Poster Number

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Long Term (4 Year) Efficacy and Safety of Tenofovir Disoproxil Fumarate (TDF) Treatment in HBeAg-Positive Patients (HBeAg+) with Chronic Hepatitis B (Study 103)

E J Heathcote[1], E J Gane[2], R A de Man[3], S Chan[4], J George[5], N Tsai[6], P Marcellin[7], A Snow-Lampart[8], D H Coombs[8], E Mondou[8], J Anderson[8]

[1]University of Toronto, Toronto, ON, Canada; [2]Middlemore Hospital, Auckland, New Zealand; [3]Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands; [4]New York Hospital at Queens, Flushing, NY, USA; [5]Storr Liver Unit, Westmead Hospital and University of Sydney, Sydney, NSW, Australia; [6]University of Hawaii, Honolulu, HI, USA; [7]Hopital Beaujon, University of Paris, Clichy, France; [8]Gilead Sciences, Durham, NC, USA.

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Tel: (650)574-3000
Fax: (650)578-9264

Introduction

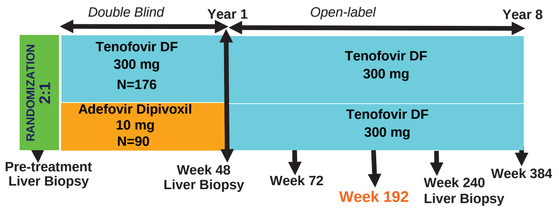
- Tenofovir DF (TDF) was approved for HIV-1 in 2001 and chronic hepatitis B (CHB) in 2008: ~ 3.5 million patient-years experience
- Week 48 Phase 3 data showed significantly greater antiviral activity of TDF compared to adefovir dipivoxil (ADV) in HBeAg+ patients: 76% vs 13%
- TDF treatment in HBeAg+ patients beyond Week 48 showed
  - Both nonviremic and viremic patients on ADV can effectively switch to TDF and achieve or maintain viral suppression (HBV DNA < 400 copies/mL), normal ALT and increasing HBeAg and HBsAg loss at Week 144
  - TDF patients treated for 144 weeks maintained HBV DNA < 400 copies/mL, normal ALT levels and experienced increasing HBeAg and HBsAg loss

Objective

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

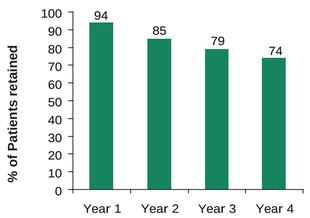
Methods

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 FTC in a fixed dose combination tablet
- 39 patients who were eligible to add FTC, 34 added and 5 did not

Figure 2. Patient Retention



% Patients completing at the end of each year

Key Eligibility Criteria

- HBeAg-positive, nucleos(t)ide naïve patients with compensated liver disease
- HBV DNA > 10^6 copies/mL; ALT>2xULN and <10xULN
- Knodell necroinflammatory score ≥ 3
- HIV-1, HDV, HCV seronegative

Assessments During Year 4

- HBV DNA, HBeAg, 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, ALT, and HBeAg loss and seroconversion

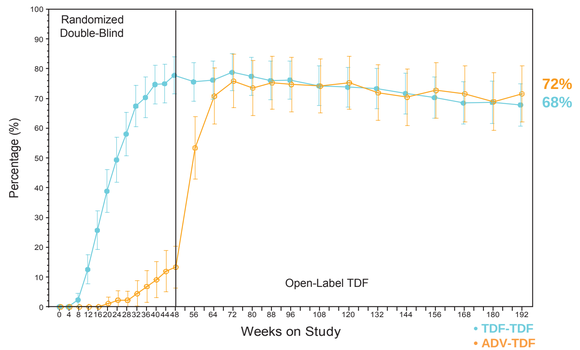
Results

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

	Randomized Treatment		Patients Entering Year 4	
	TDF (N=176)	ADV (N=90)	TDF-TDF (N=130)	ADV-TDF (N=71)
Mean Age (years)	34	34	35	34
Race Caucasian Asian	 52% 36%	 51% 36%	 53% 35%	 49% 39%
Male	68%	71%	73%	72%
Mean HBV DNA (log_{10} copies/mL)	8.64	8.88	8.62	8.75
Mean ALT (U/L)	142	155	138	168
Mean Knodell necroinflammatory score Mean Knodell fibrosis Score	8.3 2.3	8.5 2.5	8.2 2.3	8.5 2.6
Knodell fibrosis score = 4 (cirrhosis)	20%	21%	23%	22%
Viral Genotype A B C D	 24% 15% 25% 32%	 21% 11% 30% 35%	 26% 13% 25% 32%	 16% 9% 36% 35%

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

Figure 3a. LTE-TDF ANALYSIS: Long Term Evaluation, TDF



OLE-TDF: % Patients with HBV DNA ≤400 copies/mL was 71% TDF-TDF and 71% ADV-TDF

Figure 3b. On-Treatment Analysis

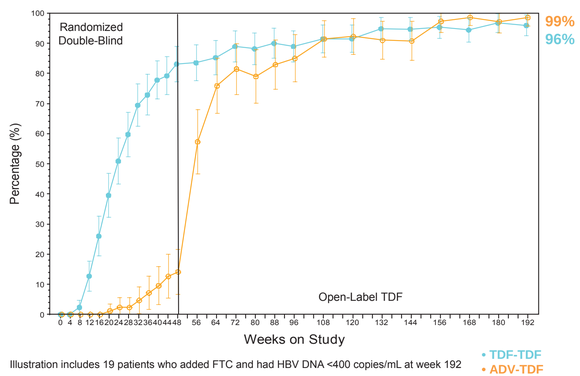


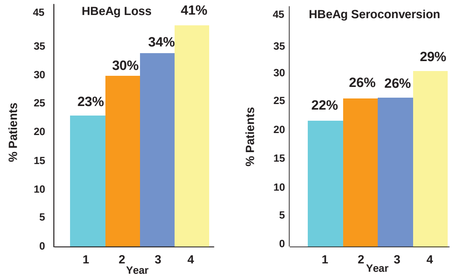
Illustration includes 19 patients who added FTC and had HBV DNA <400 copies/mL at week 192

Table 2. Week 192 Biochemical Response

	TDF-TDF	ADV-TDF
Mean ALT (U/L)	36.3	32.5
% Normalized[a] (on-treatment)	77%	80%

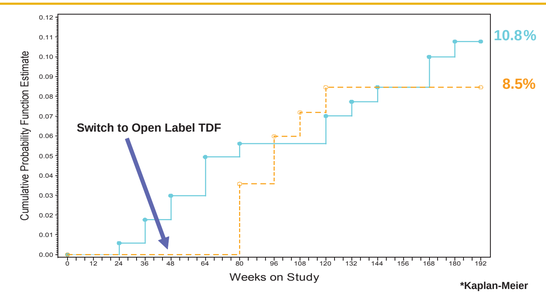
a. ALT ULN=34 for females and ULN=43 for males

Figure 4. % Patients with HBeAg Loss and Seroconversion (On-Treatment) TDF-TDF



48 of the 49 patients with HBeAg loss at week 192 were on TDF monotherapy

Figure 5. Cumulative Probability* of HBsAg Loss



*Kaplan-Meier
• TDF-TDF
• ADV-TDF

- Cumulative probability of seroconversion to anti-HBs: 7.7% TDF-TDF and 7.3% ADV-TDF
- 18/23 patients discontinued treatment for HBsAg loss; 3 patients regained HBsAg off treatment (1 patient was lost to follow up, 1 patient restarted therapy and subsequently lost HBsAg, and 1 patient remained off treatment based on HBsAg negative local laboratory results)

Table 3. Percentage of TDF-TDF Patients with HBsAg Loss

Key Characteristic	HBsAg Clearance by Year 4 n/N (%)
Genotype A or D	14/95 (15%)
HBV DNA ≥ 9 log_{10} copies/mL	12/75 (16%)
HBsAg ≥ 4.5 log_{10} IU/mL	14/90 (16%)
Knodell Necroinflammatory Score ≥ 9	13/114 (11%)

Table 4. Summary of Cumulative Open Label Safety Data Week 48 to Week 192

	TDF-TDF (N=154)	ADV-TDF (N=84)
Study Drug-Related SAE	2 (1%)	2 (2%)
Deaths	1 (<1%)	1 (<1%)
HCC	0	1
Lung cancer metastasis	1	0
Grade 3 or 4 Laboratory Abnormality	24 (16%)	14 (17%)
Discontinued due to an AE	2 (1%)[b]	0
Creatinine increased[a]	1	0
Osteoporosis[b]	1	0

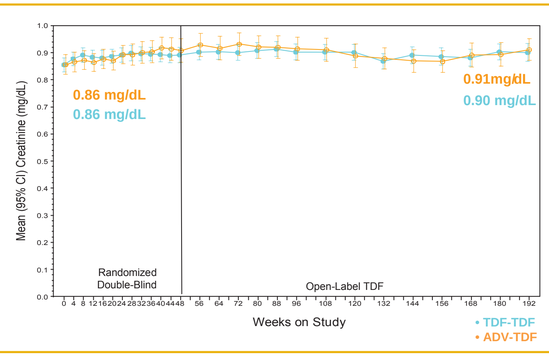
a. Unconfirmed increase in creatinine from 0.8 mg/dL to 1.3 mg/dL at Week 80 (nadir creatinine clearance 53 mL/min); increase resolved in 4 days on treatment (last available 1.1 mg/dL)
b. Osteoporosis diagnosed by DXA (no baseline DXA, no fracture)

Table 5. Summary of Cumulative Open Label Renal Safety Week 48 to Week 192

	TDF-TDF (N=154)	ADV-TDF (N=84)
Confirmed ↓ phosphorus < 2mg/dL	1 (<1%)	1 (1%)
Confirmed ≥0.5 mg/dL creatinine	1 (<1%)	2 (2%)
Confirmed creatinine clearance < 50 mL/min	0	0

- Decreases in phosphorus were transient and resolved on treatment without intervention
- Confirmed increase in creatinine:
  - TDF-TDF patient peak creatinine was 1.5 mg/dL at week 192; patient remains on treatment at full dose
  - ADV-TDF patients had an initial ≥0.5 mg/dL increase in creatinine on ADV that was confirmed after switching to TDF. One patient had an increase (grade 1) to a peak of 1.8 mg/dL (nadir creatinine clearance 44 mL/mIn); patient was dose adjusted and remains on treatment at week 192 (creatinine=1.3 mg/dL). The other patient had a peak creatinine of 1.7 mg/dL (grade 1), patient was dose reduced, and creatinine improved to 1.4 mg/dL at week 144/last available time point
  - One additional ADV-TDF patient who had a grade 1 creatinine on ADV had a transient grade 1 increase to 1.6 mg/dL at week 96 (0.1 increase from baseline). Patient remains stable and on study without interruption or modification

Figure 6. Serum Creatinine Over Time



Surveillance for Resistance: Year 4 Results[a]

- HBV DNA from 8 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 74% retention at the end of Year 4 TDF demonstrated:

- **Potent and durable antiviral activity with 99% and 96% patients on treatment at week 192 having HBV DNA <400 copies/mL**
- **41% HBeAg loss following 4 years of TDF treatment**
- **10.8% HBsAg loss following 4 years of TDF treatment**
- **No development of resistance up to year 4**
- **Stable serum creatinine over time**
- **Good tolerability over time**

Acknowledgements

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