ≤ 5xULN ALT > 5xULN	13 (13%) 61 (59%) 26 (25%)	35 (23%) 97 (63%) 22 (14%)
Mean Knodell necroinflammatory score (SD)	8.8 (1.91)	7.9 (2.29)
Knodell necroinflammatory category – n (%) 0-1 2-4 5-9 10-14 Missing	 1 (1%) 0 67 (66%) 33 (33%) 3	 1 (1%) 12 (8%) 106 (70%) 33 (22%) 3
Mean Knodell fibrosis Score (SD)	2.5 (1.24)	2.2 (1.20)
Knodell fibrosis category – n (%) 1 3 4 Missing	 38 (38%) 37 (37%) 26 (26%) 3	 71 (47%) 56 (37%) 24 (16%) 4

Table 2. Parameters at the time of HBeAg seroconversion

	HBeAg seroconversion (N=104)
Mean Time to First HBeAg Seroconversion (SD) (Weeks)	68.8 (54.91)
Mean Decline in HBsAg (SD) (Log_{10} IU/mL)	-1.01 (1.526)
Mean Decline in HBV DNA (SD) (Log_{10} copies/mL)	-5.99 (1.315)
Mean Change in ALT (SD) (U/L)	-123.2 (112.20)

- Overall, 104 patients experienced at least one event of HBeAg seroconversion during the 192 weeks
  - 72 TDF-TDF and 32 ADV-TDF

Figure 2. Median Change From Baseline in HBsAg by Seroconversion to Anti-HBe

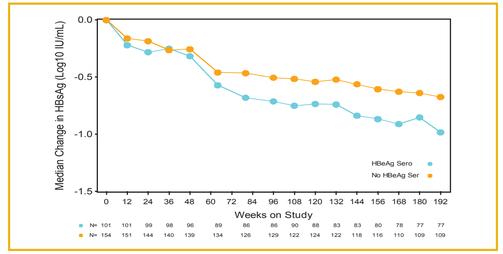


Figure 3. Median HBsAg by Genotype for Seroconverters to Anti-HBe

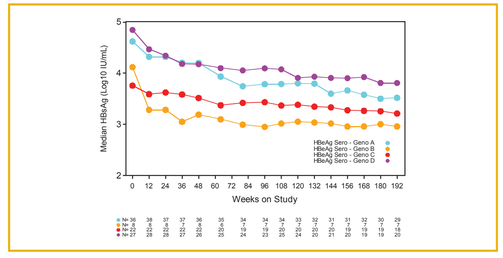


Figure 4. Median Change From Baseline in HBsAg for Genotype A & D Seroconverters vs Non-Seroconverters

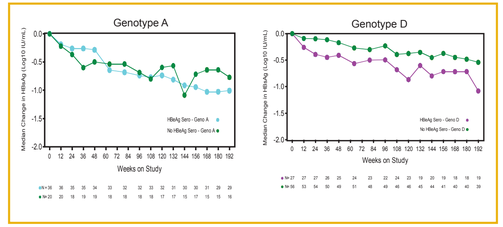


Figure 5. Median Change From Baseline in HBsAg for Genotype B & C Seroconverters vs Non-Seroconverters

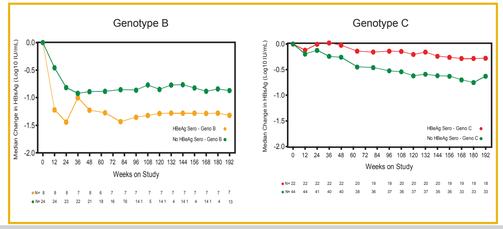


Figure 6. Median Change From Baseline in HBV DNA by Seroconversion to Anti-HBe and Treatment Arms

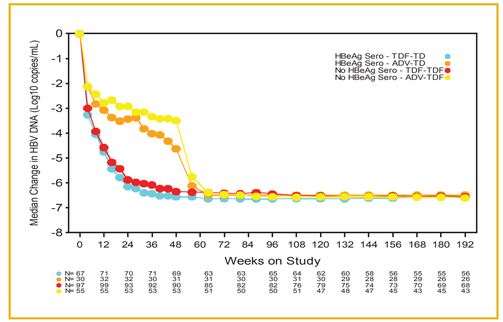


Figure 7. Median Change From Baseline in ALT by Seroconversion to Anti-HBe and Treatment Arms

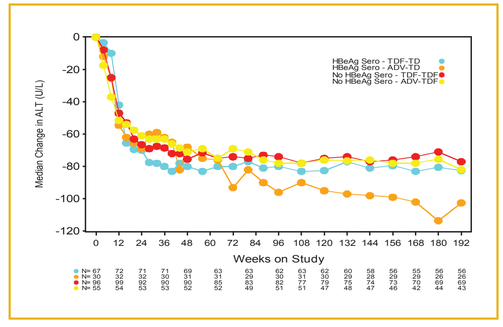


Table 3. Predictors of HBeAg Seroconversion Multivariate Model Results

In a multivariate stepwise model considering baseline factors only, the only characteristics remained in the model were:

Characteristic	Odds Ratio	95% CI for OR	P-value*
Genotype D vs A C vs A B vs A	 0.28 0.18 0.15	 (0.14, 1.45) (0.08, 1.54) (0.06, 1.66)	<0.001
HBsAg titer	0.52	(0.84, 0.32)	0.006

* The p-values are from the overall Type 3 model

- No association was found with other baseline characteristics including race, gender, HBV DNA levels, ALT levels and Knodell scores

Figure 8. Markov 2-state Estimates of Proportion of Patients with Seroconversion to Anti-HBe by Treatment Arms

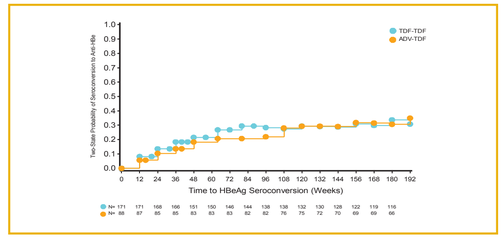
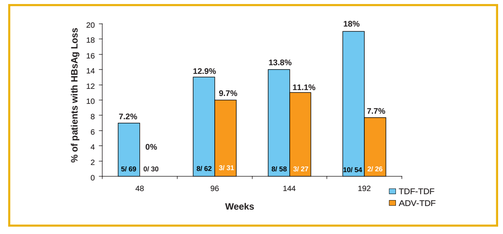


Figure 9. HBsAg Loss in Patients with HBeAg Seroconversion by Treatment Arms and Treatment Duration



Summary

- Overall, 104 HBeAg (+) patients from Study 103 experienced at least one event of HBeAg seroconversion during the 192 weeks
- Genotype A is associated with higher HBeAg seroconversion
- In the multivariate stepwise analysis, baseline genotype and HBsAg levels were associated with HBeAg seroconversion.
  - No association was found with other baseline characteristics including race, gender, HBV DNA levels, ALT levels and Knodell scores
- Proportion of HBeAg seroconverted patients with HBsAg loss increases over time

Conclusions

- **In Study 103, HBeAg seroconverison was found in all major genotypes**
- **In a multivariate model of baseline factors, only genotype and HBsAg levels were significantly predictive of HBeAg seroconversion**

Acknowledgements

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