

The Antiviral Response To Tenofovir Disoproxil Fumarate (TDF) is Comparable in Lamivudine (LAM)-Naïve and LAM-Experienced Subjects Treated for Chronic Hepatitis B (CHB)

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Introduction

- Based on data from the Phase 3 studies, GS-174-0102 (HBeAg negative) and GS-174-0103 (HBeAg positive), tenofovir DF showed superior efficacy to adefovir dipivoxil
 - At Week 48, 76% of HBeAg+ patients and 93% of HBeAg- patients receiving tenofovir DF had HBV DNA <400 c/mL (69 IU/mL)
- Both lamivudine naïve (<12 weeks treatment) and lamivudine-experienced patients were enrolled into these studies

Objective

- To evaluate the Week 48 response to tenofovir DF in the subset of lamivudine-experienced (LAM Exp) compared to lamivudine-naïve (LAM Naïve) patients enrolled in these phase 3 studies

Endpoints

- Proportion of patients with HBV DNA <400 c/mL (69 IU/mL)
- Mean HBV DNA change from baseline
- Proportion of patients with normal ALT
- Safety and tolerability

Methods

Key eligibility criteria for Studies 102 (HBeAg-) and 103 (HBeAg+)

- Age 18-69 years
- Compensated liver disease
- HBV DNA $> 10^5$ c/mL (HBeAg-) or HBV DNA $> 10^6$ c/mL (HBeAg+)
- ALT $> \text{ULN} < 10\text{xULN}$ (HBeAg-) or ALT $> 2\text{xULN} < 10\text{xULN}$ (HBeAg+)
- Knodell Necroinflammatory score ≥ 3
- HIV, HDV, HCV negative

Methods (cont'd)

Assessments

- Liver biopsies pre-treatment and between Week 44 and 48
- HBV DNA and Laboratory analyses (serum chemistry, hematology, and urinalysis) every 4 weeks
- HBeAg and HBsAg every 12 weeks
- HBV DNA measured using the Roche COBAS TaqMan assay (LLOQ=169 c/mL or 29 IU/mL)
- Resistance surveillance performed at baseline for all patients and Week 48 for all viremic patients (≥ 400 c/mL or 69 IU/mL)

Tenofovir DF Enrollment: by Study & Prior LAM Experience

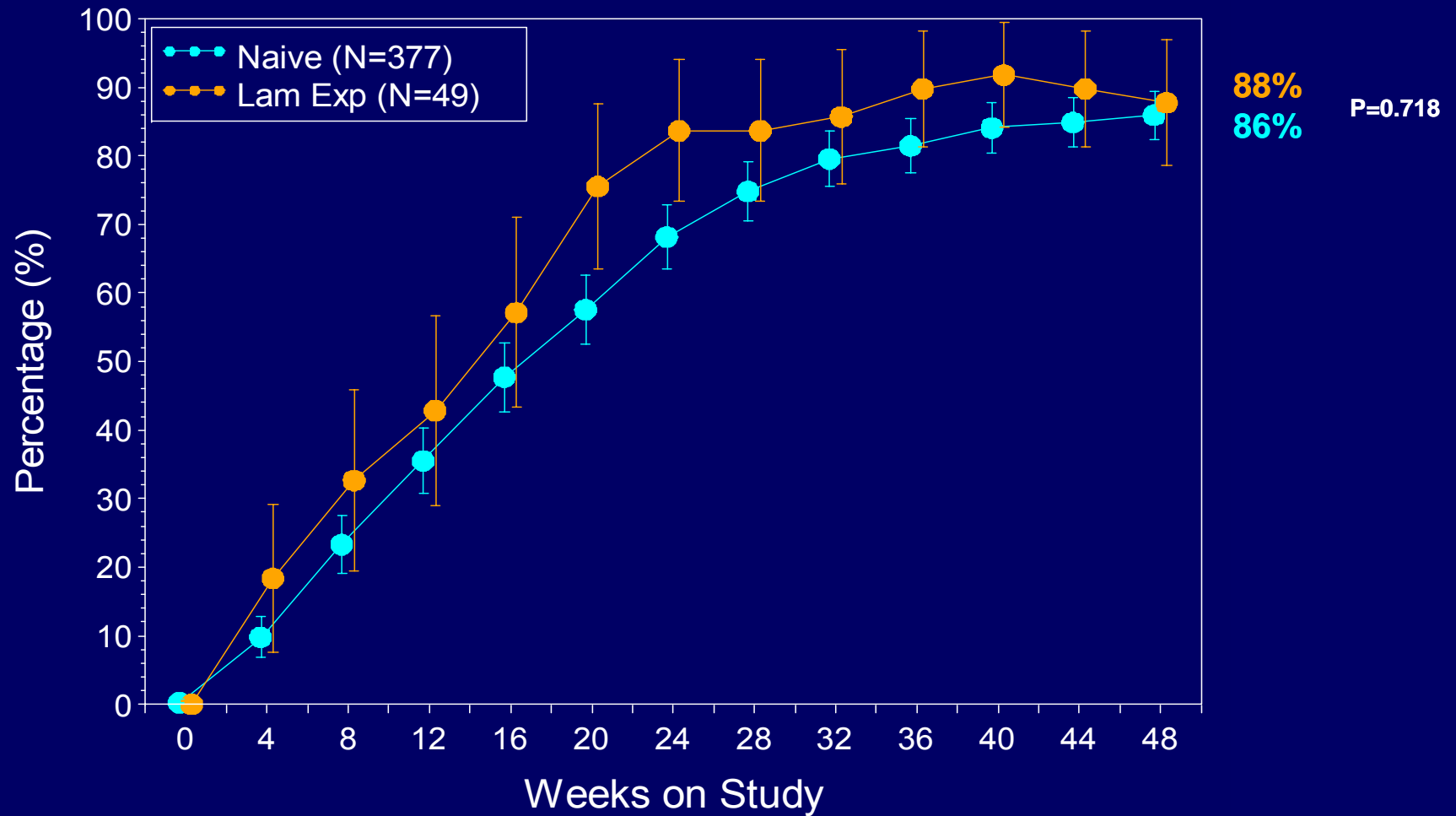
	Study 103 HBeAg Positive N=176	Study 102 HBeAg Negative N=250	Total
LAM-Naive, n	168	209	377
LAM-Experienced, n	8	41	49

- Study 102 actively enrolled both LAM experienced and LAM-naïve patients
- Study 103 enrolled 8 LAM experienced patients despite LAM-naïve inclusion criteria

Baseline Disease and Demographic Characteristics for Patients Treated with Tenofovir DF

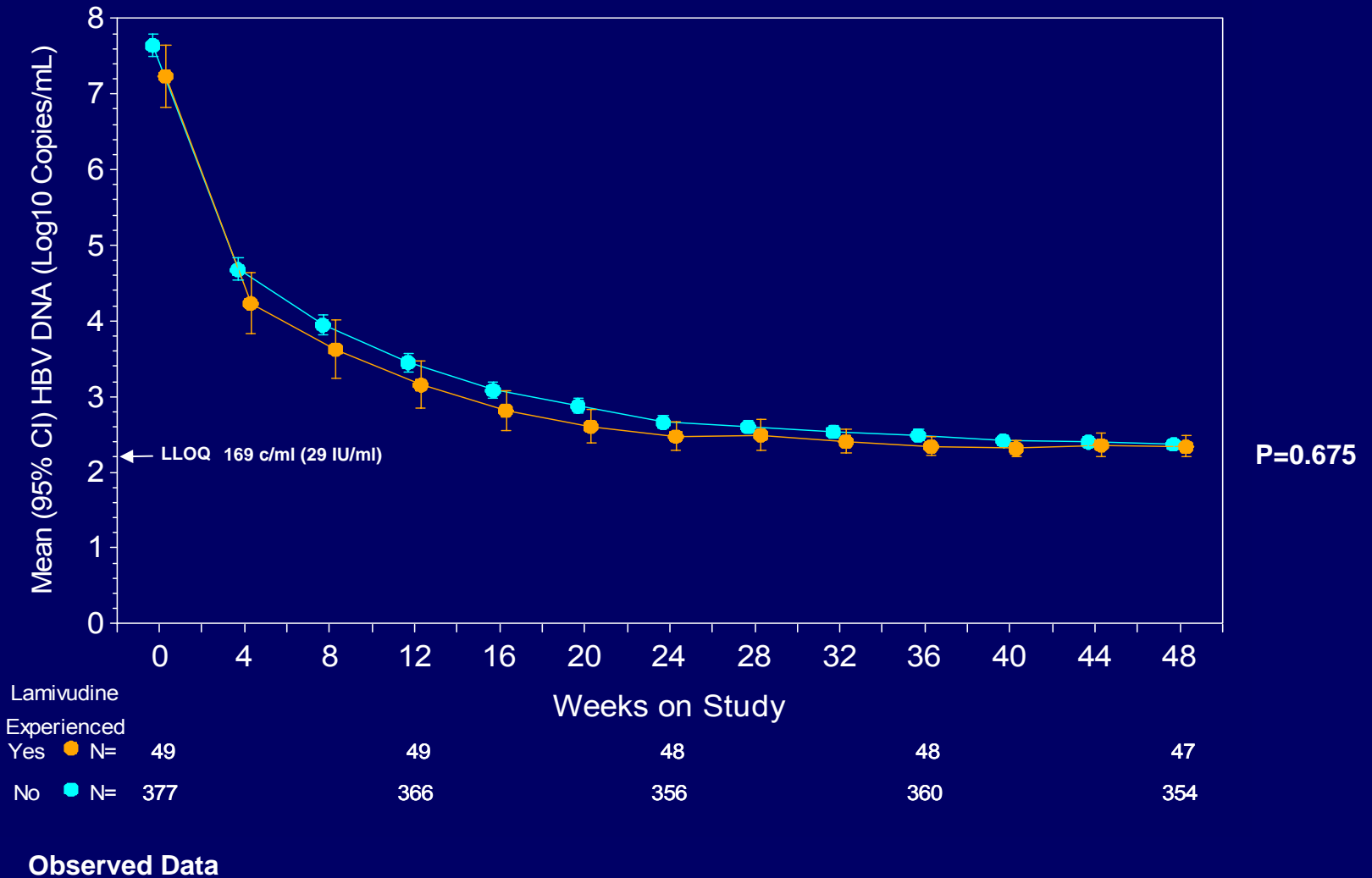
Characteristic	LAM Naive (N=377)	LAM Experienced (N=49)
Mean Age (years)	39	46
Race		
Caucasian	57%	80%
Asian	32%	16%
Male	74%	71%
Mean HBV DNA (log ₁₀ c/mL)	7.64	7.24
Mean ALT (U/L)	133	138
HBeAg Negative at Baseline	56%	80%
Mean duration of prior LAM experience (weeks)	NA	98
Mean duration off LAM prior to study (weeks)	NA	114
LAM-resistance mutations (population sequencing)	0	10%
Mean Knodell Necroinflammatory Score	8.0	8.4
Mean Knodell Fibrosis Score	2.3	2.6
Viral Genotype		
A	16%	21%
B	12%	2%
C	18%	11%
D	50%	61%

% TDF Patients with HBV DNA < 400 c/mL (69 IU/mL) by Visit (95% CI)

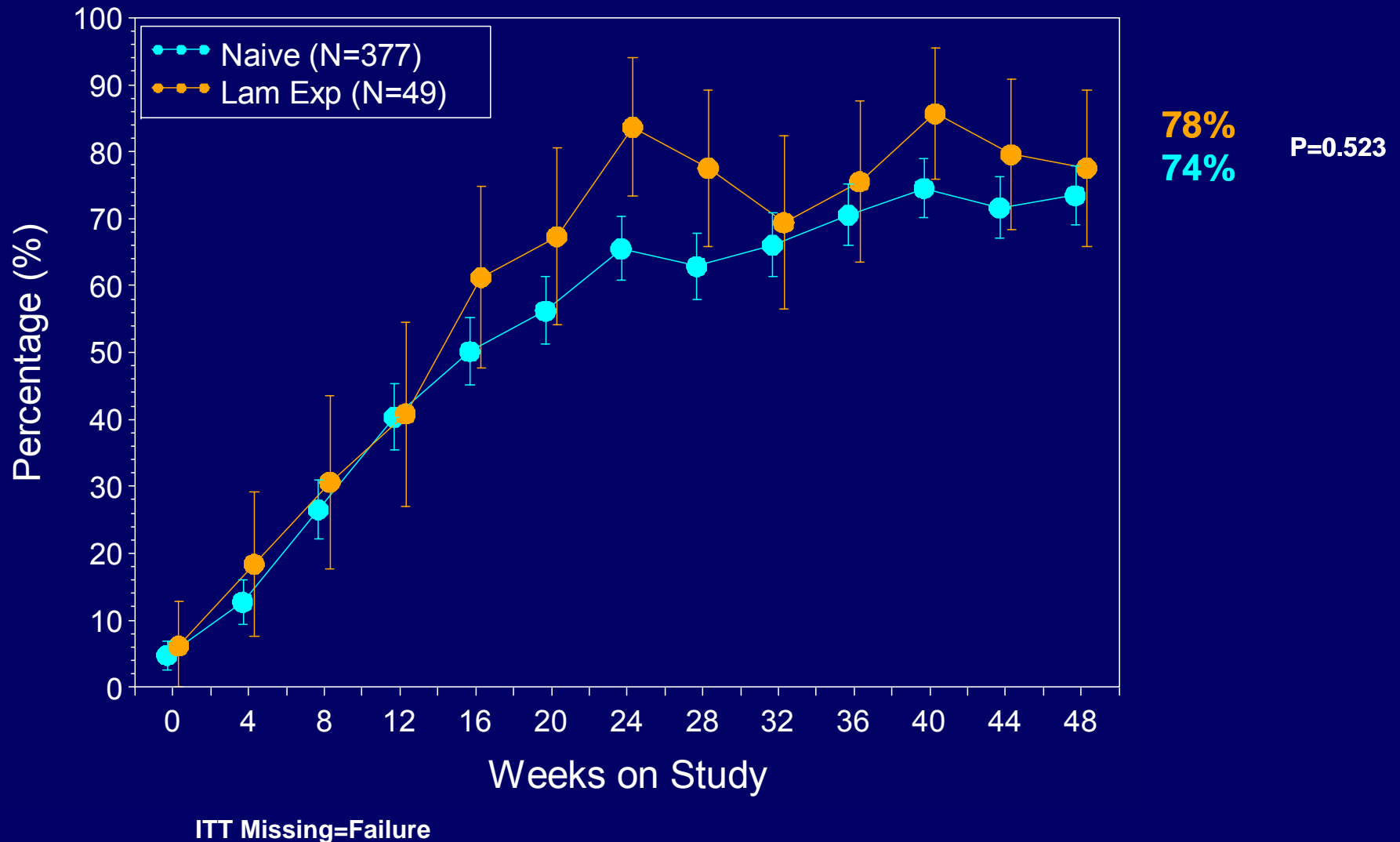


ITT Missing=Failure

Mean HBV DNA (Log₁₀ c/mL) by Visit in TDF Patients by Prior LAM Experience



%TDF Patients with Normal ALT (95% CI) by Visit



Resistance Surveillance

- No resistance to tenofovir DF was detected at Week 48 in any subject
- Across both pivotal studies 39/426 subjects had HBV DNA > 400 c/mL (69 IU/mL) at Week 48, which included 4 patients with LAM experience
- No LAM experienced or naïve patient had genotypic changes associated with resistance to tenofovir

Tenofovir DF Safety by Prior LAM Experience

	LAM Naive (N=377)	LAM Experienced (N=49)
Grade 3 or 4 AE, n (%)	32 (9)	5 (10)
Grade 3 or 4 AE considered related to TDF, n (%)	4 (1)	1 (2)
Serious AE, n (%)	21 (6)	6 (12)
Serious AE considered related to TDF, n (%)	5 (1)	2 (4)
Grade 3 or 4 Laboratory Abnormality, n (%)	72 (19)	10 (20)
Discontinuation due to AE, n (%)	5 (1)	0
Confirmed ↓ phosphorus < 2mg/dL, n (%)	5 (1)	1 (2)
Confirmed 0.5 mg/dL ↑ in creatinine, n (%)	0	0
Confirmed creatinine clearance <50 mL/min, n (%)	0	0

Conclusions

- **Tenofovir DF demonstrated potent and consistent antiviral efficacy in both LAM Exp and LAM Naive patients**
- **No mutations associated with tenofovir DF resistance were observed in either LAM Exp or LAM Naive patients**
- **Tenofovir DF was well tolerated in both LAM Exp and LAM Naive patients**

Back Up Slides

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Primary and Secondary Endpoints for TDF Patients by LAM Experience Status at Baseline

