Poster Number

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Continued Efficacy and Safety Through 4 Years of Tenofovir Disoproxil Fumarate (TDF) Treatment in HBeAg-Negative Patients with Chronic Hepatitis B (Study 102)

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Introduction

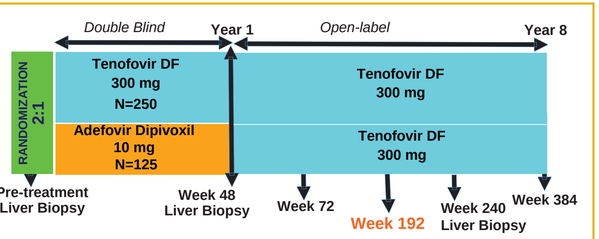
- Tenofovir DF (TDF) approved for HIV-1 in 2001 and chronic hepatitis B (CHB) in 2008: ~ 3.5 million patient-years
- Week 48 Phase 3 data showed a significantly greater antiviral activity of TDF compared to adefovir dipivoxil (ADV) in HBeAg-negative patients: 93% vs 63% HBV DNA <400 copies/mL
- TDF treatment in HBeAg-negative patients beyond Week 48 showed
  - Both viremic and nonviremic patients on ADV can effectively switch to TDF and achieve or maintain viral suppression (HBV DNA < 400 copies/mL) and normal ALT at week 144
  - TDF patients treated for 144 weeks maintained HBV DNA < 400 copies/mL and normal ALT levels

Objective

- Evaluate the efficacy and safety of up to 4 years of TDF therapy in HBeAg-negative patients

Methods

Figure 1. Study Design of Phase 3 Pivotal Study 102 HBeAg-Negative



- On/After week 72, patients with confirmed HBV DNA ≥400 copies/mL were eligible to add emtricitabine (FTC) in a fixed dose combination tablet
- Of the 12 patients who were eligible to add FTC 4 added and 8 did not; Of the 8 patients who remained on TDF 6 were <400 at week 192

Key Eligibility Criteria

- HBeAg-negative, lamivudine experienced or naïve patients with compensated liver disease
- HBV DNA > 10^5 copies/mL; ALT>ULN and <10 x ULN
- Knodell necroinflammatory score ≥ 3
- HIV-1, HDV, HCV seronegative

Assessments During Year 4

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

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 who added FTC were considered failures for all time points following FTC addition

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 FTC were considered failures for all time points following FTC addition

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 and ALT

Results

Figure 2. Patient Retention

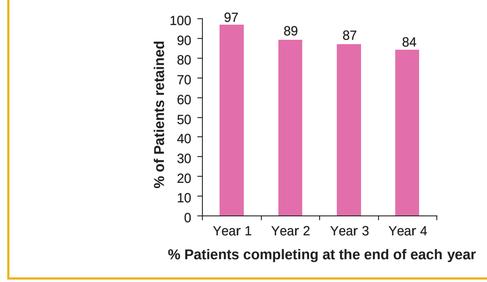
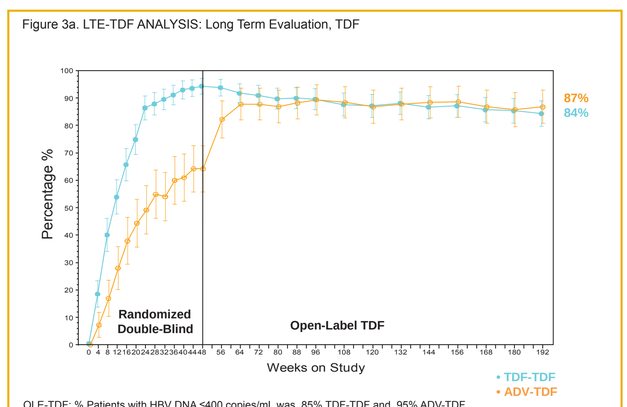


Table 1. Patients Entering Year 4 had Similar Baseline Characteristics to Patients Originally Randomized

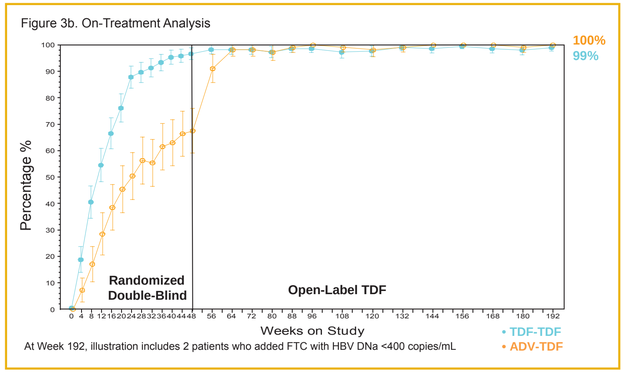
	Randomized Treatment		Patients Entering Year 4	
	TDF (N=250)	ADV (N=125)	TDF-TDF (N=218)	ADV-TDF (N=109)
Mean Age (years)	44	43	45	44
Race Caucasian Asian	 64% 25%	 65% 24%	 67% 24%	 67% 23%
Male	77%	78%	80%	78%
Prior lamivudine experience	17%	18%	18%	19%
Mean HBV DNA (log_{10} copies/mL)	6.86	6.98	6.86	7.00
Mean ALT (U/L)	128	164	131	171
Mean Knodell necroinflammatory score Mean Knodell fibrosis score	7.8 2.3	7.8 2.4	7.8 2.4	7.9 2.3
Knodell fibrosis score = 4 (cirrhosis)	19%	20%	20%	18%
Viral Genotype A B C D	 12% 9% 12% 64%	 11% 14% 10% 63%	 13% 9% 11% 64%	 12% 14% 9% 62%

FIgure 3. HBV DNA remains Suppressed with up to 4 Years of TDF Treatment (% Patients with HBV DNA <400 copies/mL)



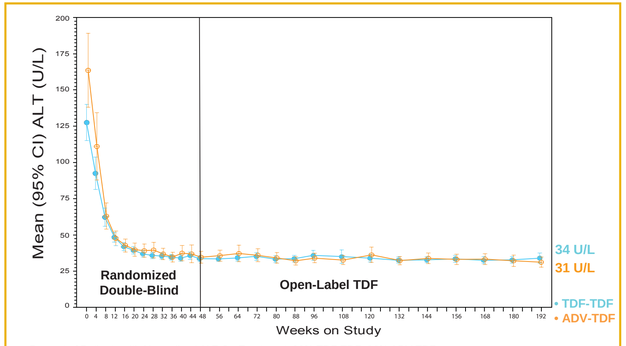
OLE-TDF: % Patients with HBV DNA ≤400 copies/mL was 85% TDF-TDF and 95% ADV-TDF

FIgure 3. HBV DNA remains Suppressed with up to 4 Years of TDF Treatment (% Patients with HBV DNA <400 copies/mL) (cont'd)



At Week 192, illustration includes 2 patients who added FTC with HBV DNa <400 copies/mL

Figure 4. Mean ALT (U/L) Over Time



Percent of Patients with Normalized ALT On-Treatment: 80% TDF-TDF; 86% ADV-TDF
ALT ULN=34 for females and ULN=43 for males

Table 2. Summary of Cumulative Open Label Safety Data from Week 48 to Week 192

	TDF-TDF (N=235)	ADV-TDF (N=112)
Study Drug-Related SAE	3 (1%)	0
Deaths	4 (2%)	1(<1%)
Cholangiocellular carcinoma	1	0
Cervical cancer metastases	0	1
Nasopharyngeal carcinoma	1	0
HCC	2	0
G3 or G4 Laboratory	35 (15%)	18 (16%)
Discontinued due to an AE	5 (2%)	0
HCC[a]	2	0
Dizziness, fatigue, lack of concentration	1	0
Septic Shock[a]	1	0
Abdominal pain	1	0

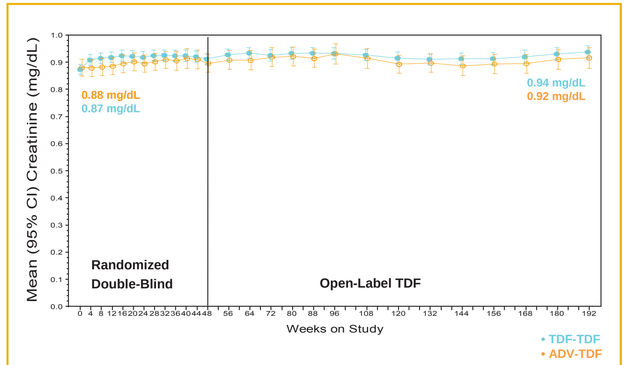
a Patients discontinued and then died of HCC (N=1) or Nasopharyngeal carcinoma (N=1) and are captured as deaths as well

Table 3. Summary of Cumulative Open Label Renal Safety Week 48 to Week 192

	TDF-TDF (N=235)	ADV-TDF (N=112)
Confirmed ↓ phosphorus < 2mg/dL	3 (1%)	2 (2%)
Confirmed ≥ 0.5 mg/dL ↑ creatinine	1 (1%)	1 (<1%)
Confirmed creatinine clearance < 50 mL/min	0	1 (<1%)

- Confirmed decreases in phosphorus were transient and resolved on treatment without intervention
- Confirmed increase in creatinine/decrease in creatinine clearance:
  - In TDF-TDF patient the creatinine increase was associated with advanced HCC/death
  - In ADV-TDF patient, increase at week 180 to peak of 1.3 mg/dL (and concurrent creatinine clearance of 48 mL/min) remains on study with a dose reduction to every other day

Figure 5. Serum Creatinine Over Time



Surveillance for Resistance: Year 4[a]

- HBV DNA from 4 viremic patients were genotypically evaluated and no patient had amino acid substitutions at a conserved site
- Therefore, no HBV pol/RT amino acid substitutions associated with tenofovir resistance were detected through 192 weeks of TDF

a. For complete details see Poster # 1365 by Snow-Lampart et al No Resistance to Tenofovir Disoproxil Fumarate (TDF) Detected Following up to 192 Weeks of Treatment in Subjects Mono-Infected with Chronic Hepatitis B Virus

Conclusions

With 84% retention at the end of Year 4 TDF demonstrated:

- **Potent antiviral activity with nearly 100% of patients on treatment at week 192 with HBV DNA <400 copies/mL**
- **No development of resistance up to Year 4**
- **Stable serum creatinine over time**
- **Good tolerability over time**

Acknowledgements

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