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

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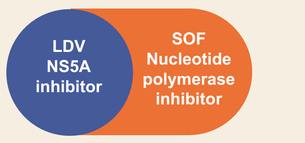
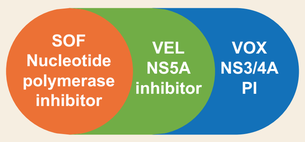
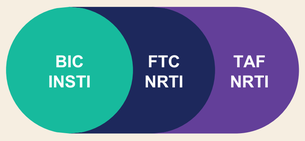
Introduction

- Hepatitis C virus (HCV)–related liver disease in HCV/HIV coinfected patients is a major cause of morbidity and mortality[1]
- It is estimated that there are ~2.3 million HIV/HCV-coinfected individuals worldwide[1]
- 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*







- Ledipasvir/sofosbuvir (LDV/SOF)
  - Once-daily, oral, fixed-dose (90/400 mg) DAA combination tablet for **HCV** genotypes 1 and 4[2]
- SOF/velpatasvir/voxilaprevir (SOF/VEL/VOX)
  - Once-daily, oral, fixed-dose (400/100/100 mg) DAA combination tablet for **HCV** genotypes 1–6[3]
- Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF)
  - Once-daily, oral, fixed-dose (50/200/25 mg) tablet regimen for treatment of **HIV**[4]

*B/F/TAF: Biktarvy®; 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 BCRP[4]

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

		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	A	B	C
B	B/F/TAF 75/200/25 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
B	B/F/TAF 50/200/25 mg	3	E	B	D
D	SOF/VEL/VOX 400/100/100 mg + VOX 100 mg*	4	E	D	B
E	B/F/TAF + SOF/VEL/VOX + VOX*	5	D	B	E
		6	D	E	B

*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_τ), maximum plasma concentration (C_{max}), and concentration at end of dosing interval (C_τ) 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

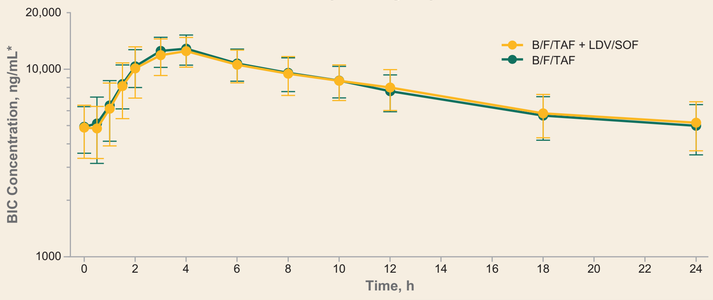
	Study 1 n=30	Study 2 n=30
Enrolled/completed, n	30/30	30/30
Sex, n (%)		
Male	20 (67)	19 (63)
Female	10 (33)	11 (37)
Mean weight, kg (range)	76.1 (56.6–99.7)	75.4 (53.0–99.0)
Race/ethnicity, n (%)		
Black	15 (50)	12 (40)
White	15 (50)	17 (57)
Other	0	1 (3)
Hispanic or Latino	19 (63)	18 (60)

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

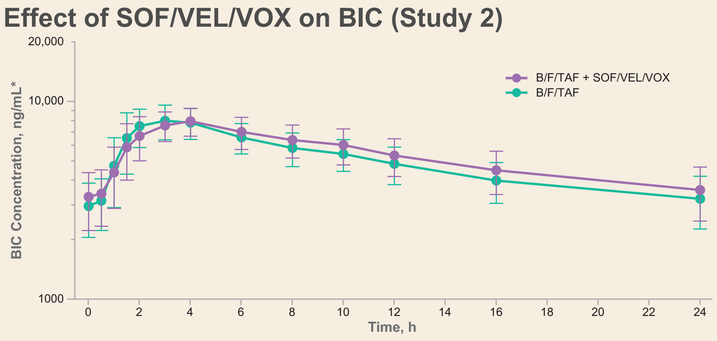
Effect of HCV DAAs on HIV ARVs

Effect of LDV/SOF on BIC (Study 1)



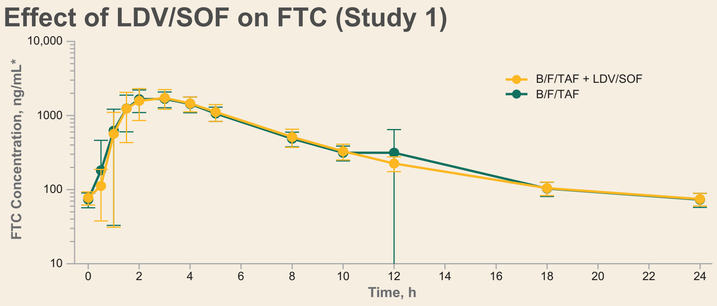
BIC Mean (%CV)†	B/F/TAF + LDV/SOF n=30	B/F/TAF n=30	GMR (90% CI)
AUC_τ, h·ng/mL	189,000 (20.8)	188,000 (19.3)	100 (97.2, 103)
C_{max}, ng/mL	13,300 (15.2)	13,600 (16.6)	98.3 (94.0, 103)
C_τ, ng/mL	5190 (29.2)	4990 (29.9)	104 (99.4, 109)

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



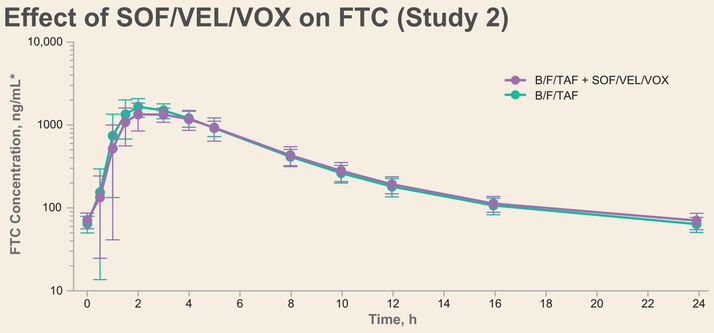
BIC Mean (%CV)†	B/F/TAF + SOF/VEL/VOX n=30	B/F/TAF n=30	GMR (90% CI)
AUC_τ, h·ng/mL	128,000 (20.1)	120,000 (19.5)	107 (103, 110)
C_{max}, ng/mL	8270 (14.7)	8530 (20.0)	97.7 (94.4, 101)
C_τ, ng/mL	3570 (30.5)	3220 (29.7)	111 (105, 117)

Effect of LDV/SOF on FTC (Study 1)



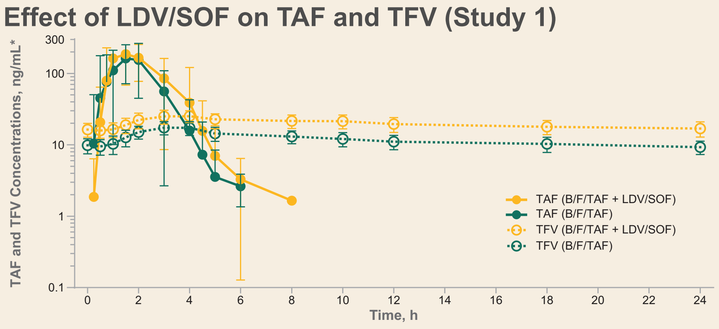
FTC Mean (%CV)†	B/F/TAF + LDV/SOF n=30	B/F/TAF n=30	GMR (90% CI)
AUC_τ, h·ng/mL	11,300 (15.0)	11,500 (20.4)	98.9 (95.5, 102)
C_{max}, ng/mL	2040 (26.6)	2010 (15.2)	99.2 (93.5, 105)
C_τ, ng/mL	74.9 (19.2)	73.4 (21.6)	103 (98.9, 107)

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



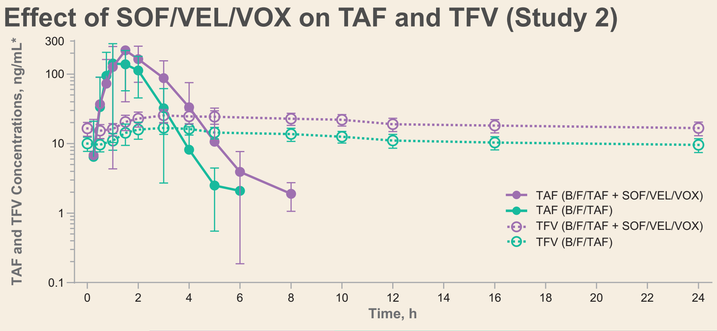
FTC Mean (%CV)†	B/F/TAF + SOF/VEL/VOX n=30	B/F/TAF n=30	GMR (90% CI)
AUC_τ, h·ng/mL	9440 (14.3)	9920 (12.1)	94.9 (93.1, 96.9)
C_{max}, ng/mL	1630 (25.6)	1830 (21.6)	88.6 (83.1, 94.3)
C_τ, ng/mL	70.5 (22.2)	63.9 (20.5)	110 (105, 116)

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)	
	TAF	TFV	TAF	TFV	TAF	TFV
AUC_τ, h·ng/mL	430 (29.3)	475 (20.8)	343 (33.6)	284 (21.0)	127 (119, 134)	167 (160, 174)
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_τ, ng/mL	—	16.9 (23.8)	—	9.30 (21.2)	—	181 (173, 190)

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



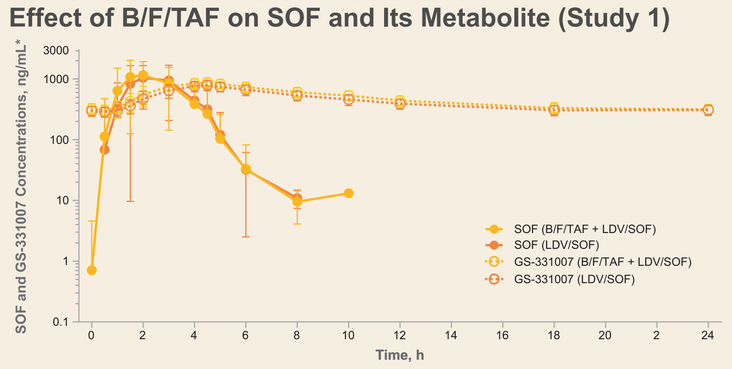
TAF/TFV Mean (%CV)†	B/F/TAF + SOF/VEL/VOX n=30		B/F/TAF n=30		GMR (90% CI)	
	TAF‡	TFV	TAF‡	TFV	TAF	TFV
AUC_τ, h·ng/mL	443 (38.2)	480 (20.0)	282 (35.5)	287 (20.2)	157 (144, 171)	167 (162, 173)
C_{max}, ng/mL	280 (61.0)	26.9 (20.8)	217 (47.8)	17.8 (21.8)	128 (109, 151)	151 (145, 158)
C_τ, ng/mL	—	16.7 (22.1)	—	9.60 (22.6)	—	174 (168, 180)

*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 alone[5]
- These increases are due to increased absorption of TAF and are not considered clinically meaningful[6-8]

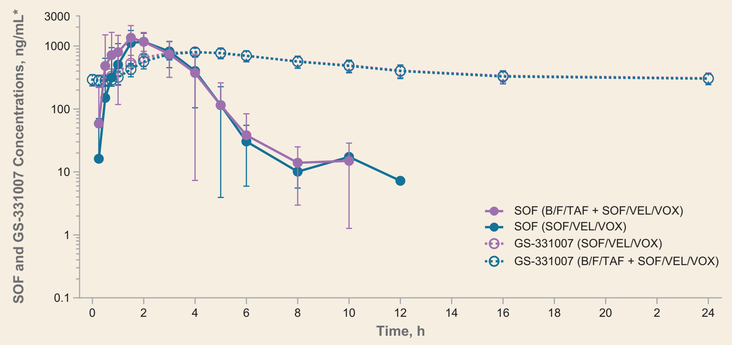
Effect of HIV ARVs on HCV DAAs

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



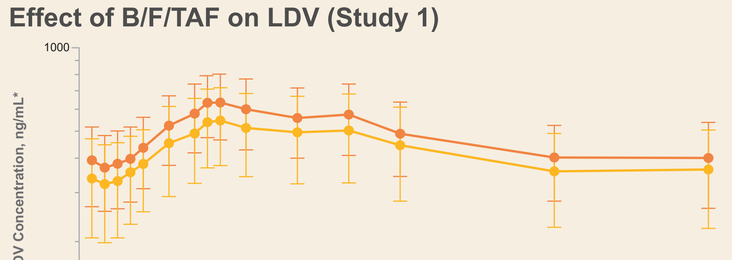
SOF/GS-331007 Mean (%CV)†	B/F/TAF + LDV/SOF n=30		LDV/SOF n=30		GMR (90% CI)	
	SOF	GS-331007	SOF	GS-331007	SOF	GS-331007
AUC_τ, h·ng/mL,	3170 (24.3)	11,600 (17.2)	2970 (24.6)	10,400 (14.9)	107 (101, 113)	111 (108, 114)
C_{max}, ng/mL	1910 (37.4)	904 (18.2)	1700 (38.2)	822 (17.7)	111 (101, 124)	110 (107, 113)
C_τ, ng/mL	—	316 (20.6)	—	308 (18.4)	—	102 (98.5, 106)

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



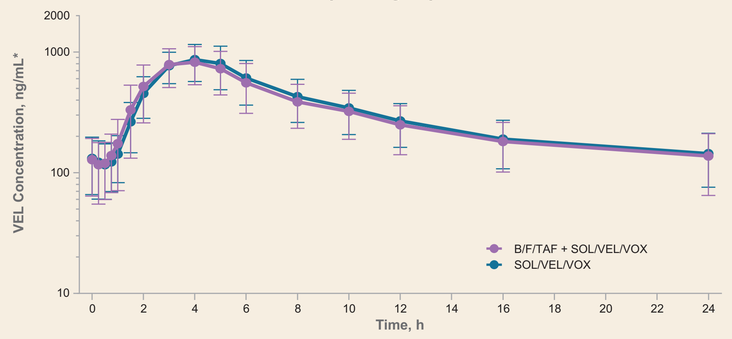
SOF/GS-331007 Mean (%CV)†	B/F/TAF + SOF/VEL/VOX n=30		SOF/VEL/VOX n=30		GMR (90% CI)	
	SOF	GS-331007	SOF	GS-331007	SOF	GS-331007
AUC_τ, h·ng/mL	3450 (27.8)	11,200 (16.3)	3130 (22.6)	10,800 (17.0)	109 (102, 115)	103 (100, 106)
C_{max}, ng/mL	1870 (48.0)	852 (15.7)	1570 (33.0)	832 (17.1)	114 (104, 125)	103 (99.5, 106)
C_τ, ng/mL	—	308 (21.3)	—	303 (19.7)	—	101 (98.1, 105)

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



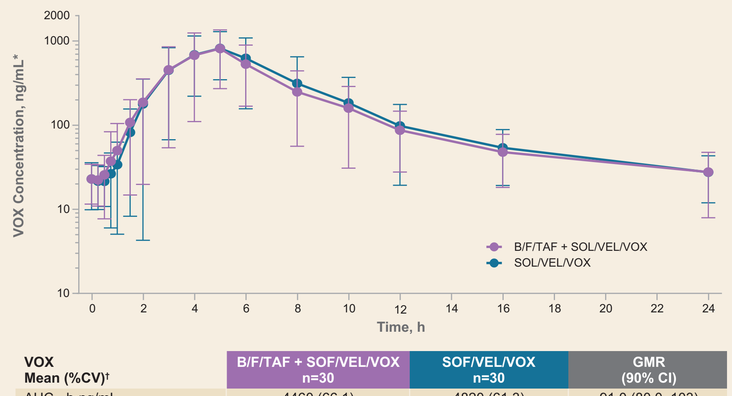
LDV Mean (%CV)†	B/F/TAF + LDV/SOF n=30	LDV/SOF n=30	GMR (90% CI)
AUC_τ, h·ng/mL	10,200 (35.0)	11,500 (28.6)	87.3 (82.6, 92.3)
C_{max}, ng/mL	567 (31.1)	656 (25.3)	85.4 (80.7, 90.3)
C_τ, ng/mL	365 (38.8)	401 (34.3)	89.9 (84.2, 96.0)

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_τ, h·ng/mL	7710 (36.4)	8050 (33.9)	95.8 (90.2, 102)
C_{max}, ng/mL	898 (31.6)	937 (29.9)	96.0 (91.2, 101)
C_τ, ng/mL	138 (52.9)	144 (47.2)	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_τ, h·ng/mL	4460 (66.1)	4820 (61.3)	91.0 (80.0, 103)
C_{max}, ng/mL	880 (69.1)	929 (55.6)	89.8 (76.4, 106)
C_τ, ng/mL	27.8 (71.4)	27.6 (56.5)	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]. Carrigtohill, Ireland: Gilead Sciences Ireland UC, 11/7/14; **3.** Vosevi [SmPC]. Carrigtohill, Ireland: Gilead Sciences Ireland UC, 7/26/17; **4.** Biktarvy [SmPC]. Cambridge, UK: Gilead Sciences International Ltd, 2018; **5.** Viread [SmPC]. Cambridge, UK: Gilead Sciences Intl Ltd, 10/16/18; **6.** Custodio JM, et al Antimicrob Agents Chemother 2016;60:5135-40; **7.** Garrison K, et al. EASL 2017, abstr FRI-187; **8.** German P, et al, Clin Pharmacokinetics 2018;57:1369-83.

Acknowledgments: We extend our thanks to the study subjects. This study was funded by Gilead Sciences, Inc.