

Four Years Efficacy and Safety of Tenofovir Disoproxil Fumarate (TDF) in Asians with HBeAg-Positive and HBeAg-Negative Chronic Hepatitis B

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Introduction

- Tenofovir DF has demonstrated durable activity in 2 pivotal studies in chronic hepatitis B through 192 weeks (4 years) of treatment.
- Asian patients comprised a substantial subset of the participants in these studies
- Evaluation of efficacy and safety in Asian patients was considered important given the prevalence of HBV infection in this population

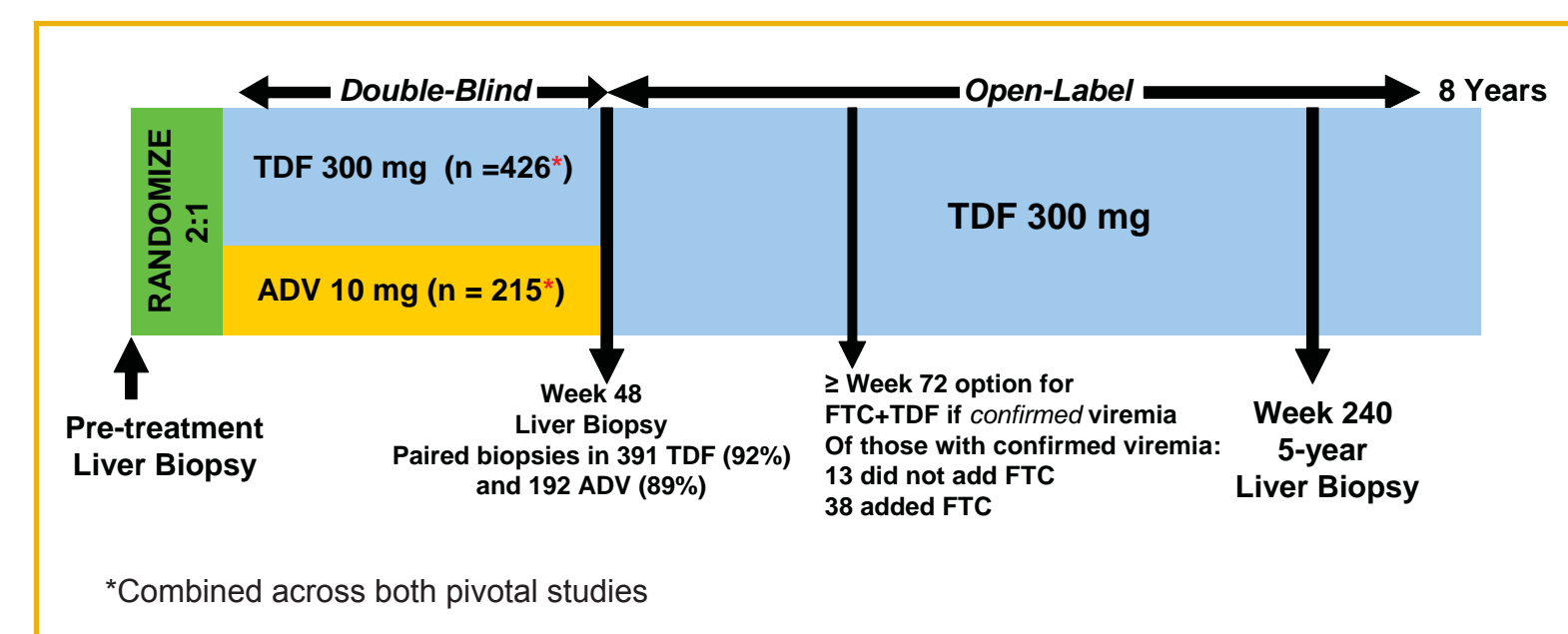
Objective

- To evaluate the efficacy and safety of tenofovir DF among Asian patients with chronic hepatitis B participating in tenofovir DF pivotal Studies 102 (HBeAg-) and 103 (HBeAg+)

Methods

- Patients were randomized 2:1 to double-blind tenofovir DF (TDF) 300 mg or adefovir dipivoxil (ADV) 10 mg once daily for 48 weeks
- Open-label tenofovir DF commenced at week 48 for those patients completing the double-blind phase
- Virologic (HBV DNA < 400 copies/mL [69 IU/mL]), biochemical, and serologic response were prospectively evaluated
- HBV DNA and safety laboratory parameters were performed every 4 weeks in year 1, every 8 weeks in year 2, and every 12 weeks thereafter with annual resistance surveillance
- Asian ethnicity was determined by self-report as recorded on the case report form

Figure 1. GS-US-174-0102 (HBeAg-) and GS-US-174-0103 (HBeAg+) Study Design



Eligibility criteria required elevated ALT[†], Knodell necroinflammatory score ≥ 3, and viremia with HBV DNA > 10⁷ copies/mL with the Roche COBAS TaqMan assay (LLOQ=169 copies/mL [29 IU/mL])

(†Upper normal limit [ULN] 34 U/L for women; 43 U/L for men)

Figure 2. Asian Patients Participating in Pivotal Studies

- 189 Asians and 452 non-Asians were enrolled across the 2 studies
- Asians comprised ~30% of all patients
 - 127/426 (30%) on TDF
 - 62/215 (29%) on ADV
- Combined study results are presented to maximize sample size
- Of 178 Asian patients eligible to continue in the Open-Label extension, 163 entered the Open-Label phase and 89% completed 192 weeks

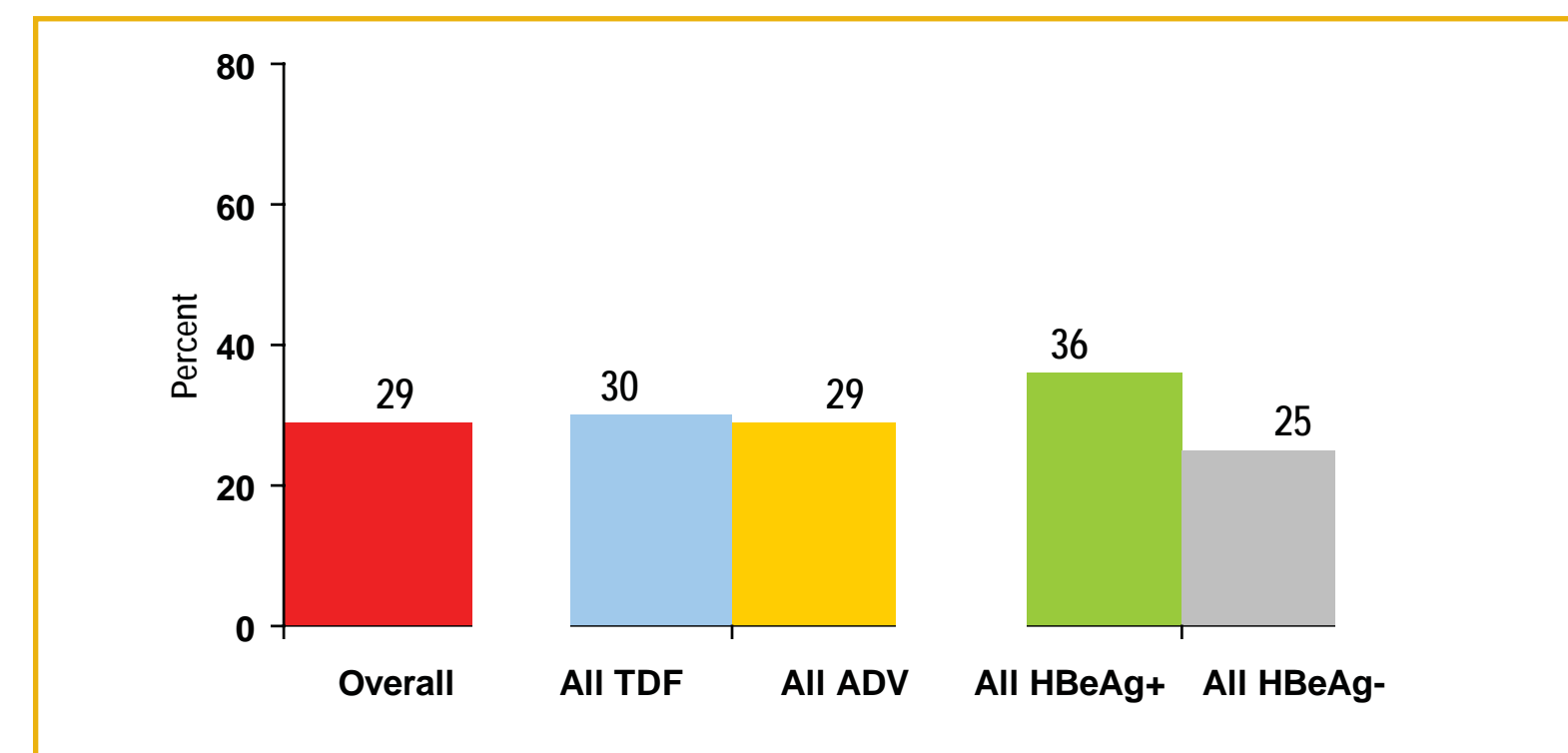


Table 1. Baseline Characteristics

Characteristic	Asian (n = 189)	Non-Asian (n = 452)
Age, yr (SD)	40 (10.9)	40 (12.4)
Weight, Kg (SD)	64.8 (13.3)	79.0 (16.6)
Male, n (%)	129 (68.3)	344 (76.1)
HBV DNA, log ₁₀ copies/mL (SD)	7.66 (1.43)	7.66 (1.52)
HBeAg+, n (%)	95 (50.3)	171 (37.8)
Knodell necroinflammation score (SD)	8.5 (2.1)	7.8 (2.3)
Cirrhosis (Knodell=4)	18%	20%
ALT, U/L (SD)	142 (133.5)	143 (106.7)
Genotype A	6%	21%
B	38%	1%
C	52%	4%
D	3%	70%

Values are means for continuous variables. ALT ULN= 34 U/L for women; 43 U/L for men

Figure 3. Percentage of Patients with HBV DNA < 400 copies/mL (69 IU/mL) (LTE-TDF)

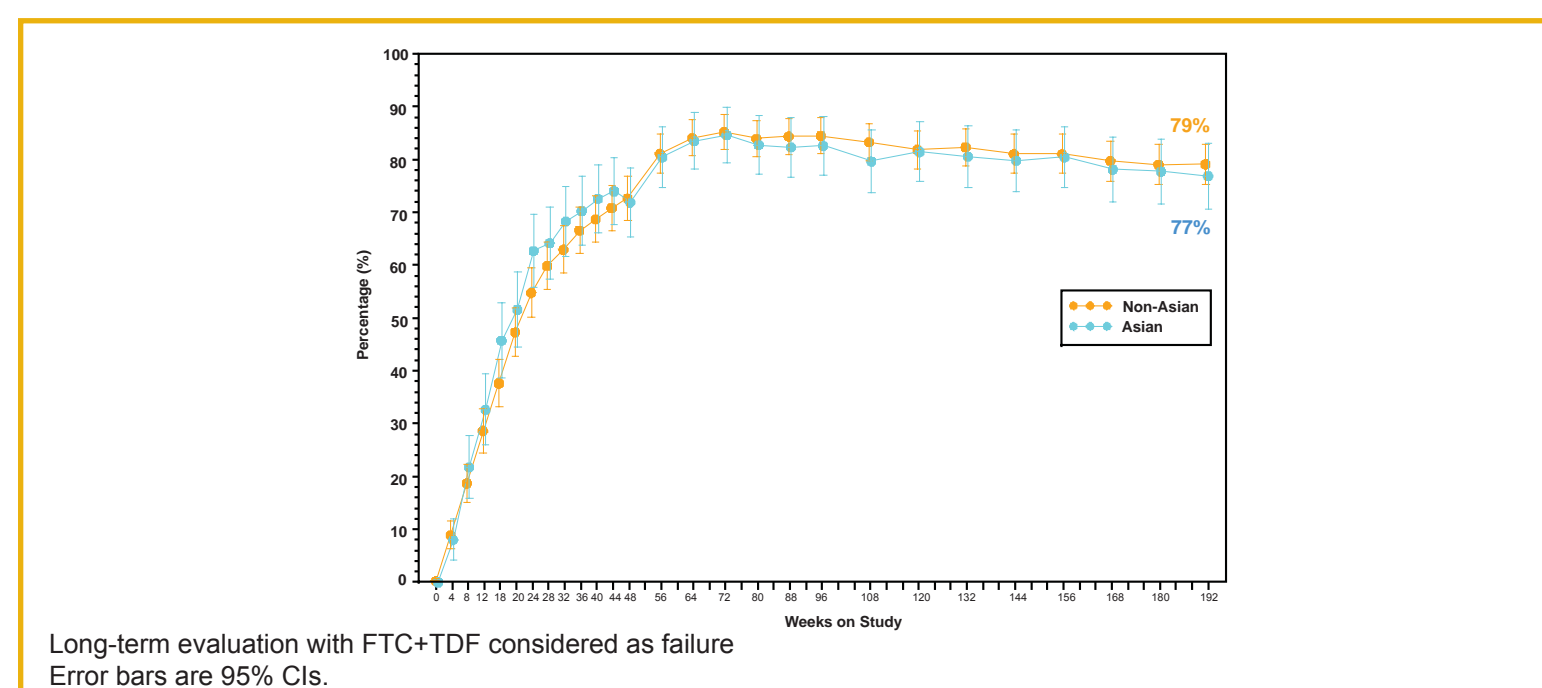


Figure 4. Percentage of Patients with HBV DNA < 400 copies/mL (69 IU/mL) at Week 192 (ITT)

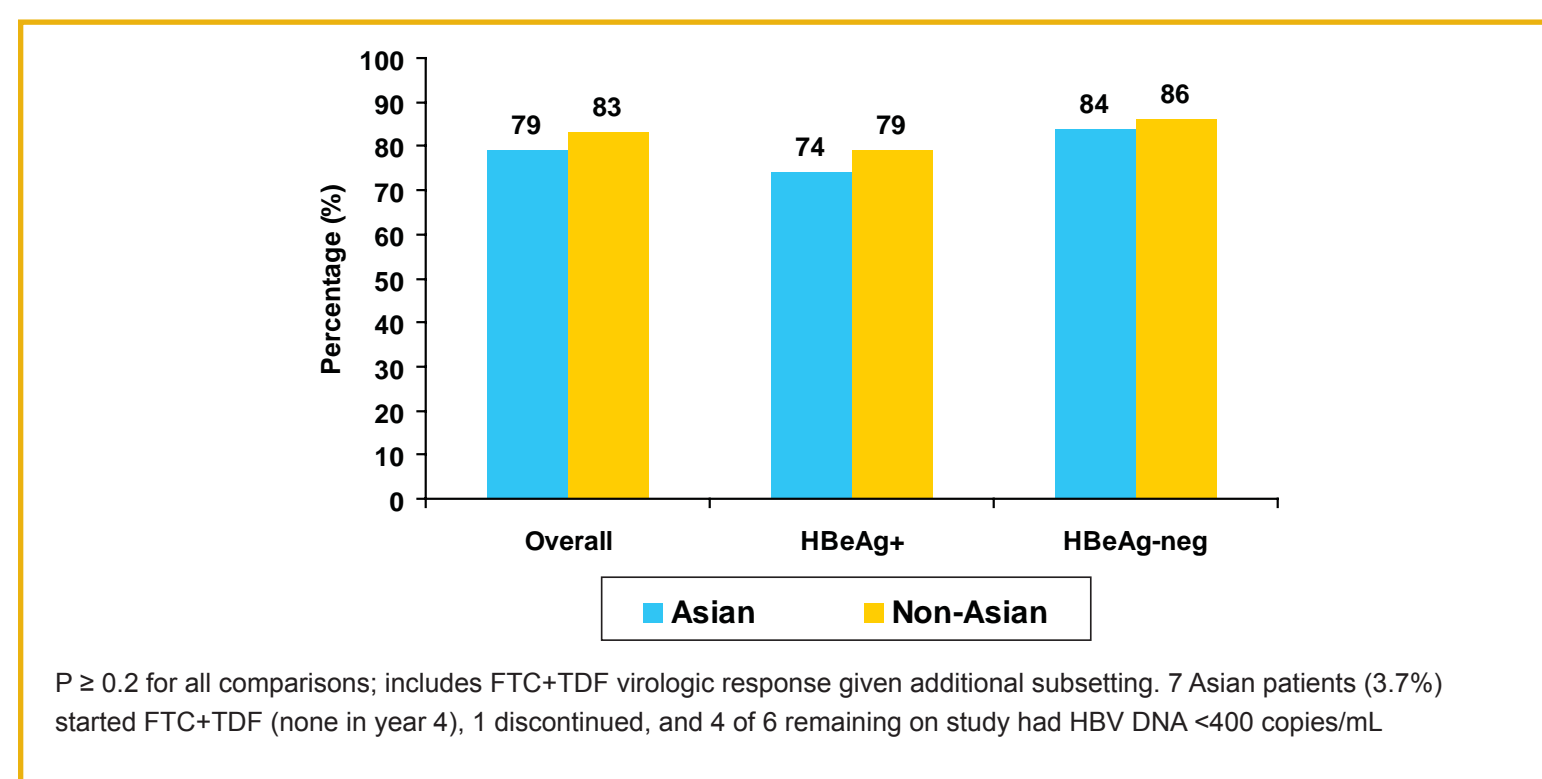
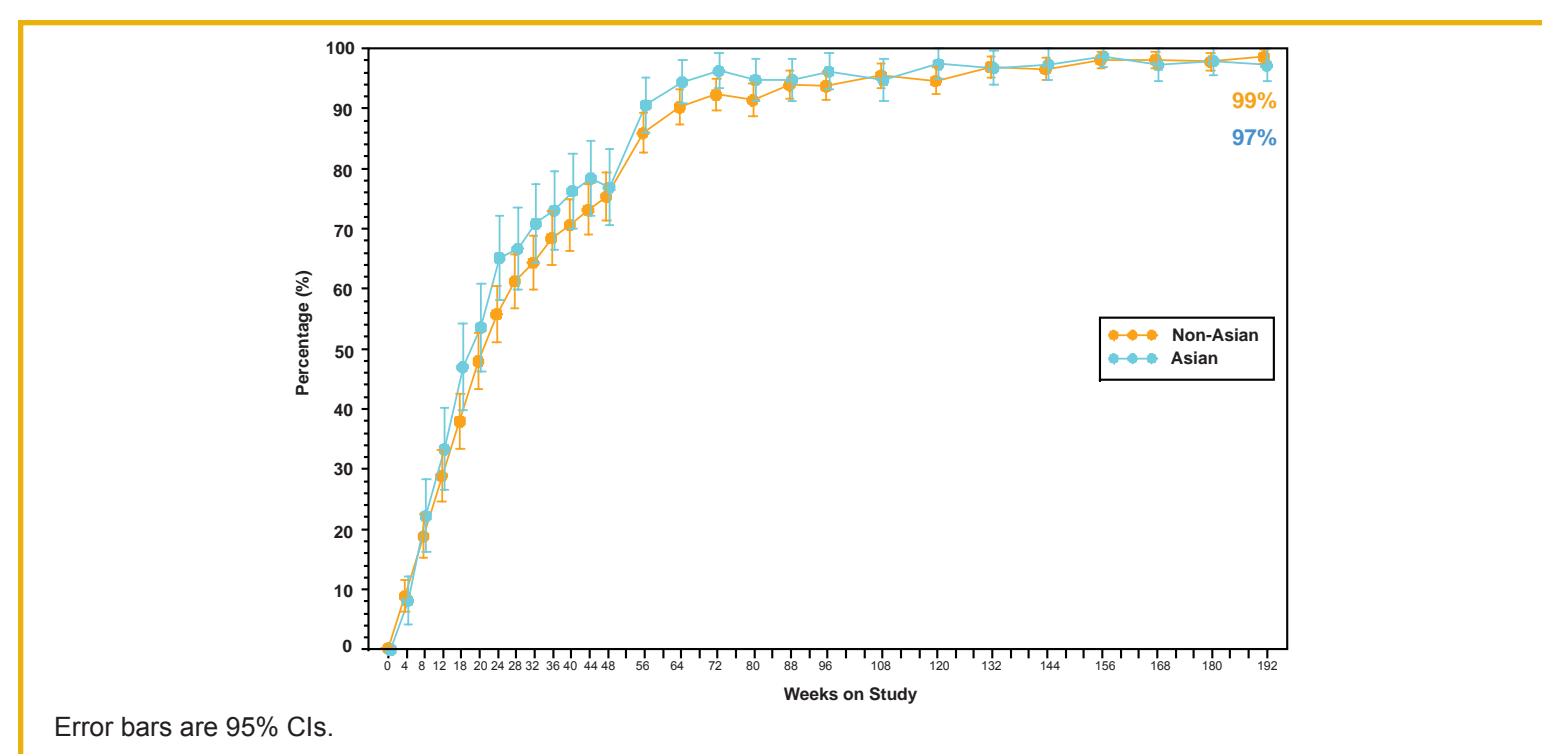


Figure 5. Percentage of Patients with HBV DNA < 400 copies/mL (69 IU/mL) (On-Treatment Analysis)



Results

Figure 6. Mean HBV DNA Over Time (log₁₀ copies/mL)

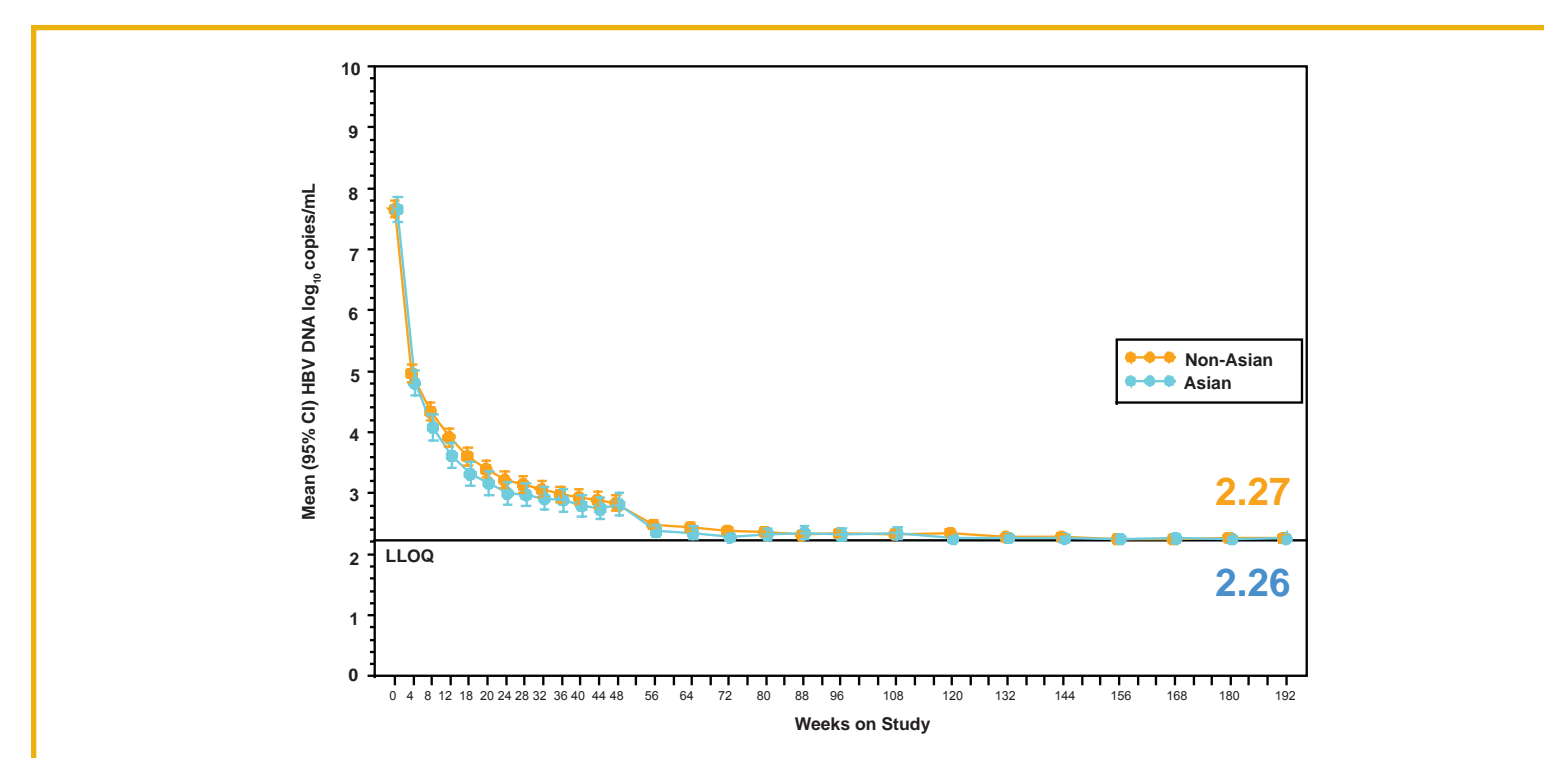


Figure 7. Percentage of Patients with Normal ALT (On-Treatment Analysis)

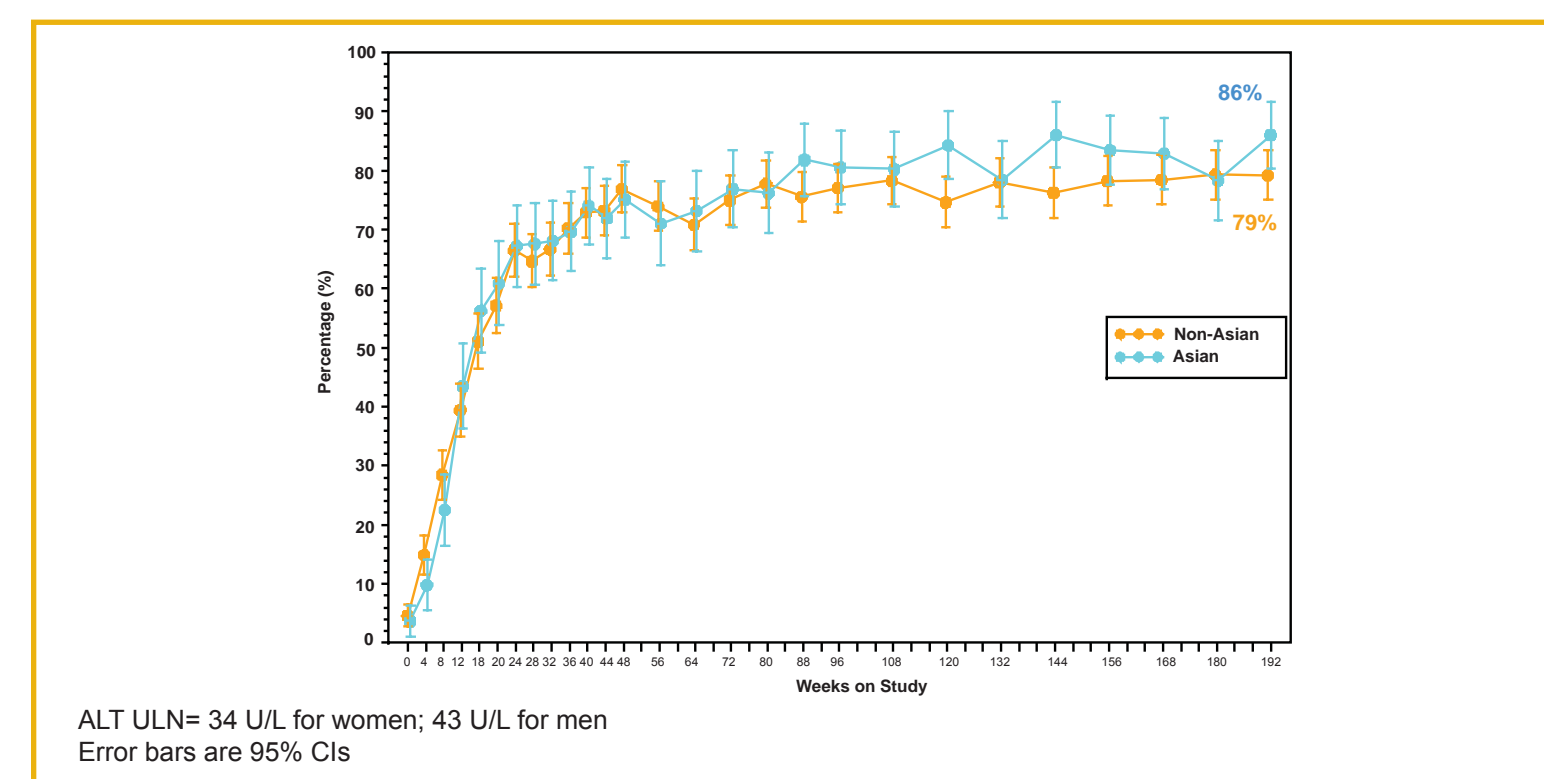


Figure 8. Mean ALT Over Time

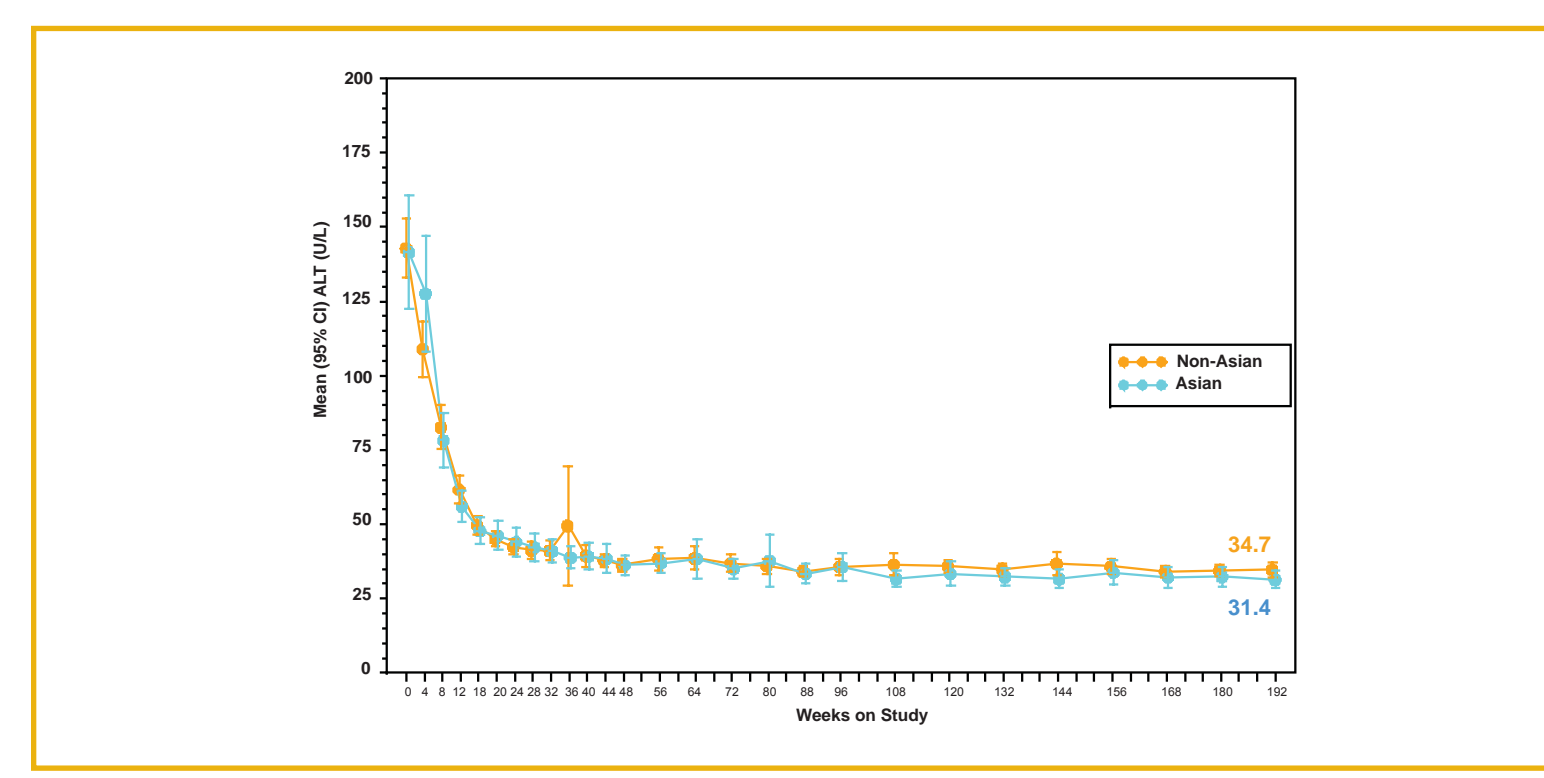


Figure 9. Serologic Response Among Asian Patients (On-Treatment Analysis)

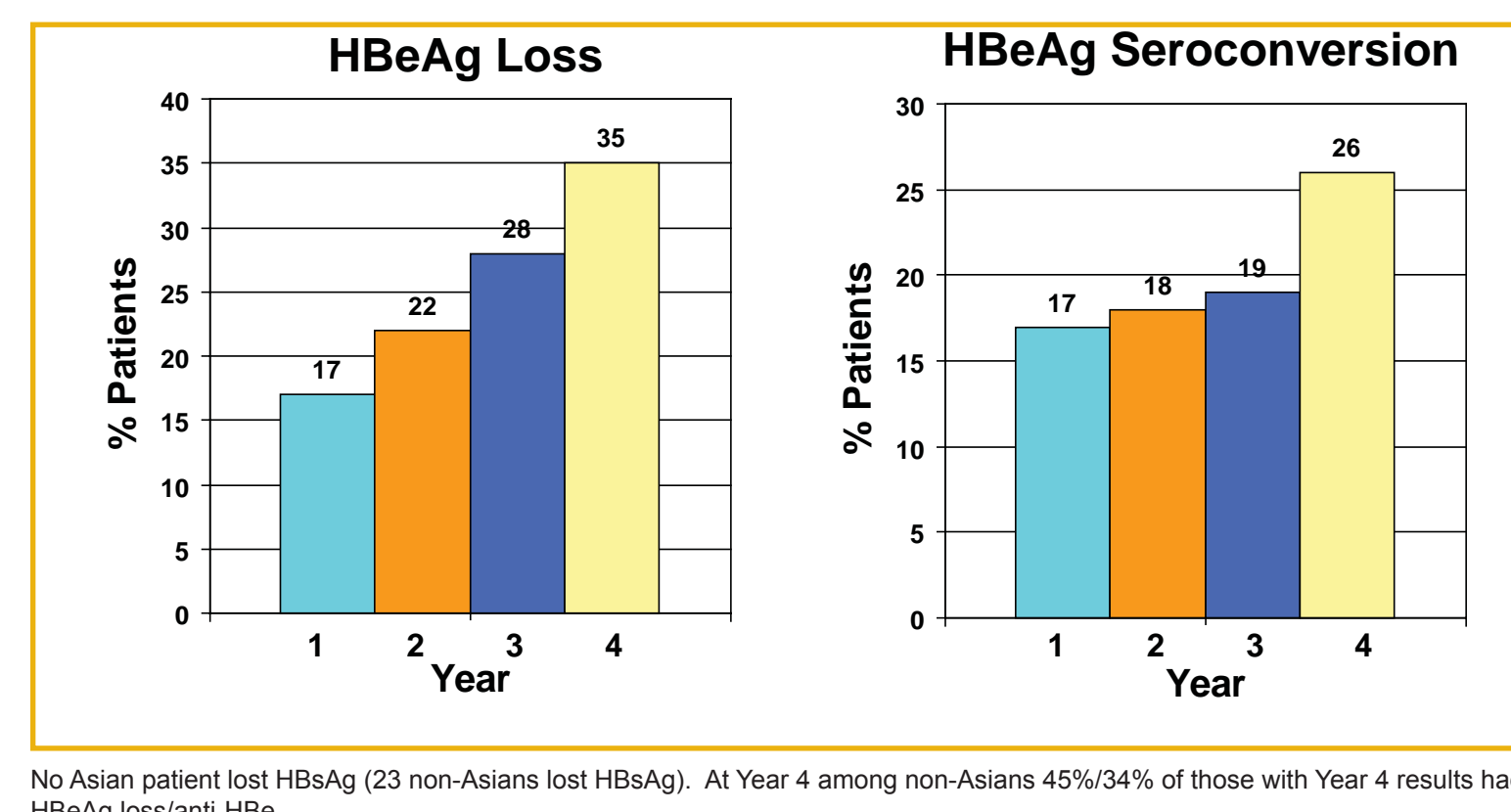


Table 2. Safety and Tolerability During Open-Label TDF Treatment

Parameter	Asians* (n = 163)	Non-Asians* (n = 422)
Grade 3/4 AEs	17 (10.4%)	50 (11.8%)
AEs causing discontinuation	2 (1.2%)	5 (1.2%)
Serious AEs	10 (6.1%)	61 (14%)
Phosphorus < 2 mg/dL	1 (0.6%)	6 (1.4%)
Creatinine ≥ 0.5 mg/dL increase	1 (0.6%)	4 (0.9%)
CrCl < 50 ml/min	0 (0%)	1 (0.2%)

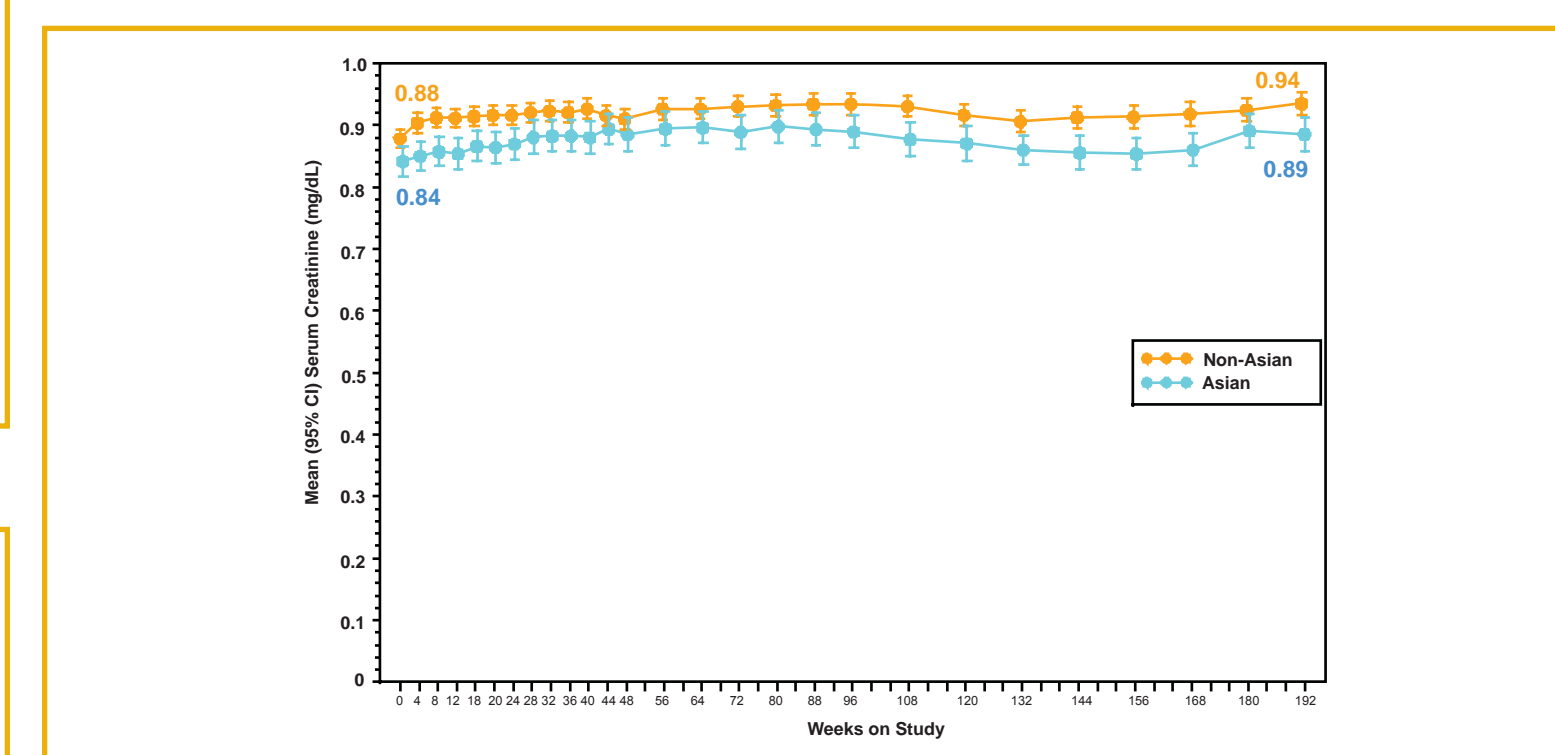
*Incidence of events during open-label TDF treatment across studies/original arms
Among Asians 2 patients had AEs resulting in discontinuation: osteoporosis diagnosed by DXA (no baseline DXA, no fracture); sepsis in the setting of poorly differentiated nasopharyngeal carcinoma (fatal)

Table 3. Grade 3/4 Laboratory Values During Open-Label TDF Treatment

Parameter	Asians* (n = 163)	Non-Asians* (n = 422)
Any Grade 3/4 Abnormality	24 (14.7%)	67 (15.9%)
ALT	4 (2.5%)	11 (2.6%)
AST	4 (2.5%)	11 (2.6%)
Prothrombin time	3 (1.8%)	18 (4.3%)
Urine glucose	9 (5.5%)	17 (4.0%)
Creatine Kinase	7 (4.3%)	6 (1.4%)

*Incidence of events during open-label TDF treatment across studies/original arms
Note: Includes Grade 3/4 laboratory parameters occurring in > 1 Asian patient

Figure 10. Serum Creatinine Over Time



TDF Resistance Surveillance

- Comprehensive Week 192 resistance surveillance is presented in Poster 1365

Conclusions

- TDF demonstrated durable antiviral activity, good tolerability, and no development of resistance over 192 weeks with no differences between Asian patients and non-Asian patients
- Antiviral efficacy and safety results in the Asian subset were similar to the overall studies

Acknowledgements Participating Centers

Australia & New Zealand D. Cheng D. Crawford P. Desmond E. Gane J. George J. Heathcote C. Meyer M. Ngy S. Roberts J. Sautchuk W. Sievert N. Stace S. Strasser F. Willett	US & Canada N. Asahi F. Anderson M. Bennett N. Bower S. Chan A. DiBiase P. Gagliardi N. Griffin S. Gordon E. J. Heathcote	US & Canada K. Hu J. Jacobson L. Jeffers K. Kaita S.S. Lee A. Lok P. Marcellin T. Miyai R. Nijm P. Prokhorov N. Sawadkhan J. Spert K. Tchernev A. Sengul M. Sherman M. Tang H. Trinh C. Trapp K. Van Rantwijk C. Wang Z. Younossi	Bulgaria, Czech Republic & Poland R. Babianska M. Bonkowski G. Gorkun A. Gladysz A. Hadziyannis C. Houpas P. Huzar R. Japane Z. Kravtsov W. Kuznetsov T. Mach P. Marcellin P. Matham S. Maus B. Moller M. Volfov	Spain, Germany & France J. Giron F. Hosten T. Hwang C. Hwang H. Hwang D. Hwang S. Kasper M. Manns H. Sasaki P. Matham S. Maus B. Moller J. Peterson M. Pineda C. Toubert C. Trapp R. Zuckovill J. Zurek S. Zurek	Greece, Turkey & Italy P. Andreone G. Daskalakis G. Geramantis S. Ganiou S. Hadziyannis G. Kitis G. Karlos S. Ozavker M. Ricetto H. Sasaki N. Taran G. Wilson
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