Drug-Drug Interactions Studies between HCV Antivirals Sofosbuvir/Velpatasvir and HIV Antiretrovirals in Healthy Volunteers

Erik Mogalian[1], Annie Luetkemeyer[2], Sarjita Naik[1], Joe Llewellyn[1], Macky Natha[1], Luisa Stamm[1], Anu Osinusi[1], Gong Shen[1], Karim Sajwani[1], John McNally[1], and Anita Mathias[1]

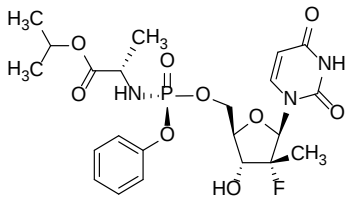
1. Gilead Sciences, Foster City, California, USA 2. University of California San Francisco Medical Center, San Francisco, California USA

Disclosures

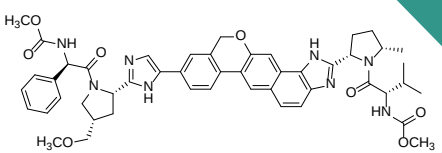
Dr Luetkemeyer has received research grants to UCSF from Abbvie, Bristol-Myers Squibb, Gilead, Merck

Sofosbuvir/Velpatasvir

SOF
Nucleotide polymerase inhibitor



- **Sofosbuvir (SOF)**
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg tablet



VEL
NS5A inhibitor

- **Velpatasvir (VEL; GS-5816)**
  - Picomolar potency against GT 1–6
  - 2nd-generation inhibitor with improved resistance profile

SOF + **VEL**

- **SOF/VEL FDC**
  - Once daily, oral, FDC (400/100 mg)
  - Treatment with SOF/VEL for 12 weeks in Phase 3 studies resulted in high SVR in patients with HCV GT 1–6

Objective and Background

- The objective of this study is to summarize the drug-drug interaction profile of SOF/VEL (400/100 mg) with HIV antiretroviral regimens (ARVs)
- SOF
  - Substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)
  - Not substrate of cytochrome P450 (CYP) or uridine diphosphate glycosyltransferase–1A1 (UGT)
  - SOF metabolite GS-331007 is not a substrate of P-gp, BCRP, renal organic anion transporter (OAT)-1, OAT3, or organic cation transporter–2
- VEL
  - Substrate of P-gp, BCRP, organic anion transport polypeptide (OATP)-1B, CYP2B6, CYP2C8, and CYP3A4
  - Inhibitor of P-gp, BCRP, and OATP1B

Methods

- SOF/VEL DDI profile evaluated using:
  - Two Phase 1, open-label, randomized, multiple-dose, cross-over studies in healthy volunteers were conducted in 9 total cohorts

Cohort 1, n=24	SOF/VEL	+	EFV/FTC/TDF
Cohort 2, n=24	SOF/VEL	+	FTC/RPV/TDF
Cohort 3, n=24	SOF/VEL	+	DTG
Cohort 4, n=30	SOF/VEL	+	FTC/TDF+RAL
Cohort 5, n=24	SOF/VEL	+	EVG/COBI/ FTC/TAF
Cohort 6, n=24	SOF/VEL	+	EVG/COBI/ FTC/TDF
Cohort 7, n=24	SOF/VEL	+	ATV/r + FTC/TDF
Cohort 8, n=30	SOF/VEL	+	DRV/r + FTC/TDF
Cohort 9, n=24	SOF/VEL	+	LPV/r + FTC/TDF

  - Steady-state pharmacokinetic (PK) samples collected over 24 hours
  - Analyses
    - Plasma concentrations: validated LC/MS/MS assays
    - PK parameters: noncompartmental methods (WinNonlin® 6.3)
    - Geometric least-squares mean ratios and 90% CIs (Test: Reference): ANOVA for AUCtau, Cmax, Ctau (as appropriate); compared against lack of PK alteration boundaries of 70−143% except for RAL (50-200%)
  - AE monitoring, clinical laboratory, physical exam, ECG evaluations

Subject Enrollment and Demographics

	SOF/VEL +								
	Cohort 1 EFV/FTC/ TDF n=30	Cohort 2 FTC/RPV/ TDF n=24	Cohort 3 DTG n=24	Cohort 4 FTC/TDF+ RAL n=30	Cohort 5 EVG/ COBI/ FTC/ TAF n=23*	Cohort 6 EVG/ COBI/ FTC/ TDF n=24*	Cohort 7 ATV/r + FTC/ TDF n=24	Cohort 8 DRV/r + FTC/ TDF n=30*†	Cohort 9 LPV/r + FTC/ TDF n=23*
Mean age, y (range)	34 (19–45)	35 (22–45)	37 (22–44)	33 (21–45)	33 (20, 44)	34 (21, 45)	34 (26, 45)	34 (20, 45)	36 (22, 44)
Mean weight, kg (range)	74 (51–103)	75 (56–92)	76 (56–100)	72 (55–92)	76 (51, 103)	76 (53, 108)	74 (56, 98)	74 (52, 90)	74 (55, 98)
Sex, n (%)									
Male	18 (60)	14 (58)	14 (58)	18 (60)	15 (63)	14 (54)	17 (71)	17 (55)	12 (50)
Female	12 (40)	10 (42)	10 (42)	12 (40)	9 (37)	12 (46)	7 (29)	14 (45)	12 (50)
Race, n (%)									
White	27 (90)	22 (92)	20 (83)	22 (73)	16 (67)	21 (81)	22 (92)	28 (90)	21 (88)
Nonwhite	3 (10)	2 (8)	4 (17)	8 (27)					
Ethnicity, n (%)									
Hispanic	30 (100)	24 (100)	23 (96)	22 (73)	13 (54)	23 (89)	22 (92)	29 (94)	22 (92)
Non-Hispanic	0	0	1 (4)	8 (27)					

*Subject withdrew consent.; †Discontinuation due to pregnancy

Safety

Subject, n (%)	SOF/VEL+			
	Cohort 1 EFV/FTC/TDF n=30	Cohort 2 FTC/RPV/TDF n=24	Cohort 3 DTG n=24	Cohort 4 FTC/TDF+RAL n=30
AEs	10 (33)	14 (58)	11 (46)	10 (33)
Grade 3-4 AE	0 (0)	0 (0)	0 (0)	0 (0)
Serious AE	0 (0)	0 (0)	0 (0)	0 (0)
Treatment D/C due to AE	1 (3)*	0 (0)	0 (0)	0 (0)
AEs >10%	5 (17)†	3 (13) †	6 (25) ‡ 5 (21) § 3 (13) †	5 (17) ‡ 5 (17) ‖ 3 (10) ¥
Grade 3-4 laboratory abnormality	3 (10)	1 (4)	2 (8)	2 (7)

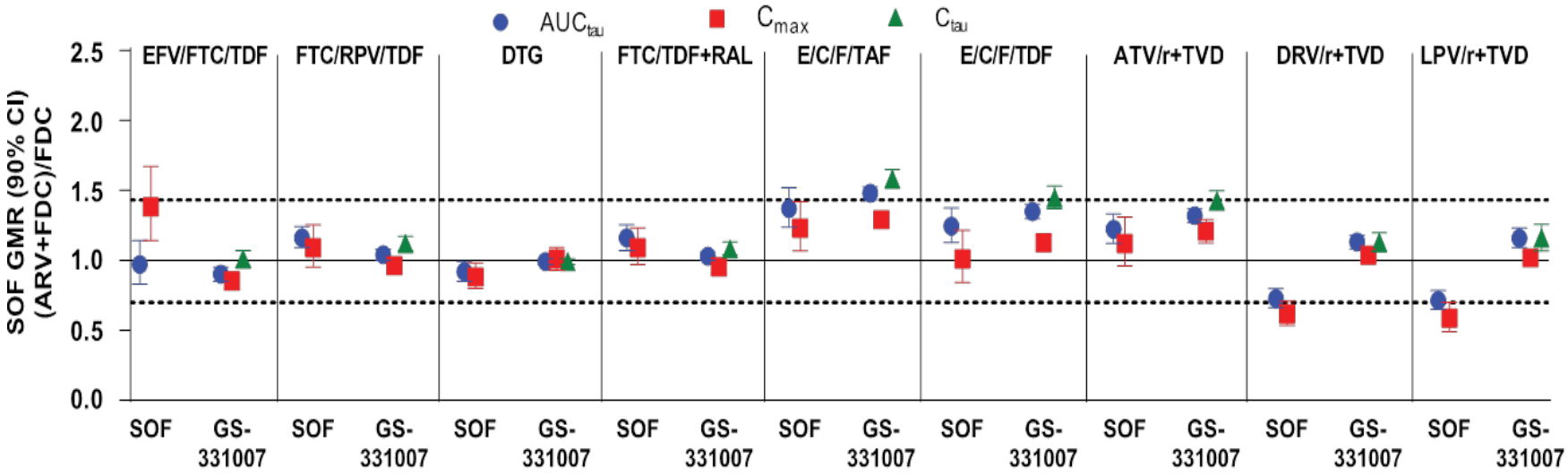
* urticaria; † constipation; ‡headache; § chapped lips; ‖ nausea; ¥ vomiting

Safety

Subjects, n (%)	SOF/VEL +				
	Cohort 5 EVG/COBI/ FTC/TAF n=23‖	Cohort 6 EVG/COBI/ FTC/TDF n=24‖	Cohort 7 ATV/r + FTC/TDF n=24	Cohort 8 DRV/r + FTC/TDF n=30‖¥	Cohort 9 LPV/r + FTC/TDF n=23‖
AEs	7 (29)	10 (39)	10 (42)	14 (45)	7 (29)
Grade 3–4 AE	0	0	0	0	0
Serious AE	0	0	0	0	0
Treatment D/C due to AE	0	0	0	0	0
AEs >10%	0	0	5 (21)*	0	0
Grade 3–4 laboratory abnormality	1 (4)†	5 (19)†	18 (75)‡	3 (10)†	2 (8)§

*Headache; similar incidence in treatment and both reference arms; †Blood in urine; ‡Blood in urine (n=1), hyperbilirubinemia (n=17). Similar incidence for subjects receiving ATV/r + FTC/TDF ± SOF/VEL; §Blood in urine (n=1), elevated LDL (n=1); ‖Subject withdrew consent; ¥Discontinuation due to pregnancy.

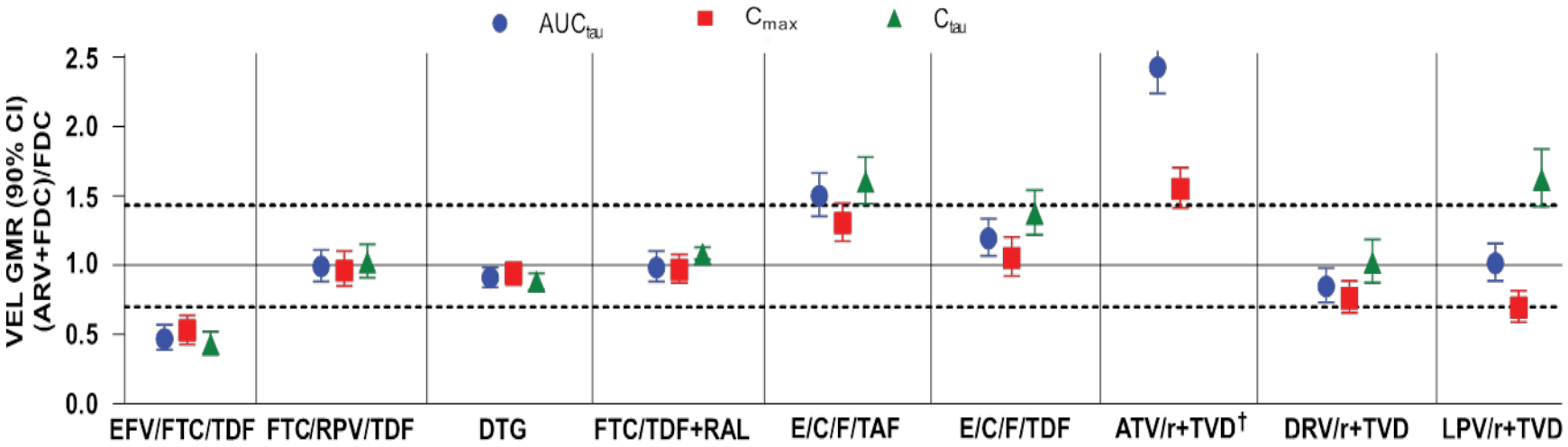
Effect of Antiretroviral Therapy on SOF and GS-331007*



*Dotted lines depict no-PK-alteration boundary.

- PK changes in SOF and GS-331007 are not clinically significant based on exposure-safety and -efficacy evaluations in Phase 3 SOF/VEL studies
- Changes in SOF exposure likely due to inhibition or induction of efflux transport (e.g., P-gp)

Effect of Antiretroviral Therapy on VEL*

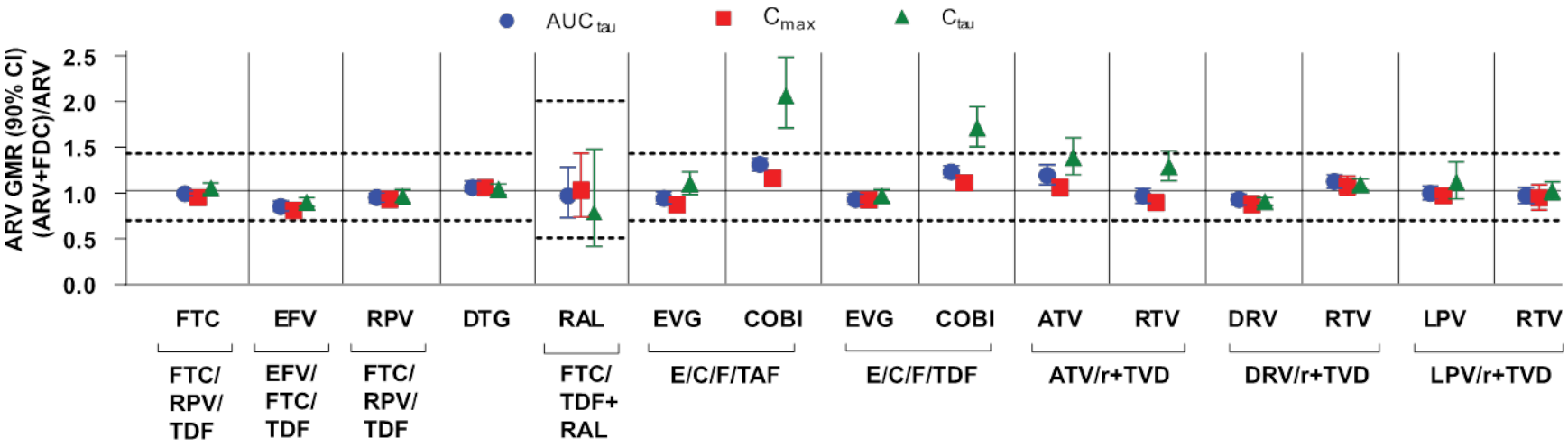


*Dotted lines depict no-PK-alteration boundary.

†Mean Ctau was 4.0 (range from 3.6 to 4.5).

- Changes in VEL exposure are explained by being a substrate of P-gp, BCRP, OATP, and CYP2B6, -2C8, and -3A4
- Co-administration of SOF/VEL with EFV/FTC/TDF resulted in ~50% decrease in VEL exposure, and EFV is not recommended with SOF/VEL
- In a separate study, VEL 500 mg was adminstered and there was no increase in adverse events compared to placebo; hence, no clinically significant DDI is expected with ATV/r+TVD

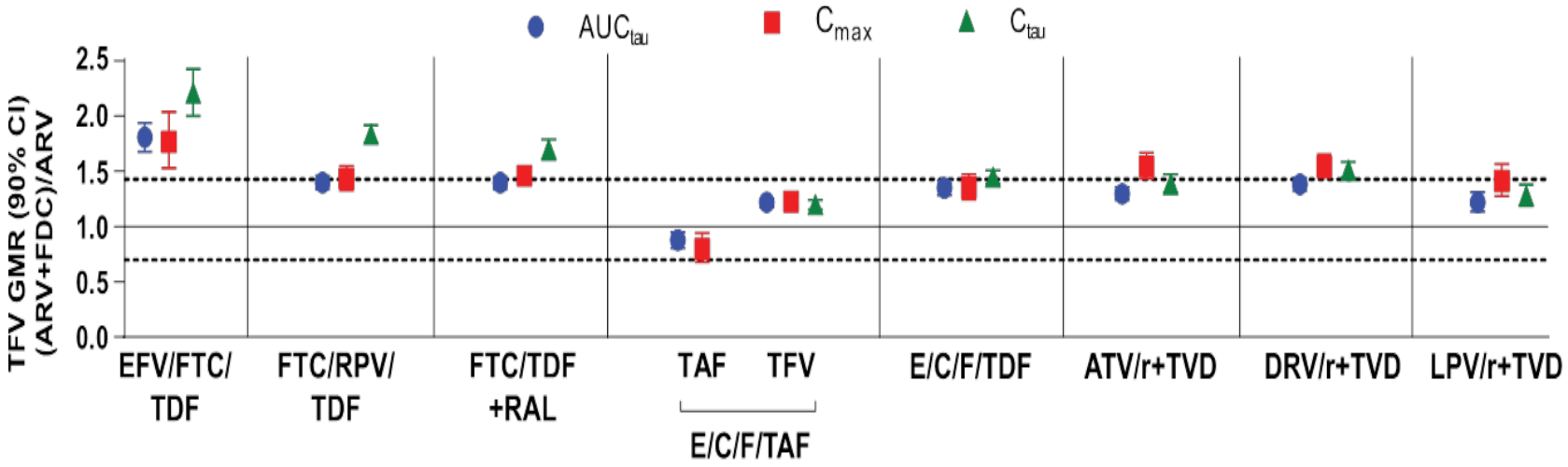
Effect of SOF/VEL on ARVs



*Dotted lines depict no-PK-alteration boundary.

- No significant effect of SOF/VEL on FTC, EFV, RPV, DTG, RAL, EVG, ATV, RTV, DRV, LPV
- Increased COBI Ctau is not expected to introduce further drug interaction potential

Effect of SOF/VEL on TFV*



*Dotted lines depict no-PK-alteration boundary.

- Co-administration of SOF/VEL with TDF-containing ARVs increased TFV exposure ~20-81%
- No significant impact of SOF/VEL on TAF or TFV derived from TAF

Conclusions

- PK Data from These and Previous Studies support the Co-administration of SOF/VEL in Co-infected Patients on the Following Agents:
  - NRTI: FTC, TAF, TDF
  - NNRTI: RPV
  - Integrase inhibitor: DTG, EVG, RAL
  - Protease inhibitor: ATV, DRV, LPV
  - PK booster: COBI, RTV
- SOF/VEL should not be administered with efavirenz
- Safety and efficacy of SOF/VEL (400/100 mg) with boosted and unboosted ARVs are being evaluated in a Phase 3 study in HIV/HCV co-infected individuals (ASTRAL-5)

Acknowledgments

- We extend our thanks to the study volunteers and research team. This study was funded by Gilead Sciences, Inc.