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# Effects of Tenofovir DF on Renal Function of Chronic HBV Patients in Three Global Randomized Studies

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## Introduction

- The efficacy of tenofovir disoproxil fumarate (TDF) for treatment of patients with chronic HBV (CHB) as well as for patients with HIV has been demonstrated
- While the effect on viral suppression is clear, cases of renal dysfunction in patients receiving TDF have been reported

## Objective

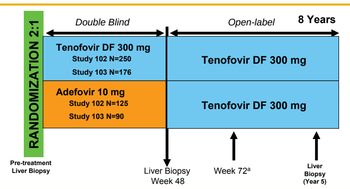
- To assess the effect of TDF on renal function across three large randomized clinical trials (Studies 102, 103, 106) in patients with chronic HBV

## Methods

- Renal parameters from 3 studies were pooled and evaluated as follows:
  - Adefovir (ADV) naïve CHB patients who initiated TDF in Studies 102 and 103 (n=426)
  - ADV experienced CHB patients who initiated TDF in Studies 102 and 103 (n=196)
  - ADV experienced CHB patients who initiated TDF in 106 (n=53) Changes from baseline in renal laboratory parameters in patients with and without baseline co-morbidities were explored:
- Changes from baseline in renal laboratory parameters in patients with and without baseline co-morbidities were explored:
  - Hypertension
  - Diabetes Mellitus
  - ADV naïve vs. ADF experienced patients

### Study Design – 102 and 103 Studies

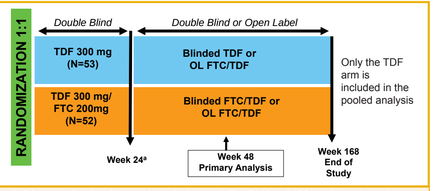
**Figure 1. Design of Phase 3 TDF Studies 102 (HBeAg-) and 103 (HBeAg+) in Chronic Hepatitis B patients**




a. Patients had the option at the discretion of the investigator to add emtricitabine 200 mg (FTC) to TDF 300 mg if confirmed to be viremic at Week 72 or beyond. Of the 51 patients that were eligible to add FTC, 34 added FTC (3 in study 102, 31 in study 103) while 17 maintained TDF monotherapy.

### Study Design – 106 Study

**Figure 2. Design of TDF Study 106 in ADV Refractory, HBeAg+ and HBeAg- Chronic Hepatitis B patients**




a. From Week 24 on, patients with confirmed plasma HBV DNA ≥ 4400 copies/mL could switch to open label (OL) FTC/TDF or discontinue from the trial and initiate commercially available; 25 patients switched to open label FTC/TDF during Year 1 (16 TDF group, 9 FTC/TDF group)

## Results

**Table 1. Demographic Characteristics**

| Baseline Characteristics | ADV Naïve Patients | ADV Experienced Patients | Overall |
|---|---|---|---|
| N | 426 | 249 | 675 |
| Median Age (yrs) (Range) | 41 (18, 68) | 41 (18, 69) | 41 (18, 69) |
| Baseline Age Group | | | |
| <50 years | 74.4% | 78.7% | 76.0% |
| ≥50 years | 25.6% | 21.3% | 24.0% |
| Race | | | |
| White | 59.4% | 57.8% | 58.8% |
| Asian | 29.8% | 32.1% | 30.7% |
| Black | 4.9% | 3.6% | 4.4% |
| Other | 5.8% | 6.4% | 6.1% |
| Sex – Male | 73.2% | 74.7% | 73.8% |
| Genotype | | | |
| A | 16.9% | 17.1% | 16.9% |
| B | 11.3% | 11.4% | 11.3% |
| C | 17.8% | 20.3% | 18.8% |
| D | 49.6% | 48.0% | 49.0% |
| Other | 4.4% | 3.2% | 4.0% |

**Table 2. Baseline Disease Characteristics**

| Baseline Characteristics | ADV Naïve Patients | ADV Experienced Patients | Overall |
|---|---|---|---|
| Percent HBeAg + | 41.1% | 43.4% | 41.9% |
| Medical History of Hypertension (%) | 15.0% | 13.3% | 14.5% |
| Medical History of Diabetes (%) | 4.9% | 5.6% | 5.2% |
| Median HBV DNA ($Log_{10}$ copies/mL) | 7.81 (2.23, 10.92) | 3.62 (2.23, 9.57) | 6.74 (2.23, 10.92) |
| Median ALT (U/L) | 105.0 (16.0, 964.0) | 33.0 (7.0, 313.0) | 74.0 (7.0, 964.0) |
| Duration of Previous Adefovir (days) | * | 336.0 (140.0, 917.0) | 336.0 (15.0, 917.0) |
| Number of Subjects with Prior Lamivudine Exposure | 56 | 60 | 116 |
| Duration of Lamivudine/ FTC Exposure (days) | 443.5** (8.0, 1846) | 733.0*** (2.0, 1828) | 609.0 (2.0, 1966) |
| **Baseline Creatinine Clearance** | | | |
| <50 mL/min | 0.2% | 0% | 0.1% |
| 50-80 mL/min | 6.6% | 9.2% | 7.6% |
| >80 mL/min | 93.2% | 90.8% | 92.3% |

*2 subjects in the ADV Naïve group received 15 days and 65 days of ADV therapy, respectively

**Table 3. Change from Baseline and Renal Events in Adefovir Naïve Subjects**

| | Naïve Subjects (N=426) | Diabetic (N=21) | Hypertensive (N=64) |
|---|---|---|---|
| Baseline Serum Creatinine (mg/dL) | 0.87<br>0.90<br>(0.7, 1.0) | 0.83<br>0.80<br>(0.7, 1.0) | 0.89<br>0.90<br>(0.8, 1.0) |
| Week 144 Serum Creatinine (mg/dL) | 0.9<br>0.9 (0.8, 1.0) | 0.89<br>0.80 (0.8, 1.0) | 0.93<br>0.90 (0.8, 1.0) |
| Baseline eGFR (mL/min) by CG* | 114.4<br>110.0<br>(94.0, 130.0) | 114.3<br>99.0<br>(94.0, 148.0) | 112.5<br>111.5<br>(91.0, 129.0) |
| Week 144 eGFR (mL/min) by CG* | 108.2<br>103.0<br>(87.0, 124.0) | 107.4<br>97.0<br>(82.0, 138.0) | 106.7<br>101.0<br>(86.0, 122.0) |
| Confirmed Increase in Creatinine ≥ 0.5 mg/dL | 2 (0.5%) | 0 | 1 (1.6%) |
| Confirmed eGFR <50 mL/min | 0 | 0 | 0 |

*Data presented as mean, median, Q1, Q3
CG = Cockcroft-Gault

**Table 4. Change from Baseline and Renal Events in Adefovir Experienced Subjects**

| | All Experienced Patients (N=249) | Diabetic (N=14) | Hypertensive (N=34) |
|---|---|---|---|
| Baseline Serum Creatinine (mg/dL)* | 0.87<br>0.90 (0.8, 1.0) | 0.96<br>0.95 (0.9, 1.1) | 0.93<br>0.90 (0.8, 1.0) |
| Week 144 Serum Creatinine (mg/dL)* | 0.9<br>0.9 (0.8, 1.0) | 0.97<br>0.90 (0.8, 1.1) | 0.98<br>1.0 (0.9, 1.1) |
| Baseline eGFR (mL/min) by CG* | 117.0<br>113.0 (96.0, 132.0) | 128.0<br>124.5 (117.0, 142.0) | 121.4<br>110.0 (86.0, 150.0) |
| Week 144 eGFR (mL/min) by CG* | 112.4<br>107.5 (92.0, 131.0) | 119.9<br>107.0 (92.0, 130.0) | 118.9<br>109.0 (81.0, 149.0) |
| Confirmed Increase in Creatinine ≥ 0.5 mg/dL | 3 (1.2%) | 1 (7.1%) | 2 (5.9%) |
| Confirmed eGFR <50 mL/min | 1 (0.4%) | 0 | 1 (2.9%) |

*Data presented as mean, median, Q1, Q3
CG = Cockcroft-Gault

**Table 5. Change from Baseline and Renal Events in Adefovir Experienced Subjects**

The change from baseline in renal parameters was evaluated in 2 subgroups of interest:

1. Older patients (≥50 years old)
2. Asian patients

| | < 50 y.o. (N=513) | ≥ 50 y.o (N=162) | Asian Patients (N=207) | Non-Asian Patients (N=468) |
|---|---|---|---|---|
| Confirmed Increase in Creatinine ≥ 0.5 mg/dl | 2 (0.4%) | 3 (1.9%) | 1 (0.5%) | 4 (0.9%) |
| Confirmed eGFR <50 mL/min | 0 | 1 (0.6%) | 0 | 1 (0.2%) |

**Figure 3. Median (IQR) Estimated GFR by CG - Overall Population**

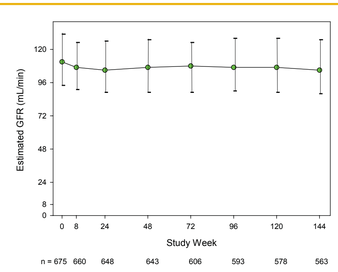



**Figure 4. Median Serum Phosphorous over 144 Weeks - Overall Population**

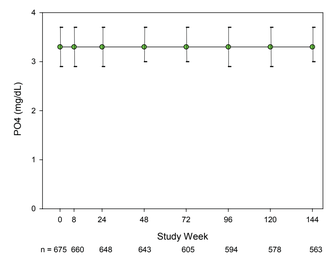



**Figure 5. Estimated GFR by CG in Patients Entering the Study with Mild Renal Impairment (50-80 mL/min)**

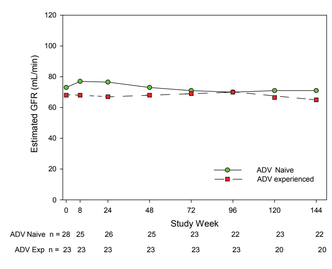



**Figure 6. Estimated GFR by CG over Time in Hypertensive Patients**

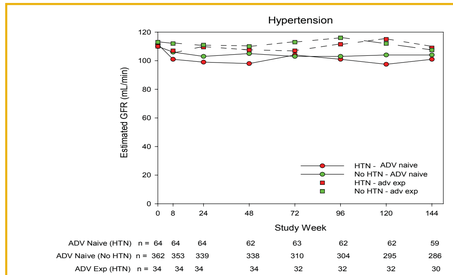
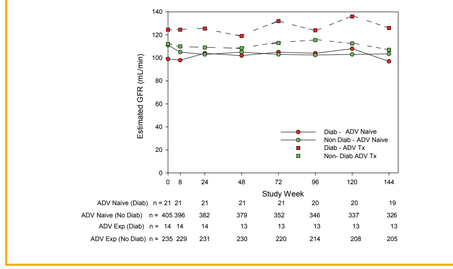



**Figure 7. Estimated GFR by CG over Time in Diabetic Patients**




### Discussion

- This analysis evaluated the renal function of 675 patients on TDF for up to 3 years
- Overall, few patients experienced a decline in renal function
  - 5/675 (0.7%) had ≥ 0.5mg/mL increase in creatinine
    - 3/5 had preexisiting hypertension
    - 1/5 had preexisting diabetes
  - 1/675 (0.1%) had a decline in eGFR to <50ml/min
    - This patient had preexisting hypertension
- The lack of a placebo group in these long term studies makes conclusions concerning the potential role of TDF in decreasing renal function more difficult to assess. Patients with diabetes and hypertension are already at risk for renal dysfunction regardless of TDF therapy