A Phase 2, Double-Blind, Randomized Study Comparing The Safety of Tenofovir Disoproxil Fumarate (TDF), Emtricitabine Plus TDF (Truvada, TVD) and Entecavir (ETV) in Subjects with Decompensated Chronic Hepatitis B Liver Disease

Interim 48 Week Data

Y-F Liaw[1], C-M Lee[2], U Akarca[3], G Papatheodoridis[4], F Wong[5], TT Chang[6], A Horban[7], C Wang[8], P Kwan[9], M Buti[10], M Prieto[11], T Berg[12], K Kitrinos[13], J Sorbel[13], E Mondou[13], D Frederick[13], F Rousseau[13], E Schiff[14]

[1]Chang-Gung Memorial Hospital – LinKou, Taoyuan Hsien, Taiwan; [2]Chang-Gung Memorial Hospital – Kaohsiung Hsien, Taiwan ; [3]Ege Universitesi Tip Fakultesi Hastanesi. Izmir, Turkey; [4]Ippokration General Hospital of Athens, Athens, Greece; [5]Toronto General Hospital, Toronto, Ontario, Canada; [6]National Chen Kun University Hospital, Tainan, Taiwan; [7]Hospital of Infectious Diseases, Warsaw, Poland; [8]Virginia Mason Medical Center, Seattle, WA, USA; [9]The Gordon and Leslie Diamond Centre, Vancouver, BC, Canada; [10]Hospital General Universitari Vall d'Hebron, Barcelona, Spain; [11]Hospital La Fe, Valencia, Spain; [12]Charite Campus Virchow-Klinikum, Berlin Germany; [13]Gilead Sciences, Durham, NC, USA; [14]University of Miami School of Medicine, Miami, FL, USA

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Eugene Schiff, MD
University of Miami School of Medicine

I have financial relationship(s) within the last 12 months relevant to my presentation with:

1. **Gilead Sciences: Scientific Advisory Board, Grant/Research support and Speaker**
2. **Bristol Myers Squibb: Scientific Advisory Board, Grant/Research support**

AND

My presentation does include discussion of off-label or investigational use

(Use of tenofovir disoproxil fumarate (TDF), TDF + emtricitabine (fixed-dose combination) and entecavir in chronic hepatitis B patients with decompensated liver disease)

Study Objectives

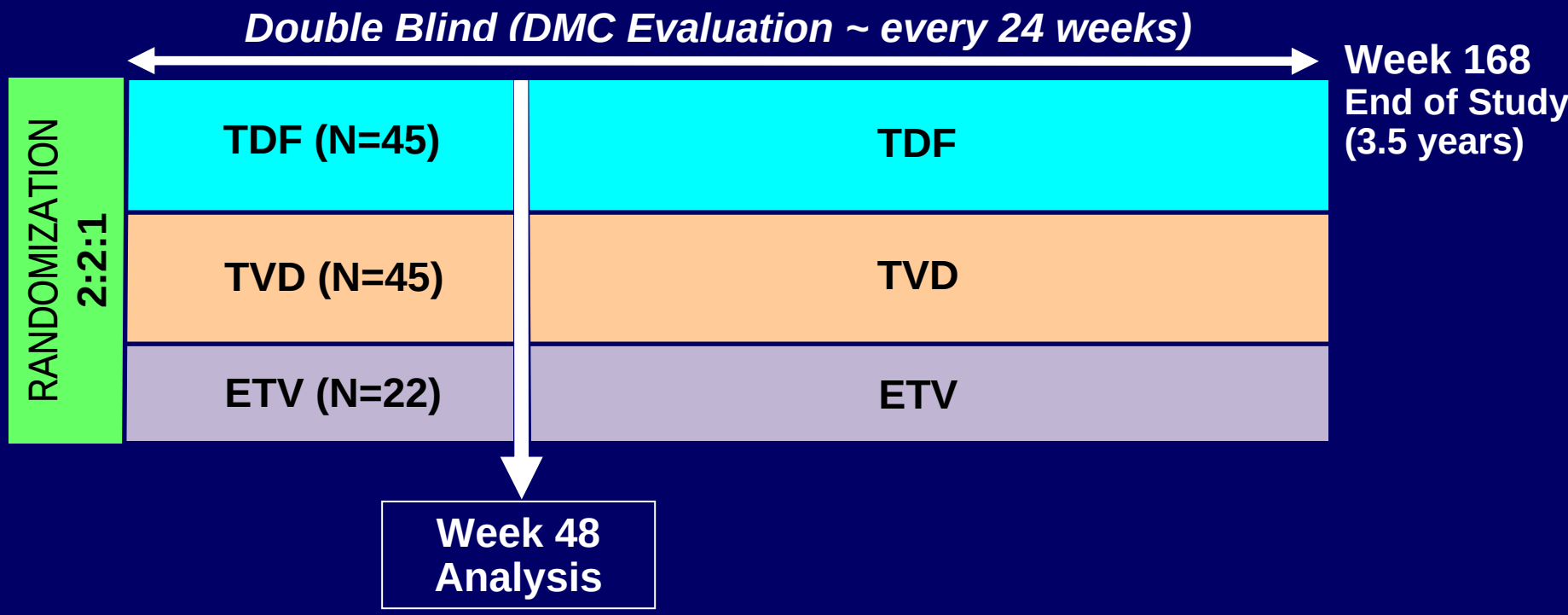
Primary objective:

- To evaluate the safety and tolerability of two tenofovir disoproxil fumarate (TDF)-containing regimens (TDF, emtricitabine [FTC] + TDF as fixed-dose combination Truvada [TVD]) compared to entecavir (ETV) in the treatment of chronic hepatitis B subjects with decompensated liver disease

Secondary objective:

- To preliminarily assess the efficacy of TDF, TVD, and ETV in the treatment of chronic hepatitis B subjects with decompensated liver disease

Study 108 Design



- Subjects meeting the criteria for insufficient decrease in plasma HBV DNA from baseline at Week 8, or had confirmed plasma HBV DNA ≥ 400 copies/mL (69 IU/mL) from Week 24 onward could begin open-label TVD
  - These subjects were considered failures in the efficacy analysis

Co-Primary Safety Endpoints

1. Proportion of subjects experiencing **tolerability failure**.

   Tolerability failure is defined as permanent discontinuation of study drug due to a treatment-emergent adverse event (AE). Any patient that temporarily discontinues study drug due to an AE but does not restart study drug was considered a tolerability failure.

2. Proportion of subjects with a confirmed increase in serum creatinine of $\geq$ 0.5 mg/dL from baseline or confirmed serum phosphorus of $<$ 2.0 mg/dL.

Patient Population

- Key eligibility criteria
  - 18–69 years of age
  - HBV DNA $\geq 10^3$ copies/mL
  - CPT score of 7–12 (inclusive) OR a past history of CPT score ≥ 7 and any CPT at screen ≤ 12
  - ALT levels $< 10 \times$ the upper limit of normal (ULN): 43 U/L for males and 34 U/L for females
  - Calculated creatinine clearance (Cockcroft-Gault) ≥ 50 mL/min
  - α-fetoprotein (AFP) ≤ 20 ng/mL and ultrasound or other imaging with no evidence of HCC, or α-fetoprotein of 21–50 ng/mL and CT/MRI with no evidence of HCC, within 6 months of screening
  - No co-infection with HCV, HIV-1, or HDV
  - No prior use of TDF or ETV
  - < 24 months prior adefovir dipivoxil (ADV)

Baseline Disease and Demographic Characteristics

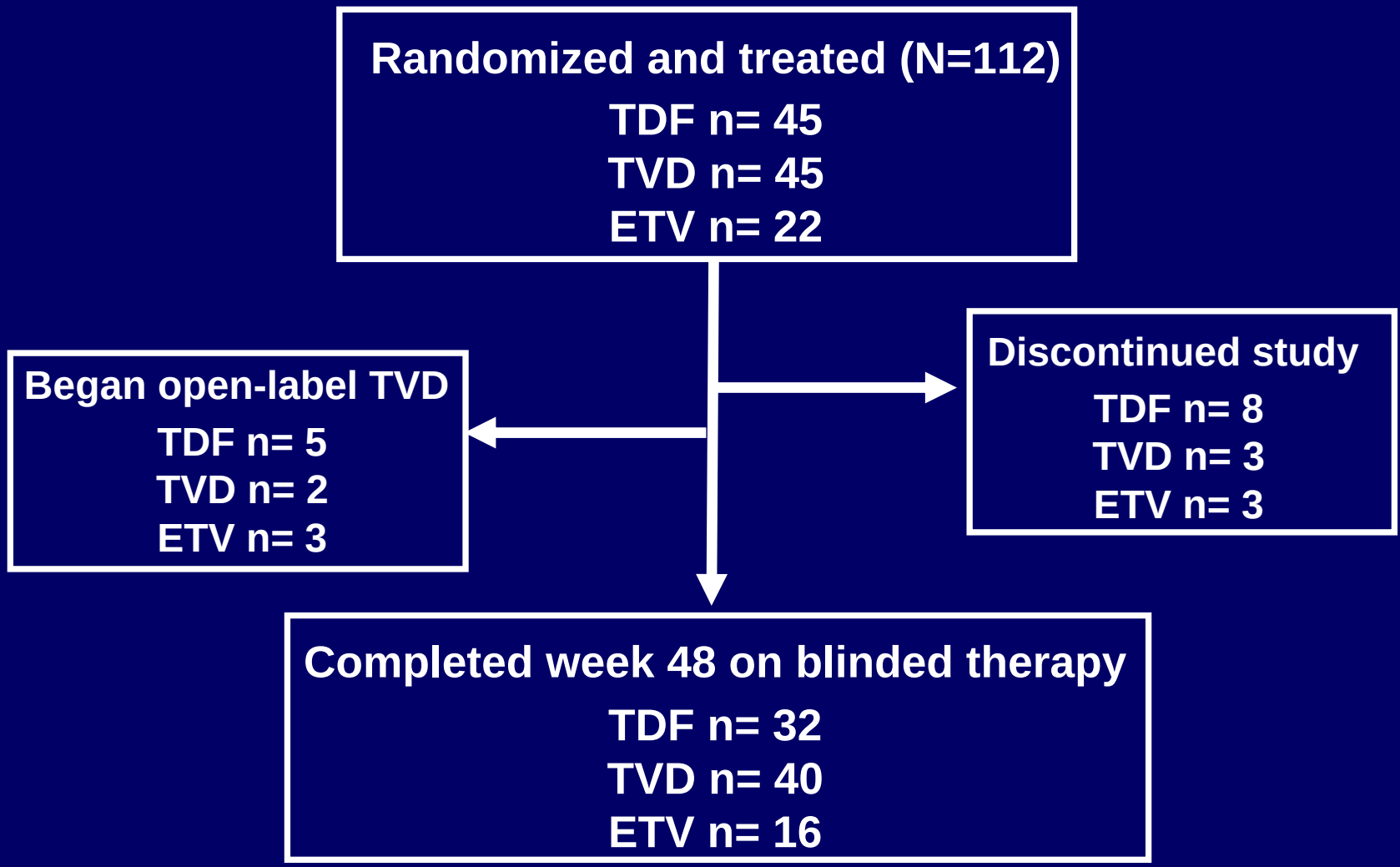
	TDF (N=45)	TVD (N=45)	ETV (N=22)
Mean Age (years)	53	49	52
Race White Asian	42% 51%	44% 53%	36% 59%
Male	82%	89%	77%
HBeAg Negative	69%	60%	68%
Median HBV DNA (log_{10} copies/mL)	5.7	6.3	5.9
% with ALT > ULN	60%	60%	77%
Median CPT score (Q1, Q3)	7 (6-8)	7 (6-9)	7 (6-8)
Median MELD score (Q1, Q3)	11.0 (9-14)	13.0 (10-17)	10.5 (9-13)

Baseline Disease and Demographic Characteristics (cont'd)

	TDF (N=45)	TVD (N=45)	ETV (N=22)
LAM- Resistance (n)*	8	10	3
HBV viral genotype (n)			
A	8	8	4
B	9	13	6
C	10	11	5
D	15	10	4
E	1	0	0
F	0	1	1
G	0	1	0
Unable to genotype	2	1	2

* 2 of the 8 subjects in the TDF arm with LAM-R at baseline also had adefovir-associated resistance mutations, rtA181T/V and rtN236T

Patient Disposition at 48 Weeks



Summary of Key Safety Results Through Week 48

	TDF (N=45)	TVD (N=45)	ETV (N=22)
Tolerability failures*	7%	4%	9%
Confirmed ≥ 0.5 mg/dL increase in creatinine or confirmed phosphorus < 2.0 mg/dL	9%[f]	7%	5%
- Confirmed ≥ 0.5 mg/dL increase in creatinine	9%	2%	5%
- Confirmed phosphorus <2.0 mg/dL	2%	4%	0

* 6 subjects discontinued due to an AE (only one DC due to AE considered related to study drug) and 1 DC'd during interruption of study drug and did not restart

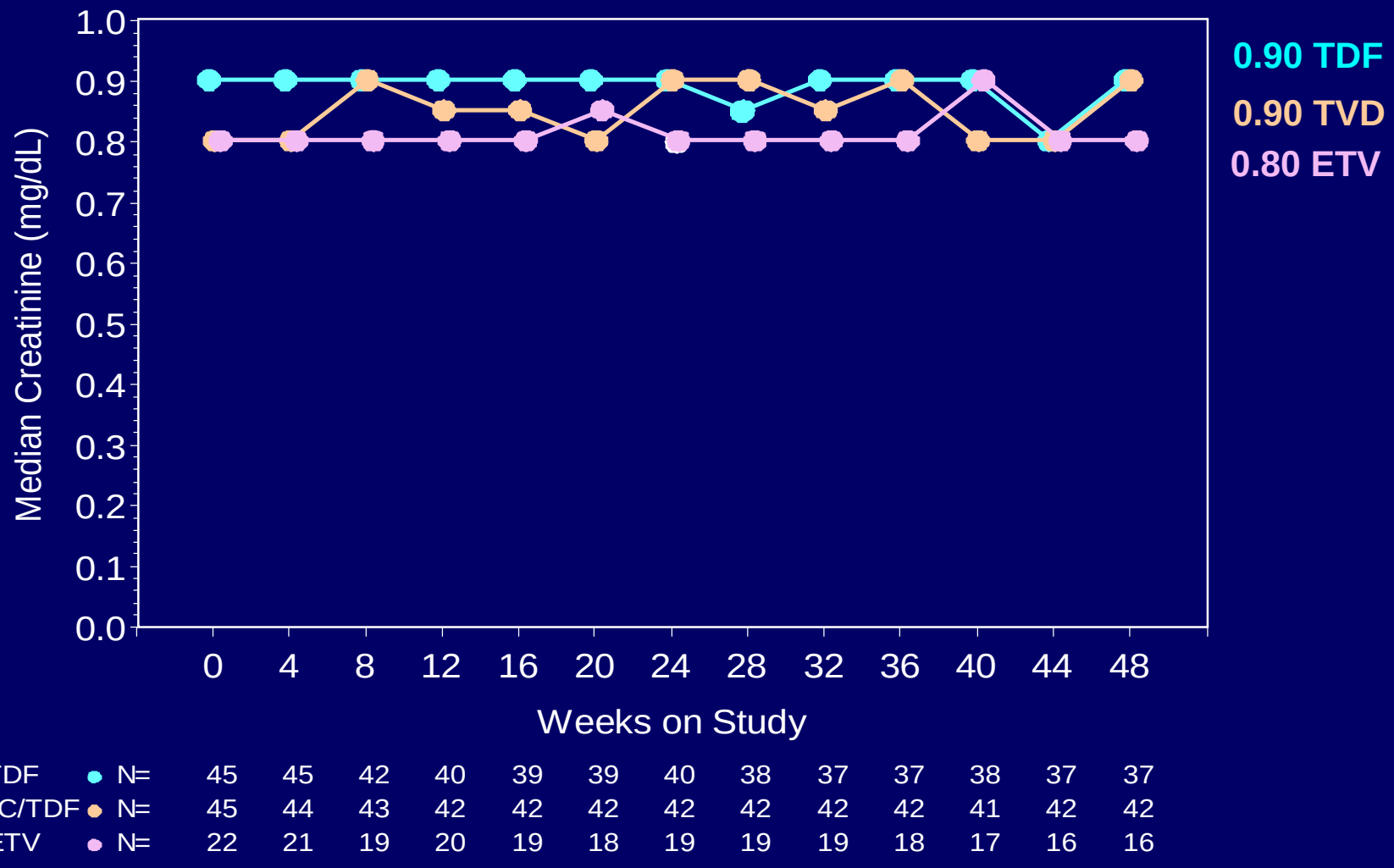
f includes the only patient reaching a coprimary endpoint after FTC/TDF switch

Summary of Key Safety Results Through Week 48 (cont'd)

	TDF (N=45)	TVD (N=45)	ETV (N=22)
Deaths*	4%	4%	9%
Grade 3/4 AEs	31%	20%	23%
Grade 3/4 study drug-related AEs	2%	0	0
SAEs	24%	42%	23%
Study drug related SAEs	2%	2%	0
AEs that resulted in discontinuation	4%	4%	9%
Grade 3/4 laboratory abnormalities	47%	51%	46%

* No death was considered related to study drug

Median Serum Creatinine (mg/dL) by Study Visit

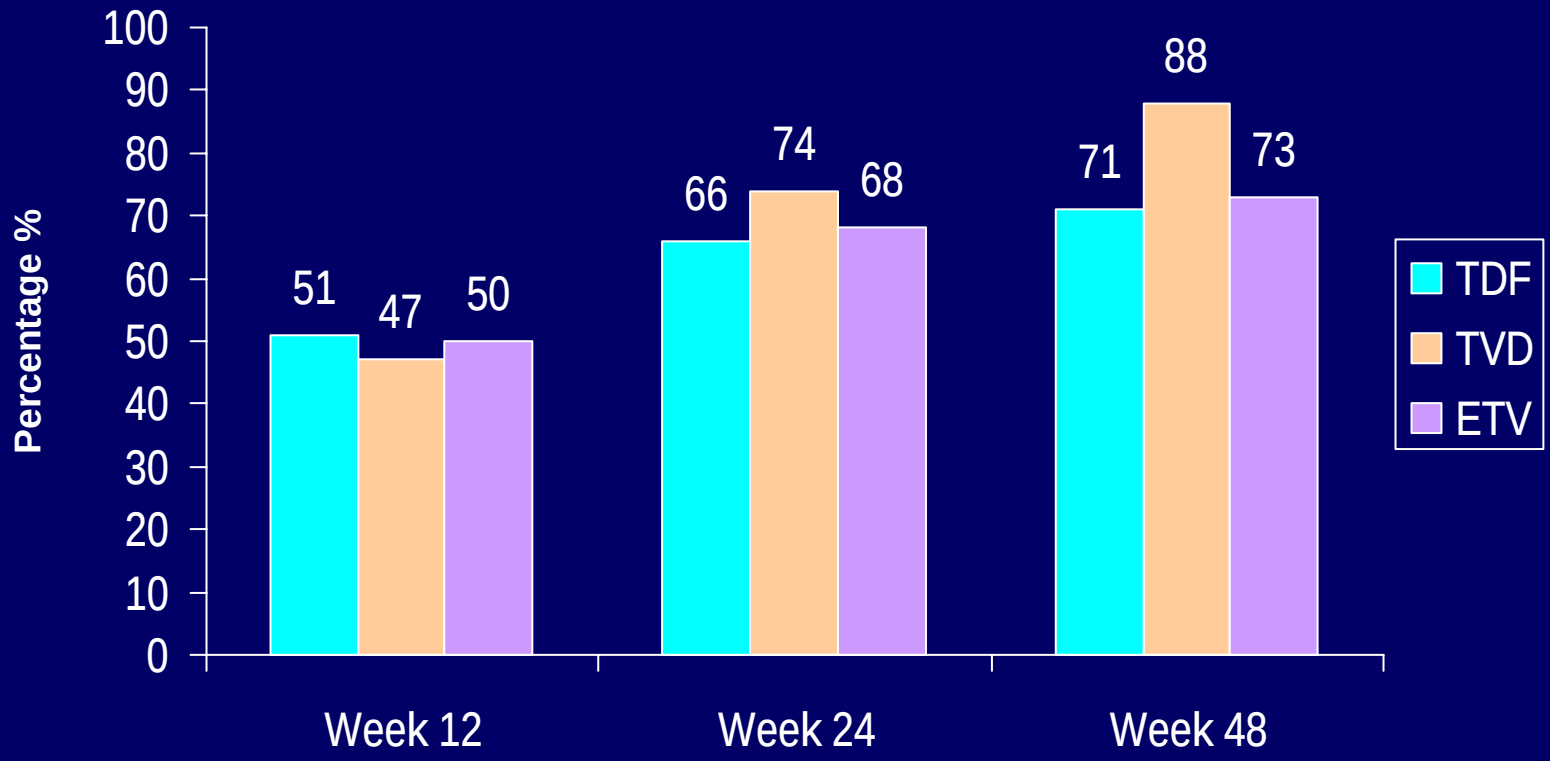


Summary of Efficacy at Week 48

	TDF (N=45)	TVD (N=45)	ETV (N=22)
% with HBV DNA < 400 copies/mL	71%	88%	73%
MELD score Median change Absolute MELD Week 48 (median)	-2.0 8	-2.0 8	-2.0 8
CPT score Mean change Absolute CPT Week 48 (median)	-1 6	-1 6	-1 5
Median ALT (U/L)	29	33	31

- An ITT noncompleter/switch = failure analysis was used
- Subjects who switched from blinded medication to open-label TVD were considered noncompleters in all 3 arms of the study
- Subjects who underwent orthotopic liver transplant (OLT) (6 total; 2 TDF, 4 FTC/TDF) are censored from the HBV DNA, serology, biochemical, MELD and CPT analyses

Percentage of Patients with HBV DNA < 400 Copies/mL (69 IU/mL): ITT: NC/S=F



Response at Week 48 by LAM Resistance

Parameter	TDF (n=45)	TVD (n=45)	ETV (n=22)
Proportion HBV DNA < 400 copies/mL by confirmed LAM-R	**4/8 (50%)**	**8/9 (89%)**	**1/3 (33%)**

- **ITT noncompleter/switch = failure analysis**
- **Subjects who had orthotopic liver transplant are censored**
  - **Hence only 9 subjects are included in the denominator of TVD arm despite 10 subjects with LAM-R at baseline**

- **12/17 (71%) on TDF-containing treatment had HBV DNA < 400 c/mL**
- **None of the subjects on TDF-containing treatment developed amino acid substitutions associated with resistance to tenofovir**

Serology at Week 48

	TDF (n=14)	FTC/TDF (n=15)	ETV (n=7)
Proportion with HBeAg loss	**21%**	**27%**	**0**
Proportion with HBeAg seroconversion	**21%**	**13%**	**0**

ITT non-completer/switch = failure analysis

- No subject experienced s loss

Conclusions Through 48 Weeks

- All treatments were well-tolerated and had comparable safety and tolerability
- The overall incidence of renal events was low and no significant renal safety difference was observed between groups in this vulnerable population
- HBeAg loss or seroconversion was only observed in the TDF containing regimens
- The combination of TDF and FTC may have a role in the treatment of patients with decompensated liver disease

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