Evaluation of Drug-Drug Interaction Between Sofosbuvir/Velpatasvir and Rifaximin in HCV-Infected Subjects with Moderate Hepatic Impairment

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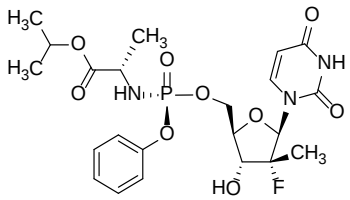
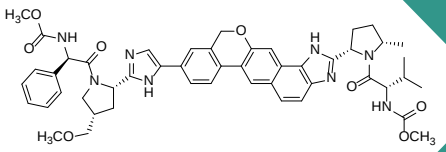
Disclosures

Erik Mogalian is an employee of Gilead Sciences, Inc.

Background: Sofosbuvir/Velpatasvir

SOF
Nucleotide polymerase inhibitor





VEL
NS5A inhibitor

SOF

VEL

- Sofosbuvir (SOF)[1,2]
  - Potent antiviral activity against HCV GT 1–6
  - GS-331007, predominant circulating metabolite
- Velpatasvir (VEL; GS-5816)[3]
  - Picomolar potency against GT 1–6
  - PK supports once-daily dosing
- SOF/VEL (400/100 mg) FDC
  - Treatment with SOF/VEL for 12 weeks in Phase 3 studies resulted in high SVR in patients with HCV GT 1–6 [4-6]
  - SOF/VEL + RBV in subjects with moderate hepatic impairment
  - Currently under regulatory review

FDC, fixed-dose combination.

1. Jacobson IM, et al. New Engl J Med 2013;368:1867-77; 2. Lawitz E, et al. New Engl J Med 2013;368:1878-87; 3. Cheng G, et al. EASL 2013, poster 1191; 4. Feld J, et al. New Engl J Med 2015;373:2599-607; 5. Foster G, et al. New Engl J Med 2015;373:2608-17; 6. Curry M, et al. New Engl J Med 2015;373:2618-28.

Background: ASTRAL-4 Study Design[1]

- Open-label, randomized (1:1:1) US study
- HCV GT 1–6 treatment-naïve or -experienced patients with Child-Pugh-Turcotte (CPT) B cirrhosis

RBV, ribavirin; SVR12, sustained virologic response 12 weeks after treatment end.

1. Curry M, et al. N Engl J Med 2015;373:2618-28.

Background: Potential for SOF/VEL DDIs

- Sofosbuvir
  - Substrate of P-gp, BCRP
- Velpatasvir
  - Substrate of P-gp, BCRP, OATP1B, CYP2B6, CYP2C8, CYP3A4
  - Inhibitor of P-gp, BCRP, OATP

Background: Rifaximin

- Indicated for use in hepatic encephalopathy
- Structural analog of rifampin
  - Induces CYP3A4 in vitro
  - Limited induction potential in healthy individuals
    - Midazolam AUC ↓8.8% following 14 days with rifaximin
- Low bioavailability (<0.4%)
- PK in Special Populations
  - Exposure in subjects with hepatic impairment increase up to 20-fold
  - "In patients with normal liver function, rifaximin at the recommended dosing regimen is not expected to induce CYP3A4. It is unknown whether rifaximin can have a significant effect on the pharmacokinetics of concomitant CYP3A4 substrates in patients with reduced liver function who have elevated rifaximin concentrations."[1]

		Child-Pugh Class		
Rifaximin PK Parameter	**Healthy Subjects n=14**	**A n=18**	**B n=7**	**C n=4**
AUC_{τ} (ng·h/mL)	12.3 ± 4.8	118 ± 67.8	161 ± 101	246 ± 120
C_{max} (ng/mL)	3.4 ± 1.6	19.5 ± 11.4	25.1 ± 12.6	35.5 ± 12.5

1. Xifaxan [package insert]. Bridgewater, NJ: Salix Pharmaceuticals, revised 2010.

Background: Rifaximin

- Drug Interaction Potential
  - "An in vitro study suggested that rifaximin is a substrate of P-glycoprotein. It is unknown whether concomitant drugs that inhibit P-glycoprotein can increase the systemic exposure of rifaximin"[1]
    - CACO-2 Monolayer[2]
      - P_{app} A→B: $1*10^{-6}$ cm/sec
      - Efflux ratio: 45-135 (reference ER: digoxin 11-12)
  - "In the presence of P-glycoprotein (P-gp) inhibitors, the efflux ratio (ER) of rifaximin decreased by 2-12 fold. Other transporters may be involved in efflux transport of rifaximin (e.g., BCRP)."

- Question: Can rifaximin act as a clinically relevant inducer of drug transporters and metabolizing enzymes in situations where high exposure can be expected?

1. Xifaxan [package insert]. Bridgewater, NJ: Salix Pharmaceuticals, revised 2010; 2. CDER Application 22-554, 2010.

Objectives

- To evaluate the effect of concomitant rifaximin use on the PK of SOF/VEL (400/100 mg) in HCV-infected subjects with decompensated cirrhosis from ASTRAL-4
  - Assess the inductive potential of rifaximin where systemic exposure is expected to be high

Methods

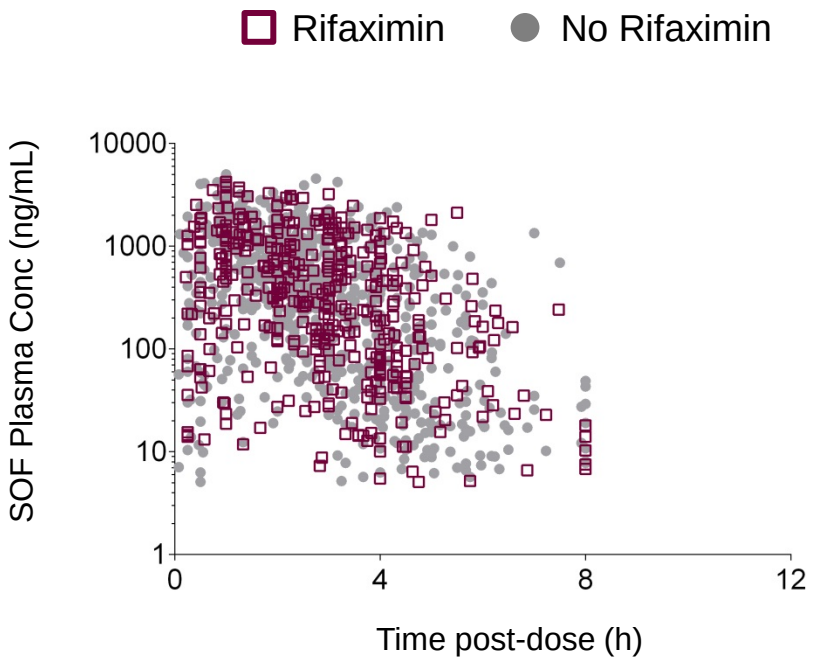
- Concomitant medication use was recorded throughout the study
- Samples to assess PK of SOF, GS-331007, and VEL PK were drawn at each on-treatment study visit
- SOF, GS-331007, and VEL exposure parameters (AUC_{tau}, C_{max}, and C_{tau}) were estimated using population PK models for each analyte
- Post hoc analysis compared PK of SOF/VEL in the presence/absence of rifaximin

Results: Subject Enrollment and Demographics

	SOF/VEL ± RBV	
	Rifaximin n=80	**No Rifaximin n=175**
Mean age, y (range)	58 (41, 70)	58 (40, 73)
Mean BMI, kg/m^2 (range)	31 (18, 56)	30 (17, 50)
Males, n (%)	58 (73)	120 (69)
White race, n (%)	73 (91)	155 (89)
Hispanic/Latino, n (%)	14 (18)	25 (14)
CPT B, n (%)	74 (93)	154 (88)

n=13 listed rifaximin as concomitant medication, but not for the entire treatment duration.

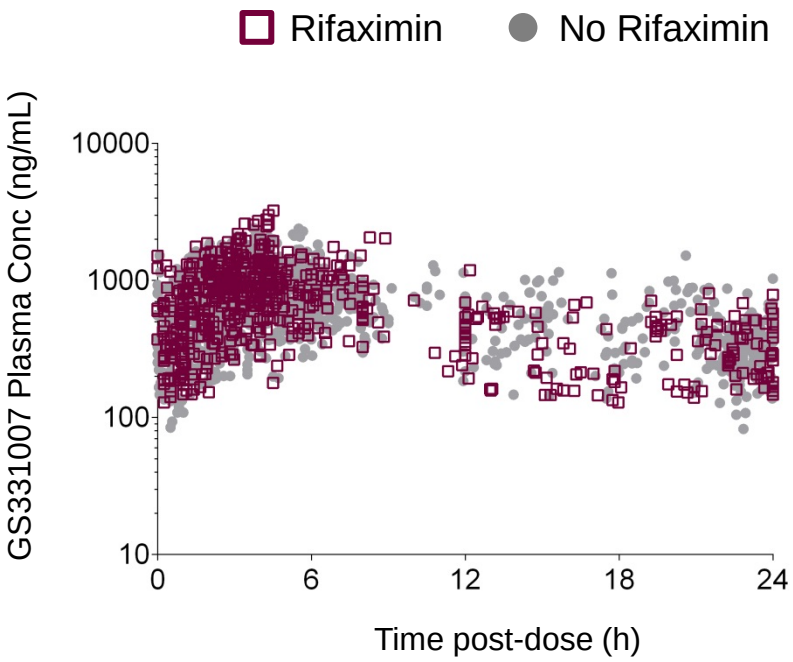
Results: SOF Pharmacokinetics



PK Parameter	Mean (%CV)		%GMR (90% CI)
	Rifaximin n=61	No Rifaximin n=135	
AUC_{tau} (ng•h/mL)	2220 (34.8)	2210 (36.9)	101 (92.4, 110)
C_{max} (ng/mL)	754 (34.5)	756 (35.1)	97.9 (88.7, 108)

- Concomitant use of rifaximin does not affect the PK of P-gp substrate SOF

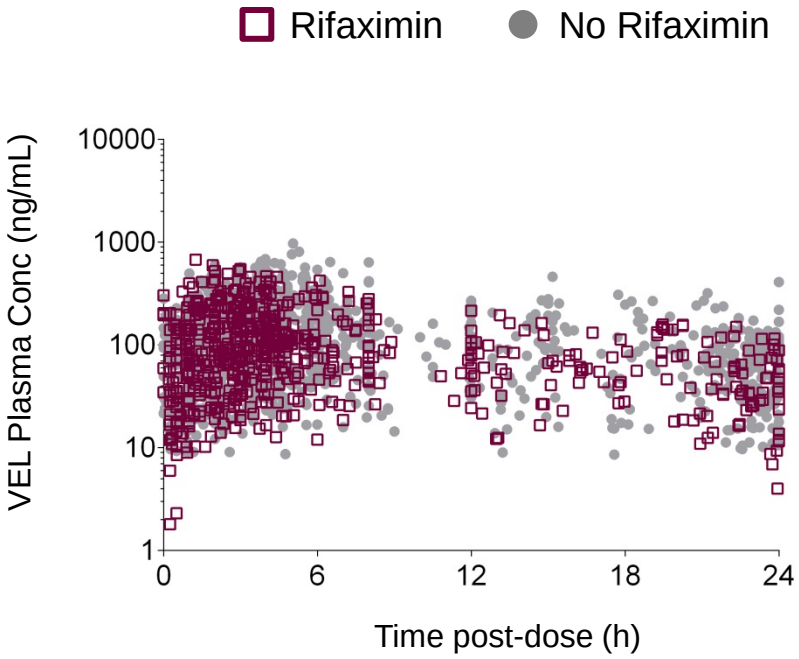
Results: GS-331007 Pharmacokinetics



PK Parameter	Mean (%CV)		%GMR (90% CI)
	Rifaximin n=80	No Rifaximin n=174	
AUC_{tau} (ng•h/mL)	13900 (39.8)	13800 (38.3)	101 (93.0, 110)
C_{max} (ng/mL)	834 (39.9)	811 (35.4)	102 (94.2, 111)

- Concomitant use of rifaximin does not affect the PK of GS-331007

Results: VEL Pharmacokinetics



PK Parameter	Mean (%CV)		%GMR (90% CI)
	Rifaximin n=79	No Rifaximin n=175	
AUC_{tau} (ng•h/mL)	1966 (51.5)	2285 (57.0)	88.4 (78.3, 99.8)
C_{max} (ng/mL)	130 (55.4)	153 (60.3)	87.4 (76.7, 99.4)
C_{tau} (ng/mL)	40 (51.9)	46 (58.6)	89.4 (79.2, 101)

- Concomitant use of rifaximin does not significantly affect the PK of P-gp and CYP substrate VEL
  - ~10% decrease in VEL exposure similar to that observed with rifaximin + midazolam in healthy subjects.

Conclusions

- Concomitant use of rifaximin with SOF/VEL ± RBV in HCV-infected subjects with moderate HI did not significantly impact the PK of SOF/VEL
- Clinically relevant induction of P-gp or CYPs by rifaximin is not expected, even in the context of high exposure situations such as in those with hepatic impairment and/or using a P-gp inhibitor

Acknowledgments

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