Poster Number

490

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Three 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 efficacy and safety in 2 pivotal studies in chronic hepatitis B through 144 weeks (3 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

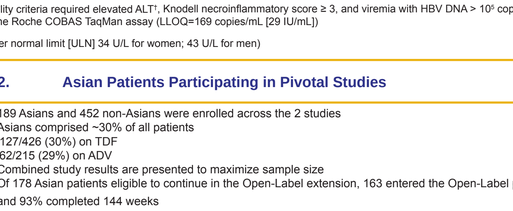
Objective

- To evaluate the efficacy and safety of tenofovir DF among Asian patients with chronic hepatitis B participating in tenofovir DF pivotal studies GS-US-174-0102 (HBeAg–) and GS-US-174-0103 (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 in year 3 with annual resistance surveillance (*creatinine clearance calculated by Cockcroft-Gault with actual body weight)
- Asian ethnicity was determined by self-report as recorded on the case report form
- Statistical methods are described in Posters 481 and 483

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



a. Combined across both pivotal studies

Eligibility criteria required elevated ALT†, Knodell necroinflammatory score ≥ 3, and viremia with HBV DNA > 10^5 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 93% completed 144 weeks

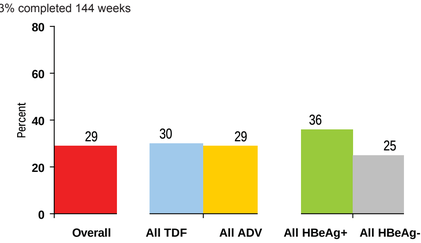


Table 1. Asian Patients: Baseline Characteristics

Characteristic	TDF (n = 127)	ADV (n = 62)
Age, yr (SD)	40 (10.8)	40 (11.2)
Weight, Kg (SD)	63.1 (11.8)	68.5 (15.3)
Male, n (%)	84 (66)	45 (73)
HBV DNA, $\log_{10}$ copies/mL (SD)	7.55 (1.43)	7.88 (1.43)
HBeAg+, n (%)	62 (49%)	33 (53%)
Knodell necroinflammation score (SD)	8.5 (2.1)	8.5 (2.1)
Cirrhosis (Knodell=4)	17%	21%
ALT, U/L (SD)	137 (131.3)	151 (138.6)
Genotype A	7 (6%)	4 (6%)
B	44 (35%)	26 (42%)
C	64 (50%)	30 (48%)
D	7 (6%)	1 (2%)

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

Results

Figure 3. Number of Patients Remaining on Studies

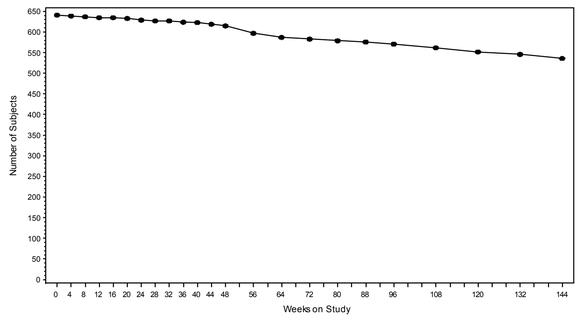
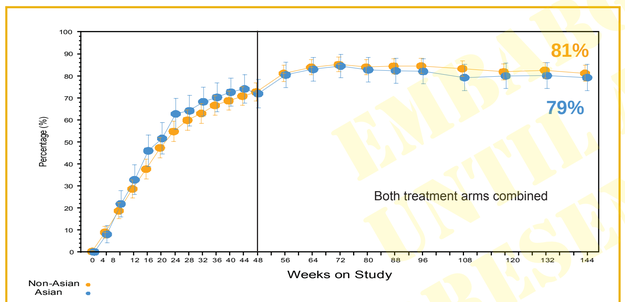


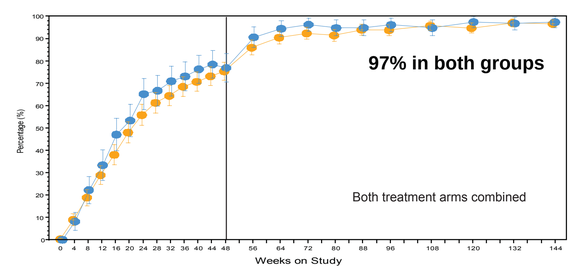
Figure 4. Percentage of Patients with HBV DNA < 400 copies/mL (69 IU/mL) (LTE-TDF)



Error bars are 95% CIs.
ITT long-term evaluation with FTC+TDF considered as failure

In the Open-Label extension population with FTC+TDF considered as failure 83% of non-Asian and 87% of Asian patients had HBV DNA < 400 copies/mL (69 IU/mL) at Week 144

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



Error bars are 95% CIs.

Figure 6. Mean HBV DNA Over Time ($\log_{10}$ copies/mL)

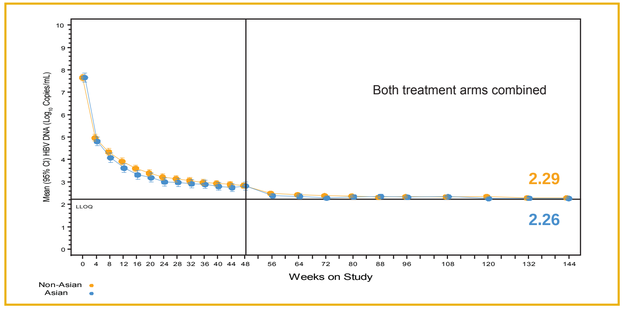
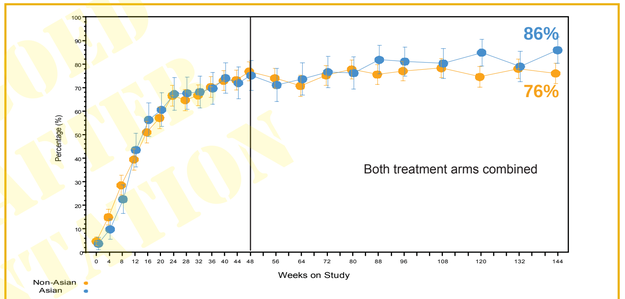


Figure 7. Percentage of Patients with Normal ALT (On-Treatment Analysis)



Error bars are 95% CIs.
ALT ULN= 34 U/L for women; 43 U/L for men

Figure 8. Mean ALT Over Time

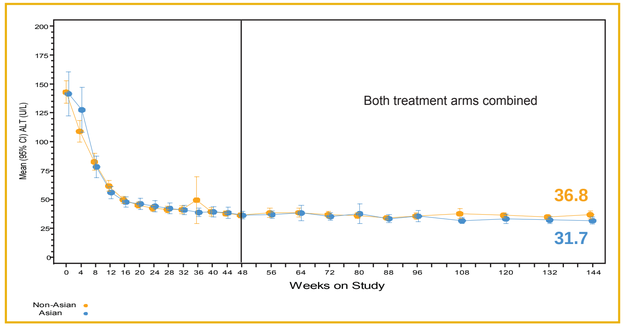
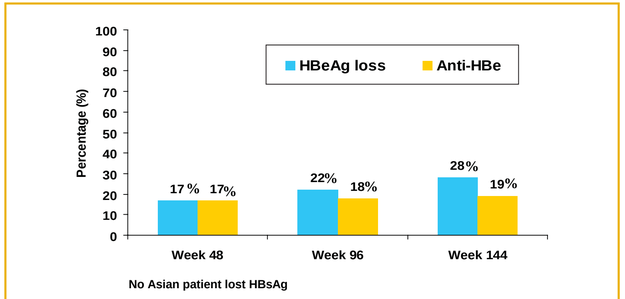


Figure 9. Serologic Response Among Asian Patients (On-Treatment Analysis)



No Asian patient lost HBsAg

Table 2. Safety and Tolerability in Patients on TDF for 144 Weeks

Parameter	Asians[a] (n = 127)	Non-Asians[a] (n = 299)
Grade 3/4 AEs	19 (15.0%)	44 (14.7%)
AEs causing discontinuation	2 (1.6%)	6 (2.0%)
Serious AEs	13 (10.2%)	42 (14.0%)
Phosphorus < 2 mg/dL	0 (0%)	7 (2.3%)
Creatinine ≥ 0.5 mg/dL increase	0 (0%)	0 (0%)
CrCl < 50 ml/min	0 (0%)	0 (0%)

a. Asians and Non-Asians originally randomized to TDF (n=426; 127 Asians; 299 non-Asians)

One Asian patient died of poorly differentiated nasopharyngeal carcinoma, and 6/189 (3.2%) had fractures (none pathologic)

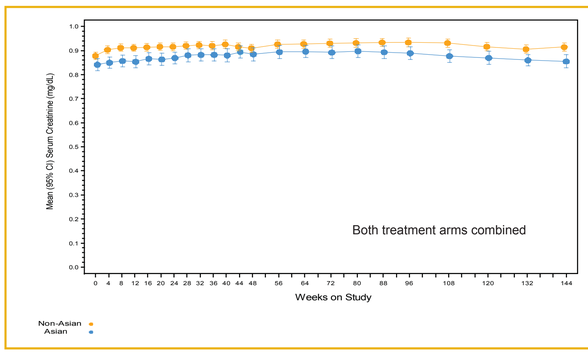
Table 3. Grade 3/4 Laboratory Values in Patients on TDF for 144 Weeks

Parameter	Asians[a] (n = 127)	Non-Asians[a] (n = 299)
Serum amylase	8 (6.3%)	14 (4.7%)
Serum lipase	2 (1.6%)	5 (1.7%)
ALT	16 (12.6%)	32 (10.7%)
AST	6 (4.7%)	19 (6.4%)
Prothrombin time	3 (2.4%)	15 (5.0%)
Urine glucose	5 (3.9%)	16 (5.4%)
Creatine Kinase	7 (5.5%)	7 (2.3%)

a. Asians and Non-Asians originally randomized to TDF (n=426; 127 Asians; 299 non-Asians)

Note: Includes Grade 3/4 laboratory parameters occurring in > 1 Asian patient

Figure 10. Serum Creatinine Over Time



TDF Resistance Surveillance

- Comprehensive Week 144 resistance surveillance is presented in Poster 480
- Across both pivotal studies 4 Asian patients had HBV DNA > 400 copies/mL (> 69 IU/mL) at Week 144
  - 1 had no change from baseline in HBV pol/RT
  - 2 had polymorphic site change
  - 1 could not be genotyped

Conclusions

- **TDF demonstrated durable antiviral efficacy, good safety and tolerability with no differences between Asian patients and non-Asian patients**
- **HBeAg loss and seroconversion are slowly increasing over time; no HBsAg loss has been observed yet in the Asian subpopulation of studies 102 and 103**