

Lack of Clinically Relevant Drug Interactions Between Bictegravir/Emtricitabine/Tenofovir Alafenamide and Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir/Voxilaprevir

Kimberly L. Garrison, Rita Humeniuk, Steve K. West, Lilian Wei, John Ling, Hiba Graham, Hal Martin, Luisa M. Stamm, Anita Mathias
Gilead Sciences, Inc., Foster City, California, USA

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, California, USA 94404
800-445-3235

Introduction

- Hepatitis C virus (HCV)-related liver disease in HCV/HIV coinfecting patients is a major cause of morbidity and mortality¹
- It is estimated that there are ~2.3 million HIV/HCV-coinfecting individuals worldwide¹
- Concomitant use of HCV direct-acting antivirals (DAAs) and HIV antiretrovirals (ARVs) may be complicated by pharmacokinetic (PK) drug-drug interactions (DDIs) in these patients

HCV Direct-Acting Antivirals and HIV Antiretrovirals*

LDV NNSA inhibitor **SOF Nucleotide polymerase inhibitor**

SOF Nucleotide polymerase inhibitor **VEL NNSA inhibitor** **VOX NS3/4A PI**

BIC INSTI **FTC NRTI** **TAF NRTI**

◆ Ledipasvir/sofosbuvir (LDV/SOF)

– Once-daily, oral, fixed-dose (90/400 mg) DAA combination tablet for HCV genotypes 1 and 4²

◆ SOF/velpatasvir/voxilaprevir (SOF/VEL/VOX)

– Once-daily, oral, fixed-dose (400/100/100 mg) DAA combination tablet for HCV genotypes 1–6³

◆ Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF)

– Once-daily, oral, fixed-dose (50/200/25 mg) tablet regimen for treatment of HIV⁴

*B/F/TAF: Biktegravi, LDV/SOF: Harvoni; SOF/VEL/VOX: Vosevi; BIC: bictegravir; FTC: emtricitabine; INSTI: integrase strand transfer inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor

- Potential mechanisms of DDIs
 - LDV, VEL, and VOX are inhibitors of drug transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)^{2,3}
 - TAF is a substrate for P-gp and BCRP⁴

Objectives

- To assess potential PK DDIs between HCV drugs (LDV/SOF or SOF/VEL/VOX) and B/F/TAF
- To evaluate the safety and tolerability of coadministration of LDV/SOF or SOF/VEL/VOX with B/F/TAF

Methods

Study Designs

Study 1: Fixed-Sequence, 3-Period, Crossover Study in Healthy Subjects

Treatment Sequence	Period 1 Days 1–10 n=30	Period 2 Days 11–20 n=30	Period 3 Days 21–30 n=30
A	LDV/SOF 90/400 mg		
B	B/F/TAF 50/200/25 mg		
C	B/F/TAF + LDV/SOF		

Study 2: Randomized, 6-Sequence, 3-Period, Crossover Study in Healthy Subjects

Treatment Sequence	Period 1 Days 1–10 n=30	Period 2 Days 11–20 n=30	Period 3 Days 21–30 n=30
1	B	E	D
2	B	D	E
3	E	B	D
4	E	D	B
5	D	E	B
6	D	B	E

*Additional 100 mg of VOX was administered to approximate VOX exposures in patients.

- Each treatment was administered for 10 d under fed conditions (standard moderate-fat breakfast: ~600 calories/27% fat)
- Intensive PK samples were collected over 24 h on the last day of each treatment period
- Plasma concentrations of BIC, FTC, TAF, tenofovir (TFV; primary circulating metabolite of TAF), SOF, GS-331007 (primary circulating metabolite of SOF), LDV, VEL, and VOX were determined using validated liquid chromatography–tandem mass spectrometry methods
- PK parameters were estimated using noncompartmental methods (WinNonlin 6.4, Certara USA, Inc., Princeton, New Jersey, USA)
- Geometric least-squares means ratios (GMR) and associated 90% confidence intervals (CIs; combination vs alone) for the PK parameters area under plasma concentration-time curve over dosing interval (AUC_{0–∞}), maximum plasma concentration (C_{max}), and concentration at end of dosing interval (C_t) were estimated and compared against lack of PK alteration boundaries of 70–143%
- Safety was assessed throughout the study (clinical laboratory tests, vital signs, and documentation of adverse events [AEs])

Results

Demographics

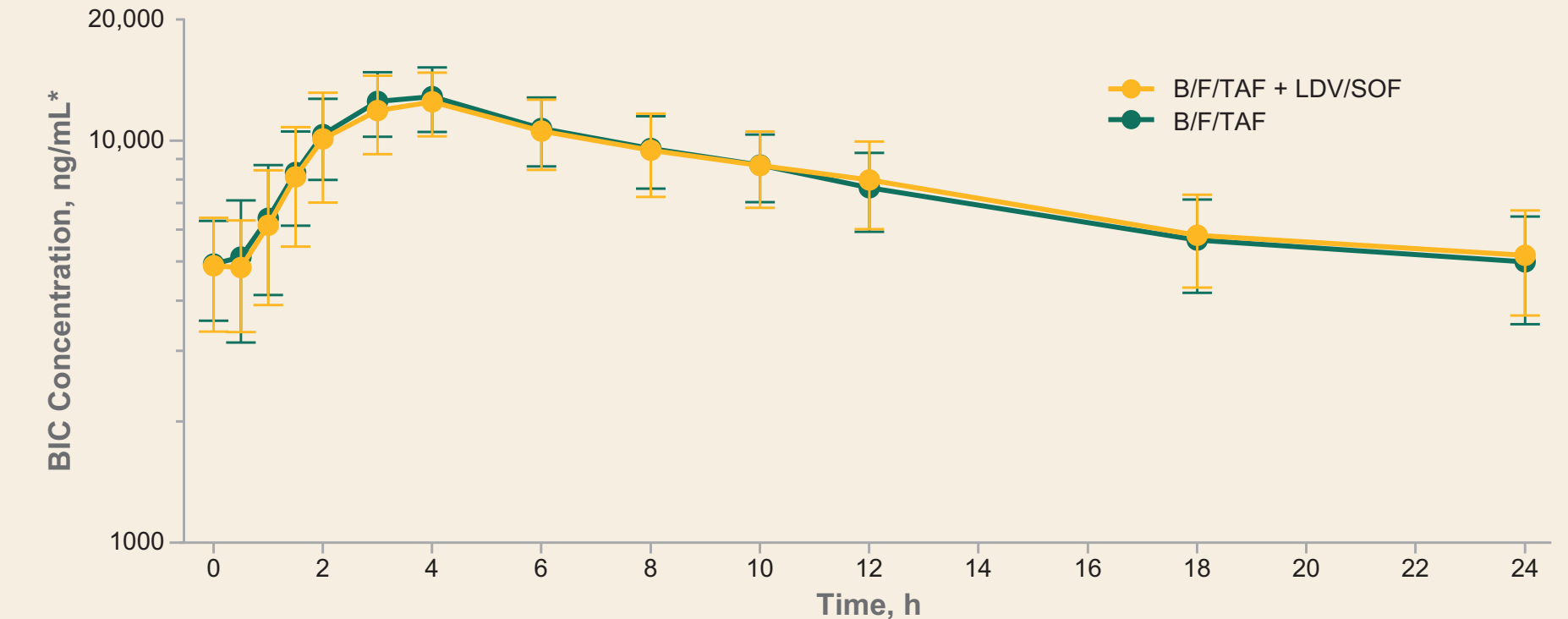
	Study 1 n=30	Study 2 n=30
Enrolled/completed, n	30/30	30/30
Sex, n (%)		
Male	20 (67)	19 (63)
Female	10 (33)	11 (37)
Mean weight, kg (range)	76.1 (56.6–99.7)	75.4 (53.0–99.0)
Race/ethnicity, n (%)		
Black	15 (50)	12 (40)
White	15 (50)	17 (57)
Other	0	1 (3)
Hispanic or Latino	19 (63)	18 (60)

Safety

- Across both studies, 28% (17/60) of subjects experienced AEs
 - No Grade 3 or 4, or serious AEs
 - No AEs leading to discontinuation
 - Headache was the only common AE (≥5%) observed across both studies (10% [6/60])
 - AE of pruritis (Grade 1) was reported in 1 subject in Study 2 receiving B/F/TAF (began Day 12; resolved Day 31)
- Laboratory abnormalities were Grades 1–2, with the exception of Grade 3 hematuria (occult blood) reported in 2 subjects with confirmed menses

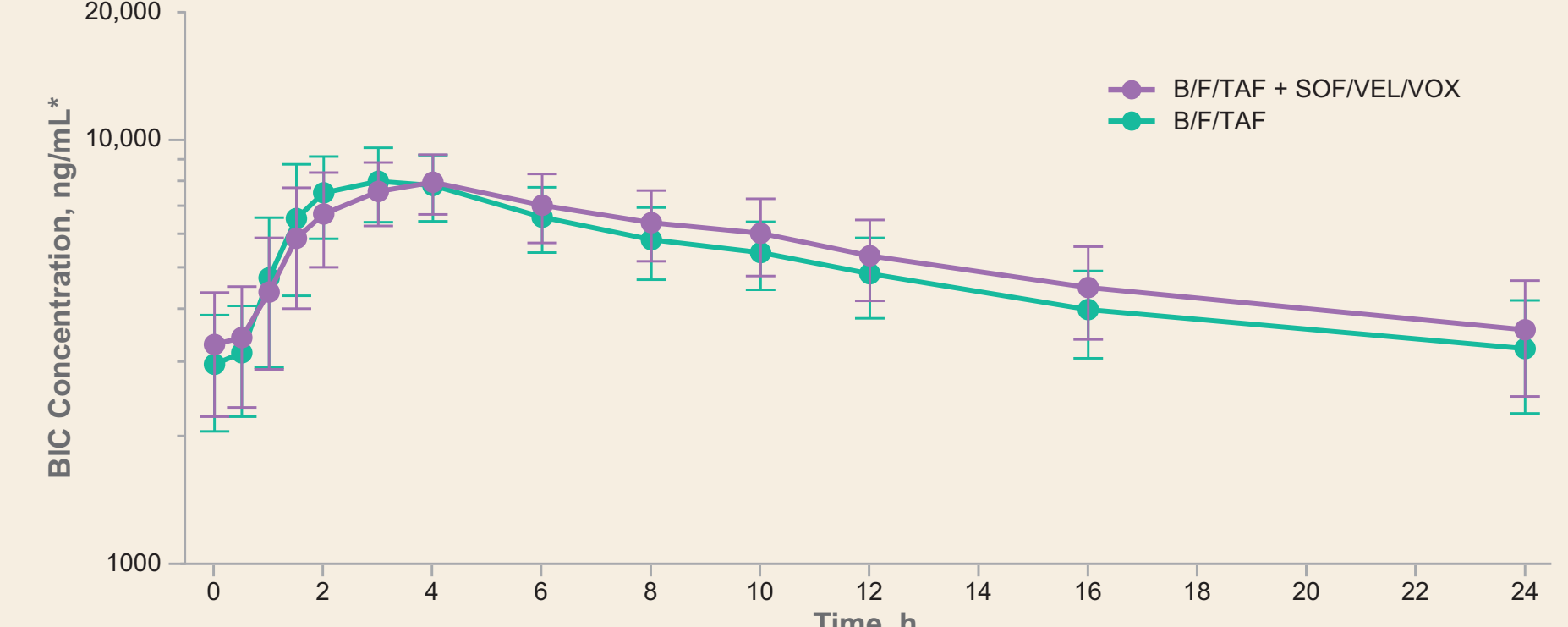
Effect of HCV DAAs on HIV ARVs

Effect of LDV/SOF on BIC (Study 1)



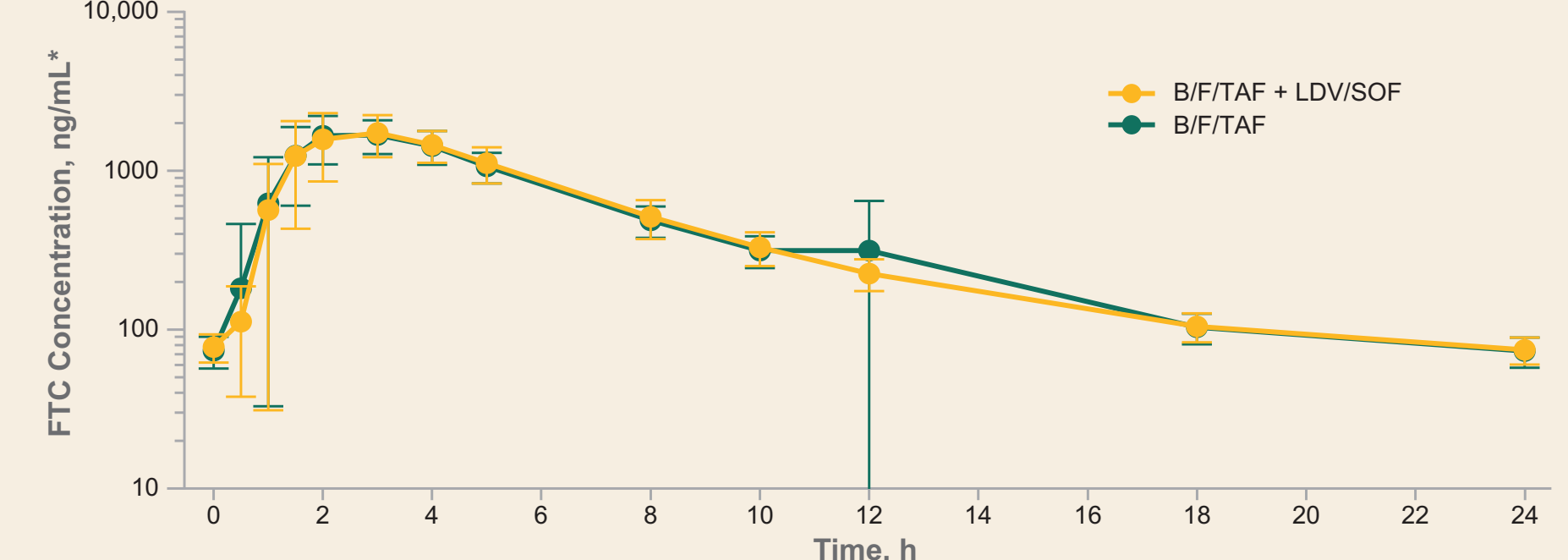
BIC Mean (%CV) [†]	B/F/TAF + LDV/SOF n=30		B/F/TAF n=30		GMR (90% CI)	
AUC _{0–∞} , h·ng/mL	189,000 (20.8)	188,000 (19.3)	100	100	97.2	(103)
C _{max} , ng/mL	13,300 (15.2)	13,600 (16.6)	98.3	98.3	94.0	(103)
C _t , ng/mL	5190 (29.2)	4990 (29.9)	104	104	99.4	(109)

Effect of SOF/VEL/VOX on BIC (Study 2)



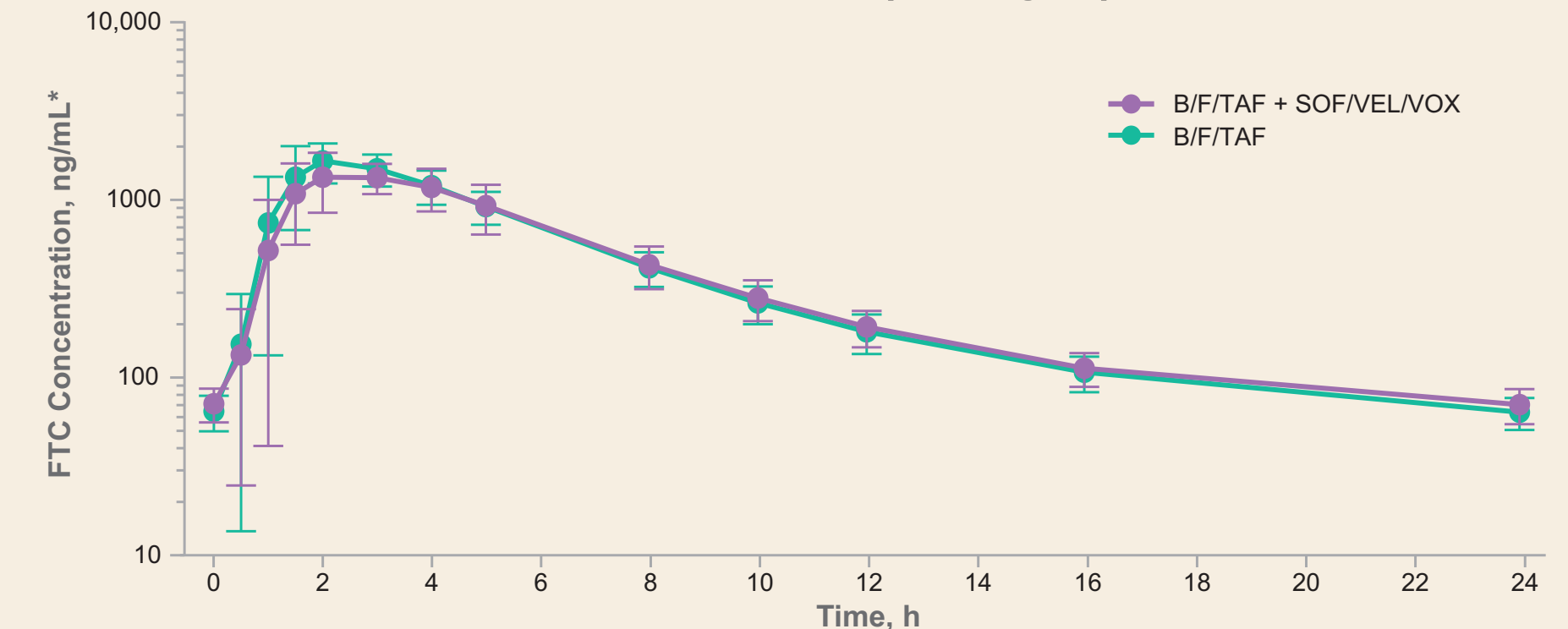
BIC Mean (%CV) [†]	B/F/TAF + SOF/VEL/VOX n=30		B/F/TAF n=30		GMR (90% CI)	
AUC _{0–∞} , h·ng/mL	128,000 (20.1)	120,000 (19.5)	107	107	103	(110)
C _{max} , ng/mL	8270 (14.7)	8530 (20.0)	97.7	97.7	94.4	(101)
C _t , ng/mL	3570 (30.5)	3220 (29.7)	111	111	105	(117)

Effect of LDV/SOF on FTC (Study 1)



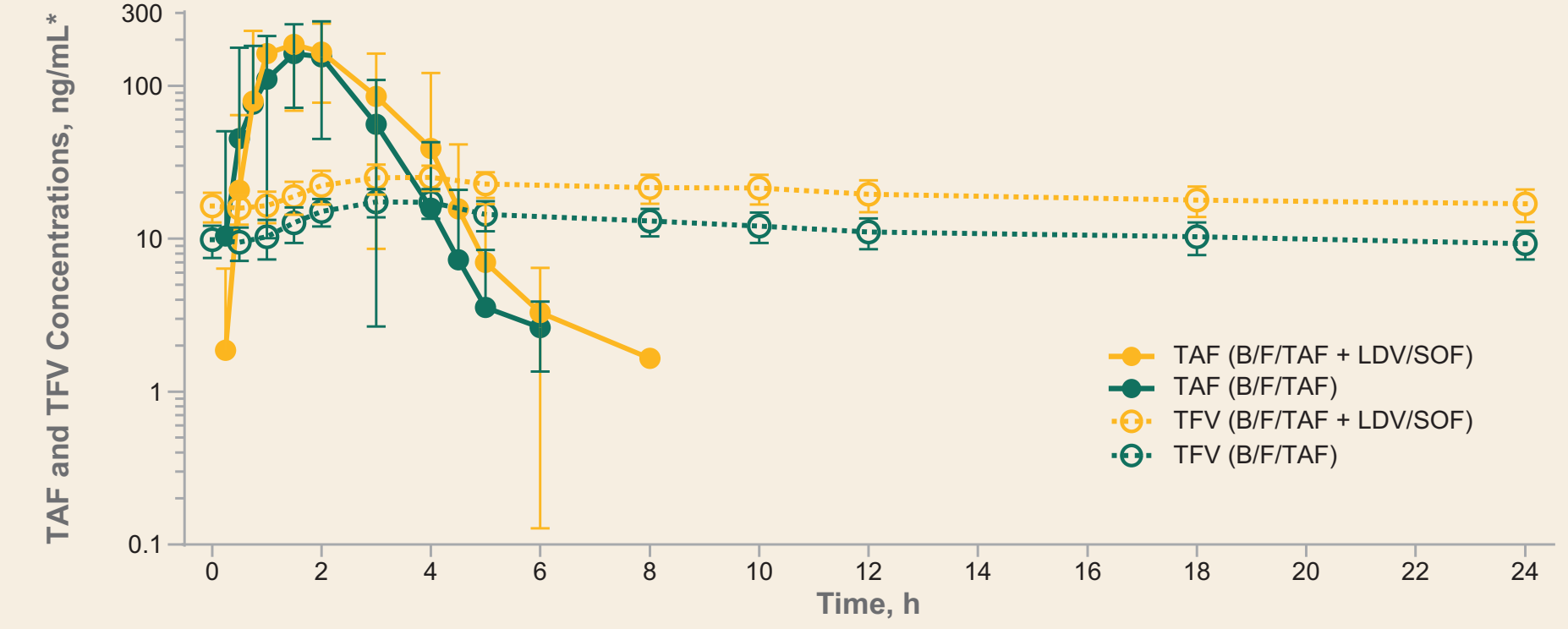
FTC Mean (%CV) [†]	B/F/TAF + LDV/SOF n=30		B/F/TAF n=30		GMR (90% CI)	
AUC _{0–∞} , h·ng/mL	11,300 (15.0)	11,500 (20.4)	98.9	98.9	95.5	(102)
C _{max} , ng/mL	2040 (26.6)	2010 (15.2)	99.2	99.2	93.5	(105)
C _t , ng/mL	74.9 (19.2)	73.4 (21.6)	103	103	98.9	(107)

Effect of SOF/VEL/VOX on FTC (Study 2)



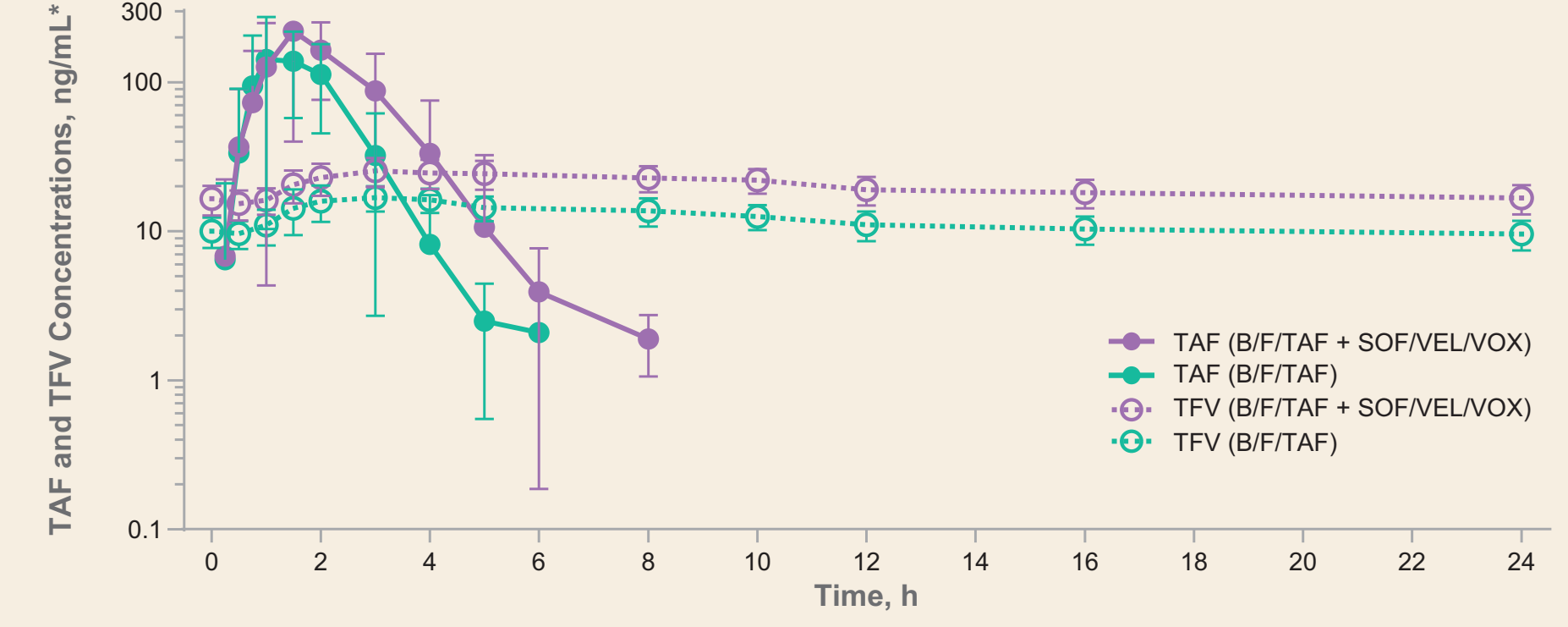
FTC Mean (%CV) [†]	B/F/TAF + SOF/VEL/VOX n=30		B/F/TAF n=30		GMR (90% CI)	
AUC _{0–∞} , h·ng/mL	9440 (14.3)	9920 (12.1)	94.9	94.9	93.1	(96.9)
C _{max} , ng/mL	1630 (25.6)	1830 (21.6)	88.6	88.6	83.1	(94.3)
C _t , ng/mL	70.5 (22.2)	63.9 (20.5)	110	110	105	(116)

Effect of LDV/SOF on TAF and TFV (Study 1)



TAF/TFV Mean (%CV) [†]	B/F/TAF + LDV/SOF n=30				B/F/TAF n=30				GMR (90% CI)	
AUC _{0–∞} , h·ng/mL	430 (29.3)	475 (20.8)	343 (33.6)	284 (21.0)	127 (119, 134)	167 (160, 174)	117	143	137	150
C _{max} , ng/mL	305 (46.0)	26.2 (19.6)	262 (49.7)	18.3 (19.5)	117 (99.5, 138)	143 (137, 150)	—	—	—	—
C _t , ng/mL	—	16.9 (23.8)	—	9.30 (21.2)	—	—	—	—	—	—

Effect of SOF/VEL/VOX on TAF and TFV (Study 2)



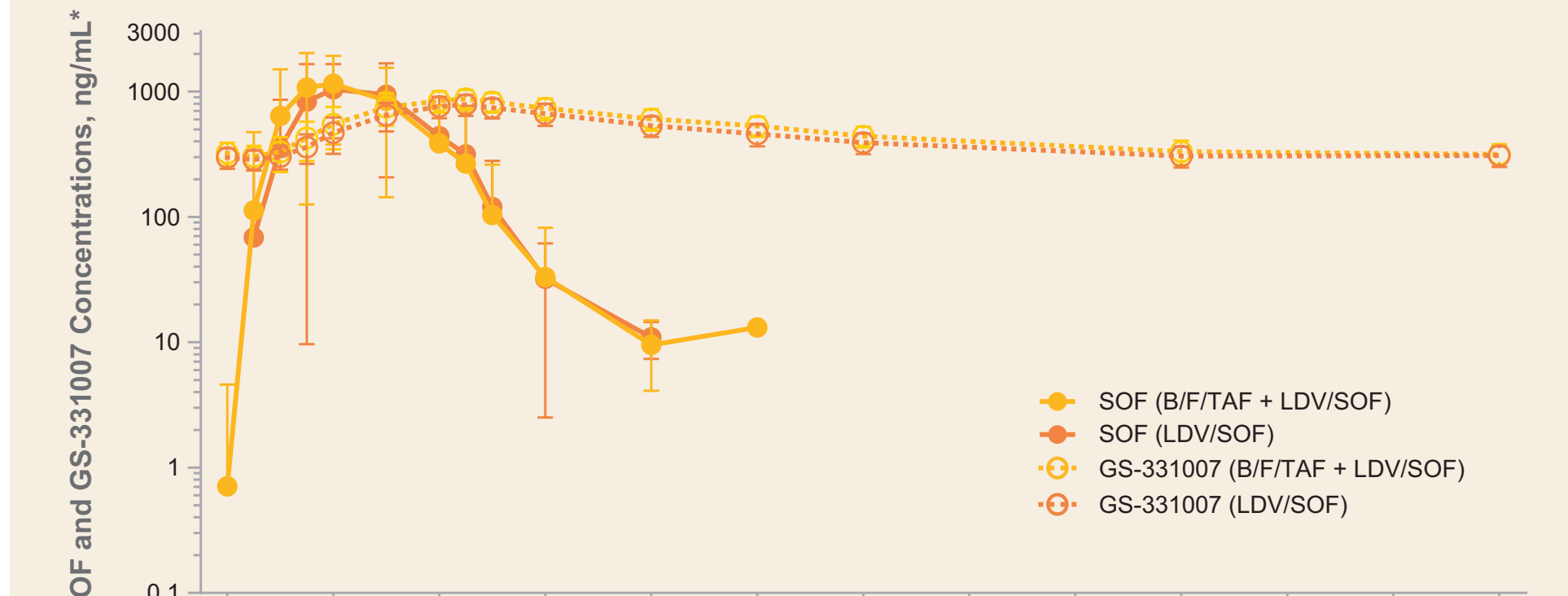
TAF/TFV Mean (%CV) [†]	B/F/TAF + SOF/VEL/VOX n=30				B/F/TAF n=30				GMR (90% CI)	
AUC _{0–∞} , h·ng/mL	443 (38.2)	480 (20.0)	282 (35.5)	287 (20.2)	157 (144, 171)	167 (162, 173)	157	167	167	174
C _{max} , ng/mL	280 (61.0)	26.9 (20.8)	217 (47.8)	17.8 (21.8)	128 (109, 151)	151 (145, 158)	—	—	—	—
C _t , ng/mL	—	16.7 (22.1)	—	9.60 (22.6)	—	—	—	—	—	—

[†]Mean (standard deviation [SD]); ^{††}Data reported to 3 significant figures; ^{†††}AUC from time 0 to last measurable concentration presented for TAF; ^{††††}% CV, % coefficient of variation.

- PK of BIC and FTC were unaltered by coadministration of B/F/TAF with LDV/SOF or SOF/VEL/VOX
- A modest increase (<2-fold) in TFV exposure was observed when B/F/TAF was coadministered with LDV/SOF
- Modest increases (<2-fold) in TAF and TFV exposures were observed when B/F/TAF was coadministered with SOF/VEL/VOX
 - TFV exposures observed when B/F/TAF was coadministered with LDV/SOF or SOF/VEL/VOX were ~4–7-fold lower than after administration of TDF alone⁵
- These increases are due to increased absorption of TAF and are not considered clinically meaningful^{6–8}

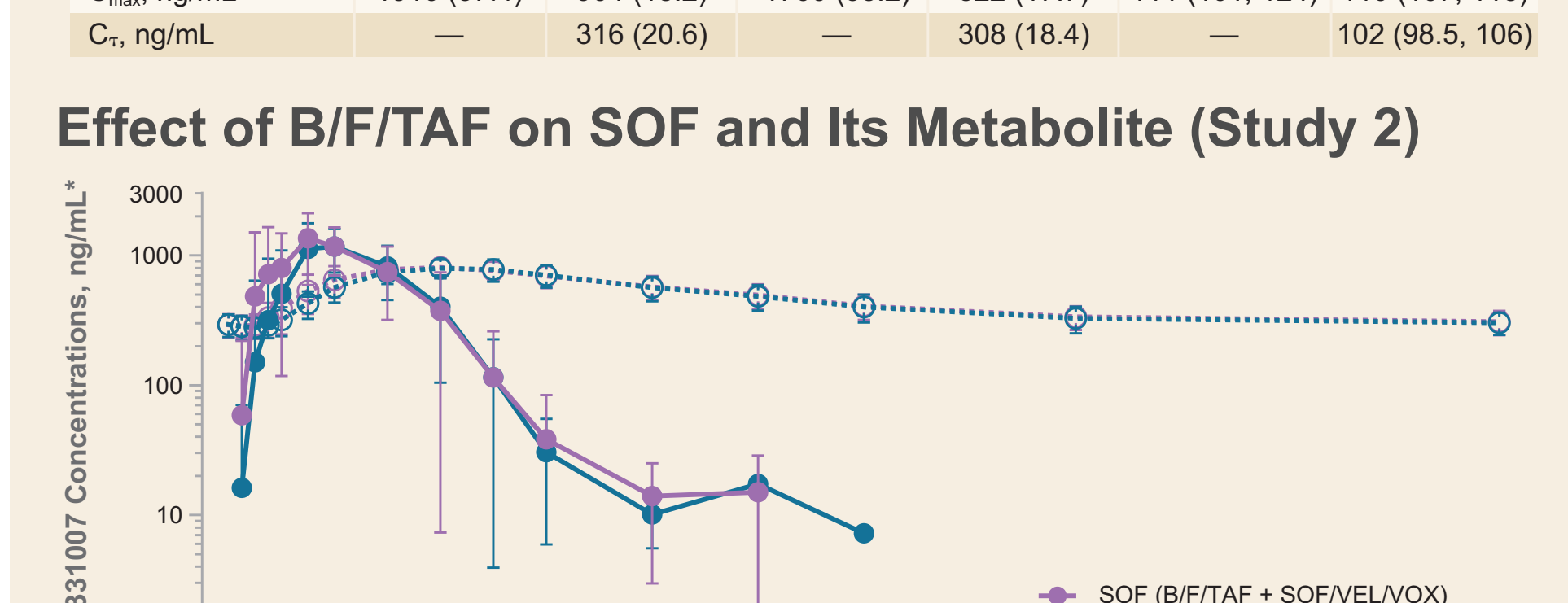
Effect of HIV ARVs on HCV DAAs

Effect of B/F/TAF on SOF and Its Metabolite (Study 1)



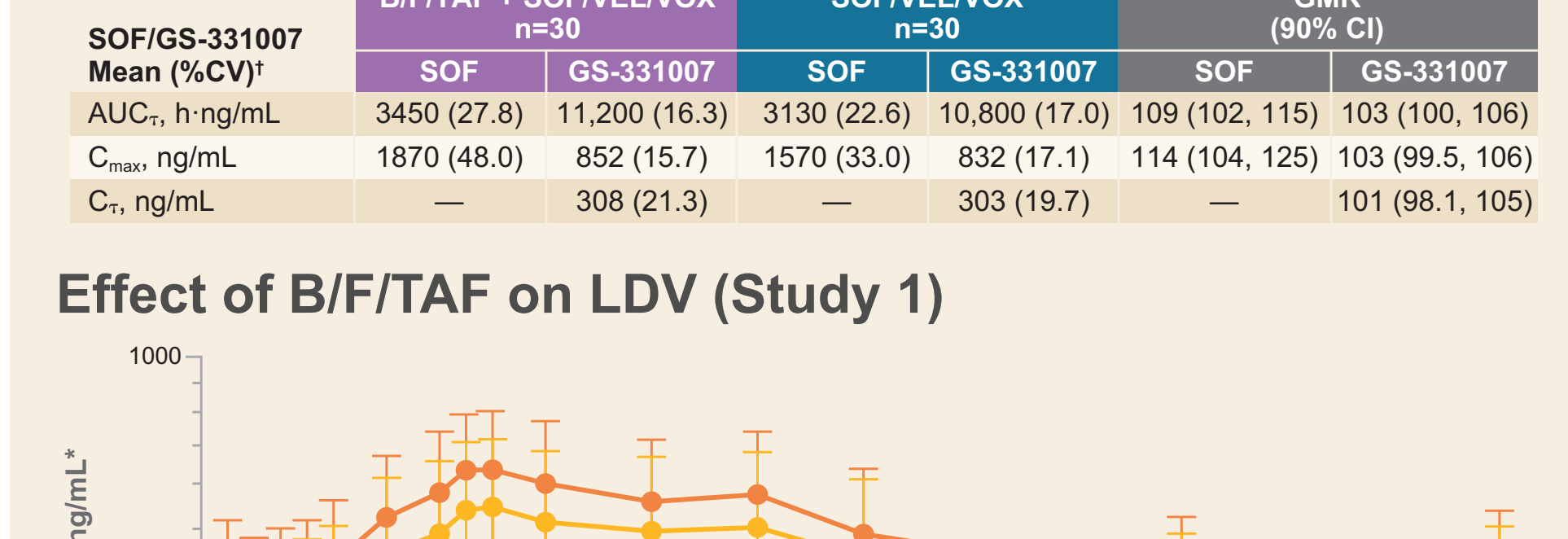
SOF and GS-331007 Mean (%CV) [†]	B/F/TAF + LDV/SOF n=30		LDV/SOF n=30		GMR (90% CI)	
AUC _{0–∞} , h·ng/mL	3170 (24.3)	11,600 (17.2)	2970 (24.6)	10,400 (14.9)	107	(101, 113)
C _{max} , ng/mL	1910 (37.4)	904 (18.2)	1700 (38.2)	822 (17.7)	111	(101, 124)
C _t , ng/mL	—	316 (20.6)	—	308 (18.4)	—	102 (98.5, 106)

Effect of B/F/TAF on SOF and Its Metabolite (Study 2)



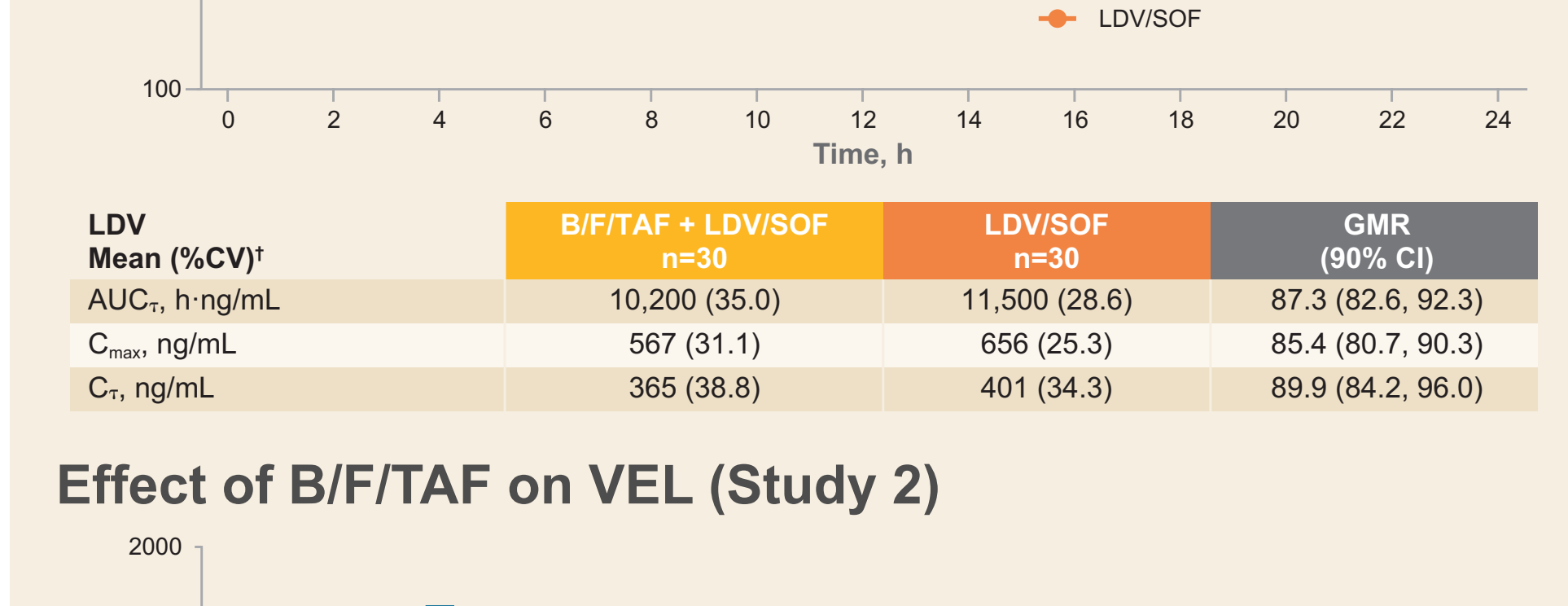
SOF and GS-331007 Mean (%CV) [†]	B/F/TAF + SOF/VEL/VOX n=30		SOF/VEL/VOX n=30		GMR (90% CI)	
AUC _{0–∞} , h·ng/mL	3450 (27.8)	11,200 (16.3)	3130 (22.6)	10,800 (17.0)	109	(102, 115)
C _{max} , ng/mL	1870 (48.0)	852 (15.7)	1570 (33.0)	832 (17.1)	114	(104, 125)
C _t , ng/mL	—	308 (21.3)	—	303 (19.7)	—	101 (98.1, 105)

Effect of B/F/TAF on LDV (Study 1)



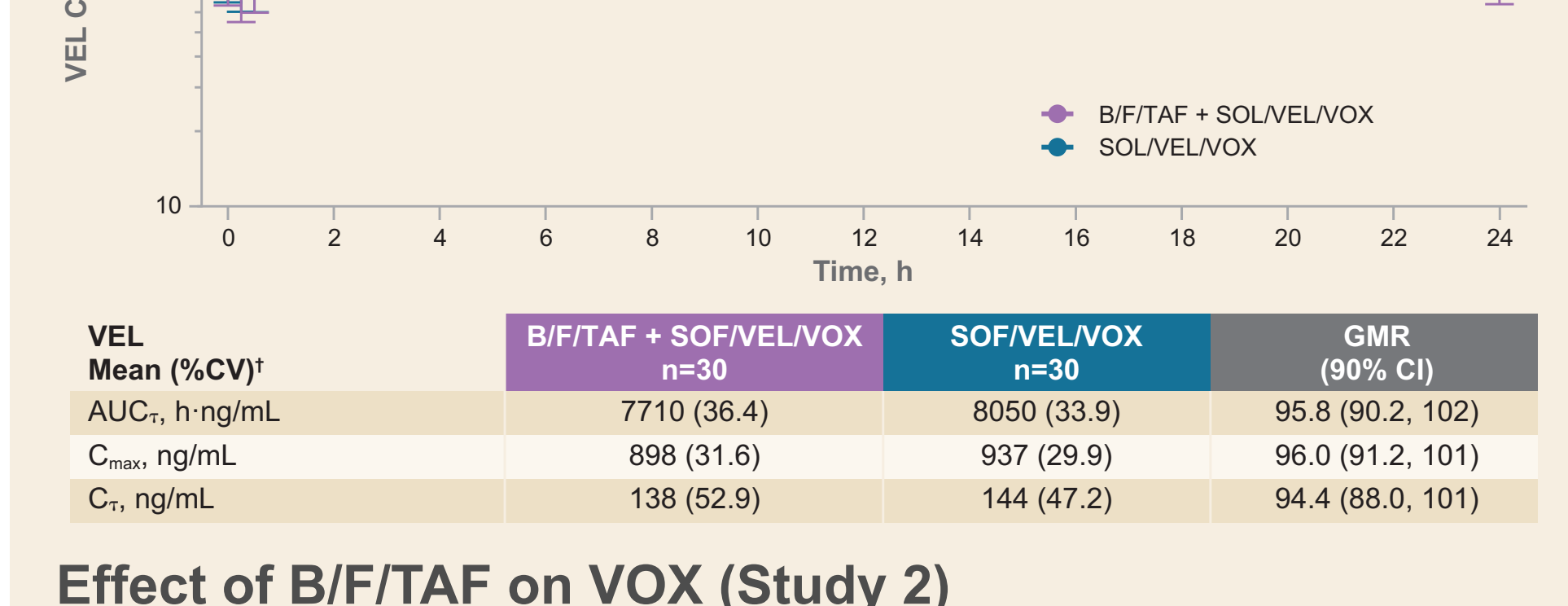
LDV Mean (%CV) [†]	B/F/TAF + LDV/SOF n=30		LDV/SOF n=30		GMR (90% CI)	
AUC _{0–∞} , h·ng/mL	10,200 (35.0)	11,500 (28.6)	87.3	87.3	82.6	(92.3)
C _{max} , ng/mL	567 (31.1)	656 (25.3)	85.4	85.4	80.7	(90.3)
C _t , ng/mL	365 (38.8)	401 (34.3)	89.9	89.9	84.2	(96.0)

Effect of B/F/TAF on VEL (Study 2)



VEL Mean (%CV) [†]	B/F/TAF + SOF/VEL/VOX n=30		SOF/VEL/VOX n=30		GMR (90% CI)	
AUC _{0–∞} , h·ng/mL	7710 (36.4)	8050 (33.9)	95.8	95.8	90.2	(102)
C _{max} , ng/mL	898 (31.6)	937 (29.9)	96.0	96.0	91.2	(101)
C _t , ng/mL	138 (52.9)	144 (47.2)	94.4	94.4	88.0	(101)

Effect of B/F/TAF on VOX (Study 2)



VOX Mean (%CV) [†]	B/F/TAF + SOF/VEL/VOX n=30		SOF/VEL/VOX n=30		GMR (90% CI)	
AUC _{0–∞} , h·ng/mL	4480 (66.1)	4820 (61.3)	91.0	91.0	80.0	(103)
C _{max} , ng/mL	880 (69.1)	929 (56.6)	89.8	89.8	76.4	(106)
C _t , ng/mL	27.8 (71.4)	27.6 (56.5)	96.7	96.7	88.3	(106)

[†]Mean (SD); ^{††}Data reported to 3 significant figures.

- PK of SOF, GS-331007, LDV, VEL, and VOX were unaltered by coadministration of B/F/TAF with LDV/SOF or SOF/VEL/VOX

Conclusions

- Study treatments were safe and well tolerated
- There were no clinically relevant changes in the PK of any components of B/F/TAF, LDV/SOF, or SOF/VEL/VOX when coadministered

References: 1. Platt L, et al. *Lancet Infect Dis* 2016;16:797-808; 2. Harvoni [SmPC], Carrigtohili, Ireland: Gilead Sciences Ireland UC, 11/7/14; 3. Vosevi [SmPC], Carrigtohili, Ireland: Gilead Sciences Ireland UC, 7/26/17; 4. Biktegravi [SmPC], Cambridge, UK: Gilead Sciences International Ltd, 2018; 5. Viread [SmPC], Cambridge, UK: Gilead Sciences Int'l Ltd, 10/16/16; 6. Custodio JM, et al. *Antimicrob Agents Chemother* 2016;60:5135-40; 7. Garrison K, et al. *EBioMedicine* 2017; abstr FRI-187; 8. German P, et al. *Clin Pharmacokinet* 2018;57:1369-83. Acknowledgments: We extend our thanks to the study subjects. This study was funded by Gilead Sciences, Inc.