Poster 180

Long-term Efficacy and Safety of Tenofovir Disoproxil Fumarate (TDF) in Children with Chronic Hepatitis B (CHB): Final Results from a Placebo-Controlled Trial

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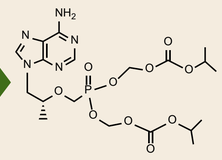
Background and Aim

TDF Study 0144

- Tenofovir disoproxil fumarate (TDF) is a potent chronic hepatitis B (CHB) treatment[1-3]
  - High viral suppression rates, favorable safety/tolerability, and no resistance documented through 8 years in adults[3]
  - Fibrosis regression and cirrhosis reversal occur in a majority of treated patients[2]
  - Potential for bone and/or renal complications in a patient subset[3]
- In children, TDF was superior to placebo at Week 48 in the proportion with HBV DNA <69 IU/mL, and was safe and well tolerated; however, bone mineral density increases were smaller than with placebo[7]

TDF
Nucleotide reverse transcriptase inhibitor

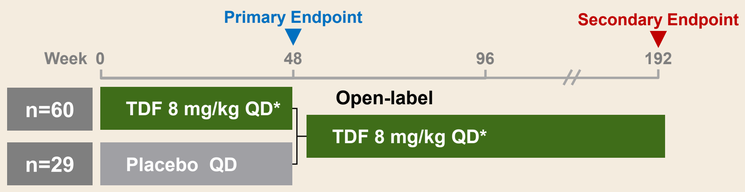


Study Aim

- To evaluate the long-term efficacy and safety of TDF compared with placebo followed by TDF treatment in children 2 to <12 years of age with CHB

Methods

Study Design



*Up to maximum of 300 mg QD; TDF tablets (150, 200, 250, or 300 mg) or powder (40 mg/g) formulation. †AASLD criteria: normal ALT ≤30 U/L for males and females 0–12 years. ALT, alanine aminotransferase; CL_{Cr}, estimated glomerular filtration rate using Schwartz formula; HBeAg, hepatitis B e antigen

- Double-blind, placebo-controlled, Phase 3 study
- Key inclusion criteria
  - Aged 2–<12 years at enrollment
  - HBeAg-positive or HBeAg-negative CHB at screening
  - HBV DNA ≥4.2 $\log_{10}$ IU/mL (≥10^5 copies/mL); ALT ≥1.5 x ULN†; CL_{Cr} ≥80 mL/min/1.73m^2
- 2:1 randomization
  - Stratified by age (2–<6 and 6–<12 years) and geographic location (N America/Europe and Asia)
- Open-label extension phase through Week 192 wherein all patients were eligible to receive TDF

Study Endpoints for Long-term Analysis

Efficacy

- **Antiviral efficacy endpoint:** HBV DNA <69 IU/mL (<400 copies/mL) at Week 192
  - COBAS® AmpliPrep/COBAS® TaqMan® HBV Test, v2.0 (LLOQ=20 IU/mL)
- **Other secondary endpoints**
  - HBV DNA <29 IU/mL at Week 192
  - ALT normalization (central laboratory and AASLD laboratory criteria)*
  - Serology (HBeAg and HBsAg loss/seroconversion)
  - Composite virologic, biochemical, and serological endpoints
- **Resistance:** Population sequencing of pol/RT for virologic breakthrough or discontinuation with viremia

Safety

- **Overall:** AEs and laboratory abnormalities (Open-label Safety Analysis Set)
- **Bone:** change in spine and whole body (minus head) BMD; bone turnover markers
- **Renal:** change in sCr, sPO_4, and CL_{Cr}, and markers of tubular function

*Central laboratory criteria: ≤34 U/L for females 1–15 years or males 1–9 years; ≤43 U/L for males 10–15 years. 2016 AASLD criteria: normal ALT ≤30 U/L for males and females 0–12 years (Terrault NA et al. Hepatology 2016;63:261-83). AE, adverse event; BMD, bone mineral density, measured by dual energy x-ray absorptiometry; HBsAg, hepatitis B surface antigen; LLOQ, lower limit of quantitation; RT, reverse transcriptase; sCr, serum creatinine; sPO_4, serum phosphate.

Results

Demographics

TDF Study 0144 (Full Analysis Set)

	TDF, n=60	Placebo→TDF, n=29
Mean age, y (range)	6 (2–11)	7 (2–12)
Male, n (%)	33 (55)	17 (59)
Asian, n (%)	41 (68)	17 (59)
White, n (%)	15 (25)	11 (38)
Asia region*, n (%)	33 (55)	16 (55)
Mean BMI, kg/m^2 (SD)	16 (2.5)	17 (2.7)
Prior HBV treatment†, n (%)	10 (17)	12 (41)‡
Mean HBV DNA, $\log_{10}$ IU/mL (SD)	8.1 (0.72)	8.1 (1.25)
HBV genotype, n (%)	A – 4 (7); B – 5 (8); C – 28 (47); D – 22 (37)	A – 2 (7); B – 1 (3); C – 11 (38); D – 15 (52)
HBeAg-positive, n (%)	56 (93)	29 (100)
Median ALT, U/L (Q1, Q3)	85 (58, 167)	97 (55, 146)
Median CL_{Cr}, mL/min/1.73 m^2 (Q1, Q3)	168 (147, 188)	166 (136, 188)

*South Korea, Taiwan, India; †Oral antivirals and/or interferon alfa; ‡p=0.012.
BMI, body mass index; Q, quartile; SD, standard deviation.

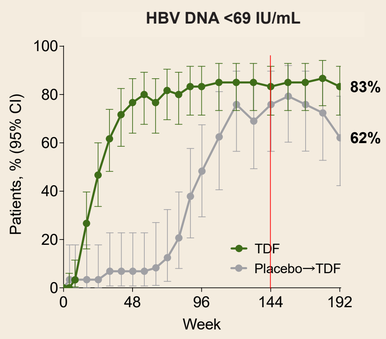
Results, cont'd

Disposition

Patients, n (%)	TDF n=60	Placebo→TDF n=29
Completed double-blind treatment	56 (93)	26 (90)
D/C double-blind study drug early	4 (7)	3 (10)
Adverse event	—	2 (7)
Noncompliance	1 (2)	—
Withdrew consent/assent	3 (5)	1 (3)
Entered open-label TDF phase	56 (93)	25 (86)
Completed open-label study drug	55 (92)	22 (76)
D/C open-label study drug early	1 (2)	3 (10)
Investigator decision	1 (2)	1 (3)
Withdrew consent/assent	—	2 (7)

D/C, discontinued.

HBV DNA Responses Over 192 Weeks



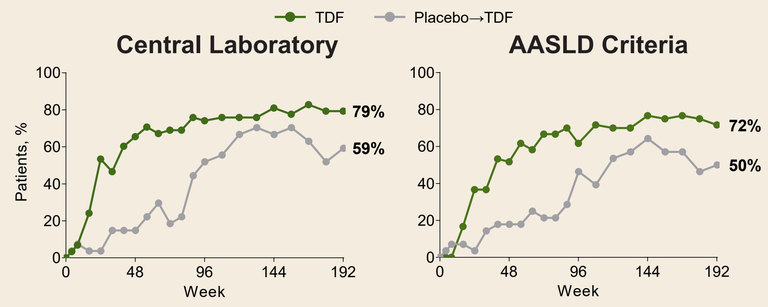
Virologic Outcomes at Week 192

Patients, n (%)	TDF n=60	Placebo→TDF n=29
HBV DNA <69 IU/mL	50 (83)	18 (62)
95% CI	72–92	42–79
HBV DNA <29 IU/mL	49 (82)	18 (62)
HBV DNA ≥69 IU/mL	10 (17)	11 (38)
≥69 IU/mL	2 (3)	2 (7)
Missing data	8 (13)	9 (31)

Results are missing equals failure from double–blind and open-label phase.
CI, confidence interval.

- High rates of virologic suppression were achieved and maintained in the TDF group
- Lower rate of viral suppression in the Placebo→TDF group is due mostly to missing data

ALT Normalization



Results are missing = failure from double-blind and open-label phase. Central lab upper limit of normal (ULN): ≤34 U/L for females 2–15 y or males 1–9 y and ≤43 U/L for males 10–15 y; AASLD criteria ULN: ≤30 U/L for males and females 0 to 12 y (Terrault NA et al. Hepatology 2016;63:261-83).

- High rates of ALT normalization were achieved and maintained in the TDF group by both methods
- Lower rates of ALT normalization at Week 192 in the Placebo→TDF group largely due to missing data

Serology at Week 192

	Patients, n/n (%)	TDF n=60	Placebo→TDF n=29
HBeAg*	Loss	30/56 (54)	10/29 (34)
	Seroconversion	19/56 (34)	10/29 (34)
HBsAg	Loss	6/60 (10)	0/29 (0)
	Seroconversion	0/60 (0)	0/29 (0)

Results are missing = failure from double-blind and open-label phase (Serologically Evaluable Full Analysis Set). *Patients who were HBeAg-positive at baseline.

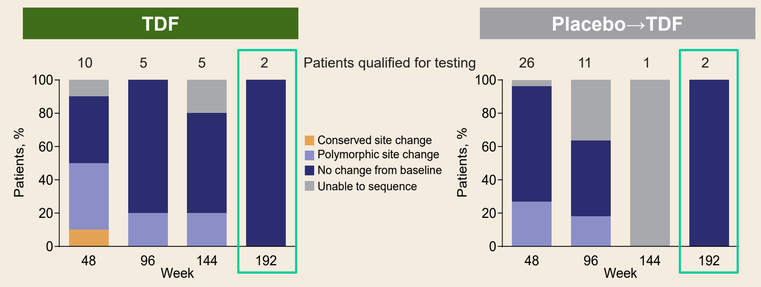
Other Efficacy Endpoints at Week 192

Patients, n/n (%)	TDF n=60	Placebo→TDF n=29
Composite of 2 endpoints: 1) HBV DNA <69 IU/mL 2) ALT normalization (central lab)	44/58 (76)	15/27 (56)
Composite of 3 endpoints: 1) HBV DNA <69 IU/mL 2) ALT normalization (central lab) 3) HBeAg loss	24/54 (44)	9/27 (33)

Results are missing = failure analysis from double-blind and open-label phase (Full Analysis Set with ALT >ULN at baseline [2 endpoints] and ALT >ULN and HBeAg-positive at baseline [3 endpoints]).

- Similar results were seen for 2 and 3 composite endpoints using ALT normalization by AASLD criteria

Resistance Analysis Through Week 192



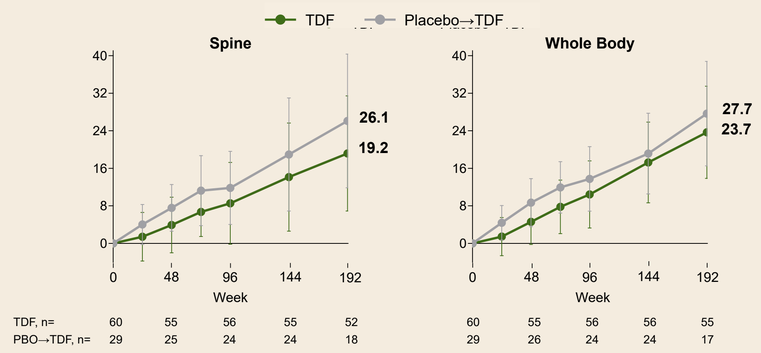
- The number of patients qualifying for sequence analysis declined over time
- No accumulation of conserved site changes was detected
- Through 192 weeks of treatment, only 2 patient in both groups qualified for phenotypic analysis
- **No patient experienced viral breakthrough or resistance to TDF during open-label phase through Week 192**

Safety (Open-label Phase)

	Patients, n (%)	TDF n=56	Placebo→TDF n=25
Adverse Events	Any AE	35 (62.5)	15 (60)
	Grade 3–4 AE*	3 (5)	3 (12)
	Serious AE†	8 (14)	3 (12)
	D/C due to AE	0	0
	Death	0	0
Laboratory Abnormalities, ≥5%	Grade 3–4	6 (11)	6 (24)
	Amylase	0	2 (8)
	Increased prothrombin time	1/42 (2)‡	1/20 (5)‡

Results from Open-label Safety Analysis Set (excludes patients who discontinued double-blind study treatment).*No Grade 3 or 4 AEs in either group were related to study drug treatment; †No SAEs in either group were related to study drug treatment. ‡Each patient experienced a single, isolated event that was not reported as an AE by the investigator.

Mean % Changes in BMD Over 192 Weeks



- Smaller mean % increases in BMD seen in the TDF vs Placebo→TDF group over 192 weeks; the clinical relevance of the differences is unknown

Renal Safety at Week 192

	TDF n=60	Placebo→TDF n=29
sCr change, mg/dL	0.12 (0.07, 0.18)	0.15 (0.07, 0.18)
PO_4 change, mg/dL	-0.1 (-0.5, 0.1)	-0.6 (-0.8, 0.1)
CL_{Cr} change, mL/min/1.73 m^2	-12.1 (-27.2, 2.4)	-5.7 (-30.6, 11.5)
Confirmed renal events, n (%)		
sCr ≥0.5 mg/dL from baseline	0	0
PO_4 <2.0 mg/dL	0	0
CL_{Cr} <70 mL/min/1.73 m^2	2 (3)	1 (3)
CL_{Cr} <50 mL/min/1.73 m^2	0	1 (3)

Continuous data are expressed as median (Q1, Q3). Confirmed events were defined as 2 consecutive visits.

- Small median declines in CLCr in both groups; few (≤3%) patients had a decline <70 mL/min/1.73 m^2
- No renal AEs reported; no study drug interruptions or discontinuations for renal events

Conclusions

- In mostly HBeAg+ pediatric patients aged 2–<12 years with CHB, long-term TDF treatment for up to 192 weeks demonstrated:
  - High rates of viral suppression, which were maintained over time
  - High rates of ALT normalization by central lab and AASLD criteria
  - Increasing rates of HBeAg loss and seroconversion; HBsAg loss was infrequent
  - No development of TDF resistance
- TDF was safe and well tolerated in pediatric patients aged 2 – <12 years
  - No Grade 3 or 4 AEs or SAEs reported were related to TDF treatment
  - Progressive increases in spine and whole-body BMD which were slightly lower for those treated with TDF vs Placebo–TDF
  - No patients experiencing a renal AE or discontinued treatment for a renal abnormality

References: **1.** Marcellin P, et al. NEJM 2008;359:2442-55; **2.** Marcellin P, et al. Lancet 2013;381:468-75; **3.** Marcellin P, et al. AASLD 2014 Oral; **4.** Terrault NA, et al. Hepatology 2018;67:1560-99; **5.** Jonas MM, et al. Hepatology 2016;63:377-87; **6.** Murray KF, et al. Hepatology 2012;56:2018-26. **7.** Chang M-H, et al. AASLD 2018, San Francisco, CA. Oral No.76.

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