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I have financial relationships within the last 12 months relevant to my presentation with:

Hoffman La Roche, Gilead Sciences, Bristol Myers Squibb and Idenix-Novartis

AND

My presentation does include discussion of off-label use of emtricitabine for the treatment of chronic hepatitis B

Two Year Tenofovir Disoproxil Fumarate (TDF) Treatment and Adefovir Dipivoxil (ADV) Switch Data in HBeAg-Negative Patients with Chronic Hepatitis B (Study 102)

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Background

- Tenofovir DF (TDF) is a nucleotide analog and obligate chain terminator
- Approved for HIV-1 in 2001: ~ 2 million patient-years of experience
- Approved for chronic hepatitis B (CHB) in 2008
- Week 48 Phase 3 data¹ showed TDF superior to adefovir dipivoxil (ADV): 93% of TDF-treated patients versus 63% ADV-treated patients had HBV DNA <400 copies/mL

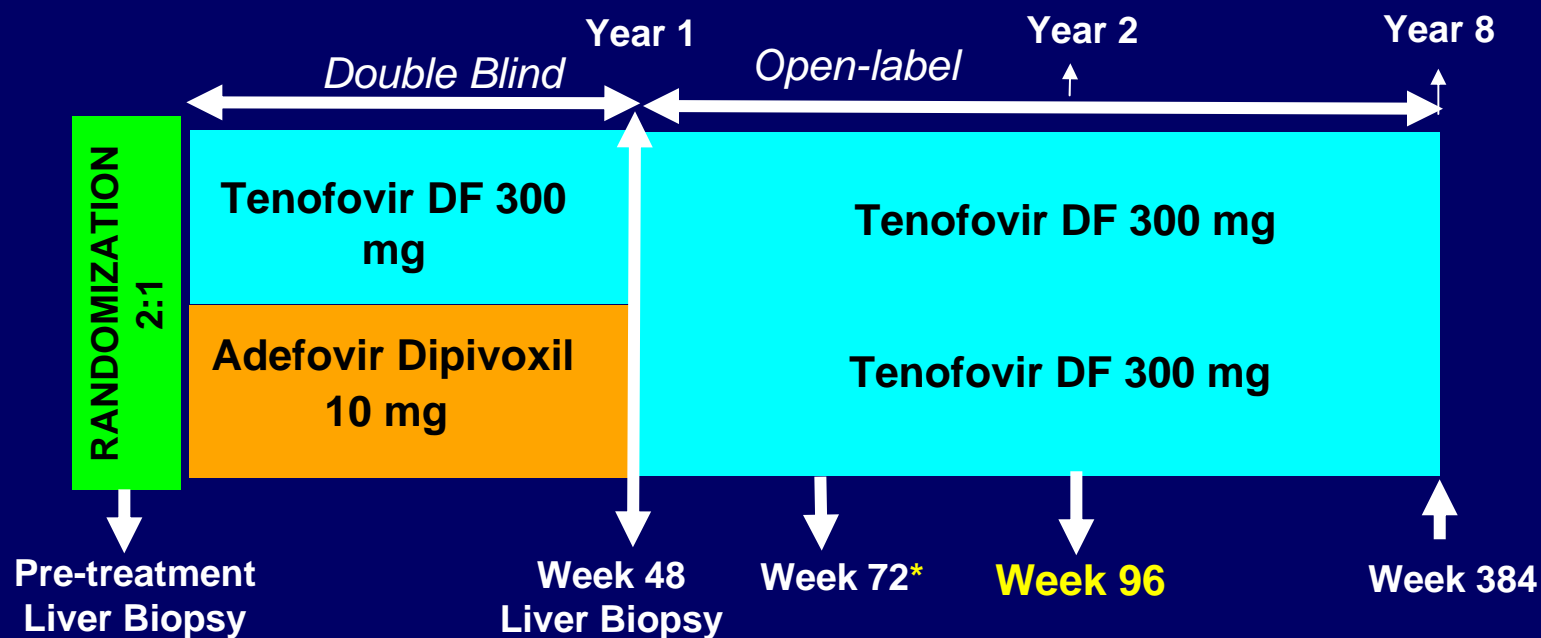
¹Marcellin, Heathcote, Buti et al 2008 NEJM 359:2442-55

Aim

To evaluate the safety and efficacy of:

- 2 years of TDF therapy
- Switch from ADV to TDF

HBeAg Negative Study 102 Design



Patients (on study)			
TDF → TDF: N= 250	235	225	89% retention
(TDF → FTC/TDF): N=		(2)*	
ADV → TDF: N=125	112	110	

*Week 72 HBV DNA \geq 400 copies/mL option to add emtricitabine (FTC) to TDF in a fixed dose tablet

Key Eligibility Criteria

- HBeAg- patients
- Age 18-69 years
- Compensated liver disease
- Lamivudine experienced or naive
- HBV DNA $> 10^5$ copies/mL
- ALT $> \text{ULN}$ and $< 10 \times \text{ULN}$
- Knodell necroinflammatory score ≥ 3
- HIV-1, HDV, HCV seronegative

Methods

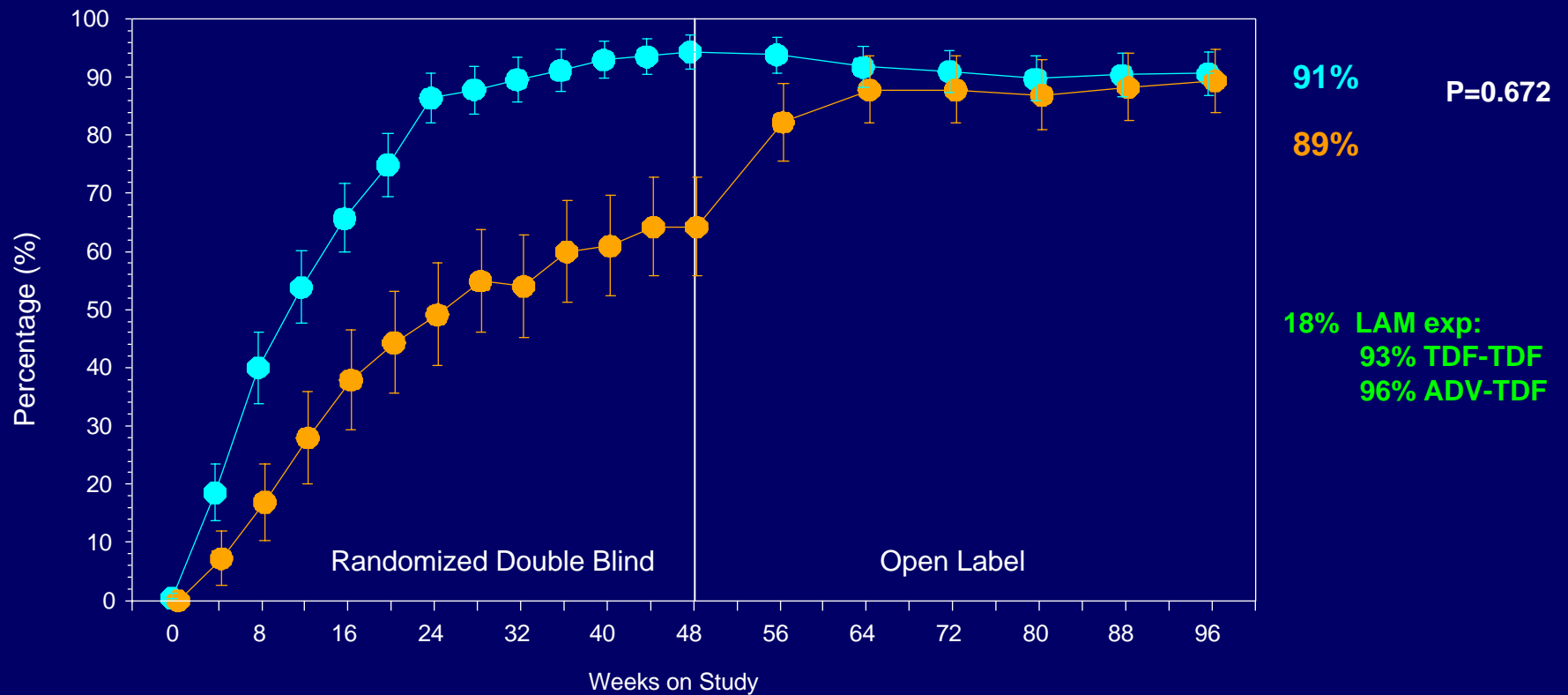
Assessments During Year 2 (after week 48 through week 96)

- HBV DNA and laboratory analyses every 8 weeks
- HBsAg every 16 weeks
- Resistance surveillance: patients with HBV DNA \geq 400 copies/mL (69 IU/mL)

Baseline Disease and Demographic Characteristics

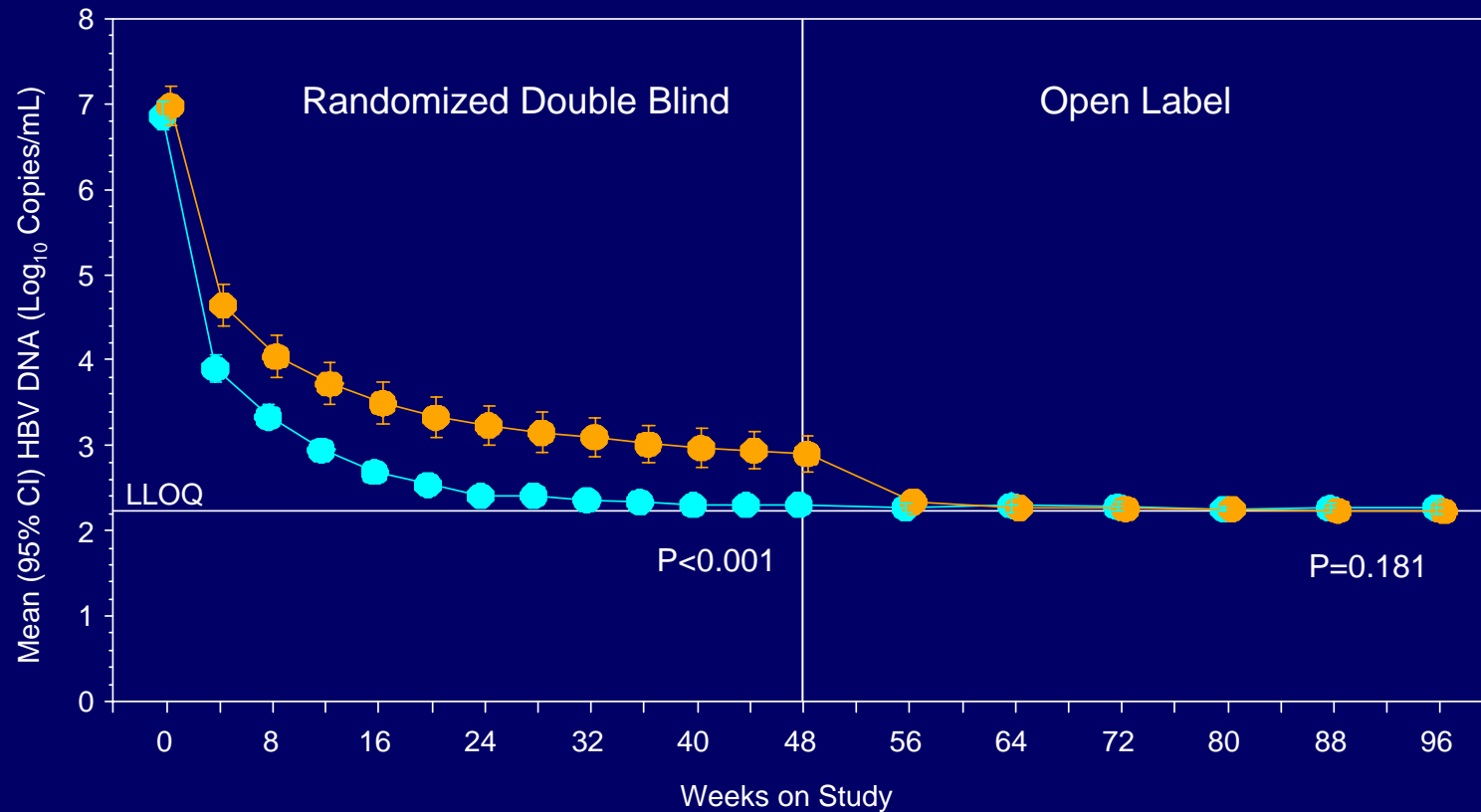
CHARACTERISTIC	TDF (N=250)	ADV (N=125)
Mean Age (years)	44	43
Race		
Caucasian	64%	65%
Asian	25%	24%
Male	77%	78%
Prior lamivudine experience	17%	18%
Mean HBV DNA (log ₁₀ copies/mL)	6.86	6.98
Mean ALT (U/L)	128	164
Mean Knodell necroinflammatory score	7.8	7.8
Mean Knodell fibrosis score	2.3	2.4
Knodell fibrosis score = 4 (cirrhosis)	19%	20%
Viral Genotype		
A	12%	11%
B	9%	14%
C	12%	10%
D	64%	63%

% Patients with HBV DNA <400 copies/mL (95% CI) (ITT)



TDF-TDF ● N=	250	245	243	248	247	242	243	234
ADV-TDF ● N=	125	125	124	120	123	123	122	122

Mean HBV DNA (\log_{10} copies/mL) (95% CI)



TDF-TDF ● N=250
 ADV-TDF ● N=125

242
 123

239
 121

242
 117

241
 117

226
 110

224
 109

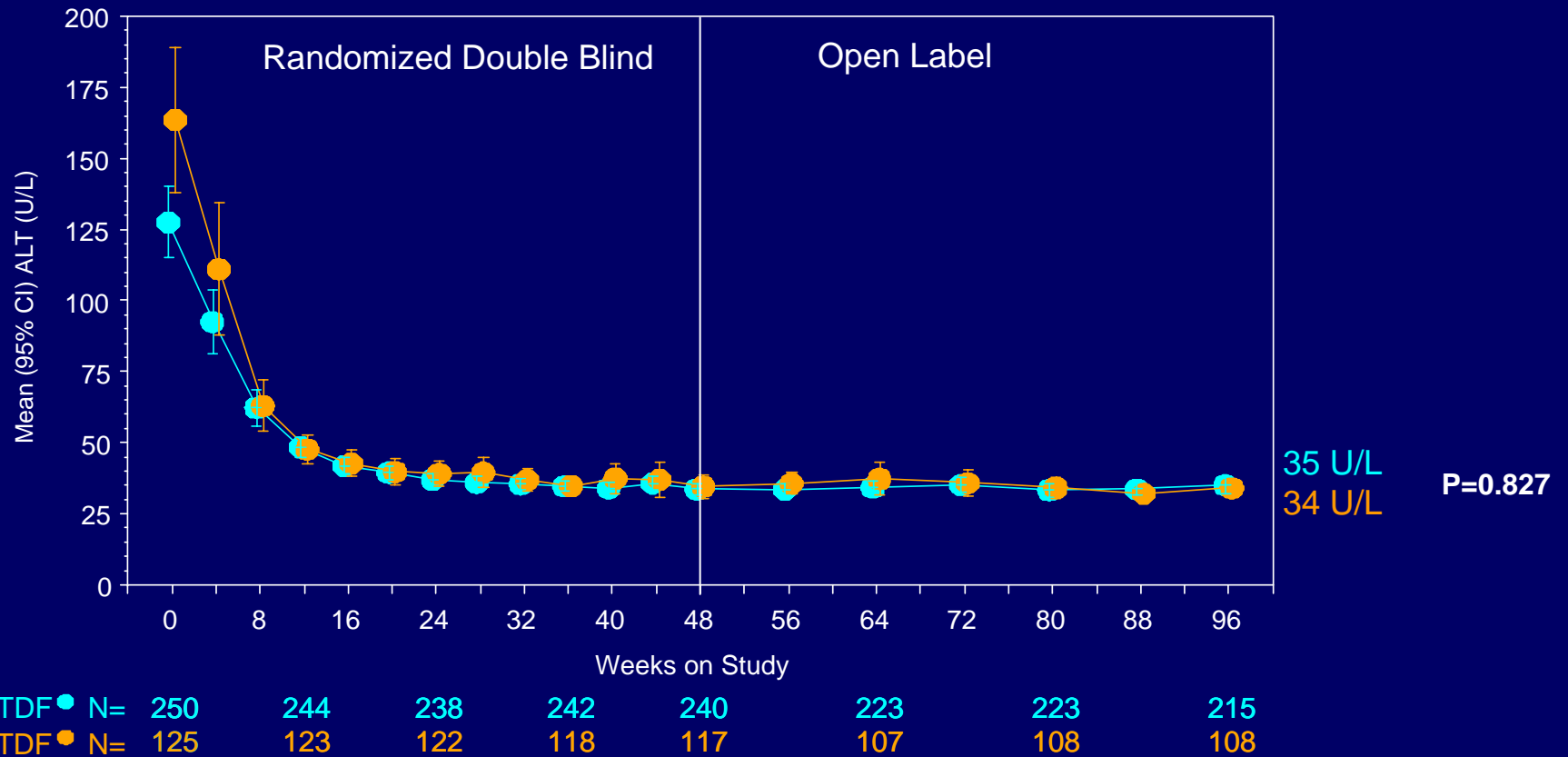
214
 109

ADV Switch Patients

HBV DNA response (below 400 copies/mL) at Week 96 for ADV patients who switched to TDF at Week 48:

- Viral suppression on ADV is maintained after switching to TDF
 - 100% of patients (76/76) were responders at Week 96
- Viral suppression of viremic patients on ADV is rapidly obtained with TDF
 - At week 64: 94%
 - At week 96: 100%

Mean ALT (U/L) (95% CI)



ULN for females=34 U/L
 ULN for males=43 U/L

Patients with Virologic Breakthrough, FTC added to TDF and HBV DNA \geq 400 copies/mL at Week 96

Patients with virologic breakthrough (defined as a confirmed 1 log₁₀ increase in HBV DNA and/or confirmed HBV DNA \geq 400copies/mL after having <400 copies/mL) between Weeks 48 and 96:

4 patients

Patients 1669 and 1674 found to be off drug

Patients 6852 and 7957 non-adherent with tenofovir drug levels BQL (below the quantifiable limit)

Patients who added FTC to TDF on/after Week 72

2 patients

Patient 7957 achieved HBV DNA <400 copies/mL at Week 96

Patient 1651 non-adherent with tenofovir levels BQL and HBV DNA >400 copies/mL at Week 96

Patients with HBV DNA \geq 400 copies/mL at Week 96:

2 patients

Patient 6852 (on TDF) non-adherent with tenofovir levels BQL

Patient 1651 (on FTC+TDF) non-adherent with tenofovir levels BQL

Resistance Surveillance

Genotyping
(HBV pol / RT)



Phenotyping
(HBV pol / RT)

All patients :

- at baseline
- yearly if ≥ 400 copies/mL (≥ 69 IU/mL)
- at discontinuation of TDF mono-therapy if ≥ 400 copies/mL

Any patient post-baseline with:

- conserved site changes in pol/RT
- virologic breakthrough
- polymorphic site changes (> 1 patient)

Resistance Surveillance Results

No resistance up to 2 years of TDF mono-therapy

No HBV pol/RT amino acid substitutions associated with TDF resistance were detected through 96 weeks of TDF monotherapy

Week 96 TDF Resistance Surveillance....

By A Snow-Lampart et al. Oral #156 "Antiviral Resistance and HBV"

March 22nd 3:50-4:05 pm (Maryland A)

Summary of Safety Data during Open Label TDF Weeks 48-96

	TDF-TDF (N=235)	ADV-TDF (N=112)
Study Drug-Related SAE	1 (<1%)	0
Deaths		
Cholangiocellular carcinoma	1 (<1%)	0
G3 or G4 Laboratory	23 (10%)	11 (10%)
Discontinue due to an AE	2 (1%)	0
HCC	1	0
dizziness, fatigue, lack of concentration	1	0
Confirmed phosphorus < 2mg/dL	2 (<1%)	1 (<1%)
Confirmed 0.5 mg/dL ↑ in creatinine	0	0
Confirmed creatinine clearance <50 mL/min	0	0

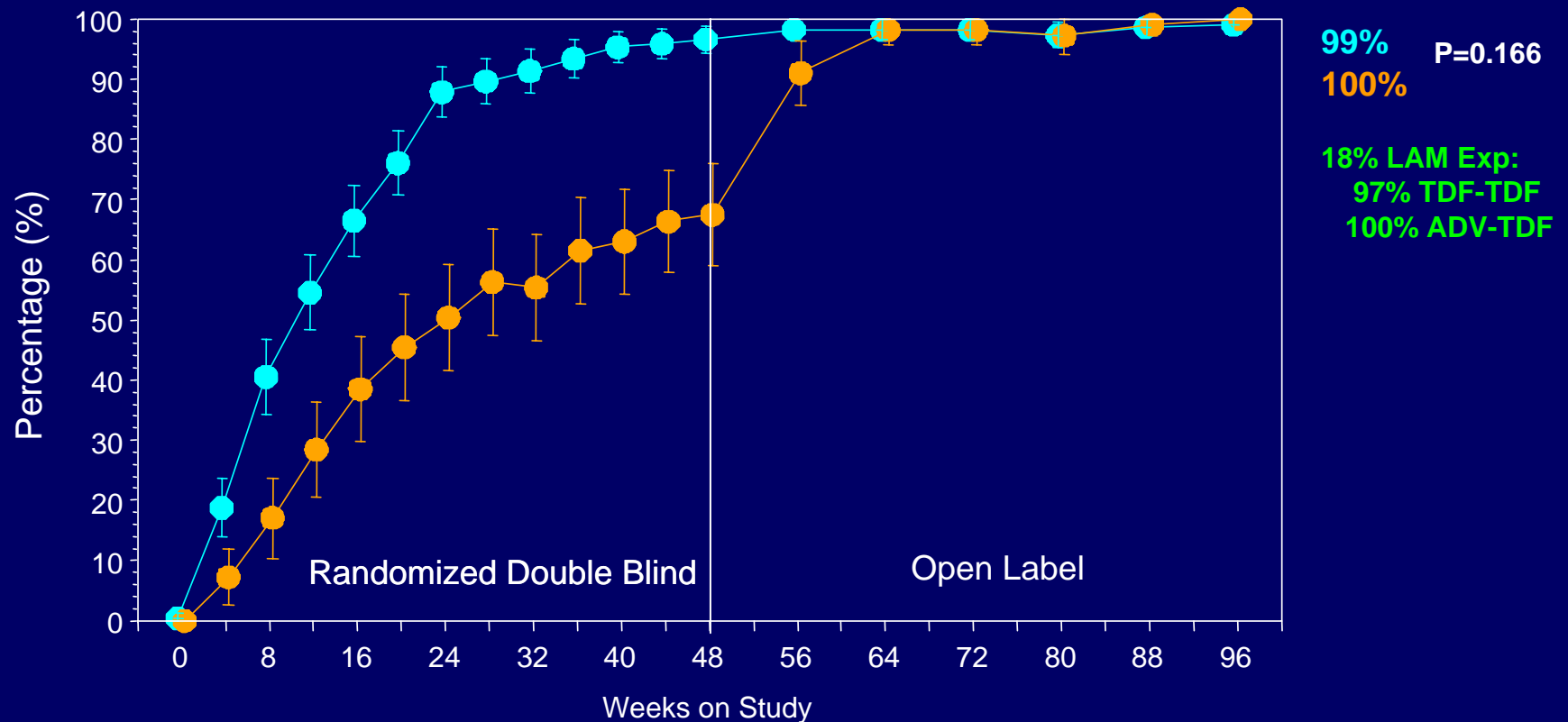
Conclusions

Week 96

- TDF demonstrated durable, potent antiviral activity through Week 96:
 - 91% of patients had HBV DNA <400 copies/mL
- No resistance to TDF monotherapy detected up to 2 years
- Patients can safely and effectively switch from ADV to TDF treatment:
 - 89% of patients had HBV DNA <400 copies/mL
- TDF was well tolerated through Week 96

Backup Slide

% Patients with HBV DNA <400 copies/mL (95% CI) (On-Treatment Analysis)



TDF-TDF	N=	250	242	239	242	241	226	224	214	~ 89% Retention
ADV-TDF	N=	125	123	121	117	117	110	109	109	