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: Final Week 168 Results

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I have financial relationships within the last 12 months relevant to my presentation with Bristol-Myers Squibb, Gilead Sciences, Human Genome Sciences, Merck, Roche, Schering Plough, Tibotec, Vertex

AND

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

FTC/TDF for the treatment of HBV

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
- The preferred treatment strategy in this heavily pretreated population remains to be defined and requires continued evaluation beyond 2 years

Study Objective

- A comparison of the long-term safety and efficacy of two ***treatment strategies*** for ADV suboptimal responders, most with prior/current lamivudine (LAM) use:
  - Compare the antiviral efficacy (HBV DNA < 400 copies/mL) 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*

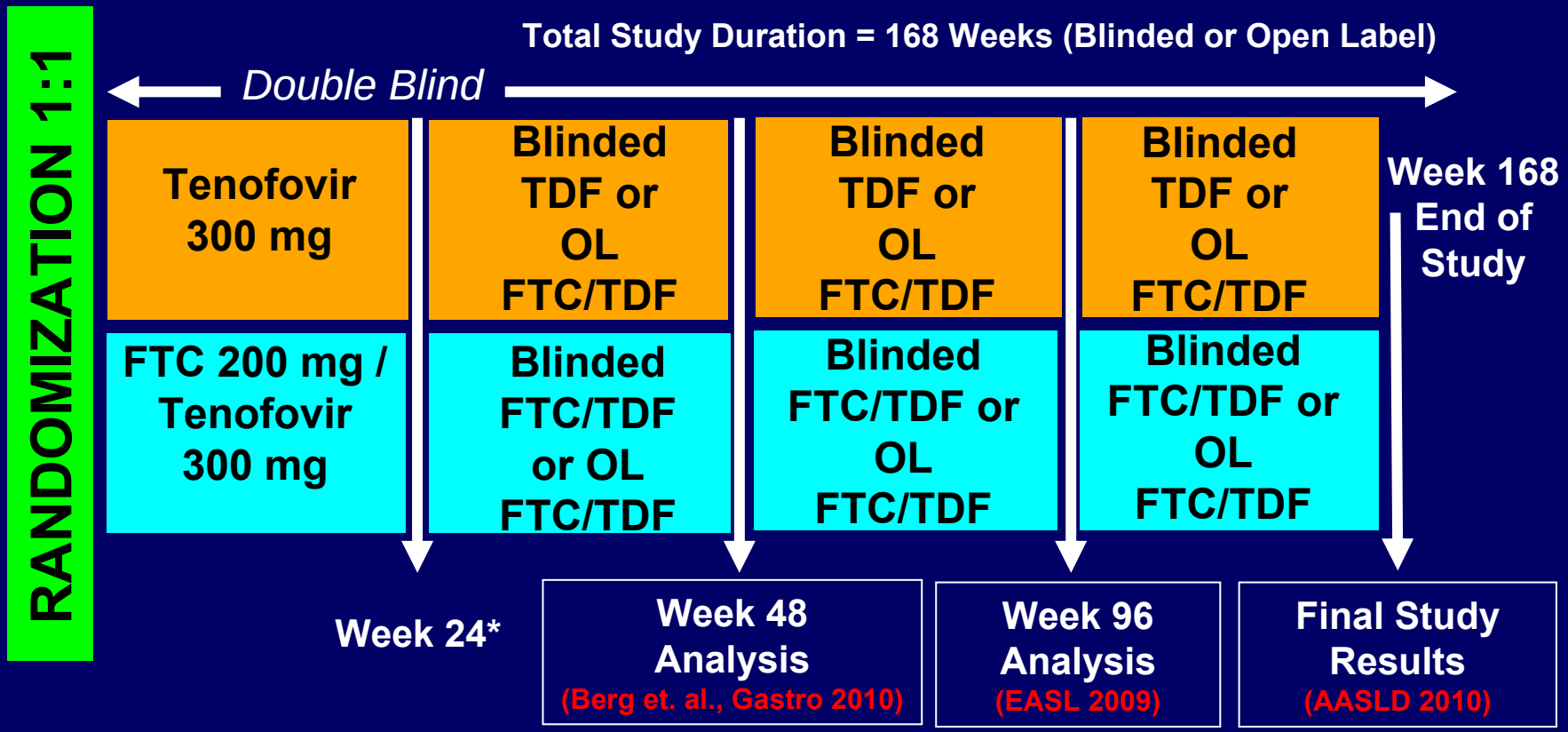
The data were analyzed by Intent to treat (ITT): virologic failure = persistent HBV DNA ≥ 400 copies/mL (69 IU/mL), or a confirmed loss of response or discontinuation (noncompleter=failure (NC=F)).

Subjects on open-label FTC/TDF will not be considered failures unless they meet the criteria described above.

Key Eligibility Criteria

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

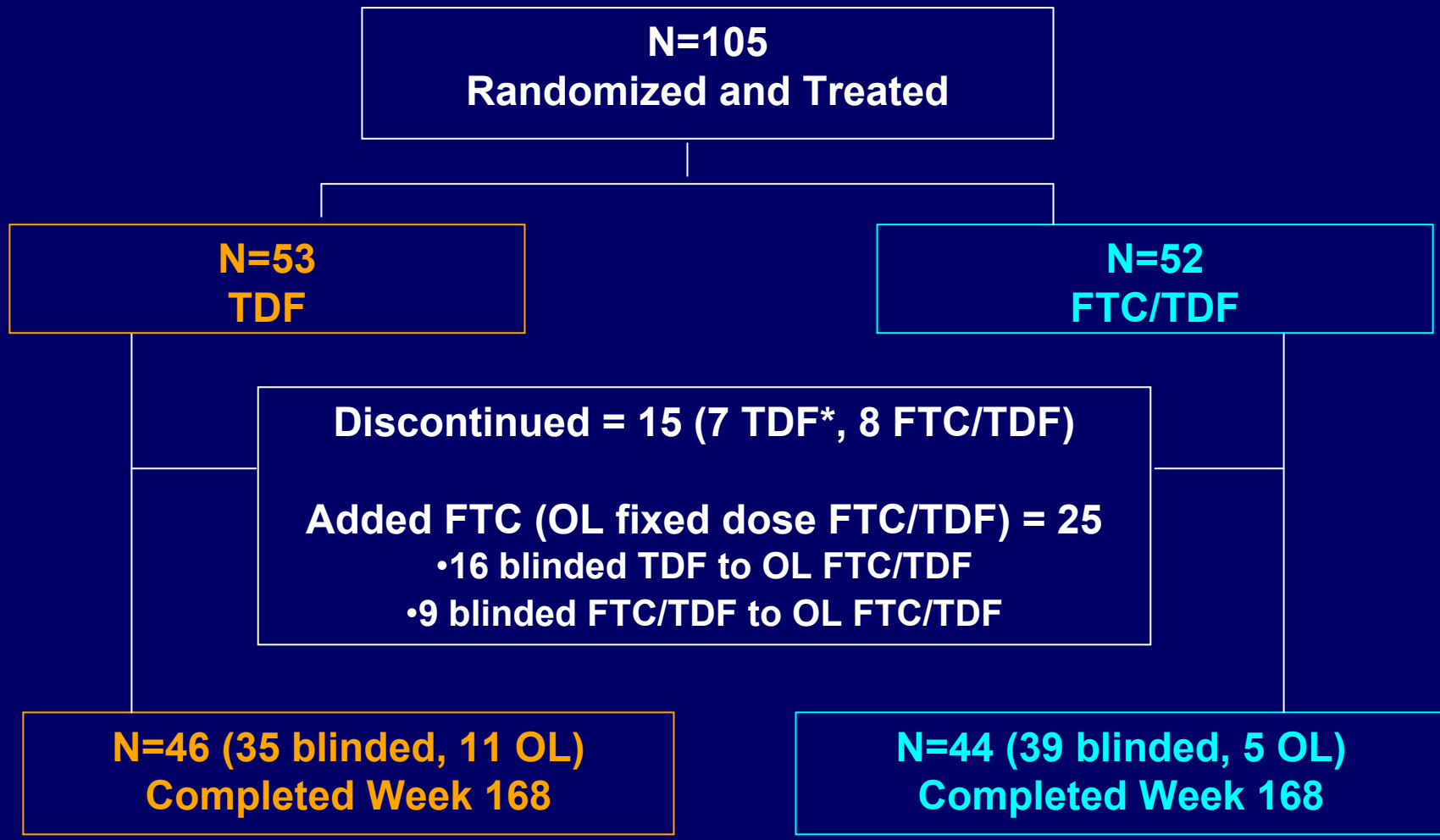
Study 106 Design



*From WK24 on, patients with confirmed HBV DNA ≥ 69 IU/mL had the option to add FTC (as fixed dose FTC/TDF) or discontinue from the trial

•TDF and FTC/TDF achieved viral suppression in 81% of patients at WK48[1], and in 89% (TDF) and 83% (FTC/TDF) at WK96[2]

Patient Disposition at 168 Weeks



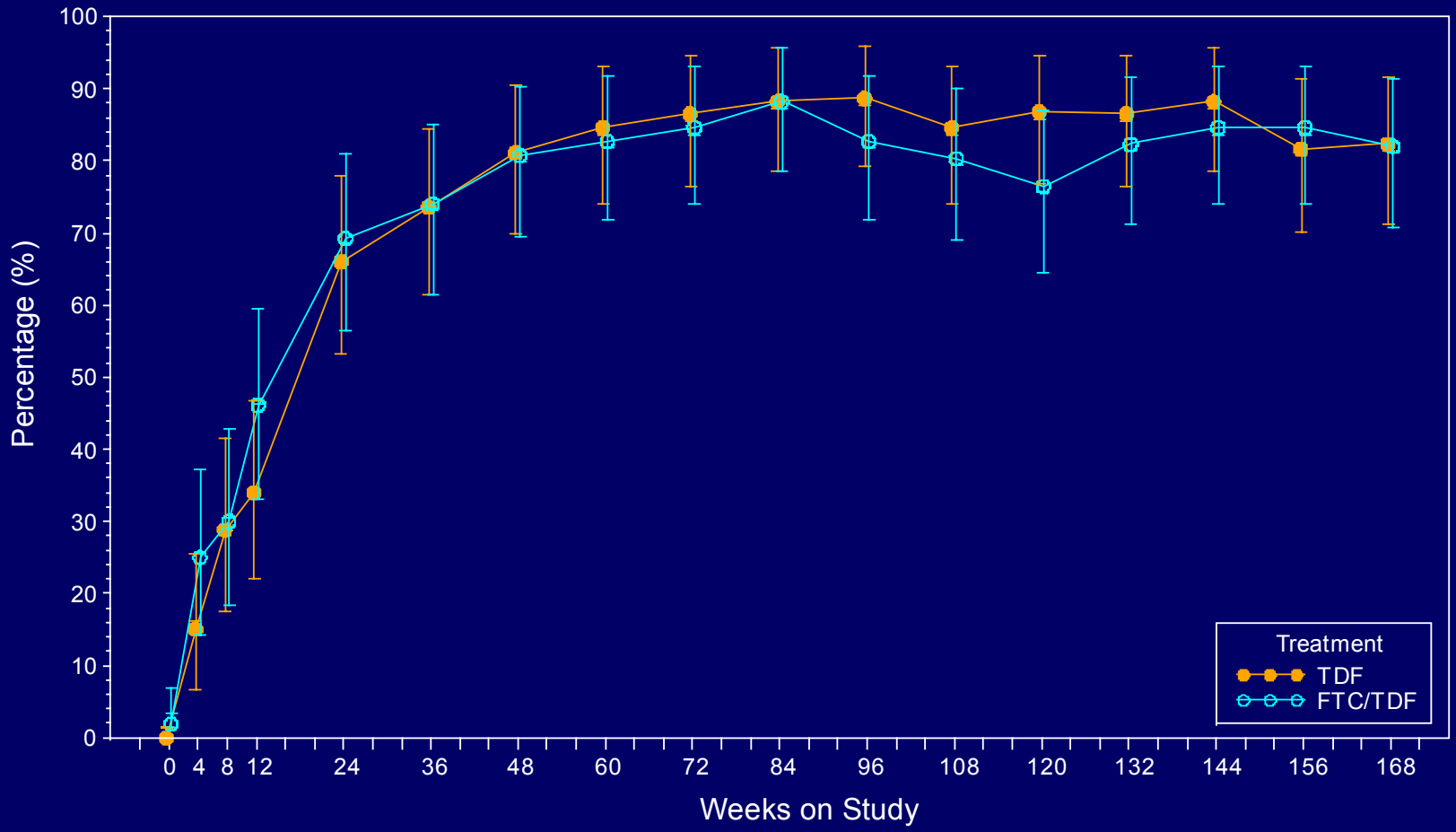
*One patient discontinued study due to HBsAg loss.

Baseline Disease and Demographic Characteristics

		TDF (N=53)	FTC/TDF (N=52)
Mean Age		40	39
Race	**White**	23 (44%)	21 (40%)
	Asian	26 (49%)	18 (35%)
Male		38 (72%)	42 (81%)
HBeAg Positive		38 (72%)	39 (75%)
Mean HBV DNA (log_{10} copies/mL) (range)		6.06 (3.41,9.57)	5.87 (2.23,9.47)
ALT > ULN		27 (51%)	26 (50%)
Prior LAM exposure (≥ 12 weeks)		30 (57%)	31 (60%)
Mean prior ADV exposure (weeks; range)		62 (20-131)	62 (29-168)
HBV Viral Genotype	**A**	11 (21%)	9 (18%)
	B	6 (11%)	4 (8%)
	C	15 (28%)	10 (20%)
	D	18 (34%)	21 (41%)
	E	2 (4%)	6 (12%)

Primary Efficacy Analysis: Comparison of the Two Treatment Strategies

% of Patients with HBV DNA < 400 copies/mL (69 IU/mL)



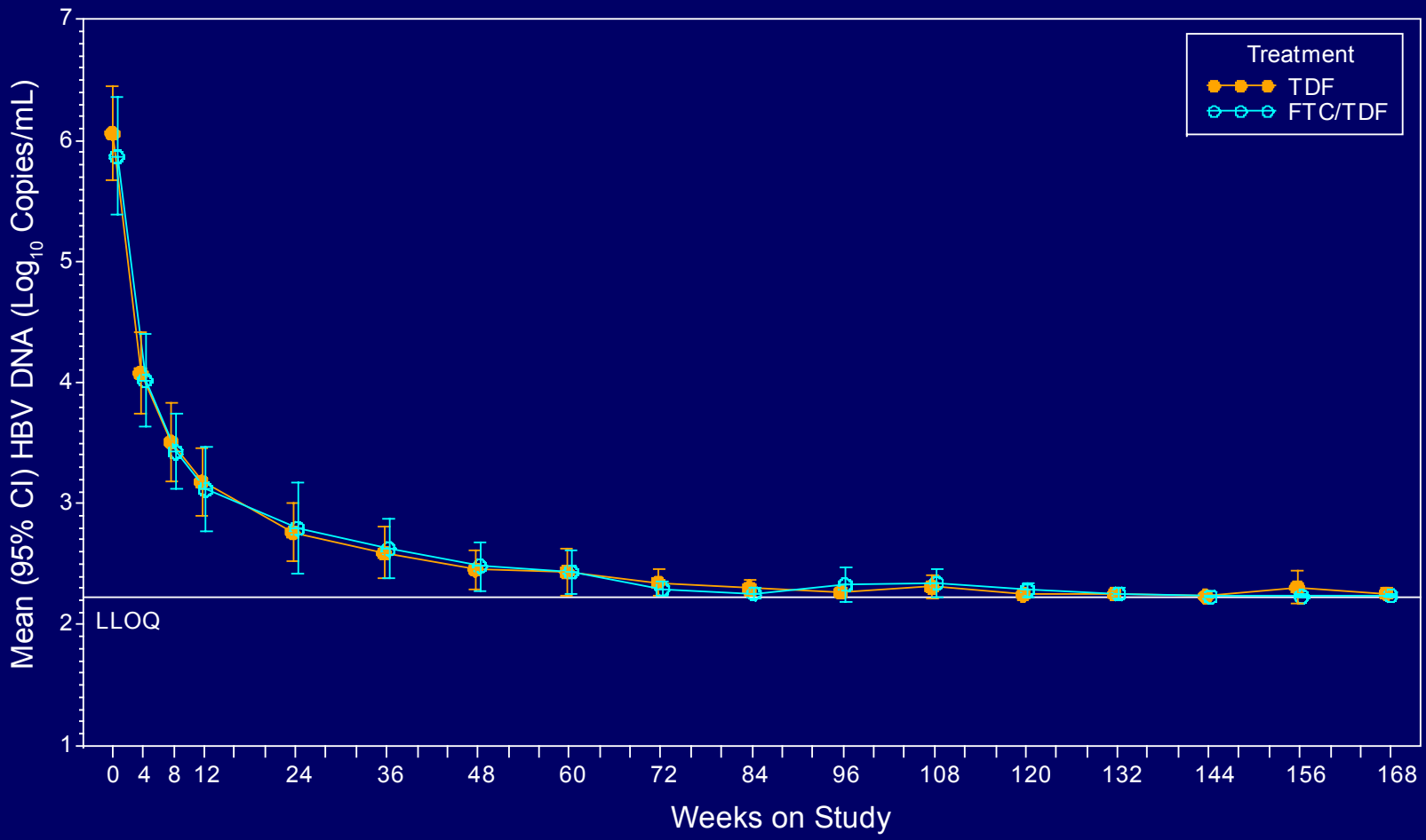
82% FTC/TDF

82% TDF

ITT: NC=F*

Proportion of patients with HBV DNA < 169 copies/mL (29IU/mL): 80% TDF and 76% FTC/TDF

Mean HBV DNA (log_{10}c/mL) by Study Visit



2.26 TDF
2.24 FTC/TDF

*** Includes patients who switched to open-label FTC/TDF fixed-dose combination**

Week 168 Serology Results*

	TDF	FTC/TDF
Proportion with HBeAg loss	**8/38 (21%)**	**9/39 (23%)**
Proportion with HBeAg seroconversion (a subset of HBeAg loss group)	**5/38 (13%)**	**5/39 (13%)**
Proportion with HBsAg loss	**3/53 (6%)**	**0**
Proportion with HBsAg seroconversion	**3/53 (6%)**	**0**

*Last Observation Carried Forward (LOCF) analysis

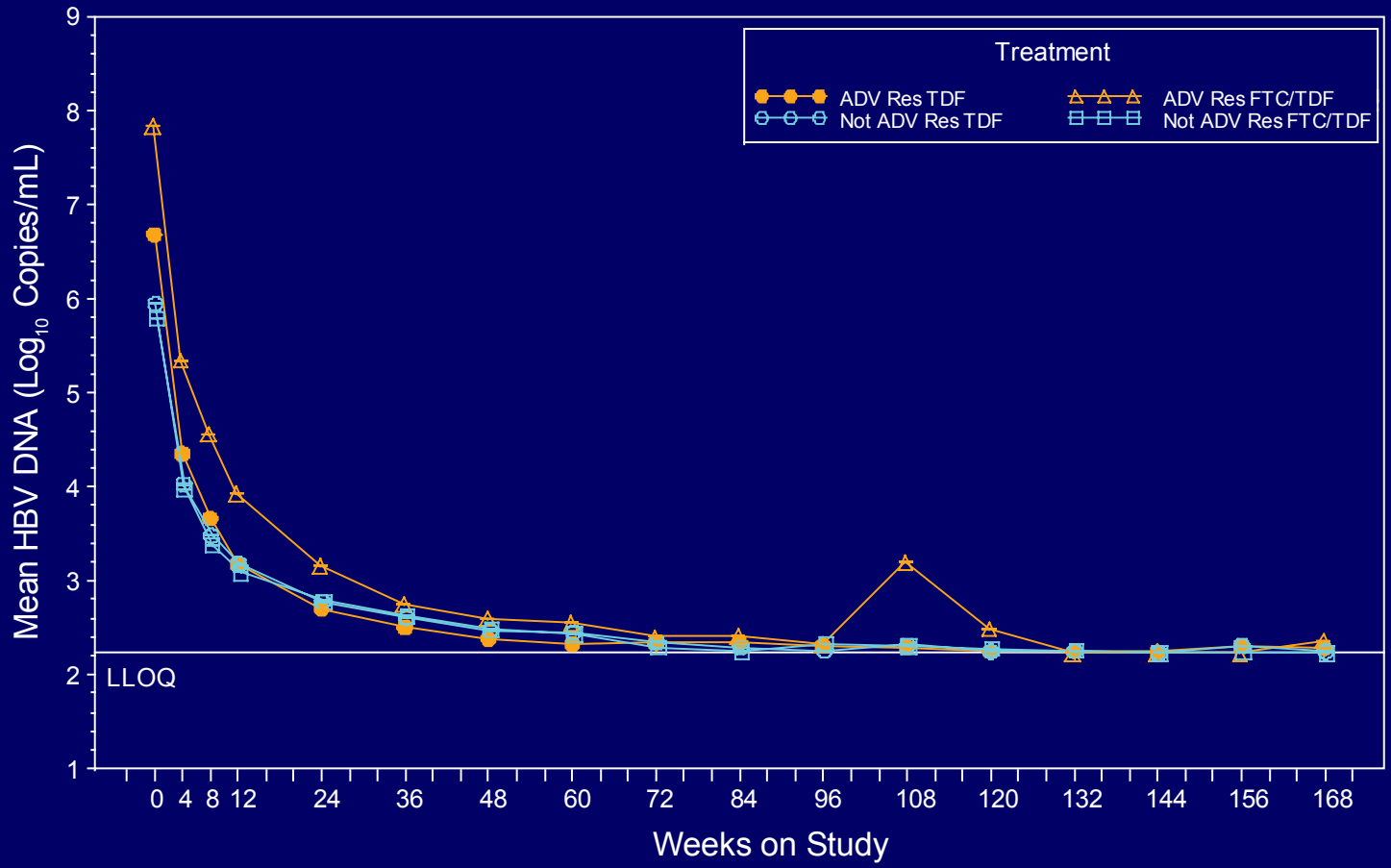
Patients who lost HBsAg/seroconverted:
Pt 3024: Asian male, HBeAg+ patient (from US site) with HBV genotype C
Pt 1006: Caucasian female, HBeAg+ patient (German site) with HBV genotype A
Pt 1036: Caucasian male, HBeAg+ patient (German site) with HBV genotype A
All remained on treatment for ~6 additional months and 2 patients were followed off treatment, without evidence of relapse.

Baseline Genotypic Analysis

Patient Population	N
All Enrolled	105
Patients with ADV-Resistance Mutations at Baseline	10 (9.5%)
rtA181V	2
rtN236T	2
rtA181T/V + rtN236T	4
rtA181T	2
Patients with LAM-Resistance Mutations at Baseline	13 (12.4%)
rtM204V/I	1
rtL180M+rtM204V/I	12
All patients with Mutations at Baseline	23 (22%)

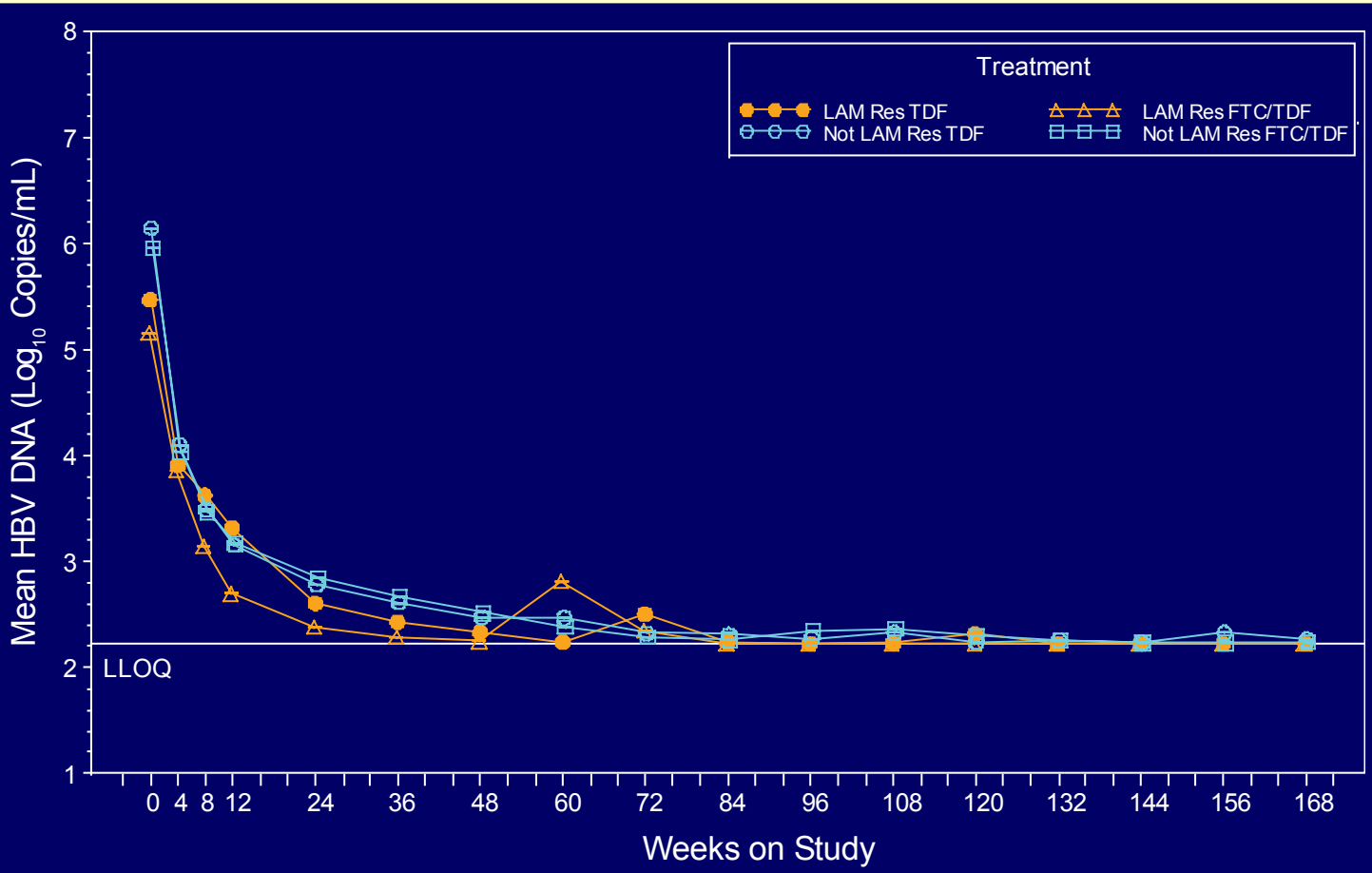
* population sequencing

Mean HBV DNA (Log_{10}c/mL) by Baseline ADV-R and Treatment



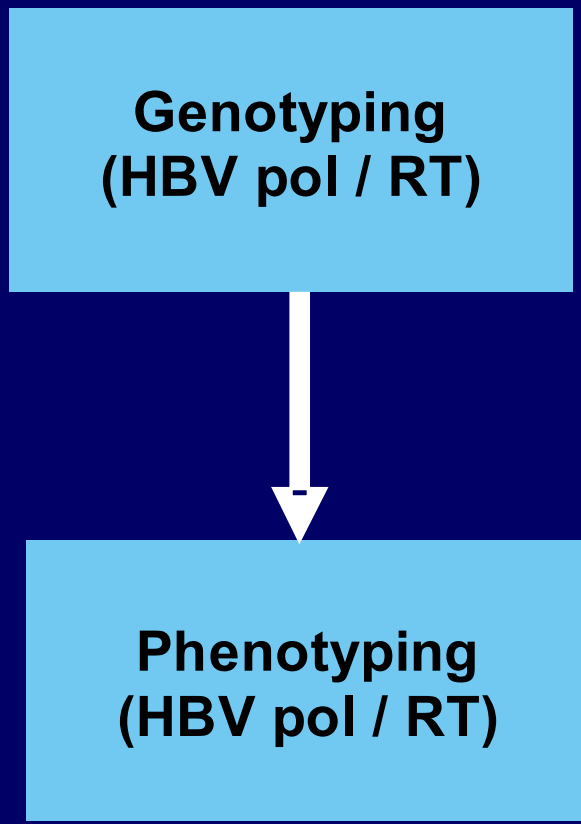
Not ADV Res FTC/TDF	□	N=	50	50	48	50	50	48	48	48	46	44	45	43	42	41	42	42	40
Not ADV Res TDF	○	N=	45	45	43	44	44	44	44	43	42	42	42	40	40	38	37	34	36
ADV Res FTC/TDF	△	N=	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
ADV Res TDF	●	N=	8	8	8	8	8	8	8	8	8	7	8	8	8	8	8	8	8

Mean HBV DNA (Log_{10}c/mL) by Baseline LAM-R and Treatment



Not Lam Res FTC/TDF	N=	46	46	44	46	46	44	44	44	42	40	41	39	38	37	38	38	36
Not Lam Res TDF	N=	46	46	44	45	45	45	45	44	43	42	43	41	41	39	38	35	37
Lam Res FTC/TDF	N=	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Lam Res TDF	N=	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7

Virology Analysis Plan for Study 106



All patients:

- at baseline
- yearly if ≥ 400 copies/mL (≥ 69 IU/mL) of HBV DNA
- before switch to OL FTC/TDF, and after discontinuation of any therapy if HBV DNA ≥ 400 copies/mL

Any patient post-baseline with:

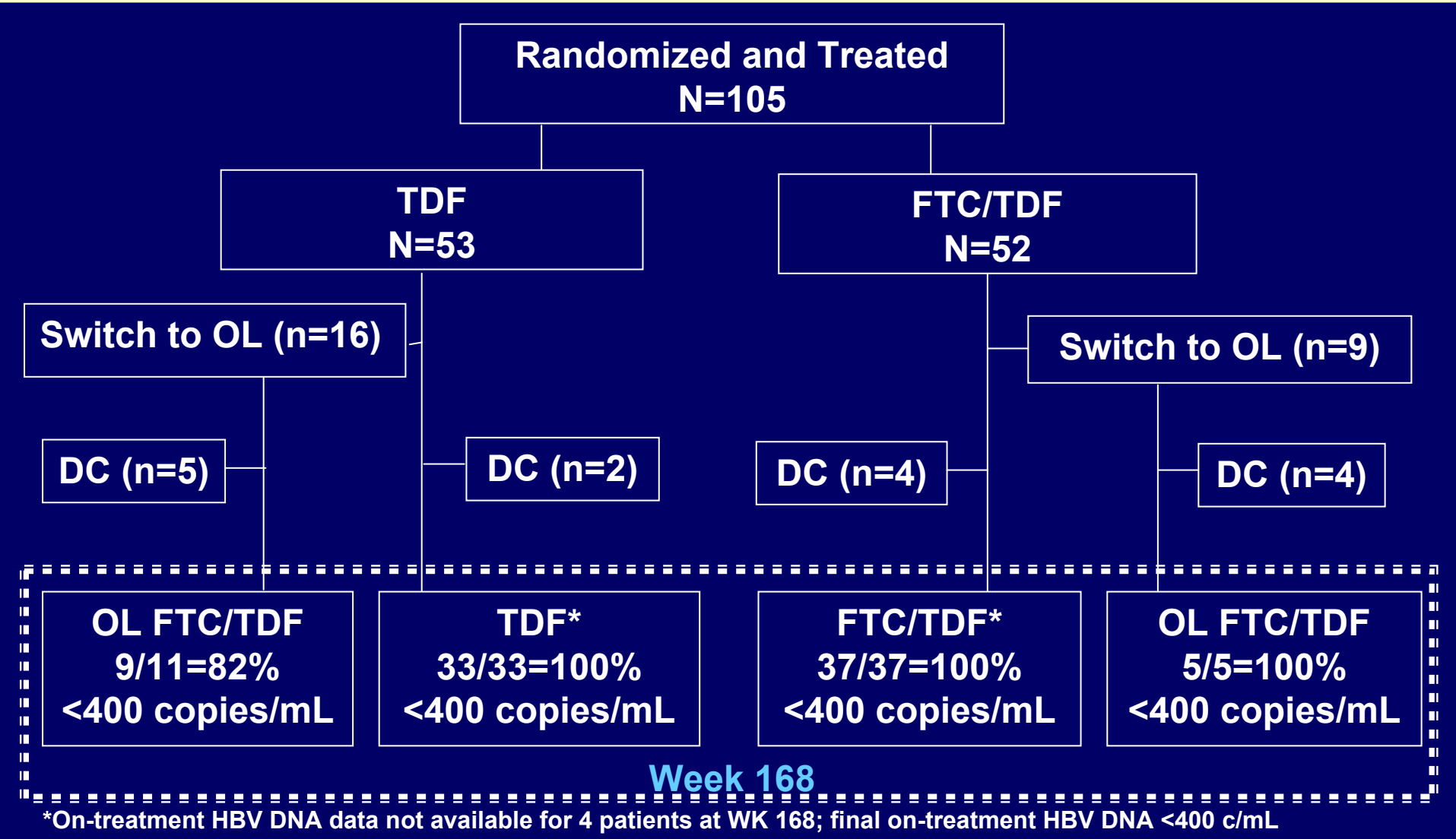
- conserved site changes in pol/RT
- virologic breakthrough[a]
- polymorphic site changes (>1 patient)

a. Defined as a confirmed 1$\log_{10}$ increase in HBV DNA and/or confirmed HBV DNA ≥ 400cp/ml after having <400 cp/mL

Resistance Surveillance

- No HBV pol/RT amino acid substitutions associated with tenofovir resistance were detected through 168 weeks of TDF or FTC/TDF therapy
- No 2 patients had the same polymorphic site change and the observed conserved site changes were transient

Proportion <400 copies/mL by Treatment Group (On-Treatment)



*On-treatment HBV DNA data not available for 4 patients at WK 168; final on-treatment HBV DNA <400 c/mL

Summary of Safety Data

	TDF (N=53)	FTC/TDF (N=52)
Adverse Event, Patients with		
Grade 3 or 4 AE	1 (2%)	4 (8%)
SAE (one considered related to study drug: ALT flare*)	6 (11%)	10 (19%)
AE that resulted in DC	0	0
Death (Pulmonary cancer with osseous metastasis)	0	1 (2%)
Laboratory Abnormalities, Patients with		
Grade 3 or 4 laboratory abnormality	10 (19%)	12 (23%)
Grade 4 ALT (>10 x ULN) and > 2 x Baseline*	0	2 (4%)
Confirmed ≥0.5 mg/dL increase in creatinine	0	0
Confirmed CrCl decline to <50mL/min	0	0
Confirmed serum phosphorus < 2mg/dL	0	0

*on-treatment ALT flare; 1 additional patient had an off-treatment ALT flare

Conclusions

- Both treatment strategies (TDF monotherapy with option to switch to combination FTC/TDF, or initial combination of FTC/TDF) were equivalent through 168 weeks in this heavily pretreated, highly viremic population
- In patients with persistent viremia on ADV (most with prior/current use of LAM) viral suppression was achieved and maintained through Week 168 in the majority (consistent with results observed at Weeks 48 and 96): 82% (TDF) and 82% (FTC/TDF)
- Virologic response was independent of pre-existing ADV- or LAM-associated mutations

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Back UP

Response by Treatment Strategy (HBV DNA <400 copies/mL [69 IU/mL]) by Resistance Mutations* at Baseline

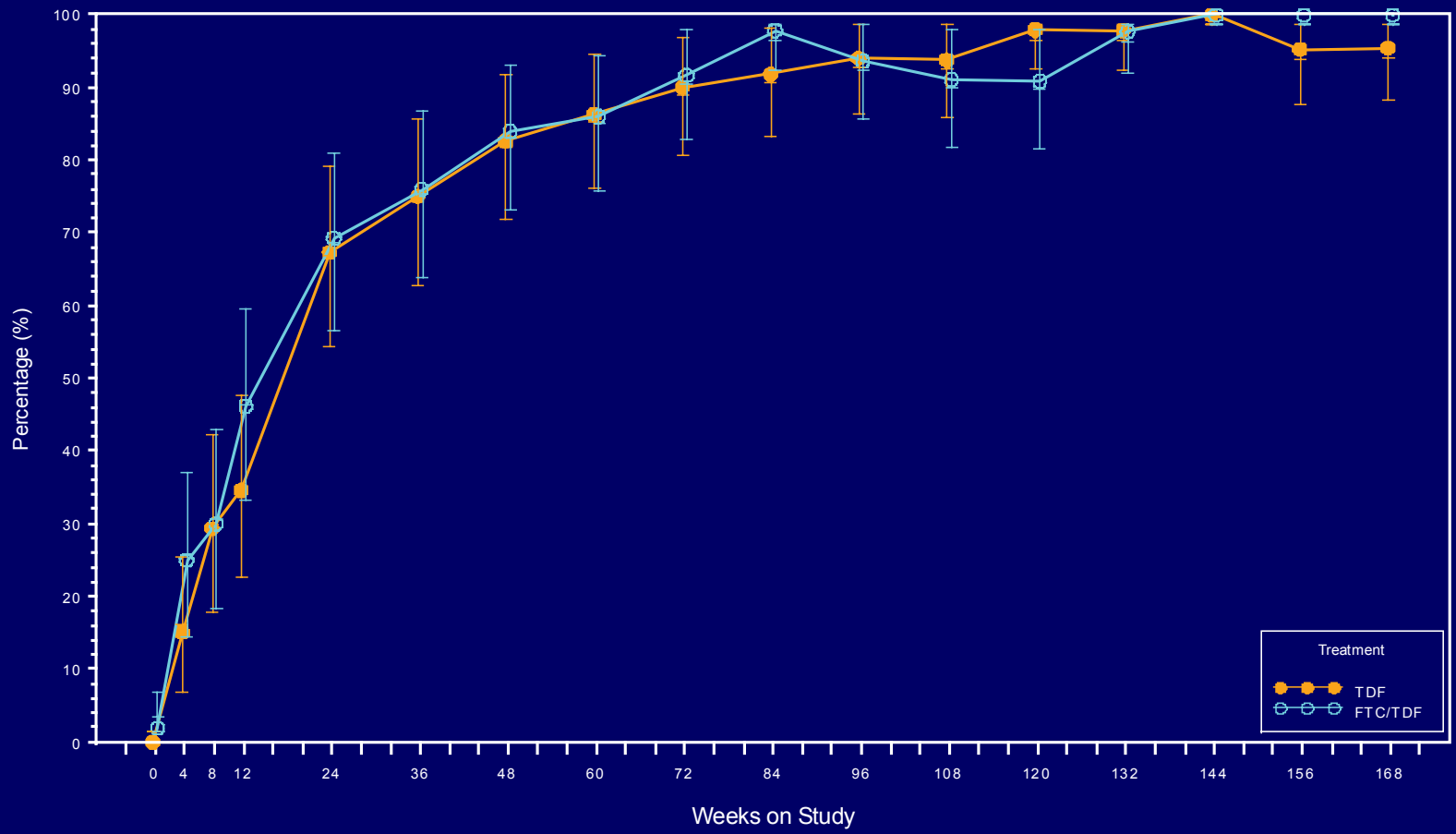
Time on Treatment	HBV DNA < 400 copies/mL ADV-resistance		HBV DNA < 400 copies/mL LAM-resistance	
	TDF	FTC/TDF	TDF	FTC/TDF
Week 48 (NC=F)	7/8 (88%)	1/2 (50%)	6/7 (86%)	6/6 (100%)
Week 96 (NC=F)	7/8 (88%)	2/2 (100%)	7/7 (100%)	6/6 (100%)
Week 168 (NC=F)	7/8 (88%)	2/2 (100%)	7/7 (100%)	6/6 (100%)

*** Resistance as identified by population sequencing**

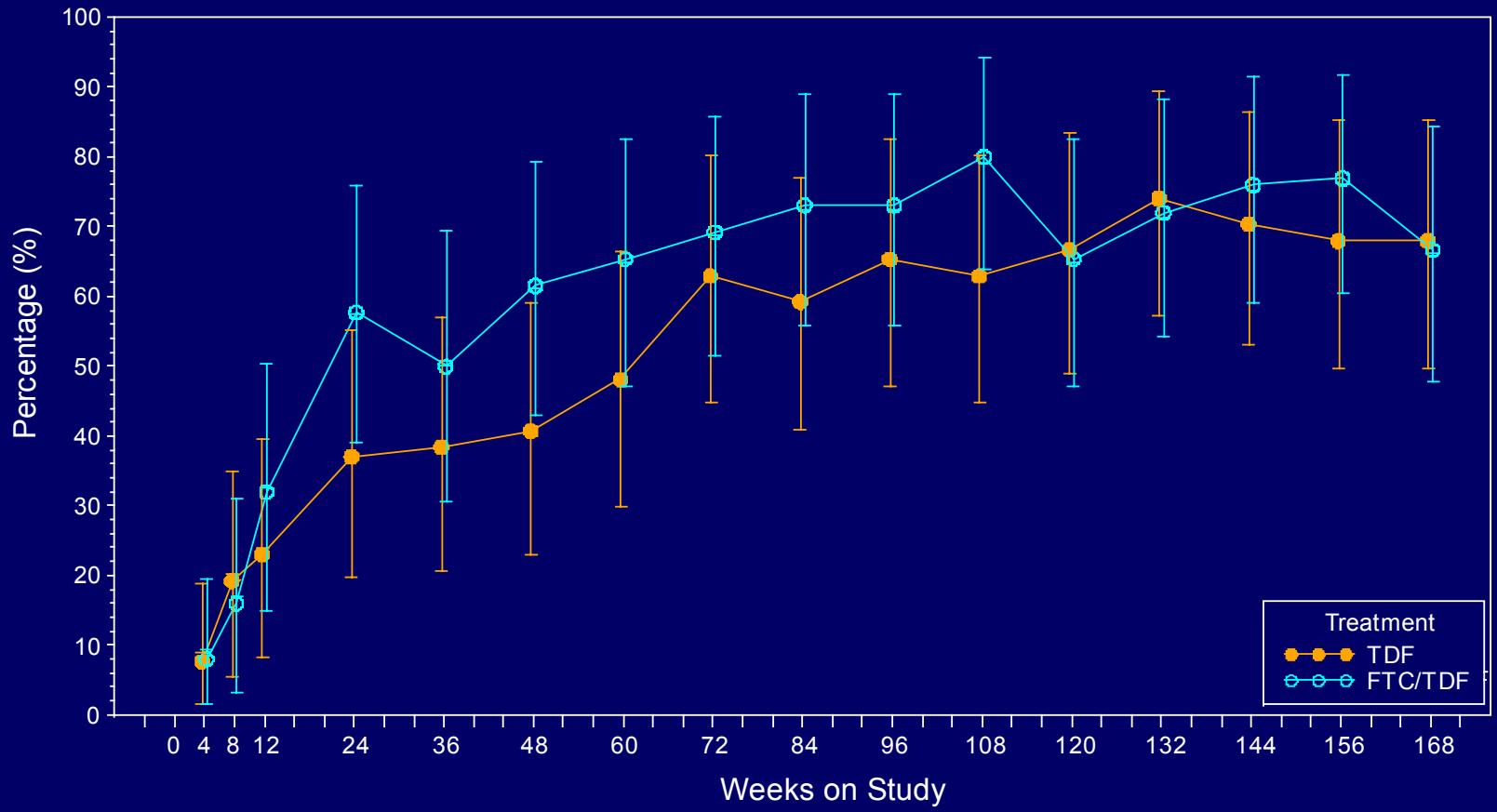
Proportion with HBV DNA <400 copies/mL by Baseline HBV DNA & Randomized Treatment

	TDF (N=39)	FTC/TDF (N=39)	TDF (N=14)	FTC/TDF (N=13)
Baseline HBV DNA	$\leq 10^7$ c/mL	$\leq 10^7$ c/mL	$>10^7$ c/mL	$>10^7$ c/mL
Week 24	31/39 (79%)	31/39 (79%)	4/13 (31%)	5/13 (39%)
Week 48	36/39 (92%)	35/38 (92%)	7/13 (54%)	7/12 (58%)
Week 96	38/38 (100%)	33/36 (92%)	9/12 (75%)	11/11 (100%)
Week 144	34/34 (100%)	34/34 (100%)	11/11 (100%)	10/10 (100%)
Week 168	33/33 (100%)	33/33 (100%)	9/11 (82%)	9/9 (100%)

Proportion of Patients with HBV DNA <400 copies/mL (On-Treatment)



Proportion of Patients with ALT Normalized* by Study Visit



68% TDF

67% FTC/TDF

ITT: NC=F

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

•(ALT ULN=34 females and ULN=43 for males