Poster Number

481

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Three Years of Tenofovir Disoproxil Fumarate (TDF) Treatment in HBeAg-Negative Patients with Chronic Hepatitis B (Study 102)

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Background

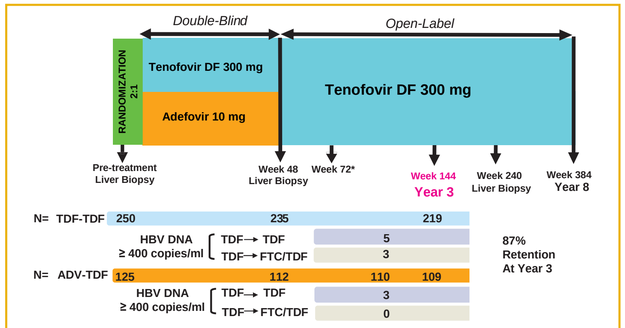
- Tenofovir DF (TDF) was approved for HIV-1 in 2001 and chronic hepatitis B (CHB) in 2008 : ~ 2.4 million patient-years of experience
- Week 48 Phase 3 data showed TDF superior to adefovir dipivoxil (ADV):
  - 93% of HBeAg-negative TDF-treated patients (versus 63% of ADV-treated patients) had HBV DNA < 400 copies/mL
- Week 96 Open-Label TDF data showed:
  - Both stable and viremic patients on ADV can effectively switch to TDF and achieve or maintain viral suppression (HBV DNA < 400 copies/mL) and normal ALT levels
  - Patients treated with TDF for 96 weeks maintained viral suppression and normal ALT levels

Objective

- Evaluate the efficacy and safety of up to 3 years of TDF therapy

Methods

Figure 1. HBeAg-Negative Study 102 Design



* Patients had the option to add FTC at the discretion of the investigator if confirmed HBV DNA ≥400 copies/ml at week 72 or beyond

Key Eligibility Criteria

- HBeAg- patients
- Age 18-69 years
- Compensated liver disease
- Lamivudine experienced or naive
- HBV DNA > 10^5 copies/mL
- ALT>ULN and <10 x ULN (females ULN=34 U/L; males ULN=43 U/L)
- Knodell necroinflammatory score ≥ 3
- HIV-1, HDV, HCV seronegative

Assessments During Year 3

- HBV DNA and laboratory analyses every 12 weeks
- HBsAg every 12 weeks
- Resistance surveillance: patients with HBV DNA ≥ 400 copies/mL (69 IU/mL)

Methods (Cont'd)

Statistical Methods

Long-Term Evaluation, TDF only analysis [LTE-TDF]

- Patients discontinuing the study early and missing data due to death; safety, tolerability, or efficacy; loss to follow-up; or for any other reason who were failures for the endpoint or had an ongoing AE at the last on-study visit were considered failures.
- Patients missing data at random or who discontinued for administrative reasons with HBV DNA <400 copies/mL with no ongoing AEs were excluded for visits after discontinuation.
- Patients with HBsAg loss who discontinued the study for any reason and met the endpoint criteria at the last on-study visit had the last value carried forward (LOCF) and were included in the analysis as a success.
- Patients who added emtricitabine were considered failures at all time points following the addition of emtricitabine

Open-Label Extension, TDF only analysis [OLE-TDF]

- Includes only those patients who entered the open label extension
- Employs an intent-to-treat missing=failure approach
- Patients who added emtricitabine were considered failures at all time points following the addition of emtricitabine

On-Treatment Analysis [observed data, missing=excluded]

- Excludes patients with missing data from both the numerator and denominator at each applicable time point for the analyses of HBV DNA, ALT, and HBeAg loss and seroconversion

Results

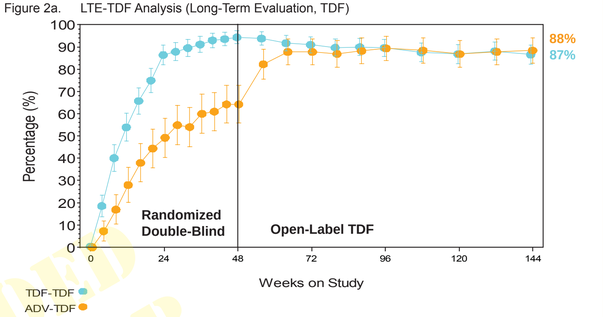
Table 1. Baseline Characteristics of Patients Entering Year 3 Similar to Patients Randomized

	Randomized Treatment		Patients Entering Year 3	
	TDF (N=250)	ADV (N=125)	TDF-TDF (N=223)	ADV-TDF (N=110)
Mean Age (years)	44	43	45	44
Race				
Caucasian	64%	65%	66%	67%
Asian	25%	24%	24%	23%
Male	77%	78%	80%	77%
Prior lamivudine experience	17%	18%	18%	20%
Mean HBV DNA (log_{10} copies/mL)	6.86	6.98	6.83	6.99
Mean ALT (U/L)	128	164	130	171
Mean Knodell necroinflammatory score	7.8	7.9	7.8	7.9
Mean Knodell fibrosis score	2.3	2.4	2.4	2.4
Knodell fibrosis score = 4 (cirrhosis)	19%	20%	20%	18%
Viral Genotype				
A	12%	12%	13%	12%
B	9%	14%	9%	14%
C	12%	10%	11%	9%
D	64%	62%	65%	63%

Results (Cont'd)

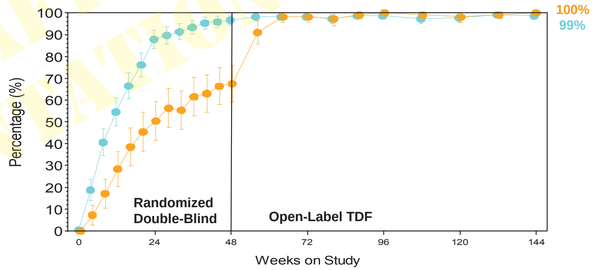
Figure 2. HBV DNA remains Suppressed with up to 3 Years of TDF Treatment (% Patients with HBV DNA <400 copies/mL)

Figure 2a. LTE-TDF Analysis (Long-Term Evaluation, TDF)



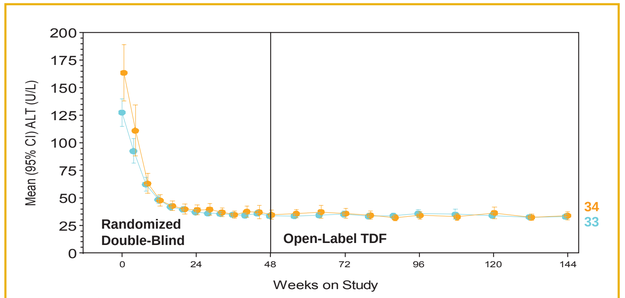
- OLE-TDF Analysis: % Patients with HBV DNA ≤400 copies/mL was 88% TDF-TDF and 96% ADV-TDF

Figure 2b. On-Treatment Analysis



- Illustration includes 3 patients who had HBV DNA <400 copies/mL at week 144 on FTC + TDF

Figure 3. Mean ALT (U/L) Over Time



Percent of Patients with Normalized ALT On-Treatment: 83% TDF-TDF; 77% ADV-TDF

Surveillance for Resistance

- Overall HBV DNA from 4 viremic patients were genotypically evaluated and no patient had amino acid substitutions in a conserved site region
- Therefore, no HBV pol/RT amino acid substitutions associated with TDF resistance were detected through 144 weeks of TDF

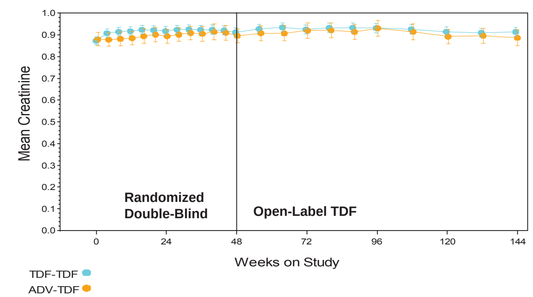
For complete details see Poster # 480 by Snow-Lampart et al. Resistance Surveillance for up to 144 Weeks in HBeAg+ and HBeAg- Hepatitis B Patients Treated with Tenofovir DF Showed No Relationship Between Virologic Breakthrough and Emergence of Genotypic Changes in HBV Polymerase

Table 2. Summary of Cumulative Open Label Safety Data through Week 144

	TDF-TDF (N=235)[a]	ADV-TDF (N=112)[a]
Study Drug-Related SAE	1 (<1%)	0
Deaths	2 (<1%)	1 (<1%)
metastatic liver carcinoma	1 (<1%)	0
cervical cancer metastases	0	1(<1%)
nasopharyngeal carcinoma	1 (<1%)	0
Grade 3 or Grade 4 Laboratory Abnormality	32 (14%)	17 (15%)
Discontinue due to an AE	3 (1.3%)	0
HCC	1	0
dizziness, fatigue, lack of concentration	1	0
septic shock	1	0
Confirmed phosphorus < 2mg/dL	2 (<1%)	1 (<1%)
Confirmed 0.5 mg/dL increase from baseline in creatinine	0	0
Confirmed creatinine clearance < 50 mL/min	0	0

a. N's reflect the number of patients who entered the open label extension

Figure 4. Creatinine Over Time



HBsAg Serology Results

- As of week 144 no patient has lost HBsAg

Conclusions

At Year 3, 87% of patients remained on treatment demonstrating

- **durable and potent antiviral activity, i.e., 99% of patients had HBV DNA <400 copies/mL**
- **no resistance to TDF**
- **a favorable tolerability profile**

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