Evaluation of Transporter and Cytochrome P450-Mediated Drug-Drug Interactions Between Pan-Genotypic HCV NS5A Inhibitor GS-5816 and Phenotypic Probe Drugs

Erik Mogalian, Polina German, Chris Yang, Lisa Moorehead, Diana Brainard, John McNally, Jennifer Cuvin, Anita Mathias

Gilead Sciences, Foster City, CA

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Disclosures

- I am an employee of Gilead Sciences, Inc

GS-5816

- Novel HCV NS5A inhibitor
- Picomolar potency against HCV GT 1–6[1]
- PK supports once-daily dosing[2]
- High SVR rates were demonstrated in treatment-naïve subjects with GT1-6 HCV infection treated for 12 weeks with GS-5816 + SOF[3]
- Generally safe and well tolerated

1. Cheng G, et al. EASL 2013, poster 1191; 2. German P, et al. EASL 2013, poster 1195; 3. Everson G, et al. EASL 2014, oral presentation: Safety and Efficacy of Treatment with the Interferon-Free, Ribavirin-Free Combination of Sofosbuvir + GS-5816 for 12 Weeks in Treatment-Naive Patients with Genotype 1-6 HCV Infection.

GS-5816 Preclinical Characterization

In vitro

- GS-5816 is slowly metabolized by CYP3A4, 2C8, and 2B6
- GS-5816 does not inhibit CYP enzymes
- No induction of transporters/metabolizing enzymes by AhR/PXR
- GS-5816 showed at least weak inhibition of P-gp, BCRP, OATP1B1, OATP1B3

Efflux/Uptake Transporter Inhibition (IC_{50}, µM)				
P-gp	**BCRP**	**OATP1B1**	**OATP1B3**	**MRP2**
20.6	0.30	1.5	0.26	>40

In vivo

- Predominantly excreted in feces as parent and metabolites
- <1% of dose excreted in urine

Objectives

Primary

- To evaluate the effect of GS-5816 on OATP, BCRP, and P-gp substrates using phenotypic probes
- To evaluate the effect of CYP3A/2C8/P-gp inducers or inhibitors on the PK of GS-5816
- To evaluate the effect of a selective OATP1B1/1B3 inhibitor and a mixed transport inhibitor on the PK of GS-5816

Secondary

- To evaluate the safety of GS-5816 when administered with probe drugs

Methods: Study Design

- Phase 1, open-label, single- and multiple-dose, 5-cohort, crossover study in healthy subjects
  - GS-5816 as a perpetrator of interaction
    - Pravastatin (OATP substrate)
    - Rosuvastatin (OATP/BCRP substrate)
    - Digoxin (P-gp substrate)
  - GS-5816 as a victim of interaction
    - Rifampin (multiple-dose, CYP/P-gp inducer)
    - Ketoconazole (multiple dose, CYP/P-gp inhibitor)
    - Rifampin (single-dose, OATP inhibitor)
    - Cyclosporine (OATP/MRP2/P-gp inhibitor)
- Subjects expressing reduced function OATP1B1 variants (*5 and *15 haplotypes) excluded

Methods

- All treatments were administered under fasting conditions
- PK samples collected over 72 hours for pravastatin and 96 hours for all other analytes
- Plasma or blood (cyclosporine) concentrations measured using LC/MS/MS
- PK parameters estimated by noncompartmental analysis (WinNonlin 6.3, Pharsight)
- Geometric-least squares means ratios and 90% confidence intervals (Test:Reference) estimated for AUC and C_{max}
  - 70-143% bounds for all analytes except for digoxin (80-125%)

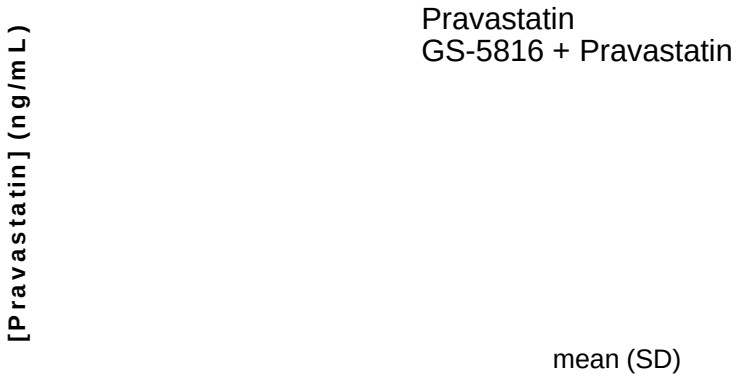
Results: Demographics

Subjects	Cohort 1 Pravastatin Rosuvastatin GS-5816	Cohort 2 Digoxin GS-5816	Cohort 3 Rifampin GS-5816	Cohort 4 Ketoconazole GS-5816	Cohort 5 Rifampin Cyclosporine GS-5816
Enrolled, n	18	22	12	12	12
Completed, n	18	21	12	12	12
Male sex, %	61	64	50	50	67
Mean age, y (range)	33 (22, 44)	34 (18, 45)	35 (25, 44)	30 (22, 40)	38 (28, 45)
Mean BMI, kg/m^2 (range)	27 (20, 30)	26 (20, 30)	26 (21, 30)	24 (19, 29)	27 (24, 30)
Race, %					
White	72	77	83	58	58
Black	28	23	17	42	42
Ethnicity, %					
Hispanic	94	73	100	58	67
Not Hispanic	6	27	0	42	33

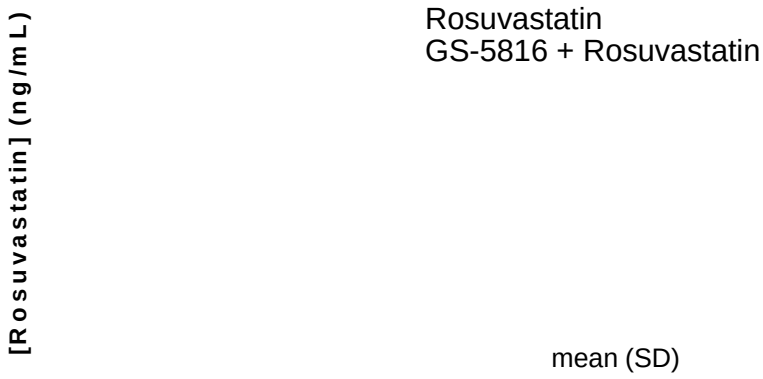
Results: Safety

- GS-5816 alone or with probe drugs were generally well tolerated
- 14 subjects (18%) experienced ≥1 AE
- All AEs were Grade 1 (mild) in severity except one Grade 3
  - One Grade 3 AE (panic attack) led to treatment discontinuation in a subject following digoxin administration but before receiving GS-5816
  - Headache and dysmenorrhea only AEs reported in >1 subject

GS-5816 Effect on OATP or OATP/BCRP Substrates



	Test/Ref GMR (90% CI)
AUC_{inf}	1.35 (1.18, 1.54)
C_{max}	1.28 (1.08, 1.52)



	Test/Ref GMR (90% CI)
AUC_{inf}	2.69 (2.46, 2.94)
C_{max}	2.61 (2.32, 2.92)

- GS-5816 may be classified as a weak OATP inhibitor and moderate BCRP inhibitor
  - Inhibition likely presystemic only

GS-5816 Effect on P-gp Substrates

	Test/Ref GMR% (90% CI)
AUC_{inf}	1.34 (1.13, 1.60)
C_{max}	1.88 (1.71, 2.08)

- GS-5816 may be classified as a weak P-gp inhibitor
  - Inhibition likely presystemic only
- Consistent with digoxin standard of care, therapeutic monitoring is recommended during use with GS-5816

Effect of Potent CYP/P-gp Induction on GS-5816

	Test/Ref GMR% (90% CI)
AUC_{inf}	0.18 (0.15, 0.22)
C_{max}	0.29 (0.23, 0.37)

- GS-5816 is subject to significant induction by enzyme/drug transport systems
- GS-5816 should not be administered with potent inducers of CYP/P-gp

Effect of Potent CYP/P-gp Inhibition on GS-5816

	Test/Ref GMR% (90% CI)
AUC_{inf}	1.71 (1.35, 2.18)
C_{max}	1.29 (1.02, 1.64)

- Inhibition of enzyme/drug transport systems only modestly affects GS-5816
- GS-5816 can be administered with potent inhibitors of CYP/P-gp

Effect of OATP or Mixed-Transporter Inhibitor on GS-5816

	Test/Ref GMR (90% CI)
AUC_{inf}	1.46 (1.17, 1.83)
C_{max}	1.28 (1.05, 1.56)

	Test/Ref GMR (90% CI)
AUC_{inf}	2.03 (1.51, 2.71)
C_{max}	1.56 (1.22, 2.01)

- GS-5816 may be classified as a substrate of OATP and P-gp
- GS-5816 can be administered with OATP and mixed-transporter inhibitors

Conclusions

- GS-5816 with or without probe drugs was safe and well tolerated
- As a perpetrator of interactions
  - GS-5816 is a weak (P-gp and OATP) to moderate (BCRP) transport inhibitor
  - Transport inhibition appears presystemic in nature
  - Clinically relevant DDIs between GS-5816 and P-gp, OATP, and CYP450 substrates are not anticipated
- As a victim of interactions
  - GS-5816 disposition is affected by inhibitors and more so inducers of enzyme/transport systems
  - GS-5816 can be administered with potent CYP/P-gp inhibitors without dose adjustment
  - Use of potent CYP/P-gp inducers with GS-5816 is not recommended
  - GS-5816 can be administered with OATP and mixed-transporter inhibitors
  - Relative contribution of enzyme and transporters will be elucidated pending results from human mass balance study

Acknowledgments

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