# 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 data[1] 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 data[2] 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-negative[3] and 78% of HBeAg-positive[4] patients had HBV DNA <400 copies/mL (<69 IU/mL) (ITT)

## Objective

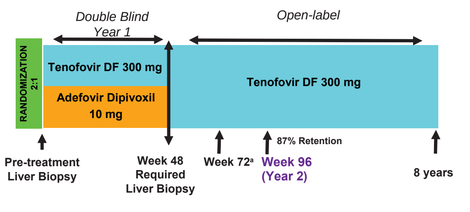
- To evaluate the response to 96 weeks (2 years) of TDF treatment in the subset of lamivudine-experienced compared to lamivudine-naïve patients with chronic hepatitis B enrolled in the phase 3 studies 102 and 103

## 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**




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

## Methods

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

- Age 18-69 years
- Compensated liver disease
- HBV DNA > $10^5$ copies/mL[a] (HBeAg-negative) or HBV DNA > $10^6$ 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

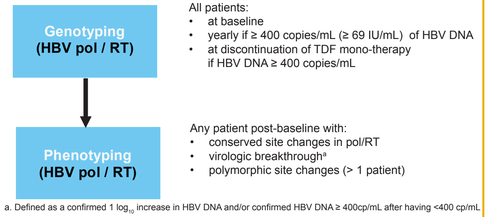
### Monitoring During Year 1 & Year 2

- 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**




a. Defined as a confirmed 1 $\log_{10}$ increase in HBV DNA and/or confirmed HBV DNA ≥ 400cp/mL after having <400 cp/mL

## 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)**

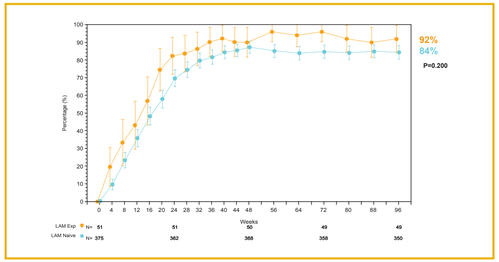
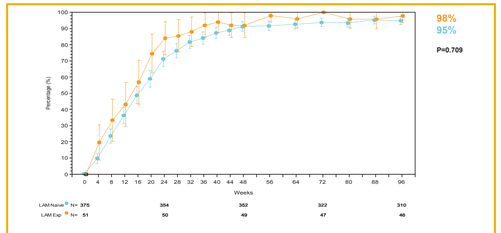



**Figure 4. HBV DNA < 400 copies/mL (On-Treatment Analysis)**




• Only 1 LAM experienced patient was >400 copies/mL at Week 96
•Patient remained on TDF through Week 96 and was non-adherent (TDF levels BQL)

**Figure 5. Mean HBV DNA ($\log_{10}$copies/mL)**

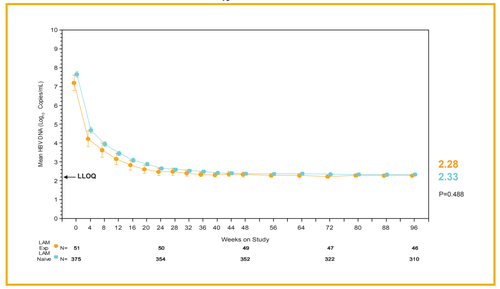
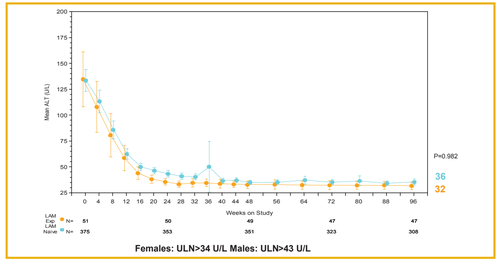



**Figure 6. Mean ALT (U/L)**




Females: ULN>34 U/L Males: ULN>43 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 patients[5]

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

| | LAM-Naive (N=375) | LAM-Experienced (N=51) |
|---|---|---|
| Serious AE, n (%)<br>Serious AE considered related to TDF, n (%) | 34 (9.1%)<br>7 (1.9%) | 8 (15.7%)<br>2 (3.9%) |
| Grade 3 or 4 AE, n (%)<br>Grade 3 or 4 AE considered related to TDF, n (%) | 47 (12.5%)<br>4 (1.1%) | 8 (15.7%)<br>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-naive 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-naive 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**

## 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. Manns M, Jeffers L, Dalekos G et al. The Antiviral Response To Tenofovir Disoproxil Fumarate (TDF) is Comparable in Lamivudine (LAM)-Naïve and LAM-Experienced Subjects Treated for Chronic Hepatitis B (CHB) presented at EASL 2008 (#1587).
3. 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).
4. 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).
5. Snow-Lampart A, Chappell B, Curtis M et al Week 96 Resistance Surveillance for HBeAg Positive and Negative Subjects with Chronic HBV Infection Randomized to Receive Tenofovir DF 300 mg QD presented at AASLD 2008 (Poster 977)

## Acknowledgements

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