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Tenofovir Disoproxil Fumarate (TDF) Versus Emtricitabine Plus TDF (FTC/TDF) for Treatment of Chronic Hepatitis B (CHB) in Patients with Persistent Viral Replication Receiving Adefovir Dipivoxil

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Introduction

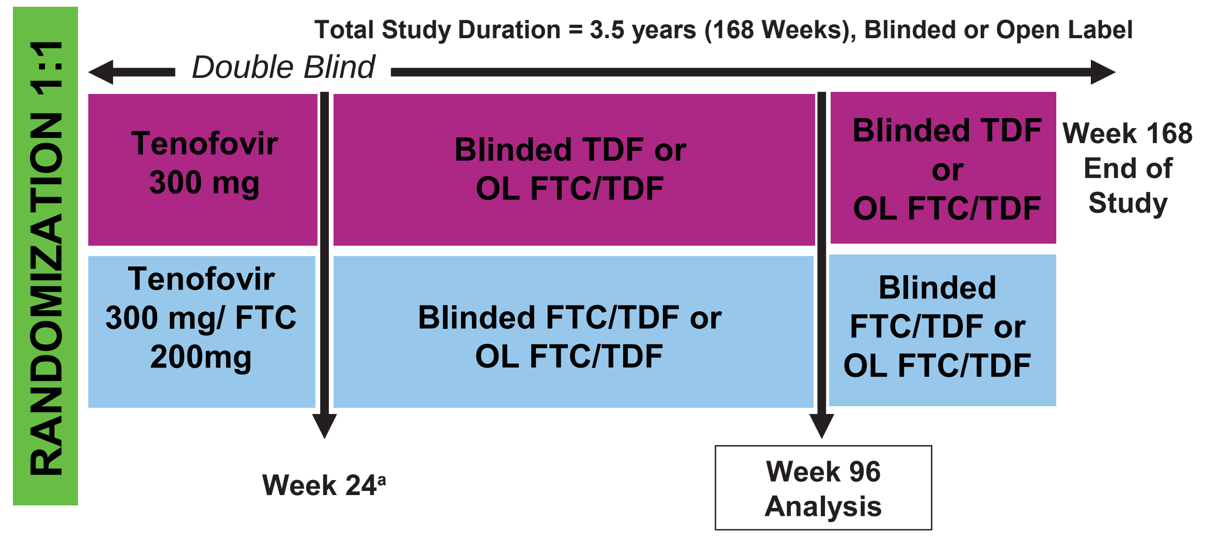
- Virologic suppression by adefovir dipivoxil (ADV) is incomplete in some cases, resulting in persistent viremia on treatment
- Options include switching to a single more potent drug or to two drugs with different resistance pathways
- TDF and FTC/TDF were well tolerated and achieved complete viral suppression in 81% of patients at week 48 in this population[1]
- The preferred treatment strategy in this heavily pretreated population remains to be defined and requires continued evaluation beyond 1 year[1]

Methods

Study Objectives

Compare the efficacy and safety/tolerability of TDF monotherapy versus the fixed dose combination of emtricitabine-tenofovir (FTC/TDF) for the treatment of chronic hepatitis B infection in patients with suboptimal antiviral efficacy on ADV (most with prior/current lamivudine [LAM] use)
96 Week Data

Figure 1. Study 106 Design



a. From Week 24 on, patients with confirmed (within 4 weeks) plasma HBV DNA ≥ 69 IU/mL could add FTC (open-label fixed dose combination FTC/TDF) or discontinue from the trial and initiate commercially available therapy

Primary Efficacy Analysis

- A comparison of two treatment strategies for ADV suboptimal responders, most with prior/current lamivudine (LAM) use
  - Compare the antiviral efficacy of
    - Monotherapy with TDF 300 mg QD (with option to add FTC 200 mg versus
    - Fixed-dose combination of FTC 200 mg + TDF 300 mg QD

This analysis will consider patients as virologic failure if they have persistent HBV DNA ≥ 400 copies/mL (69 IU/mL), or a confirmed loss of response or discontinuation prior to Week 96. The addition of FTC to TDF (FTC/TDF fixed dose combination) will be analyzed by pure Intent to treat (ITT) noncompleter=failure (NC=F), i.e., subjects on open-label FTC/TDF will not be considered failures unless they meet the criteria described above.

Methods (cont'd)

Secondary Efficacy Analysis

This analysis will consider patients as virologic failure if they have persistent HBV DNA ≥ 400 copies/mL (69 IU/mL), or a confirmed loss of response, premature discontinuation from study prior to Week 96 or if they begin open-label FTC/TDF (fixed-dose combination) regardless of their original treatment assignment (i.e., subjects randomized to FTC/TDF who begin open-label FTC/TDF are counted as virologic failures, as are those who add FTC to DTF monotherapy)

Patient Population

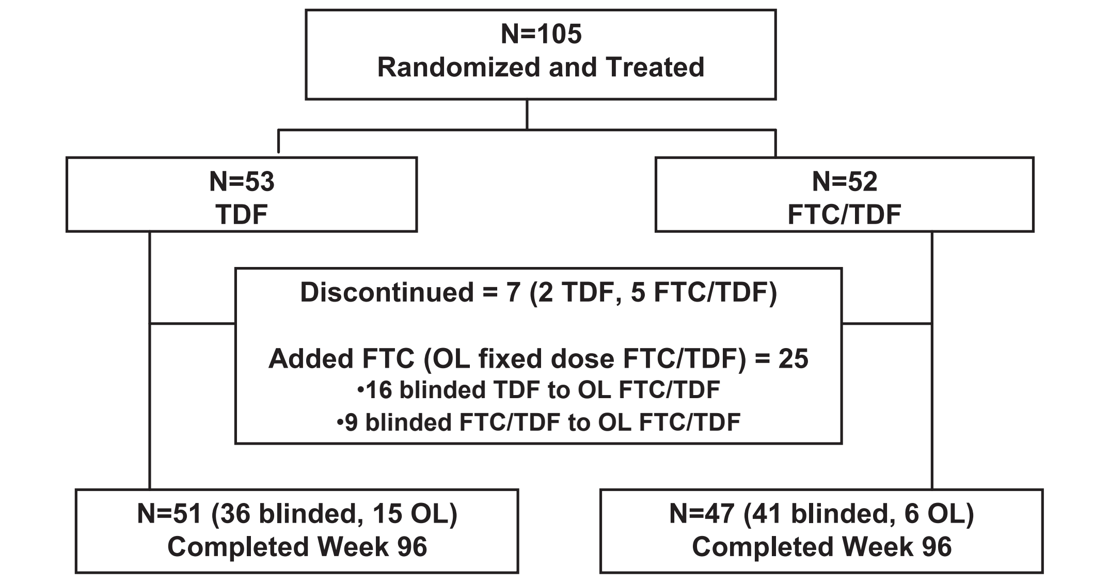
- Key eligibility criteria
  - 18–69 years of age
  - HBeAg positive or negative
  - Currently treated with ADV 10 mg QD (for ≥ 24 weeks but ≤ 96 weeks)
  - Concomitant and past treatment with lamivudine permitted
  - HBV DNA ≥ 172 IU/mL (1000 copies/mL) (Roche Cobas TaqMan Assay, lower limit of quantification 29 IU/mL [169 copies/mL])
  - ALT levels < 10 x the upper limit of normal (ULN)
  - Compensated liver disease; no evidence of HCC
  - No co-infection with HCV, HIV, or HDV

Results

Table 1. Baseline Disease and Demographic Characteristics

	TDF (N=53)	FTC/TDF (N=52)
Mean Age	40	39
Race White Asian	23 (44%) 26 (49%)	21 (40%) 18 (35%)
Male	38 (72%)	42 (81%)
HBeAg Positive	38 (72%)	39 (75%)
Mean HBV (log10 copies/mL)	6.06	5.87
ALT > ULN	27 (51%)	26 (50%)
Prior LAM exposure (≥ 12 weeks)	30 (57%)	31 (60%)
Mean prior ADV exposure (weeks; range)	62 (20-131)	59 (29-128)
HBV Viral Genotype (n)		
A	11	9
B	6	4
C	15	11
D	18	21
E	2	6

Figure 2. Patient Disposition at 2 years



N=105
Randomized and Treated

N=53
TDF

N=52
FTC/TDF

Discontinued = 7 (2 TDF, 5 FTC/TDF)

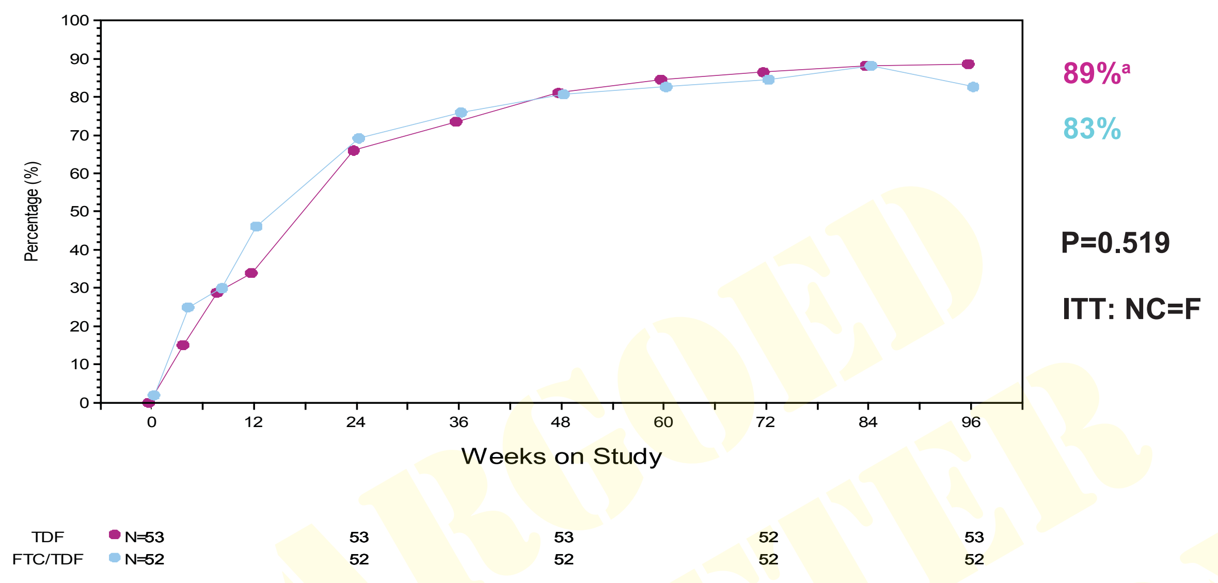
Added FTC (OL fixed dose FTC/TDF) = 25
•16 blinded TDF to OL FTC/TDF
•9 blinded FTC/TDF to OL FTC/TDF

N=51 (36 blinded, 15 OL)
Completed Week 96

N=47 (41 blinded, 6 OL)
Completed Week 96

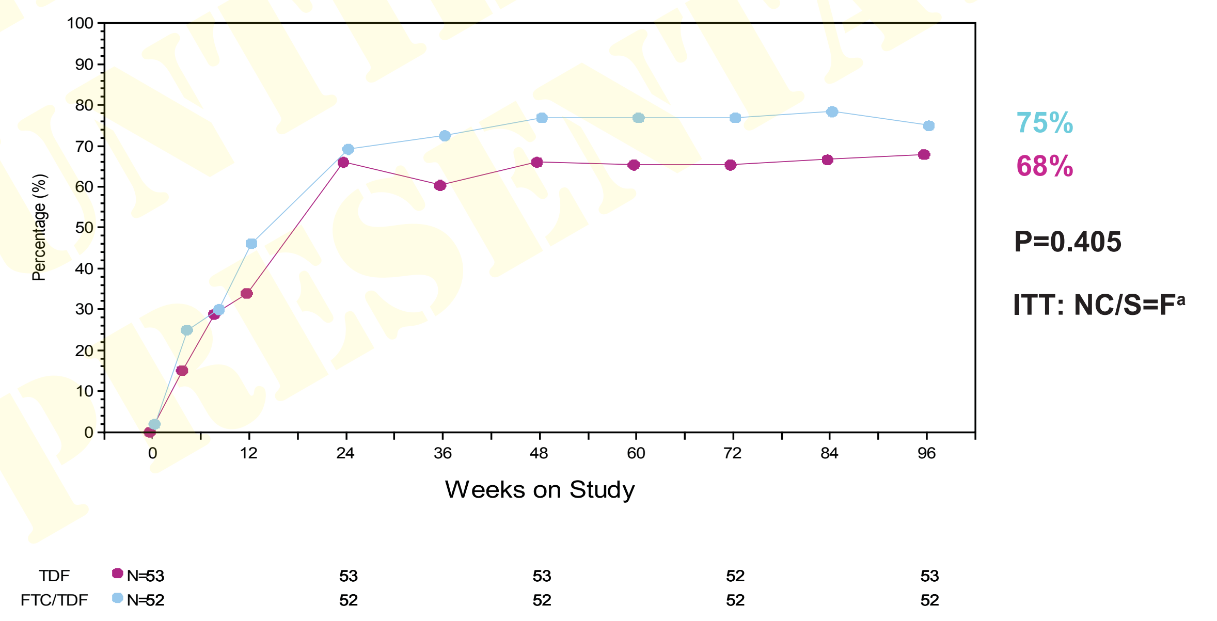
Results (cont'd)

Figure 3. Primary Efficacy Analysis: Comparison of the Two Treatment Strategies% of Patients with HBV DNA < 400 copies/mL (69 IU/mL)



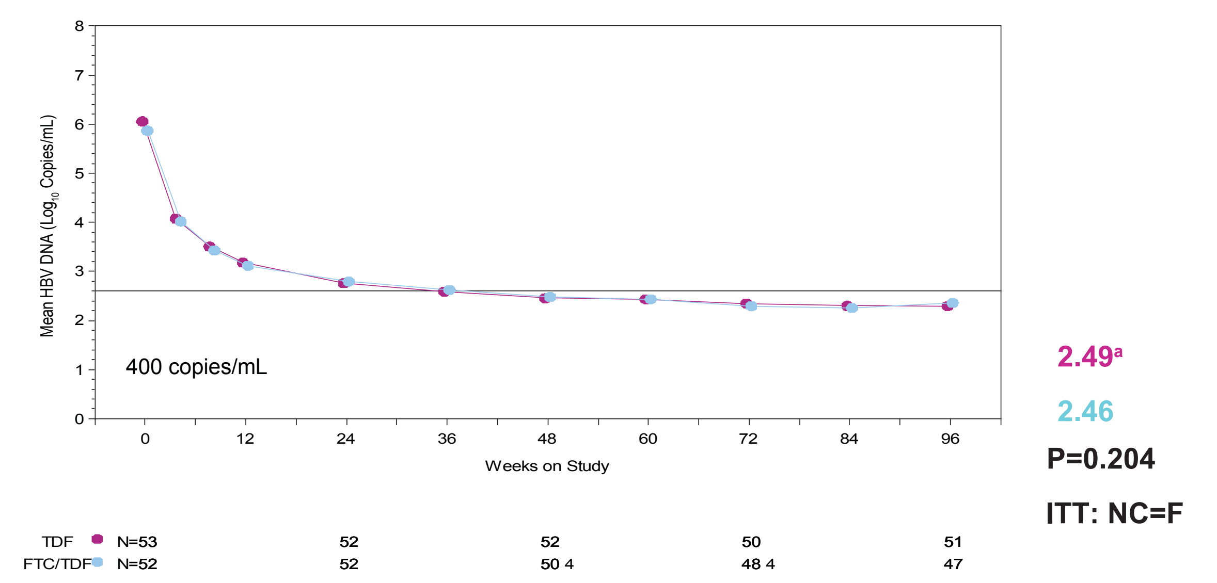
a. Includes 15 subjects who added FTC as FTC/TDF fixed-dose combination

Figure 4. Secondary Efficacy Analysis: Comparison of Antiviral Efficacy of Monotherapy versus Combination Therapy% patients with HBV DNA < 400 copies/mL (69 IU/mL)



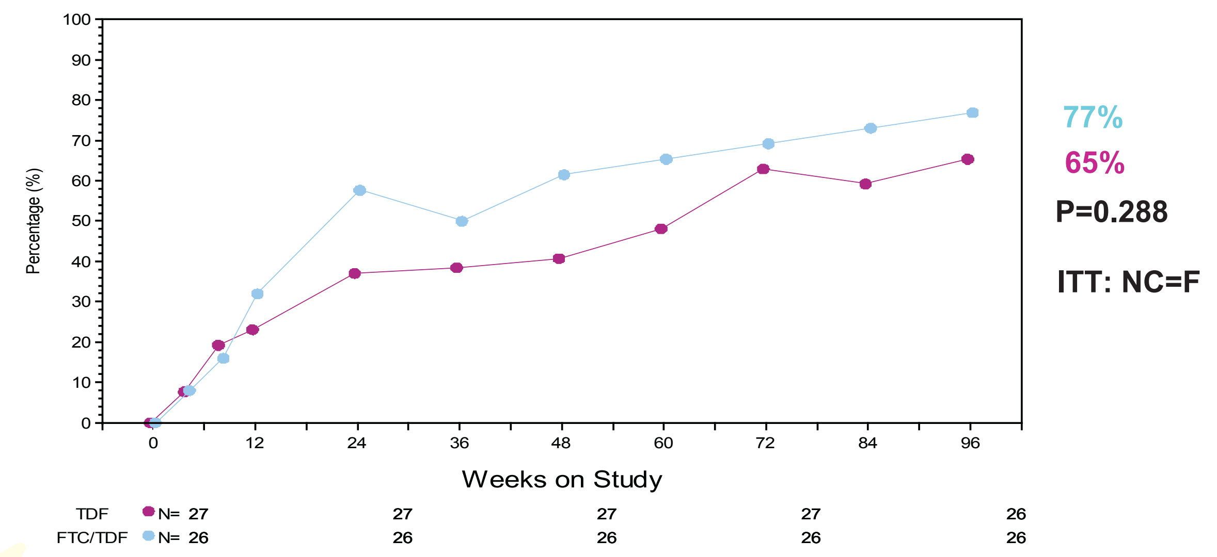
a. All subjects who began OL FTC/TDF are considered failures

Figure 5. Mean HBV DNA ($\log_{10}$) by Study Visit



a. Includes 15 subjects who added FTC as FTC/TDF fixed-dose combination

Figure 6. Proportion of Patients with ALT Normalized[a] by Study Visit



a. defined as ALT value at or below ULN for patients with baseline ALT above ULN

Table 2. Week 96 Results (cont'd)

	TDF (N=53)	FTC/TDF (N=52)
Proportion with HBeAg loss	5/38 (13%)	6/39 (15%)
Proportion with HBeAg seroconversion	3/38 (8%)	5/39 (13%)
Proportion with HBsAg loss	2/53 (4%)	0
Proportion with HBsAg seroconversion	1/53 (2%)	0

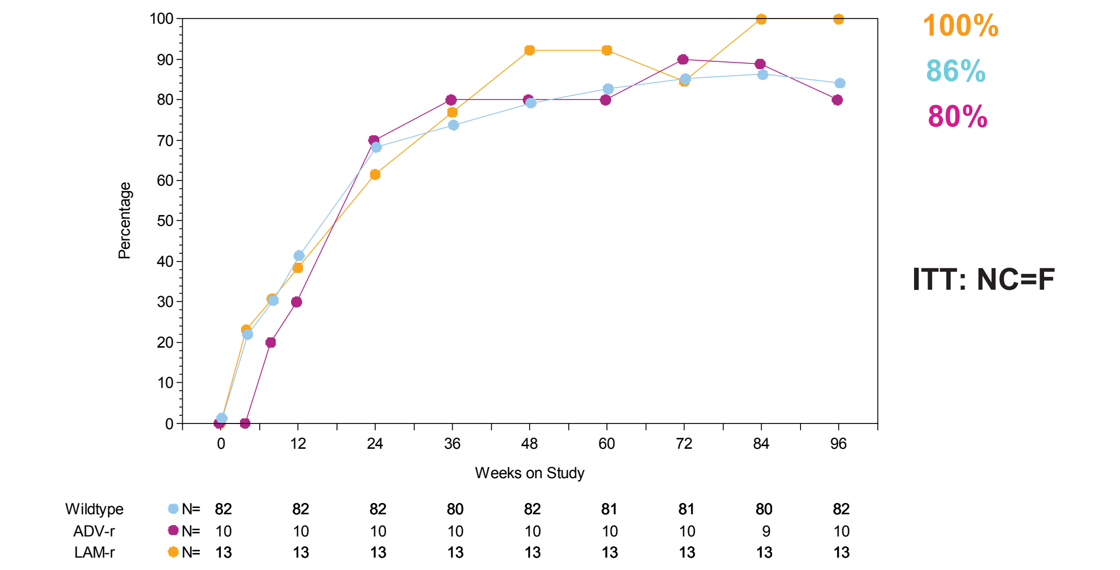
ITT non-completer = failure analysis

Table 3. Baseline Genotypic Analysis[a]

Patient Population	N
All Enrolled	105
Patients with ADV-Resistance Mutations at Baseline	8 (7.6%)
rtA181V	2
rtN236T	2
rtA181T/V + rtN236T	4
Patients with LAM-Resistance Mutations at Baseline	13 (12.4%)
rtM204V/I	1
rtL180M+rtM204V/I	12
Patients with rtA181T at Baseline	2 (1.9%)
All patients with Mutations at Baseline	23 (22%)

a. population sequencing

Figure 7. Response (HBV DNA <400 copies/mL [69 IU/mL] at Week 96) by Resistance Mutations at Baseline



- ADV-r group includes the 2 patients with rtA181T at baseline

ITT non-completer = failure analysis

Table 4. Response by Treatment Strategy (HBV DNA <400 copies/mL [69 IU/mL]) at Week 96 by Resistance Mutations at Baseline

HBV DNA < 400 copies/mL	ADV-r		LAM-r	
	TDF	FTC/TDF	TDF	FTC/TDF
Week 48 (NC=F)	7/8 (88%)	1/2 (50%)	6/7 (86%)	6/6 (100%)
Week 96 (NC=F)	7/8 (88%)	2/2 (100%)	7/7 (100%)	6/6 (100%)

Table 4. Summary of Safety Data

	TDF (N=53)	FTC/TDF (N=52)
Adverse Event, % patients with		
Grade 3 or 4 AE	1 (2%)	5 (9%)
SAE (none reported as related to study drug)	4 (8%)	8 (15%)
AE that resulted in DC	0	0
Laboratory Abnormalities, Subject with		
Any G3/4 abnormality (total events)	7 (13%)	9 (17%)
G4 (ALT >10 x ULN) and > 2 x Baseline	0	2 (4%)
Confirmed 0.5 mg/dL increase in creatinine	0	0
Confirmed CLcr decline to <50mL/min	0	0
Confirmed serum phosphorus < 2mg/dL	0	0

Conclusions

- **Both treatment strategies (TDF monotherapy with option to add FTC as combination FTC/TDF, or initial combination of FTC/TDF) were equivalent through 96 weeks of follow-up in this heavily pretreated, highly viremic population**
- **There is a non significant trend favoring combination for antiviral efficacy when considering subjects who added FTC or switched from blinded FTC/TDF to open-label as failures**
- **In patients with incomplete viral suppression on ADV majority with prior/current LAM use, the complete viral suppression noted in most patients at Week 48 on TDF or FTC/TDF (81% in both arms) was maintained at Week 96 (89% TDF; 85% FTC/TDF)**
- **Virologic response was independent of pre-existing ADV- or LAM-associated mutations**

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References

1. Berg et al, EASL 2008;