Abstract # O_24 and O_25

Evaluation of Transporter and Cytochrome P450-Mediated Drug-Drug Interactions with the Pan Genotypic HCV NS3/4A Protease Inhibitor Voxilaprevir (GS-9857) or Sofosbuvir/Velpatasvir/Voxilaprevir and Phenotypic Probe Drugs

Brian J. Kirby, James Taylor, Luisa M. Stamm, Qinghua Song, Helen Wei, Yizhao Li, Dina Alhelawe, K-H John Ling, and Anita Mathias

Gilead Sciences, Foster City, CA

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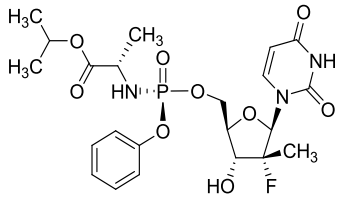
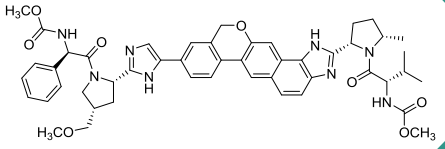
Disclosures

All authors are employees of Gilead Sciences, Inc.

Background

SOF Nucleotide polymerase inhibitor





VEL NS5A inhibitor

SOF Nucleotide polymerase inhibitor → VEL NS5A inhibitor → VOX NS3/4A Protease inhibitor

- **Sofosbuvir (SOF)**[1,2]
  - Potent antiviral activity against HCV GT 1–6
- **Velpatasvir (VEL)**[3-5]
  - Picomolar potency against HCV GT 1–6
  - 2nd-generation NS5A inhibitor with improved resistance profile
- **Voxilaprevir (VOX, GS-9857)**
  - HCV NS3/4A protease inhibitor with potent antiviral activity against HCV GT 1–6[6]
  - Improved resistance profile compared with other HCV protease inhibitors[6]
- **SOF/VEL/VOX FDC**
  - Once daily, oral, FDC (400/100/100 mg) for HCV infection
  - In evaluation in four Phase 3 studies

1. Jacobson IM, et al. N Engl J Med 2013;368:1867-77; 2. Lawitz E, et al. N Engl J Med 2013;368:1878-87; 3. Cheng G, et al. EASL 2013, poster 1191; 4. German P, et al. EASL 2013, poster 1195; **5.** Lawitz E, et al. J Viral Hepat 2015;22:1011-9; 6. Taylor JG, et al. EASL 2015, poster 899.

Background – DDI Mechanism

Known or Potential DDI Mechanism		SOF (Non-Clinical and Clinical)[7]	VEL (Non-Clinical and Clinical)[8]	VOX (Non-Clinical)
Drug Transporters	P-gp/BCRP	Substrate	Substrate/Inhibitor	Substrate/Inhibitor
	OATPs	-	Substrate/Inhibitor (OATP1B)	Substrate/Inhibitor
Drug Metabolizing Enzymes	CYP3A4	-	Substrate	Substrate
	CYP2C8	-	Substrate	Substrate
	CYP2B6	-	Substrate	-

7. Sovaldi® USPI, Revised 2015. 8. Mogalian E, et al. Poster FRI-168 EASL 2016

Objectives

- Primary
  - VOX as an object of DDIs:
    - To identify the contribution of drug transporters and CYP enzymes to the pharmacokinetics of VOX in healthy volunteers
  - SOF/VEL/VOX as a precipitant of DDIs:
    - To characterize the effect of the combination of SOF/VEL/VOX on P-gp, BCRP, and OATP activity in healthy volunteers to guide concomitant medication use in HCV-infected patients
- Secondary
  - To evaluate the safety and tolerability of administration of VOX, or SOF/VEL/VOX with phenotypic transporter or CYP probe substrates or inhibitors

Methods

Study 1: VOX as a Substrate of P-gp/BCRP, OATPs, or CYPs

Cohort 1, n=24	Rifampin (RIF) 600 mg Single Dose: OATP inhibitor Cyclosporine A (CsA) 600 mg Single Dose: P-gp/OATP/MRP2 Inhibitor
Cohort 2, n=24	Voriconazole (VORI) 200 mg BID 4 days: CYP3A Inhibitor Gemfibrozil (GFZ) 600 mg BID 4 days: CYP2C8 Inhibitor
Cohort 3, n=24	Rifampin (RIF) 600 mg QD 7 days prior to VOX: CYP/P-gp Inducer
Cohort 4, n=24	Grapefruit Juice (GFJ) 300 mL: Intestinal OATP inhibitor

- Phase 1 randomized open-label, single- and multiple-dose study in healthy volunteers
- VOX 100 mg single dose fasted (Cohort 1), or fed (moderate-fat meal Cohorts 2-4)
- Single dose PK samples collected over 96 hours for VOX
- Analyses
  - Plasma concentrations: validated LC/MS/MS assays
  - PK parameters: noncompartmental methods (WinNonlin® 6.3)
  - Percent geometric least-squares mean ratios (%GMRs) and 90% CIs (Test: Reference): ANOVA for AUC_{inf}, AUC_{last}, and C_{max}; compared against lack of PK alteration boundaries of 70−143%
- AE monitoring, clinical laboratory, physical exam, ECG evaluations

Methods

Study 2: SOF/VEL/VOX as an inhibitor of P-gp, BCRP or OATPs

Cohort 1, n=20	Rosuvastatin (ROS) 10 mg Single Dose: BCRP/OATP Substrate Pravastatin (PRA) 40 mg Single Dose: OATPSubstrate
Cohort 2, n=36	Dabigatran Etexilate (DE) 75 mg Single Dose: P-gp Substrate

- Phase 1 randomized open-label, multiple-dose study in healthy volunteers
- SOF/VEL/VOX 400/100/100 mg + 100 mg VOX QD 10 days administered fed
  - to match systemic exposure observed in HCV-infected subjects administered SOF/VEL/VOX 400/100/100 mg.
- Single dose PK samples collected over 96 hours for ROS, PRA, Total and Unconjugated (Free) Dabigatran (DAB: Dabigatran Etexilate metabolite)
- Analyses
  - Plasma concentrations: validated LC/MS/MS assays
  - PK parameters: noncompartmental methods (WinNonlin® 6.3)
  - Percent geometric least-squares mean ratios (%GMRs) and 90% CIs (Test: Reference): ANOVA for AUC_{inf}, AUC_{last}, and C_{max}; compared against lack of PK alteration boundaries of 70−143%
- AE monitoring, clinical laboratory, physical exam, ECG evaluations

Subject Enrollment and Demographics

	VOX				SOF/VEL/VOX	
	RIF (SD), CsA	VORI, GFZ	RIF (MD)	GFJ	ROS, PRA	DE
Enrolled/completed, n	26/22[a]	24/23[b]	24/24	24/23[b]	20/19[b]	36/36
Mean age, y (range)	33 (22, 44)	34 (22, 45)	34 (25, 45)	32 (20, 44)	37 (25, 43)	33 (19, 45)
Mean BMI, kg/m^2 (range)	25.6 (21.5, 30.0)	26.2 (20.9, 30.0)	25.7 (19.4, 30.0)	25.4 (19.2, 29.5)	26.7 (20.2, 29.6)	26.0 (19.0, 29.9)
Sex (male/female), n	14/12	18/6	16/8	7/17	10/10	26/10
White race, n (%)	12 (46)	8 (33)	10 (42)	4 (17)	13 (65)	24 (67)
Hispanic/Latino, n (%)	6 (23)	3 (12.5)	5 (21)	3 (13)	11 (55)	30 (83)

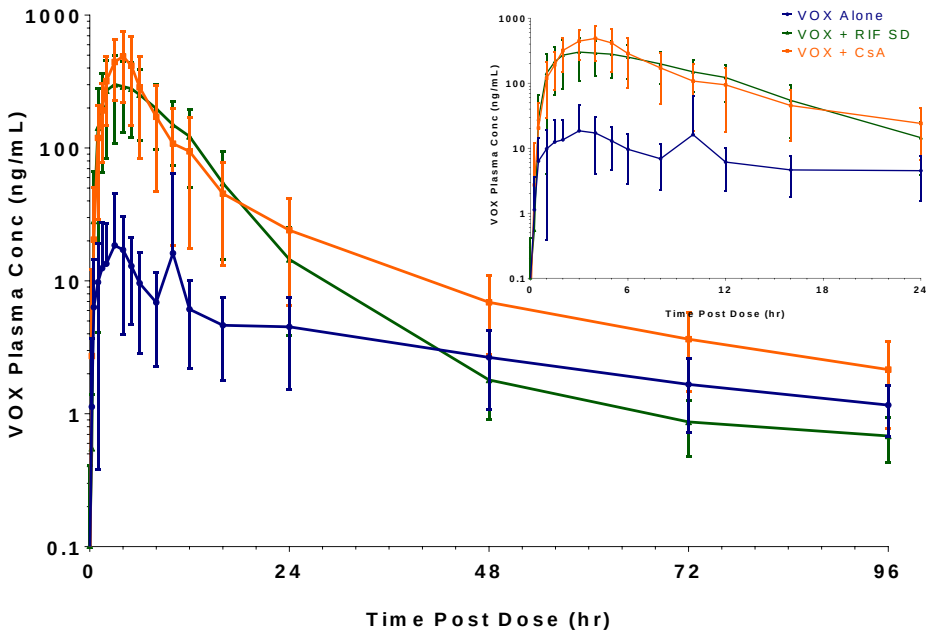
[a] Discontinuations due to Investigator discretion (n = 2), adverse event (n = 1, grade 1 headache), pregnancy (n = 1)
[b] Subject withdrew consent

Results: Safety

Subjects, n (%)	VOX				SOF/VEL/VOX	
	RIF (SD), CsA (n=26)	VORI, GFZ (n=24)	RIF (MD) (n=24)	GFJ (n=24)	ROS, PRA (n=20)	DE (n=36)
AEs	18 (69)	8 (33)	24 (100)	5 (21)	4 (20)	4 (11)
Grade 3–4 AE	0	0	0	0	0	0
Serious AE	0	0	0	0	0	0
Treatment D/C due to AE	1 (4)	0	0	0	0	0

- The majority of AEs were Grade 1 and none were related to study drug
- Overall, the most common AEs were chromaturia, nausea and headache

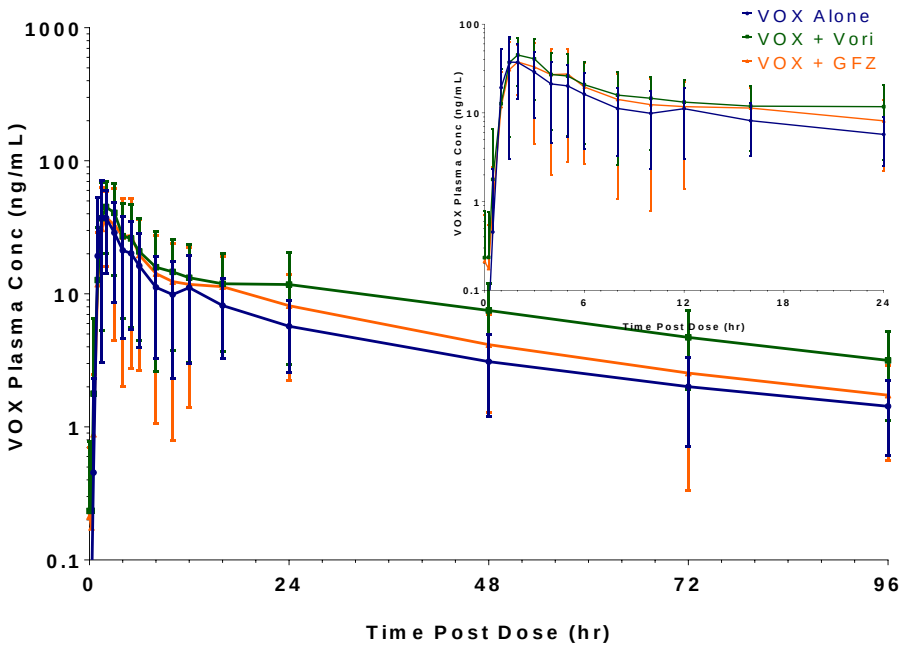
Effect of CsA or RIF SD on VOX PK



VOX PK Param.	%GMR (90%CI)	
	RIF (SD)	CsA
AUC_{inf}	791 (620, 1010)	940 (737, 1200)
AUC_{last}	948 (734, 1220)	1100 (854, 1420)
C_{max}	1110 (823, 1500)	1900 (1410, 2560)

- VOX exposure significantly increased by potent hepatic OATP inhibition by single dose RIF (AUC_{inf} ↑7.9-fold, C_{max} ↑11-fold) or CsA (AUC_{inf} ↑9.4-fold, C_{max} ↑19-fold).
- VOX exposure increased to a lesser extent (<2-fold) by intestinal P-gp inhibition (determined by assessing differential effect of single doses of CsA and RIF)

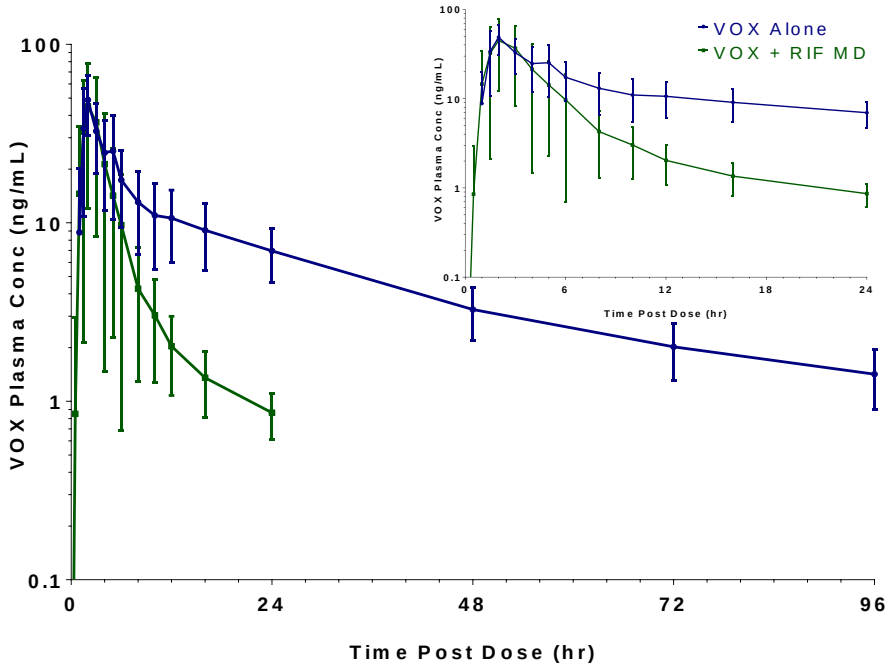
Effect of VORI or GFZ on VOX PK



VOX PK Param.	%GMR (90%CI)	
	VORI	GFZ
AUC_{inf}	184 (166, 203)	111 (101, 123)
AUC_{last}	171 (154, 190)	116 (104, 128)
C_{max}	113 (98.0, 131)	97.9 (84.6, 113)

- Potent inhibition of CYP3A (VORI) resulted in a modest increase 1.8-fold in VOX AUC_{inf} with no change in C_{max}.
- Minimal contribution of pre-systemic CYP3A on VOX exposure
- Potent inhibition of CYP2C8 (GFZ) had no effect on VOX exposure

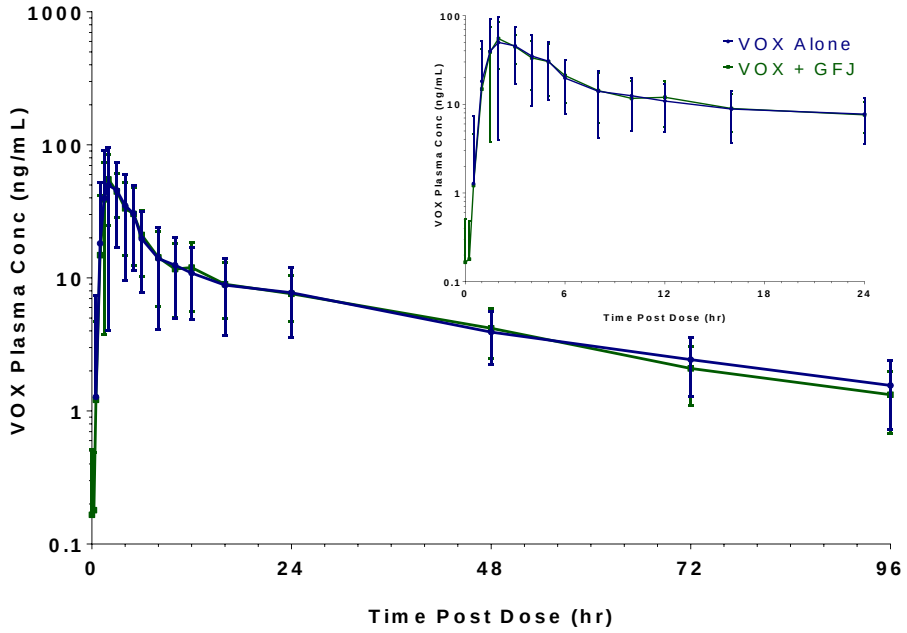
Effect of Multiple Dose RIF on VOX PK



VOX PK Param.	%GMR (90%CI) RIF (MD)
AUC_{inf}	27.0 (23.2, 31.4)
AUC_{last}	28.3 (24.3, 33.0)
C_{max}	91.4 (76.0, 110)

- Potent induction of CYPs and P-gp by multiple dose RIF significantly reduces VOX systemic exposure (AUC_{inf} by ↓73%) with no change in VOX C_{max} (minimal pre-systemic contribution).

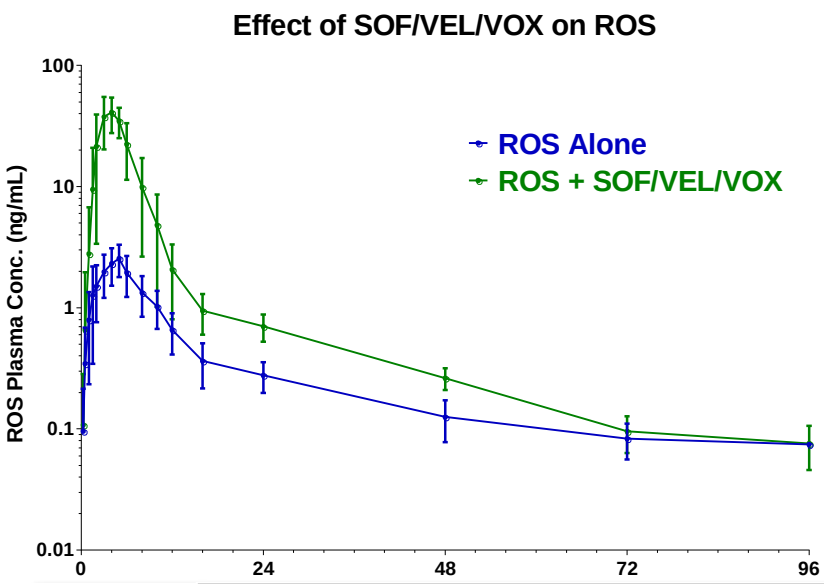
Effect of Grapefruit Juice on VOX PK

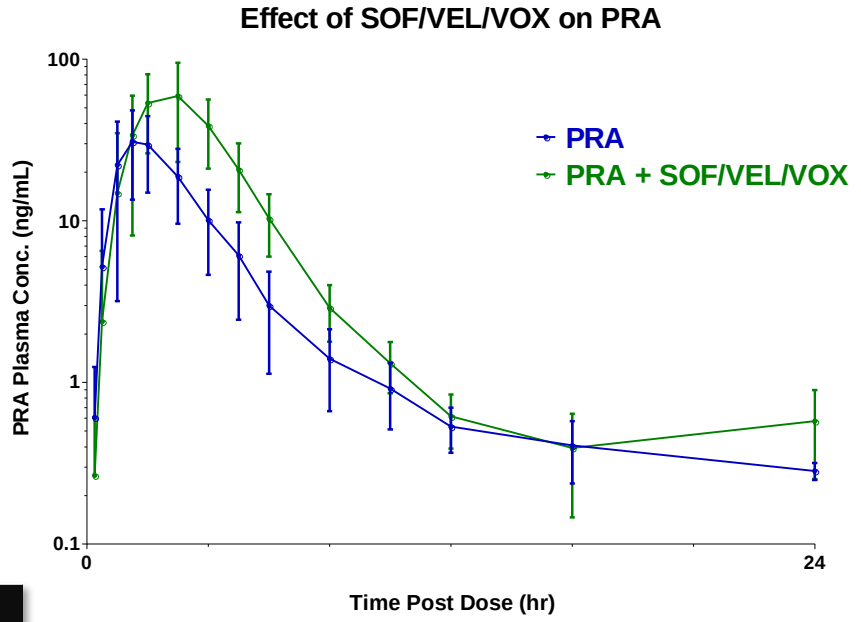


VOX PK Param.	%GMR (90%CI) GFJ
AUC_{inf}	101 (94.6, 109)
AUC_{last}	102 (94.6, 111)
C_{max}	95.4 (81.9, 111)

- Intestinal OATP inhibition by Grapefruit Juice had no effect on VOX exposure when administered with food.

Effect of SOF/VEL/VOX on ROS or PRA PK

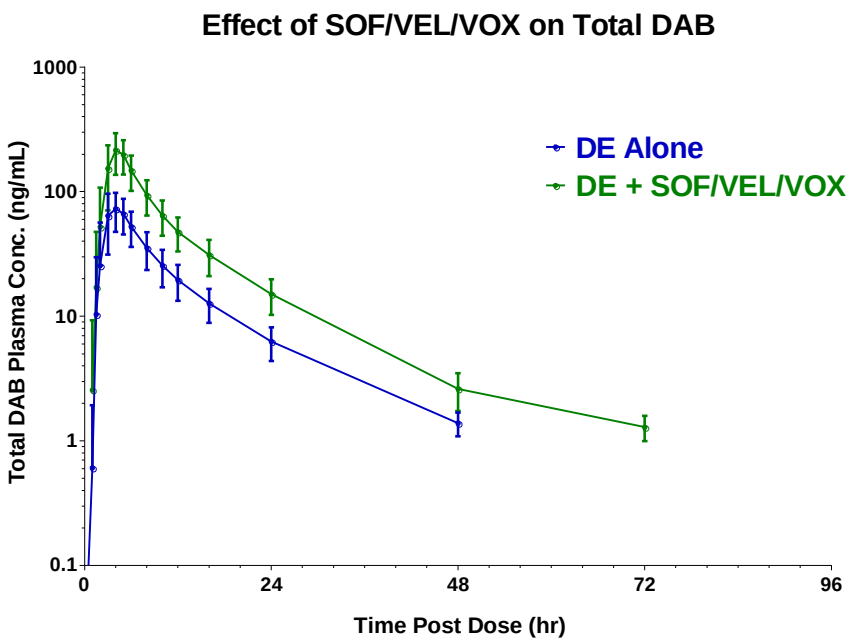


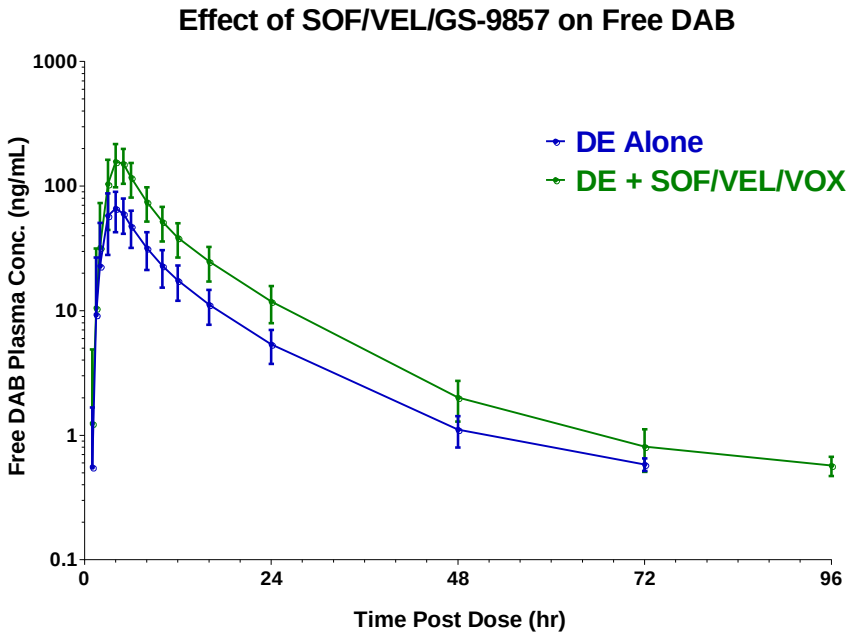


PK Param.	%GMR (90%CI)	
	ROS	PRA
AUC_{inf}	738 (668, 818)	216 (179, 260)
AUC_{last}	817 (733, 910)	218 (181, 263)
C_{max}	1890 (1620, 2200)	189 (153, 234)

- SOF/VEL/VOX significantly inhibited BCRP (ROS) and to a lesser extent OATP (PRA)

Effect of SOF/VEL/VOX on DAB PK





PK Param.	%GMR (90%CI)	
	Total DAB	Free DAB
AUC_{inf}	261 (241, 282)	222 (204, 241)
AUC_{last}	269 (247, 292)	224 (206, 244)
C_{max}	287 (261, 315)	234 (212, 259)

- SOF/VEL/VOX is a P-gp inhibitor (Total or Free DAB)

Summary and Conclusions

- Hepatic OATP plays a significant role in the pharmacokinetics of VOX with P-gp and CYP3A contributing to a lesser extent; VOX is not sensitive to intestinal OATP inhibition when administered fed.
  - VOX may be coadministered with potent P-gp inhibitors with caution, or inhibitors of CYP3A or 2C8 without dose modification.
  - Coadministration of VOX with potent hepatic OATP inhibitors, or potent or moderate inducers of CYPs and P-gp is not recommended.
  - Future studies will inform dosing recommendations with moderate hepatic OATP inhibitors
- The combination of SOF/VEL/VOX is an inhibitor of intestinal BCRP and to a lesser extend OATP and P-gp.
  - These results will support dosing recommendation in HCV-infected subjects for us of concomitant medications that are sensitive substrates of these transporters
- Coadministration of VOX, or SOF/VEL/VOX with phenotypic transporter or CYP probe substrates or inhibitors was safe and well tolerated

Acknowledgments

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