Safety and Tolerability of 96 Weeks of Tenofovir Disoproxil Fumarate (TDF) Treatment in HBeAg Negative and Positive Patients Infected with Chronic Hepatitis B (CHB)

44th Annual Meeting of the
European Association for the Study of the Liver
April 22 - 26, 2009
Copenhagen, Denmark

P Marcellin[1], E J Heathcote[2], I Jacobson[3], P Mathurin[4], E Gane[5], P Buggisch[6], P Husa[7] Z Krastev[8], J Sorbel[9], J Anderson[9], E Mondou[9] and F Rousseau[9]

[1]University of Paris, Clichy France; [2]University of Toronto, Toronto ONT, Canada; [3]Weill Medical College of Cornell University, New York, NY; [4]Service d'Hepato-Gastroenterologie, Hopital Claude Huriez, CHRU Lille, Lille, France; [5]Middlemore Hospital, Auckland New Zealand; [6]Medizinische Universitatsklinik Eppendorf, Hamburg Germany; [7]University Hospital,BRNO, Czech Republic; [8]University Hospital "St Ivan Rilsky", Sofia, Bulgaria; [9]Gilead Sciences, Durham NC USA

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Tel: 1-800 -Gilead 5
Fax: (650)578-9264

Introduction

- Tenofovir DF (TDF) is a nucleotide analog and obligate chain terminator
- Approved for HIV-1 in 2001: ~ 2 million patient-years of experience
- Approved for chronic hepatitis B (CHB) in 2008
- TDF was well tolerated through 48 weeks of treatment in the Phase 3 CHB studies 102 and 103
- Week 48 Phase 3 data[1] showed that TDF had superior antiviral efficacy to adefovir dipivoxil (ADV) in the pivotal studies 102 and 103:
  - 93% vs 63% (HBeAg-negative) and 76% vs 13% (HBeAg-positive) patients achieved HBV DNA <400 copies/mL (69 IU/mL) (ITT)
- TDF continues to demonstrate durable, potent antiviral efficacy at Week 96[2,3]:
  - 91% of HBeAg-negative patients and 78% of HBeAg-positive patients had HBV DNA <400 copies/mL (ITT)

Objective

To evaluate the overall safety of 96 weeks (2 years) of treatment with TDF in both HBeAg-positive and HBeAg-negative patients enrolled in the phase 3, pivotal studies 102 and 103

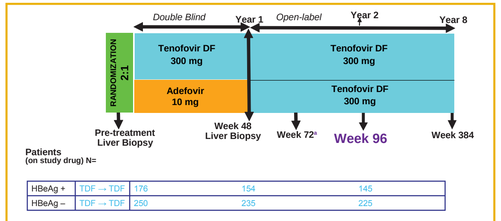
Safety Endpoints

Safety and tolerability

- Deaths
- Serious Adverse Events (SAEs)
- Grade 3 or 4 Adverse Events (AEs)
- Related SAEs and Grade 3 or 4 AEs
- (AEs) leading to study drug discontinuation
- Grade 3 or 4 laboratory abnormalities
- Renal tolerability (confirmed increase ≥ 0.5 mg/dL in creatinine; creatinine clearance <50 ml/min; phosphorus < 2mg/dL)
- Resistance Mutations

Methods

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



a. Week 72 HBV DNA ≥ 400 copies/mL option to add emtricitabine (FTC) to TDF in a fixed dose tablet

Safety monitoring:

- Patient visits every 4 to 8 weeks
- Monitored for SAEs and AEs
- Standard laboratory tests, e.g., liver function tests, serum chemistries and hematology
- Resistance

Results

Table 1. Overall Summary of TDF Safety

Adverse Event Category or Death, n (%)	Year 1: Double Blind TDF (N=426)	Year 2: Open Label TDF (N=389)
Any Serious AE	27 (6.3%)	17 (4.4%)
Any Grade 3 or 4 AE	37 (8.7%)	21 (5.4%)
Any Grade 2, 3, 4 AE	128 (30.0%)	94 (24.2%)
AEs considered related to study drug:		
Any Serious AE	7 (1.6%)	2 (0.5%)
Any Grade 3 or 4 AE	5 (1.2%)	0
Any Grade 2, 3, 4 AE	23 (5.4%)	5 (1.3%)
AEs resulting in study drug discontinuation	5 (1.2%)	3 (0.8%)
Deaths[a]	0	1 (0.3%)

a. Cholangiocellular carcinoma

Results (cont'd)

Table 2. AEs Resulting in Permanent Discontinuation of TDF

AEs, n (%)	Considered Related to TDF (Yes/No)	Year 1: Double Blind TDF (N=426)	Year 2: Open Label TDF (N=389)
Any AE resulting in study drug discontinuation		5 (1.2%)	3 (0.8%)
Bladder Neoplasm	No	1 (0.2%)	0
Cervix Carcinoma	No	1 (0.2%)	0
Fatigue	Yes	1 (0.2%)	0
Feeling hot	Yes	1 (0.2%)	0
Anorexia	Yes	1 (0.2%)	0
Hepatocellular Carcinoma	No	0	1 (0.3%)
Creatinine[a] Increased	Yes	0	1 (0.3%)
Disturbance in attention, fatigue, and dizziness	Yes	0	1 (0.3%)

a. Patient did not have a confirmed 0.5 mg/dL increase in creatinine or confirmed creatinine clearance <50 mL/min.

Table 3. Treatment Emergent Grade 3 or 4 Clinical AEs

Grade 3 or 4 AE[a], n (%)	Year 1: Double Blind TDF (N=426)	Year 2: Open Label TDF (N=389)
Hepatocellular Carcinoma	3 (0.7%)	1 (0.3%)
Abdominal Pain/ Abdominal Pain Upper	2 (0.5%)	1 (0.3%)
Angina Pectoris	0	2 (0.5%)
Back Pain	0	2 (0.5%)
Transient Ischaemic Attack	0	2 (0.5%)

a. Clinical AEs occurring in more than 1 patient in either Year 1 or Year 2

- No Grade 3 or 4 Clinical AE was considered related to TDF

Table 4. Treatment Emergent SAEs Considered Related to TDF

SAE, n (%)	Year 1: Double Blind TDF (N=426)	Year 2: Open Label TDF (N=389)
Any study drug related SAE	7 (1.6%)	2 (0.5%)
ALT Flare[a]	6 (1.2%)	0
Thrombocytopenia	1 (0.2%)	0
Facial Spasm	0	1 (0.3%)
Renal Impairment[b]	0	1 (0.3%)

a. Per protocol, on-treatment ALT flares were considered SAEs (ALT >2 x baseline and >10 x ULN); events were transient, occurred within 4-8 weeks of initiating therapy, no evidence of decompensation and associated with profound and continued decreases in HBV DNA
b. Patient did not have a confirmed 0.5 mg/dL increase in creatinine or confirmed creatinine clearance <50 mL/min.

Table 5. Treatment Emergent Grade 3 or 4 Laboratory Abnormalities

Laboratory Parameter with a Grade 3 or 4 (occurring in >1 patient in either Year 1 or Year 2)	Year 1: Double Blind TDF (N=426)	Year 2: Open Label TDF (N=389)
Any Grade 3 or 4 laboratory abnormality	19%	8.7%
ALT[a]	10.1%	0.8%
AST	4.2%	1.0%
Amylase	3.8%	1.5%
Urine Glucose[b]	2.6%	2.8%
Creatine Kinase	1.9%	1.0%
Hyperglycemia	1.2%	0.5%
Lipase	0.9%	0.8%
Phosphorus	0.7%	0
Total Bilirubin	0.7%	0.3%
Neutrophils	0.5%	0.3%
Prothrombin Time	0.5%	1.8%

a. A total of 11 patients experienced on-treatment ALT flares during Year 1 and 1 patient during Year 2. Five of the 8 HBeAg-positive patients with an ALT flare also experienced HBeAg seroconversion. Year 2 ALT flare associated with an increase in HBV DNA and was thought to be related to non-compliance.
b. Over the 2 year period a total of 18 patients had a Grade 3 or 4 urine glucose; 12/18 were diabetics; 18/18 patients had ≥Grade 2 elevations of serum glucose on study

Table 6. Renal Laboratory Parameters

Confirmed[a] Creatinine or Phosphorus, n (%)	Year 1: Double Blind TDF (N=426)	Year 2: Open Label TDF (N=389)
Serum Creatinine Confirmed increase from baseline of ≥ 0.5 mg/dL	0	0
Serum Phosphorus Confirmed decrease to <2mg/dL	1.4%	0.5%
Creatinine Clearance Confirmed decrease to <50mL/min	0	0

a. defined as two consecutive visits

- None of the patients with a confirmed decrease in phosphorus had a concurrent and/or clinically significant increase in creatinine or decrease in creatinine clearance.

Virologic Safety

- No HBV pol/RT amino acid substitutions associated with TDF resistance were detected through 96 weeks of TDF monotherapy in HBeAg-negative and HBeAg-positive patients

Conclusions

- **The safety and tolerability profile of tenofovir DF was good and did not show any new or unexpected adverse events in the HBV–infected population**
- **The renal safety of tenofovir DF was good and confirms the profile established in patients with HIV-infection**
- **The virologic safety profile of tenofovir DF remains excellent with 0% resistance at 2 years**

References

1. Marcellin P, Heathcote J, Buti M et al Tenofovir Disoproxil Fumarate versus Adefovir Dipivoxil for Chronic Hepatitis B. NEJM 2008, Vol 359, pg 2442-2455.
2. Marcellin P, Buti M, Krastev Z et al . Two Year Tenofovir Disoproxil Fumarate (TDF) Treatment and Adefovir Dipivoxil (ADV) Switch Data in HBeAg-Negative Patients with Chronic Hepatitis B (Study 102) presented at AASLD 2008 (#146).
3. Heathcote J, Gane E, DeMan R et al. Two Year Tenofovir Disoproxil Fumarate (TDF) Treatment and Adefovir Dipivoxil (ADV) Switch Data in HBeAg-Posite Patients with Chronic Hepatitis B (Study 103) presented at AASLD 2008 (#158).

Acknowledgements

Special thanks to all participating investigators and patients in the GS-US-174-0102 and GS-US-174-0103 studies.