

## Introduction

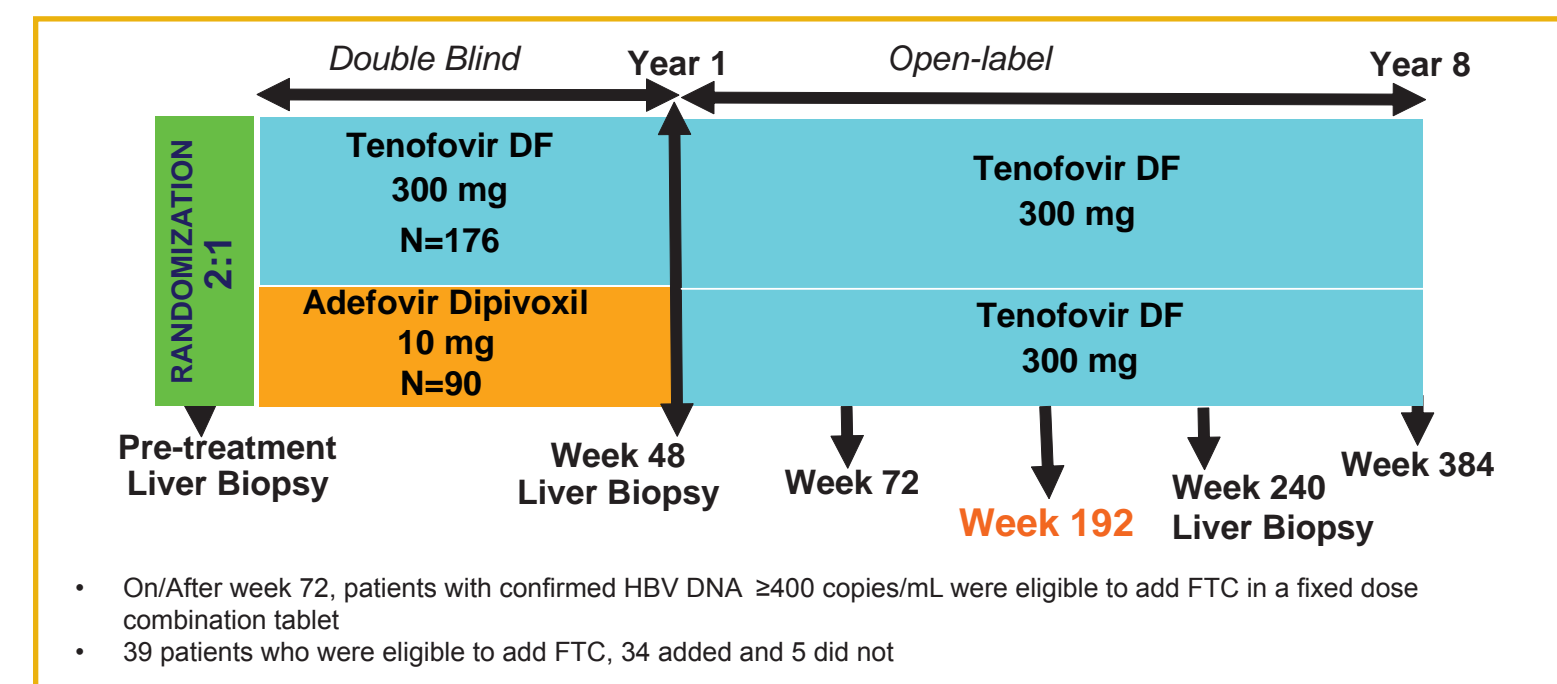
- Tenofovir DF (TDF) was approved for HIV-1 in 2001 and chronic hepatitis B (CHB) in 2008: ~ 3.5 million patient-years experience
- Week 48 Phase 3 data showed significantly greater antiviral activity of TDF compared to adefovir dipivoxil (ADV) in HBeAg+ patients: 76% vs 13%
- TDF treatment in HBeAg+ 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

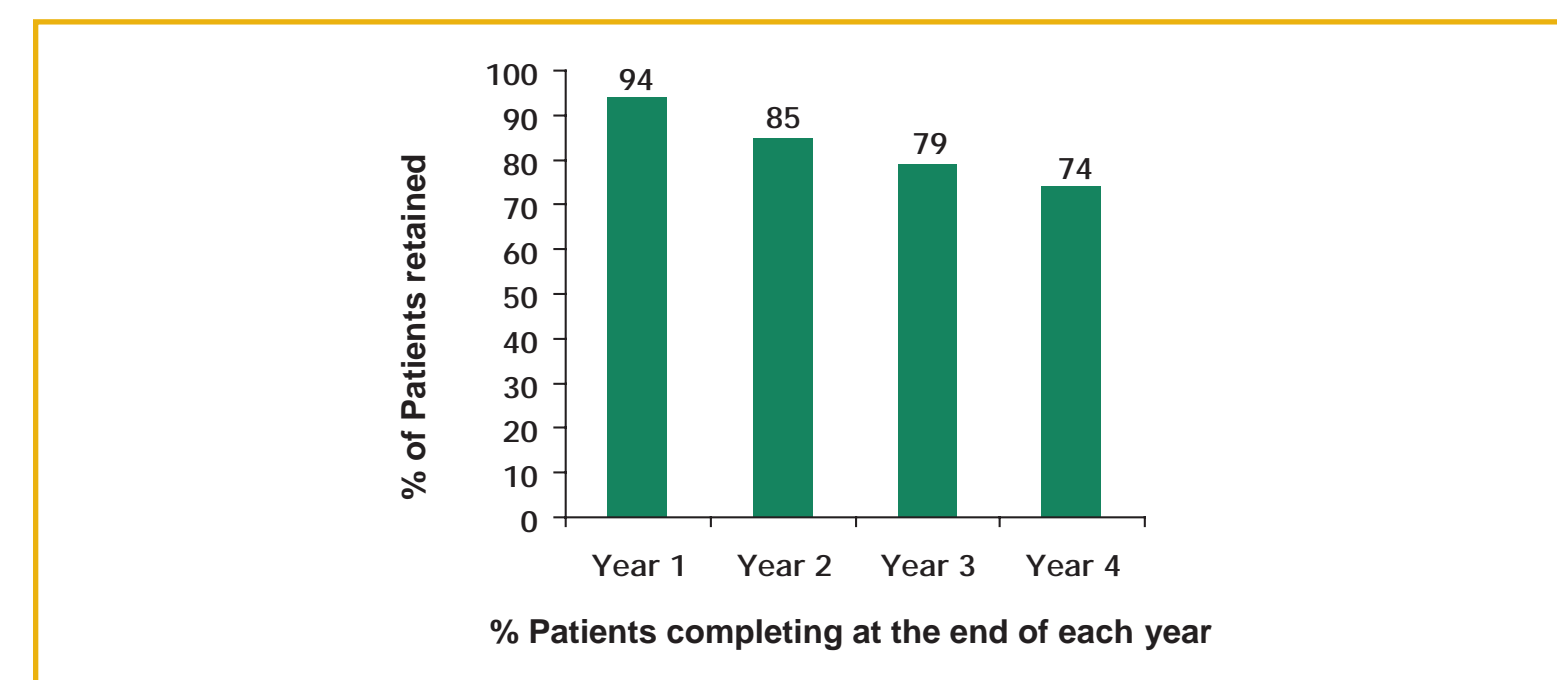
- Evaluate the efficacy and safety of up to 4 years of TDF therapy in HBeAg+ patients

## Methods

**Figure 1. Study Design of Phase 3 Pivotal Study 103 HBeAg+**



**Figure 2. Patient Retention**



### Key Eligibility Criteria

- HBeAg-positive, nucleos(t)ide naïve patients with compensated liver disease
- HBV DNA >  $10^8$  copies/mL; ALT > 2xULN and < 10xULN
- Knodell necroinflammatory score  $\geq 3$
- 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  $\geq 400$  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

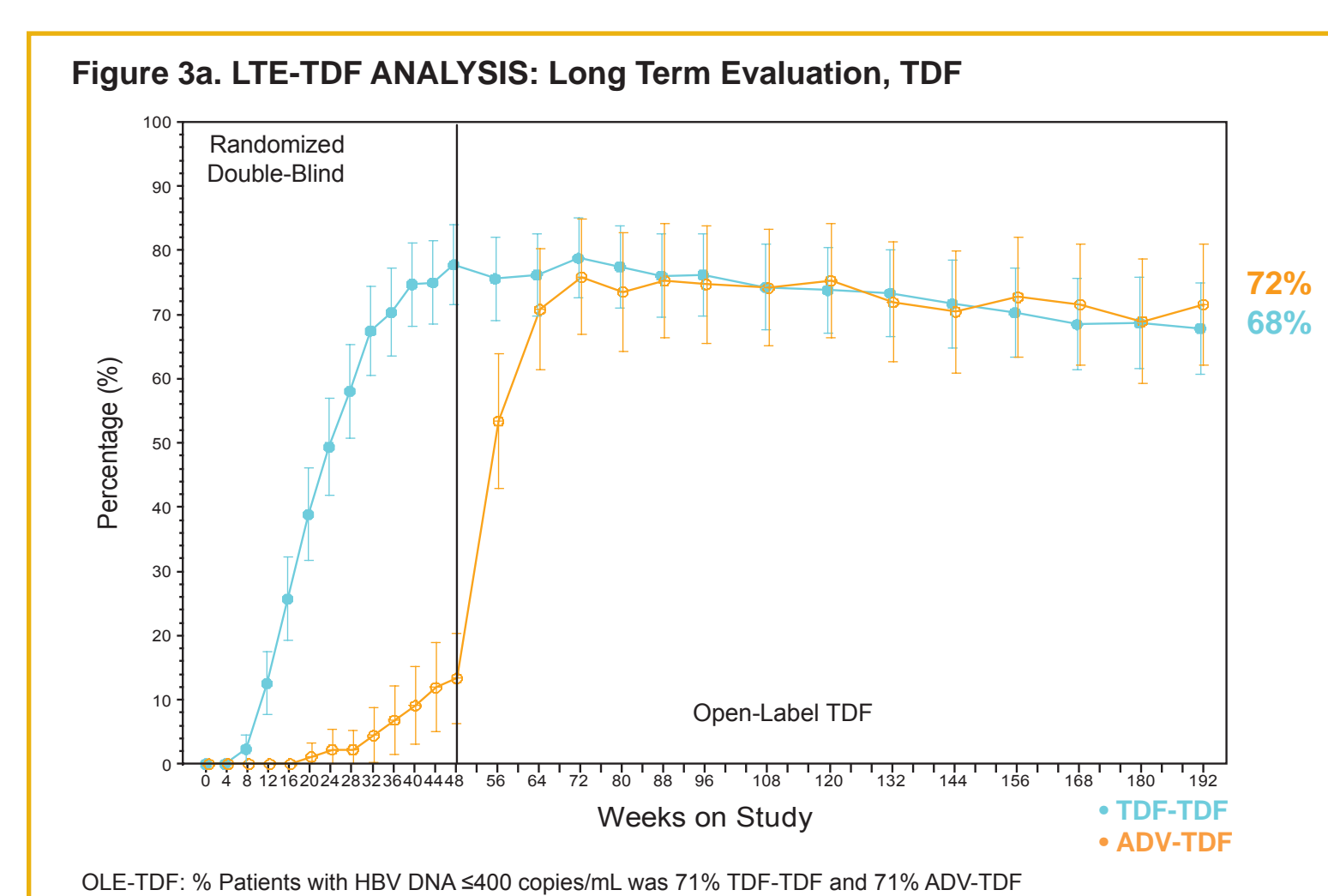
#### On-Treatment Analysis [observed data, missing=excluded]

- 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

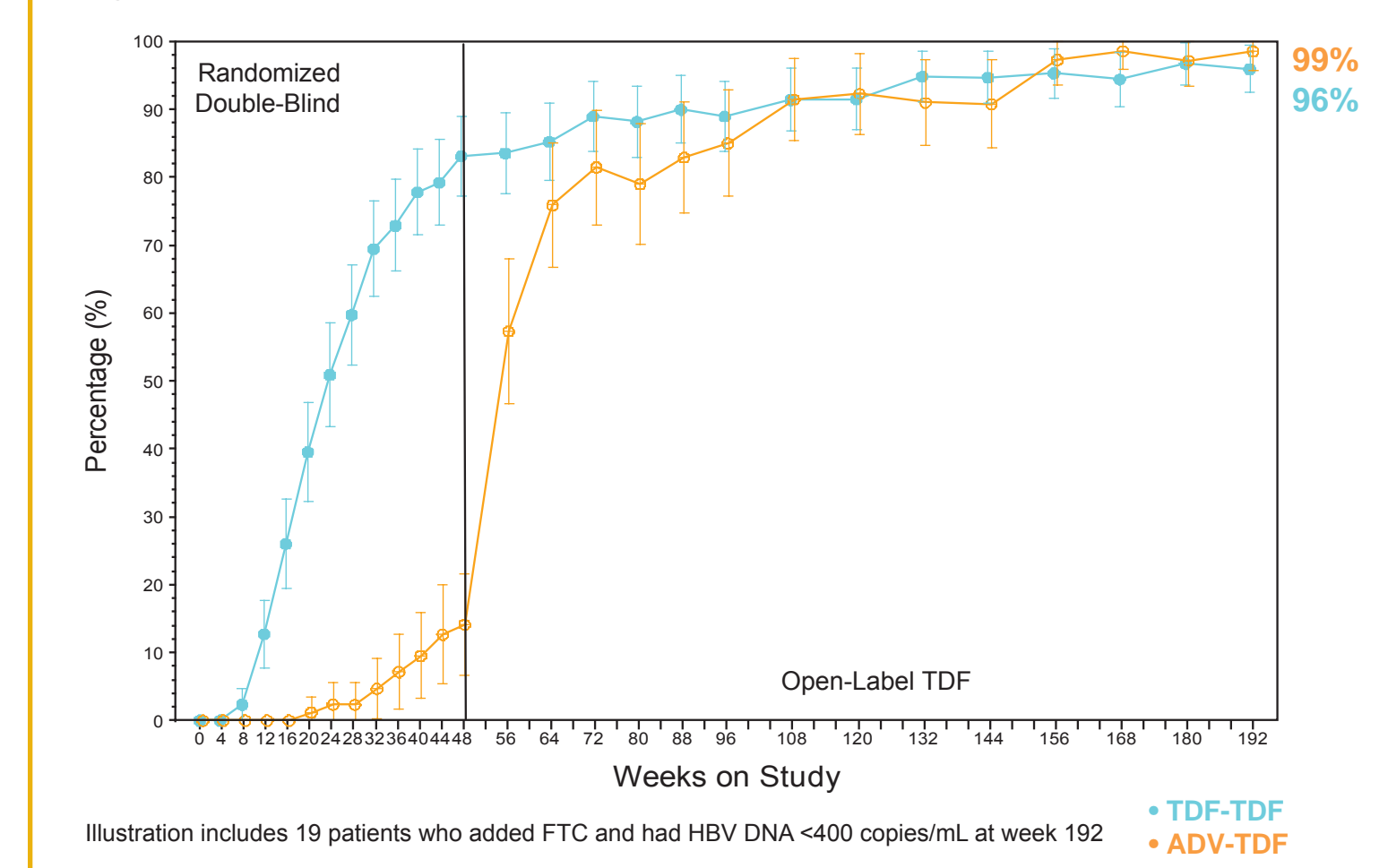
**Table 1. Patients Entering Year 4 had Similar Baseline Characteristics to Patients Originally Randomized**

|  | 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                                  | 52%                  | 51%        | 53%                      | 49%            |
| Asian                                      | 36%                  | 36%        | 35%                      | 39%            |
| Male                                       | 68%                  | 71%        | 73%                      | 72%            |
| Mean HBV DNA (log <sub>10</sub> copies/mL) | 8.64                 | 8.88       | 8.62                     | 8.75           |
| Mean ALT (U/L)                             | 142                  | 155        | 138                      | 168            |
| Mean Knodell necroinflammatory score       | 8.3                  | 8.5        | 8.2                      | 8.5            |
| Mean Knodell fibrosis Score                | 2.3                  | 2.5        | 2.3                      | 2.6            |
| Knodell fibrosis score = 4 (cirrhosis)     | 20%                  | 21%        | 23%                      | 22%            |
| Viral Genotype                             |                      |            |                          |                |
| A  | 24%                  | 21%        | 26%                      | 16%            |
| B  | 15%                  | 11%        | 13%                      | 9%             |
| C  | 25%                  | 30%        | 25%                      | 36%            |
| D  | 32%                  | 35%        | 32%                      | 35%            |

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



**Figure 3b. On-Treatment Analysis**



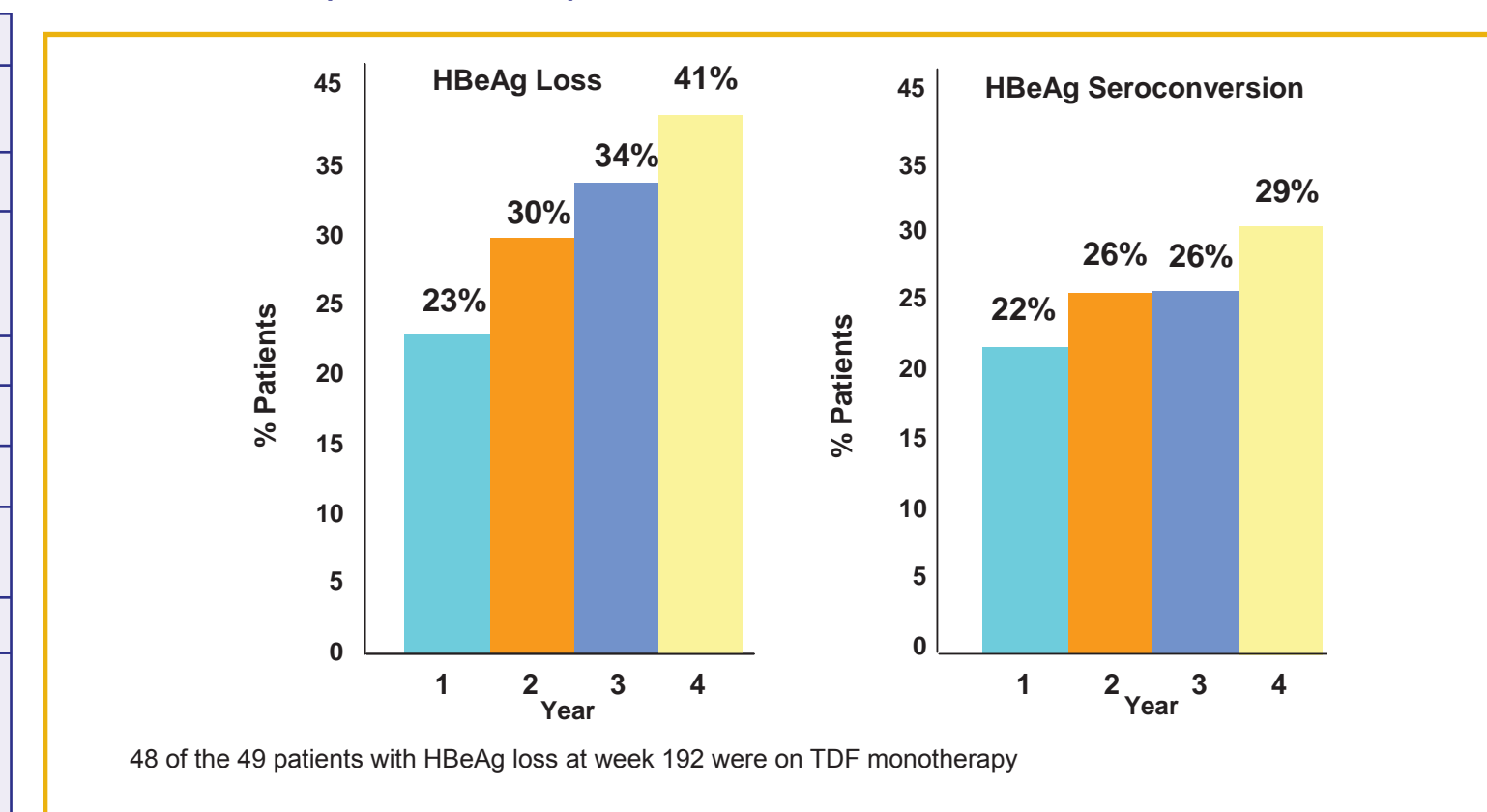
**Table 2. Week 192 Biochemical Response**

|  | TDF-TDF | ADV-TDF |
|--|---------|---------|
| Mean ALT (U/L)                           | 36.3    | 32.5    |
| % Normalized <sup>a</sup> (on-treatment) | 77%     | 80%     |

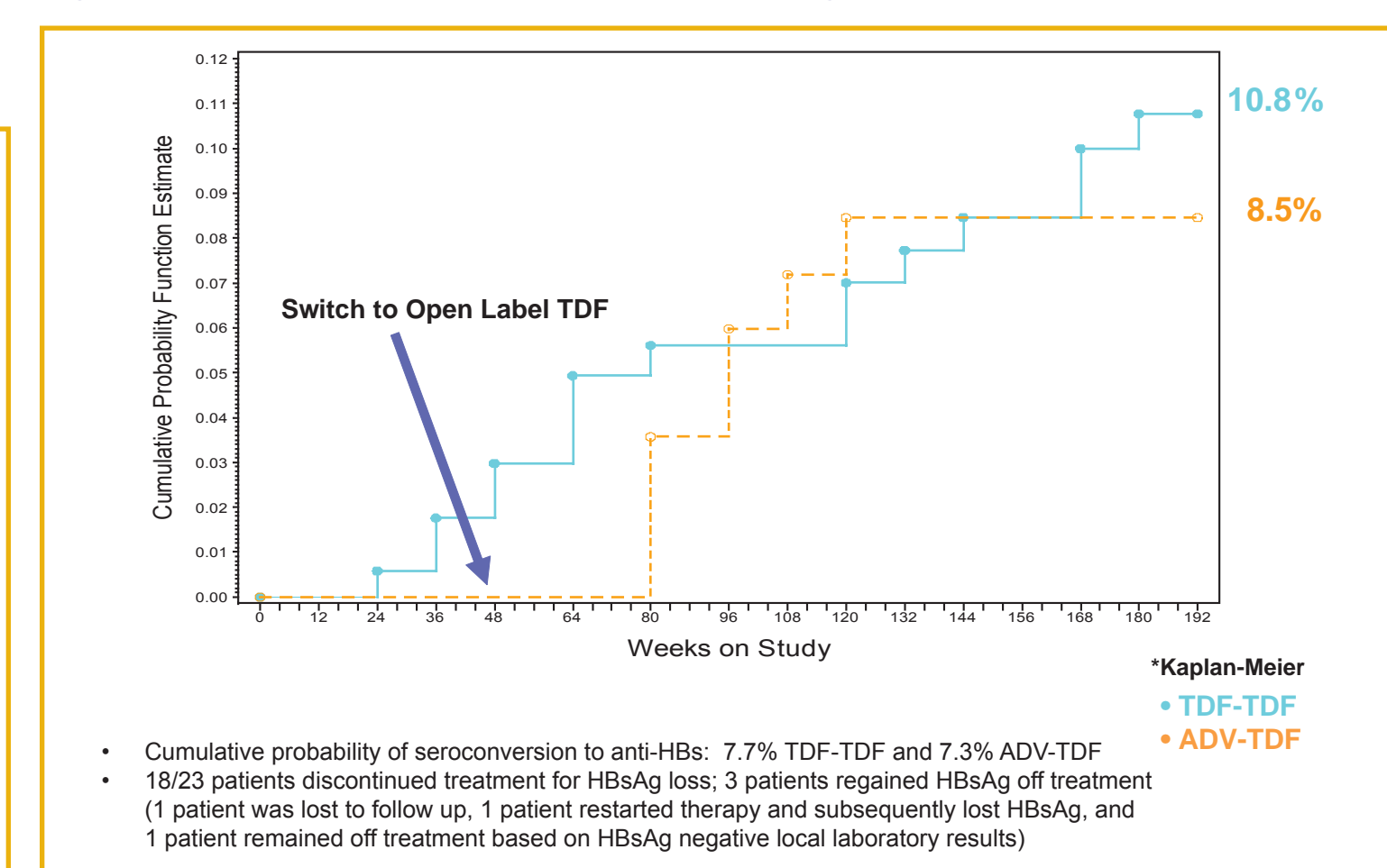
a. ALT ULN=34 for females and ULN=43 for males

## Results

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



**Figure 5. Cumulative Probability\* of HBsAg Loss**



**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 $\geq 9$ log <sub>10</sub> copies/mL | 12/75 (16%)                       |
| HBsAg $\geq 4.5$ log <sub>10</sub> IU/mL     | 14/90 (16%)                       |
| Knodell Necroinflammatory Score $\geq 9$     | 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%) <sup>a</sup> | 0              |
| Creatinine increased <sup>a</sup>   | 1                   | 0              |
| Osteoporosis <sup>b</sup>           | 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)

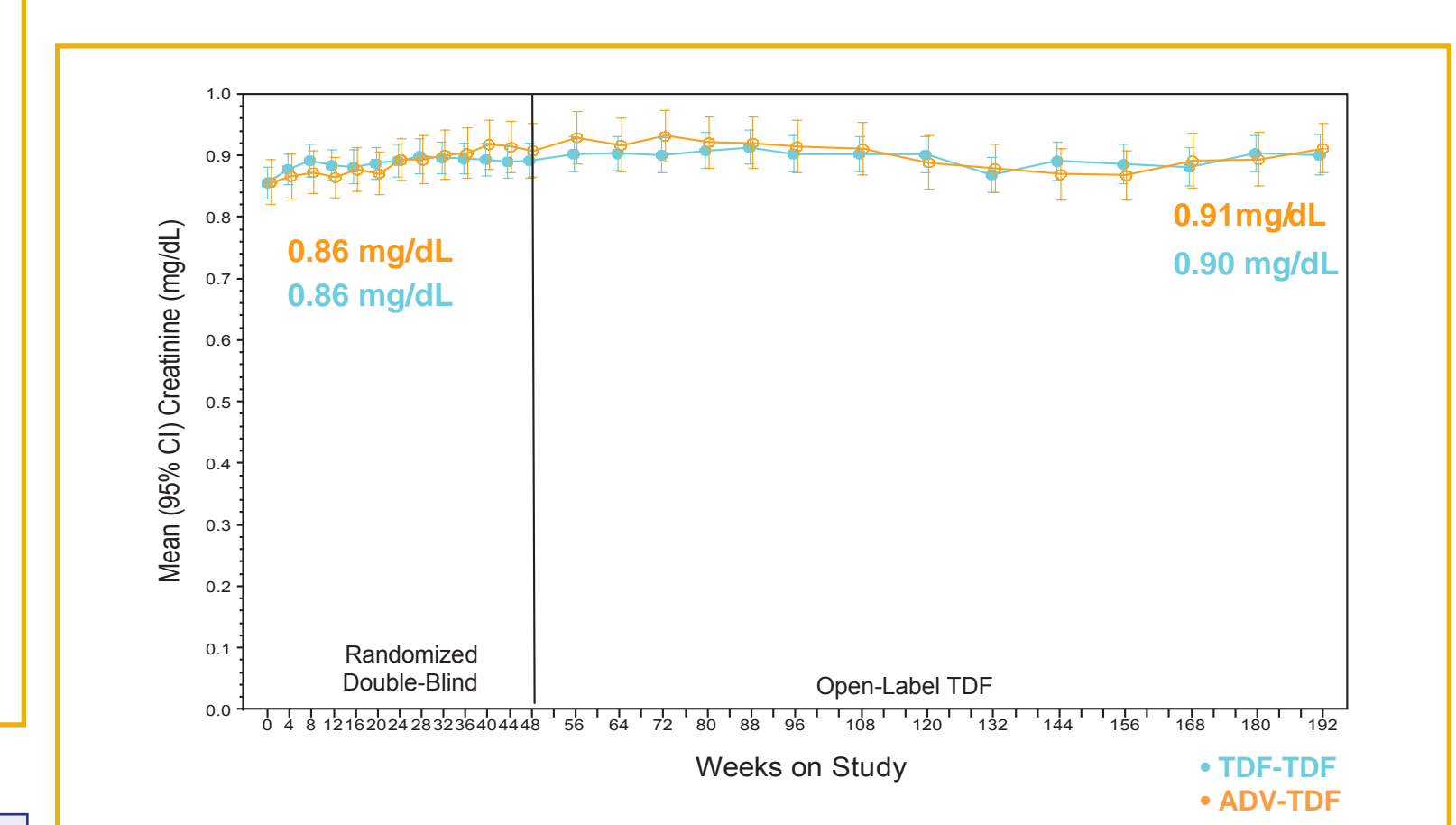
b. Osteoporosis diagnosed by DXA (no baseline DXA, no fracture)

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

|  | TDF-TDF (N=154) | ADV-TDF (N=84) |
|--|-----------------|----------------|
| Confirmed $\downarrow$ phosphorus < 2mg/dL | 1 (<1%)         | 1 (1%)         |
| Confirmed $\geq 0.5$ 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  $\geq 0.5$  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<sup>a</sup>

- 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

- Special thanks to all participating investigators and patients in study GS-US-174-0103