

Safety and Efficacy of 96 Weeks of Tenofovir Disoproxil Fumarate Therapy in Lamivudine Experienced Patients

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Introduction

- Tenofovir DF (TDF) is a nucleotide analog and obligate chain terminator
- Approved for chronic hepatitis B (CHB) in 2008
- Week 48 Phase 3 data¹ showed that TDF had superior antiviral efficacy to adefovir dipivoxil (ADV) in studies 102 (HBeAg-negative patients) and 103 (HBeAg-positive patients):
 - 93% vs. 63% (HBeAg-negative) and 76% vs. 13% (HBeAg positive) with HBV DNA <400 copies/mL (<69 IU/mL) (ITT)
- Week 48 data² also showed a similar virologic response for TDF-treated patients with prior lamivudine-experience versus lamivudine-naïve patients:
 - 88% of lamivudine-experienced versus 86% of lamivudine naïve patients had HBV DNA <400 copies/mL (<69 IU/mL) (ITT)
- Week 96 antiviral efficacy data demonstrates durable and potent activity in both HBeAg-negative and HBeAg-positive patients:
 - 91% of HBeAg-negative³ and 78% of HBeAg-positive⁴ patients had HBV DNA <400 copies/mL (<69 IU/mL) (ITT)

Objective

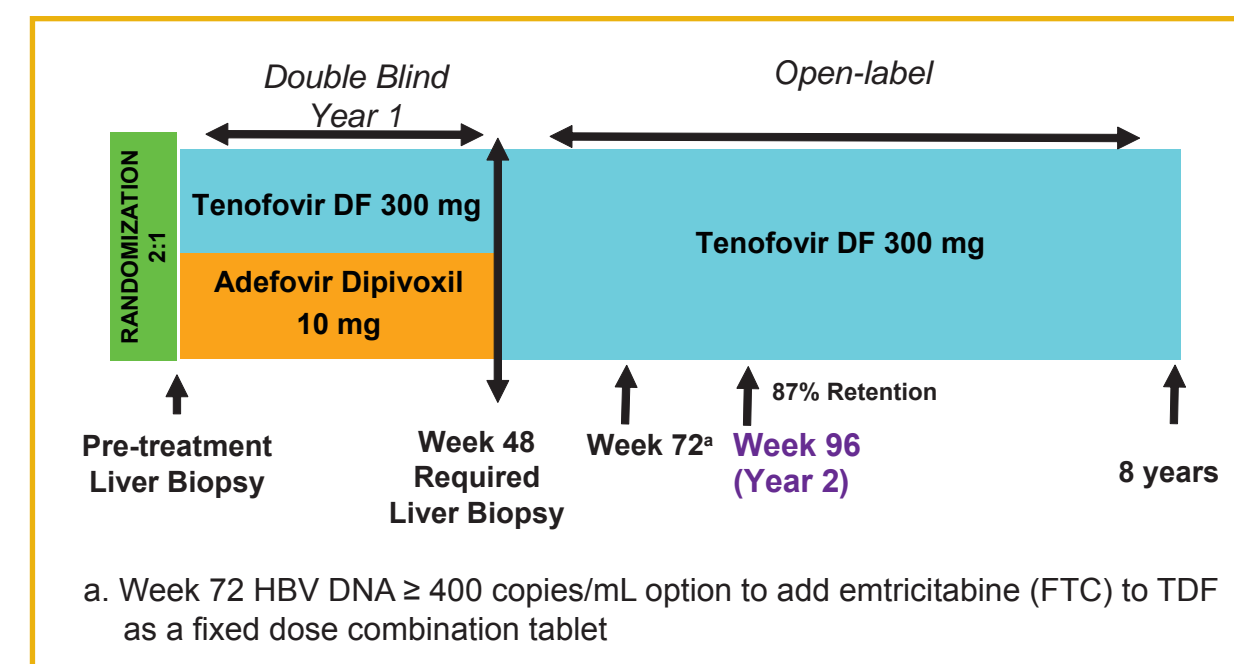
- To evaluate the response to 96 weeks (2 years) of TDF treatment in the subset of lamivudine-experienced compared to lamivudine-naïve patients with chronic hepatitis B enrolled in the phase 3 studies 102 and 103

Endpoints

- HBV DNA <400 copies/mL (<69 IU/mL) (tested at Week 96)
- HBV DNA over time
- ALT over time
- Safety and tolerability
- Resistance

Methods

Figure 1. Study Design of Phase 3 Pivotal Studies 102 and 103



Methods

Key eligibility criteria for Studies 102 (HBeAg-negative) and 103 (HBeAg-positive)

- Age 18-69 years
- Compensated liver disease
- HBV DNA > 10⁵ copies/mL^a (HBeAg-negative) or HBV DNA > 10⁶ copies/mL (HBeAg-positive)
- ALT > ULN < 10xULN (HBeAg-) or ALT > 2xULN < 10xULN (HBeAg+)
- Knodell necroinflammatory score ≥ 3
- HIV, HDV, HCV sero-negative

a. 5.82 IU/mL=1 copy/mL

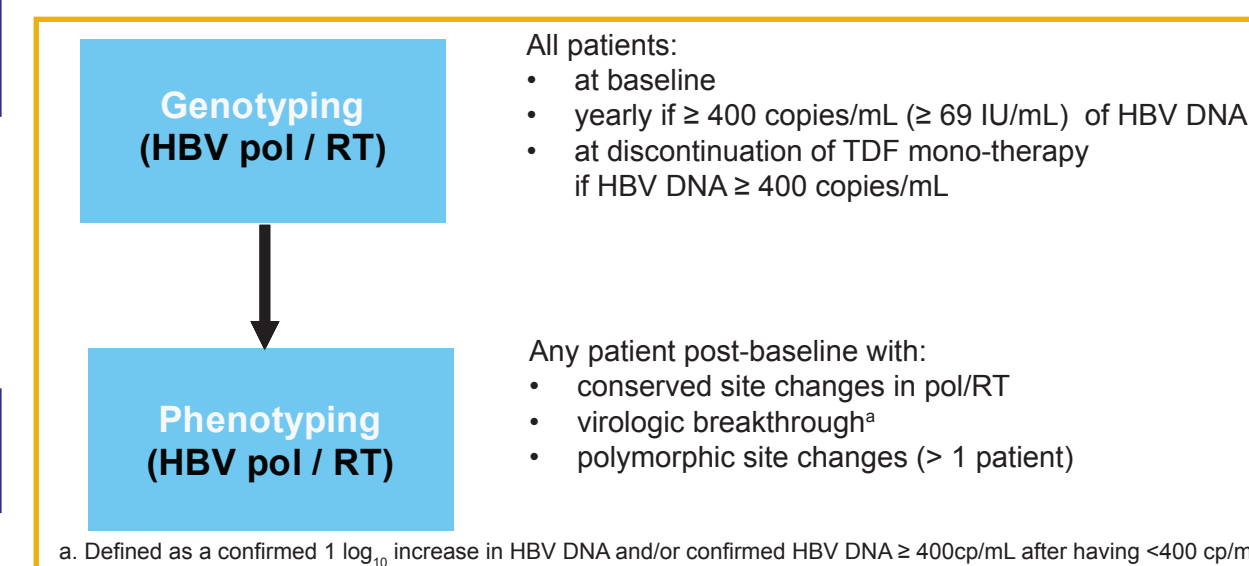
Monitoring During Year 1 & Year 2

- HBV DNA and laboratory analyses every 4 to 8 weeks
- HBeAg (HBeAg-patients only) and HBsAg every 12 to 16 weeks

Resistance surveillance

- Patients with HBV DNA ≥ 400 copies/mL (≥ 69 IU/mL)
- Population di-deoxy sequencing of serum HBV pol/RT
 - Covers AA 1-344 of pol/RT (AA 1-266 of HBsAg)
 - Able to detect AA substitutions present at ≥ 25% of viral quasi-species population
- Phenotypic analyses were conducted in HepG2 cells transiently transfected with a pool of recombinant HBV plasmid DNA derived from patient serum HBV

Figure 2. Virology Analysis Plan for Studies 102 and 103



Results

Table 1. TDF Enrollment: by Study & Prior LAM Experience

	Study 103 HBeAg Positive N=176	Study 102 HBeAg Negative N=250	Total
LAM-Naive, n	168	207	375
LAM-Experienced ^a , n	8	43	51

a. LAM-experienced includes patients with >12 weeks of either lamivudine (N=49) or emtricitabine (N=2) experience

- Study 102 actively enrolled both LAM-experienced and LAM-naïve patients
- Study 103 enrolled 8 LAM-experienced patients despite LAM-naïve inclusion criteria

Results (cont'd)

Table 2. Baseline Demographic and Disease Characteristics

Characteristic	LAM-Naive (N=375)	LAM-Experienced (N=51)
Mean Age (years)	39	45
Race		
Caucasian	57%	78%
Asian	32%	16%
Male	74%	71%
Mean HBV DNA (log ₁₀ c/mL)	7.65	7.2
Mean ALT (U/L)	133.5	134.7
Mean duration (weeks) of prior LAM experience (min, max)	NA	95.9 (13, 264)
Mean duration (weeks) off LAM prior to study (min, max)	NA	115.5 (17, 251)
LAM-resistance mutations (population sequencing)	0	10%
Mean Knodell Necroinflammatory Score	8.0	8.3
Mean Knodell Fibrosis Score	2.3	2.6
Viral Genotype		
A	16%	20%
B	12%	2%
C	18%	11%
D	49%	63%

Figure 3. HBV DNA < 400 copies/mL (ITT Analysis)

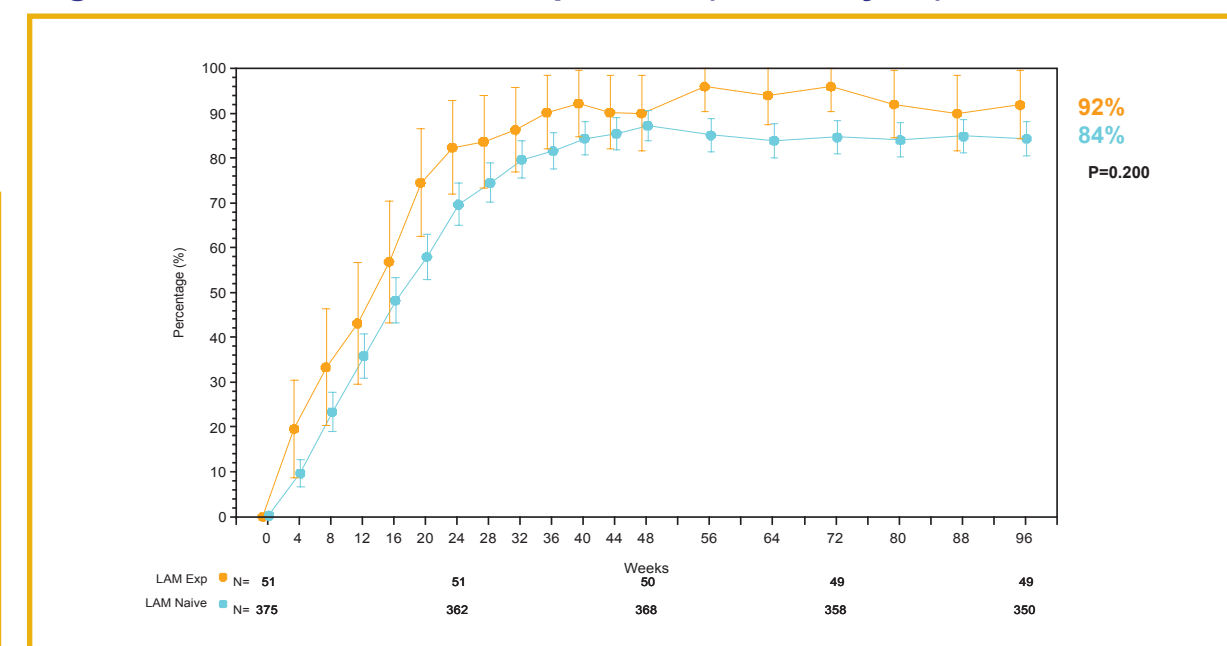


Figure 4. HBV DNA < 400 copies/mL (On-Treatment Analysis)

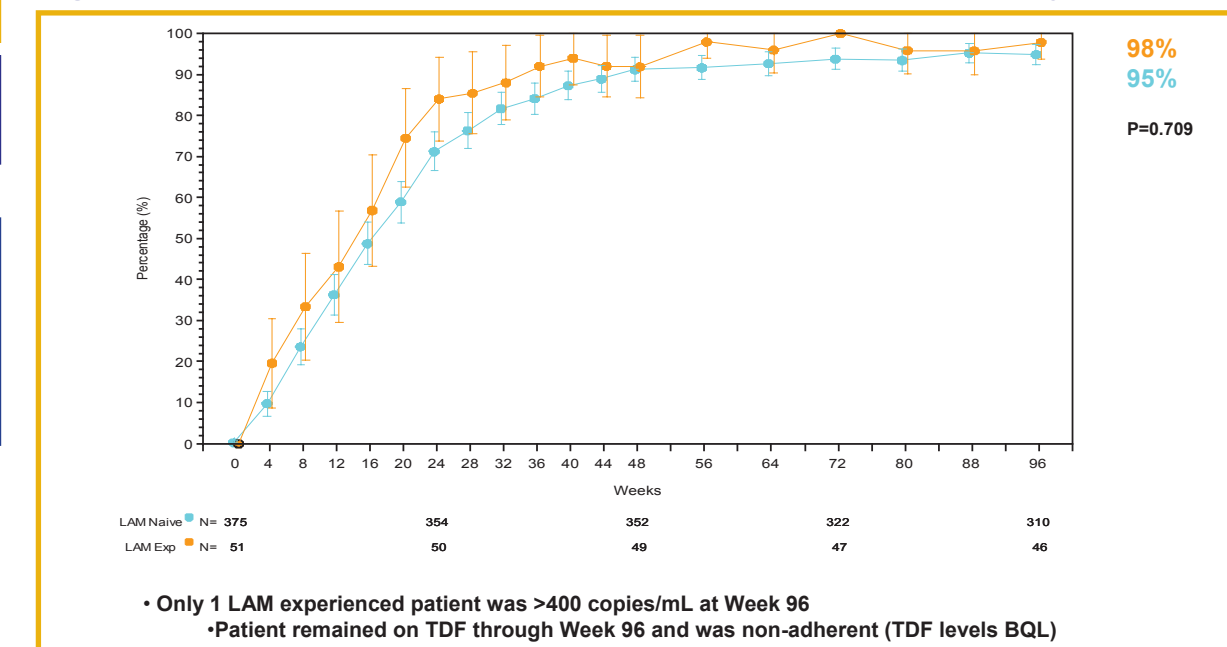


Figure 5. Mean HBV DNA (log₁₀ copies/mL)

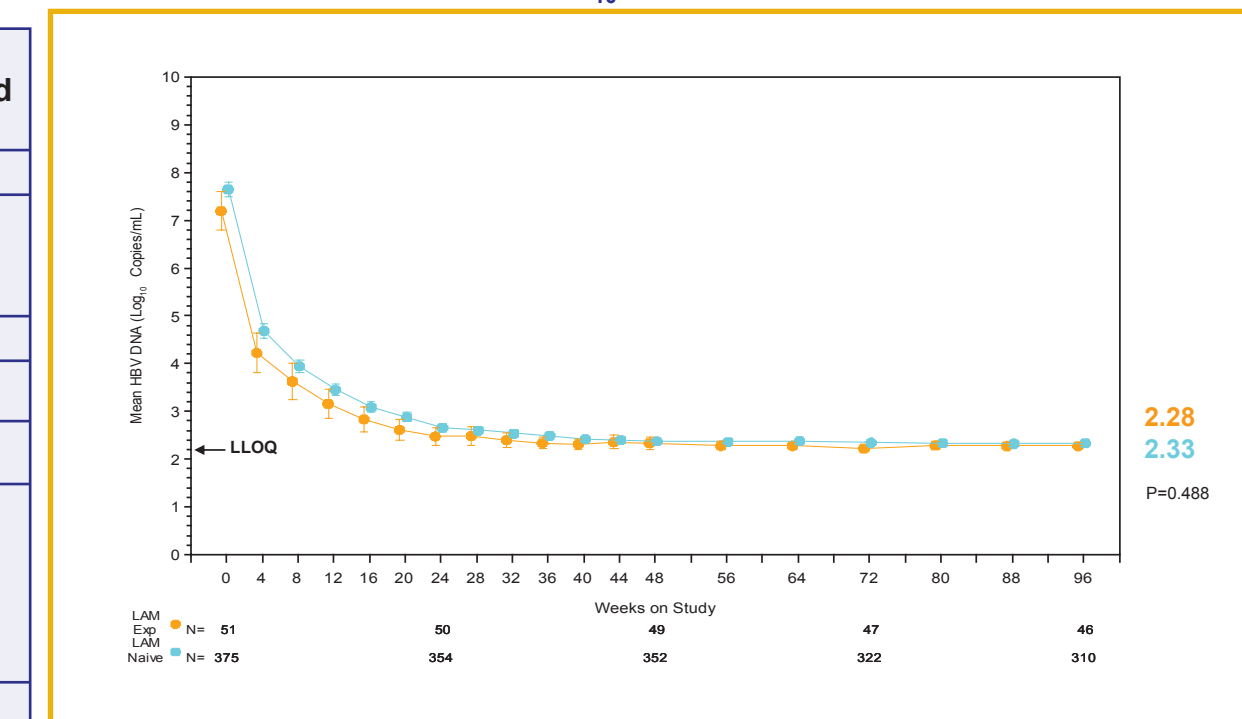
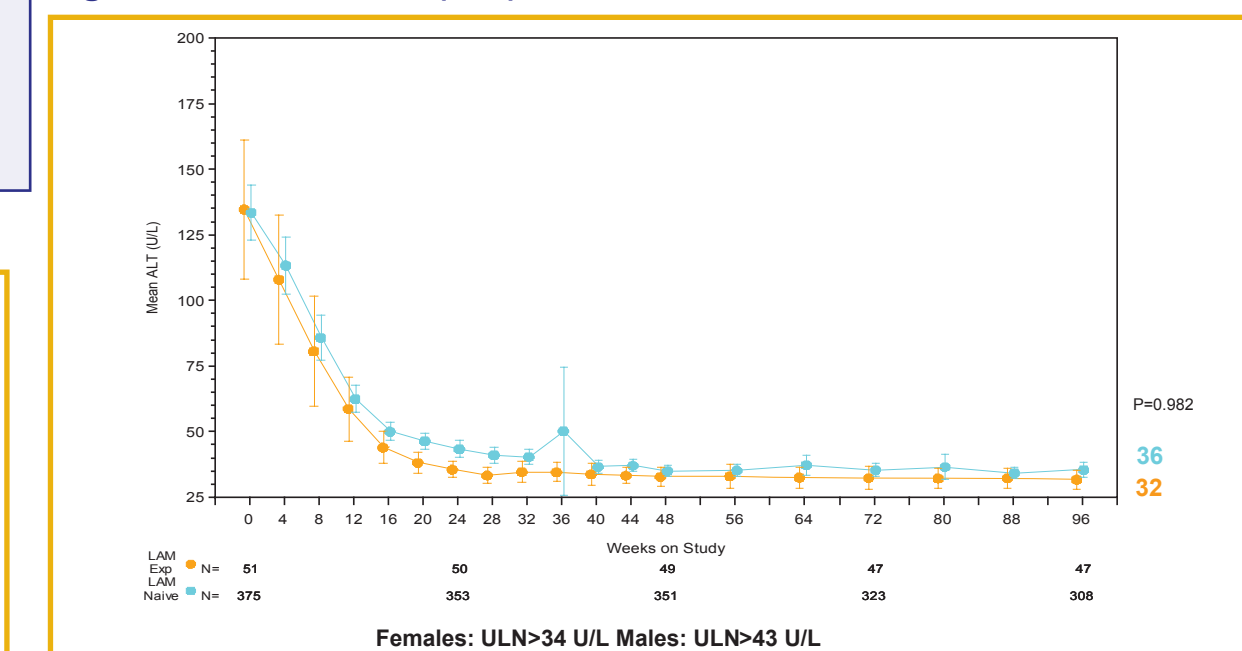


Figure 6. Mean ALT (U/L)



Resistance Surveillance Results

No HBV pol/RT amino acid substitutions associated with TDF resistance were detected through 96 weeks of TDF monotherapy in either LAM-experienced or LAM-naïve patients⁵

Table 3. Cumulative Safety by Prior LAM Experience: 96 Weeks of TDF Treatment

	LAM-Naive (N=375)	LAM-Experienced (N=51)
Serious AE, n (%)	34 (9.1%)	8 (15.7%)
Serious AE considered related to TDF, n (%)	7 (1.9%)	2 (3.9%)
Grade 3 or 4 AE, n (%)	47 (12.5%)	8 (15.7%)
Grade 3 or 4 AE considered related to TDF, n (%)	4 (1.1%)	1 (2.0%)
Grade 3 or 4 laboratory abnormality, n (%)	90 (24%)	13 (25.5%)
Discontinuation due to AE, n (%)	8 (2.1%)	0
Confirmed phosphorus < 2mg/dL, n (%)	6 (1.6%)	1 (2.0%)
Confirmed 0.5 mg/dL ↑ in creatinine, n (%)	0	0
Confirmed creatinine clearance < 50 mL/min, n (%)	0	0

Conclusions

- TDF demonstrated potent and durable antiviral efficacy in both LAM-experienced and LAM-naïve patients
 - 92% of LAM-experienced patients treated for 96 weeks had HBV DNA <400 copies/mL (ITT)
- TDF was well tolerated up to 96 weeks in both LAM-experienced and LAM-naïve patients
- No HBV pol/RT amino acid substitutions associated with TDF resistance were detected through 96 weeks of TDF monotherapy in either LAM-experienced or LAM-naïve patients

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