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Population Pharmacokinetic Modeling of Sofosbuvir, an NS5B Polymerase Inhibitor, and Its Metabolites in Patients With Hepatitis C Virus Infection

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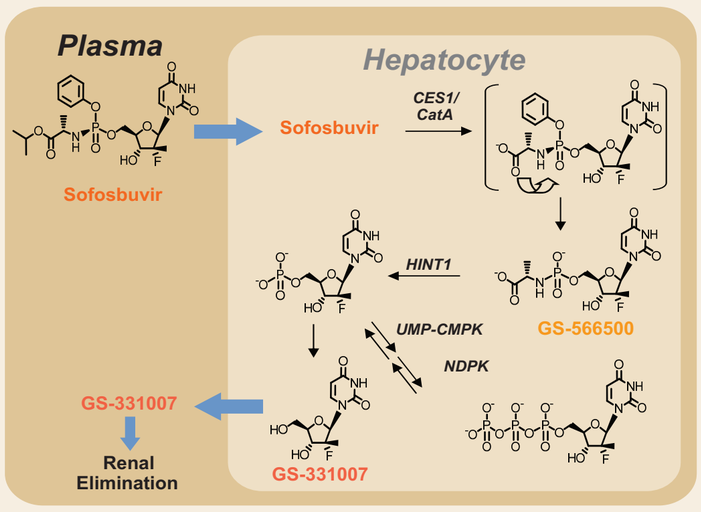
Introduction

- Sofosbuvir (SOF)
  - Potent, once-daily, orally administered, nucleotide analog prodrug, hepatitis C virus (HCV)-specific nucleotide NS5B polymerase inhibitor (chain terminator)
  - Antiviral activity and clinical efficacy in HCV genotypes 1–6
  - High genetic barrier to resistance and high sustained virologic response rates
  - Approved in USA, EU, and other regions for the treatment of chronic HCV as a component of an antiviral treatment regimen
  - Provides an option for treatment-experienced patients who previously had no recommended or approved treatment options
  - Shows promise for patients awaiting liver transplantation and those with HCV/HIV coinfection
  - Since the launch of SOF in December 2013, >310,000 patients (including ≥50,000 in lower-income countries) have received an HCV medication containing SOF

Sofosbuvir Intracellular Activation



CatA, cathepsin A; CES1, carboxylesterase 1; HINT1, histidine triad nucleotide binding protein; NDPK, nucleoside diphosphate kinase; UMP-CMPK, uridine monophosphate-citidine monophosphate kinase. Adapted from Murakami E, et al.[1]

- SOF is activated by sequential metabolic pathways including:
  - Low-affinity and high-capacity hydrolases (CES1, CatA, and HINT1)
  - Nucleotide phosphorylation (UMP–CMPK and NDPK)
- Only SOF can enter hepatocytes and be converted to active triphosphate (GS-461203)
- SOF can also undergo extrahepatic metabolism to form GS-331007 (predominant circulating metabolite), principally eliminated in urine
- GS-331007 accounts for >90% of systemic drug exposure and is the primary analyte of interest in clinical trials

Objectives

- To develop a mechanistic integrated population pharmacokinetic (PK) model for SOF, GS-566500, and GS-331007, and evaluate the impact of covariates on their PK

Methods

- Data
  - Pooled from 8 studies conducted in HCV-infected patients (N=1288)
  - Log-transformed data used in the analysis
- Covariates included in the analysis
  - Age, gender, race, body weight, ethnicity, creatinine clearance (CLCR) or estimated glomerular filtration rate, cirrhosis status, interleukin-28B status, ribavirin (RBV) use, food, and concomitant medications
- Modeling software and settings
  - NONMEM® 7.3, FO (ICON Development Solutions, Hanover, Maryland, USA)
  - TIBCO Spotfire S+ 8.2 (TIBCO Software, Palo Alto, California, USA)

Model Development

Dataset checking and cleaning

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Base model building

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Covariate exploratory analysis

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Covariate model building (forward selection, backward deletion)

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Model validation (internal)

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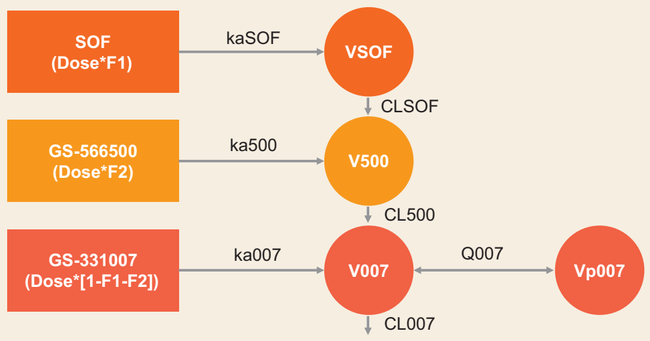
Post-hoc analysis and simulations

- Base model established using complete dataset
- Covariate screening
  - Log-linear regression or analysis of variance
  - Significant clinical effect: relative effect size outside of 90–110% of nominal value
- Covariate model building: forward addition ($p < 0.001$) followed by backward deletion ($p < 0.001$) based on likelihood ratio test
- Model evaluation
  - Statistical criteria
  - Successful covariance step
  - Sensitivity analysis
  - Stability of minimization
  - Goodness-of-fit diagnostics

Results

Final Model Structure



- Integrated mechanistic PK model for SOF
  - SOF absorption in the gut as SOF, GS-566500, and GS-331007 according to the fractions F1, F2, and F3, where F1 + F2 + F3 = 1
  - Analytes absorbed into central volumes VSOF, V500, and VC007 by 1st-order rate constants kaSOF, ka500, and ka007, respectively, with additional absorption lag times
  - SOF is metabolized into GS-566500, GS-566500 is metabolized into GS-331007, and GS-331007 (with a peripheral distribution compartment) is cleared from the body

Significant Covariates in Final Model

Sofosbuvir

- Sex was identified as a significant covariate for SOF clearance (CL)
- Drug absorption was slower (lower Ka) in the presence of food

GS-566500

- CRCL was identified as a significant covariate for GS-566500 CL

GS-331007

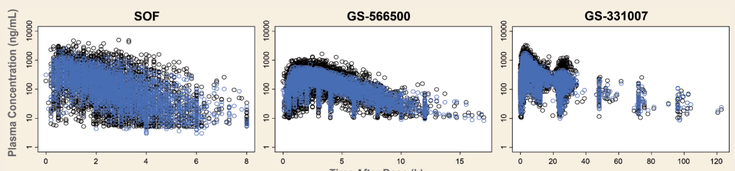
- Sex and CRCL were identified as significant covariates for GS-331007 CL
- Sex was identified as a significant covariate for GS-331007 volume of distribution
- Drug absorption was slower (lower Ka) in the presence of food and faster (higher Ka) with concomitant administration of methadone

$$KASOF_i = exp(\theta_1 + \theta_{20} \cdot fasted + \eta_{KASOF})$$
$$CLSOF_i = exp(\theta_4 + \theta_{25} \cdot female + \eta_{CLSOF})$$
$$VSOF_i = exp(\theta_5 + \eta_{VSOF})$$
$$ALAG1_i = exp(\theta_{14})$$
$$F_{SOF} = \frac{exp(\theta_{12})}{1 + exp(\theta_{12})}$$

$$KA500_i = exp(\theta_2 + \eta_{KA500})$$
$$CL500_i = exp(\theta_6 + \theta_{19} \cdot log(\frac{CLCR}{110}) + \eta_{CL500})$$
$$V500_i = exp(\theta_7 + \eta_{V500})$$
$$F_{500} = \frac{exp(\theta_{12} + \theta_{13})}{1 + exp(\theta_{12} + \theta_{13})} - F_{SOF}$$

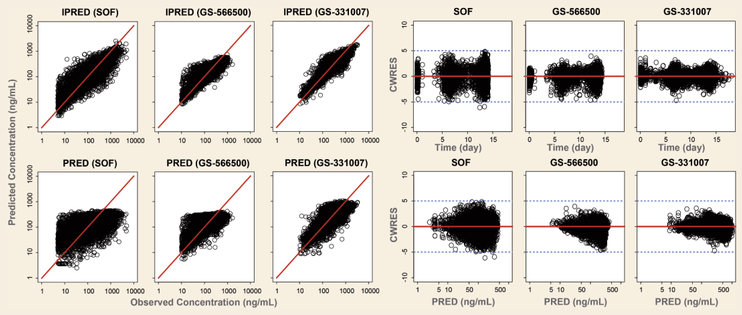
$$KA007_i = exp(\theta_3 + \theta_{16} \cdot fasted + \theta_{22} \cdot CMMDN + \eta_{KA007})$$
$$CL007_i = exp(\theta_8 + \theta_{17} \cdot log(\frac{CLCR}{110}) + \theta_{18} \cdot female + \eta_{CL007})$$
$$V007_i = exp(\theta_9 + \theta_{21} \cdot female + \eta_{V007})$$
$$Q007_i = exp(\theta_{10})$$
$$VP007_i = exp(\theta_{11})$$
$$ALAG3_i = exp(\theta_{15})$$
$$F_{007} = 1 - F_{SOF} - F_{500}$$

Model Predicted vs Observed Concentration-Time Plots*



*Observed concentrations (*black*) and individual fits (*blue*) were in good agreement.

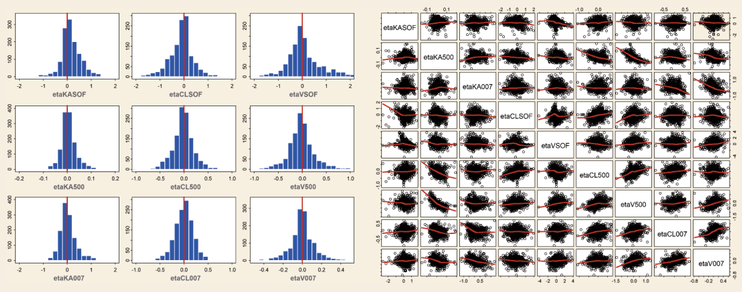
Diagnostic Plots



- Good agreement between predicted concentrations and measured concentration
- No bias in residuals over time and predicted concentration

Random Effects Were Normally Distributed and Centered to 0

Correlation of η's

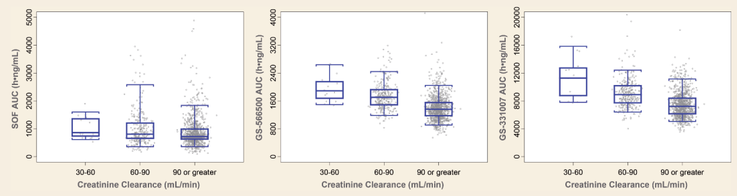


Final Model Parameters

	PK Parameters and Baseline Covariates		Baseline Covariate Value	Estimate	Change From Typical, %	Interindividual Variability
SOF	Typical CLSOF (male), L/h			78.26	—	66.9
	Female			*64.98*	*-17.0*	—
	Typical VSOF, L			17.29	—	239.2
	Typical KASOF (without regard to food), h^{-1}			0.622	—	72.9
	Fasted			*0.925*	*48.7*	—
	Typical lag time, h			0.186	—	—
	F1, %			13.24	—	—
GS-566500	Typical CL500 (CLCR 110 mL/min) (L/h)			81.45	—	32.2
	CLCR, mL/min	5th percentile	*68.5*	*64.25*	*-21.1*	—
		95th percentile	*172.8*	*102.1*	*25.4*	—
	Typical V500, L			101.5	—	56.6
	Typical KA500, h^{-1}			0.228	—	17.9
	F2 (%)			23.58	—	—
GS-331007	Typical CL007 (male; CLCR 110 mL/min), L/h			27.66	—	27.7
	CLCR (mL/min)	5th percentile	*68.5*	*22.46*	*-18.8*	—
		95th percentile	*172.8*	*33.75*	*22.0*	—
	Female			*22.97*	*-17.0*	—
	Typical V007 (without regard to food), L			56.26	—	43.6
	Fasted			*24.44*	*-56.6*	—
	Typical KA007 (without regard to food), h^{-1}			0.034	—	84.0
	Fasted			*0.077*	*123.9*	—
	Methadone use			*0.016*	*-53.2*	—
	Typical Q007			7.029	—	—
	Typical VP007			308.0	—	—
	Typical lag time, h			0.239	—	—
	F3, %			63.18	—	—
	Residual variability as coefficient of variation, %			56.5		

- Estimated relative % of doses absorbed from the gut on a molar basis: 13.2% (SOF), 23.6% (GS-566500), and 63.2% (GS-331007)
- Low relative fraction absorbed as SOF is consistent with the 4-fold increase in SOF exposure observed in the presence of the potent P-glycoprotein inhibitor cyclosporine
- All volume, CL, and absorption rate parameters were estimated accurately (precision <10%)

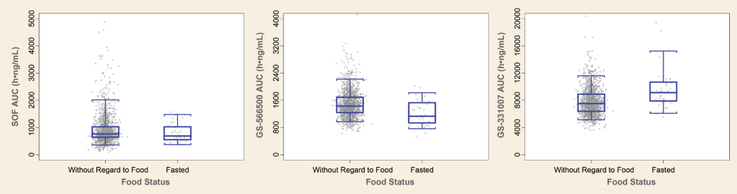
Impact of Creatinine Clearance on Exposures of SOF and Metabolites



AUC, area under concentration time curve.

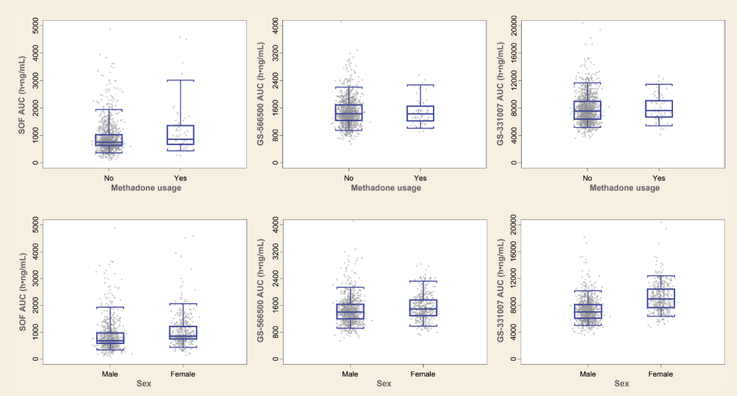
- Increased CLCR was strongly correlated with decreased exposures for GS-566500 and GS-331007, and less so for SOF
- These findings are consistent with those of the dedicated renal impairment study and the individual GS-331007 population PK analysis included in the SOF and SOF/ledipasvir New Drug Application/Marketing Authorization Application (NDA/MAA) submissions

Impact of Food on Exposures of SOF and Metabolites



- Modest effect of food on AUC: higher for SOF (10.8%) and GS-566500 (26.6%), and lower for GS-331007 (-17.6%)
- Effect of food was confounded by food requirement for coadministration of RBV ± pegylated interferon
- The decrease in GS-331007 AUC for a dosing interval (AUC_T) is comparable to the impact of RBV coadministration of GS-331007 on AUC_T observed in the SOF/ledipasvir New Drug Application/Marketing Authorization Application individual and integrated models

Impact of Sex and Methadone Use on Exposures of SOF and Metabolites



- Impact of methadone use on SOF and SOF metabolite exposures was not considered clinically meaningful
- Modest trend for females to have higher AUCs than males: comparable to that observed in the individual GS-331007 population PK analysis, which was not considered clinically meaningful

Conclusions

- SOF, GS-566500, and GS-331007 PK were adequately described by an integrated mechanistic PK model
- The covariates tested did not have a clinically meaningful impact on SOF and its metabolites exposures
- Relative to the individual model, this integrated model provided further insight on the conversion of SOF to its metabolites
- Following PK/PD analyses based on exposures derived from the integrated population-PK model corroborate the previous findings based on exposures derived from the individual population-PK models and substantiate the use of GS-331007 as a valid exposure marker for E-R analysis in comparison to SOF and GS-566500

Reference

1. Murakami E, et al. J Biol Chem 2010;285:34337-47.

Acknowledgment

This study was funded by Gilead Sciences, Inc.

Disclosures

F. Jin, B. Kirby, B. Kearney, and **A. Mathias:** Gilead (employment, equity ownership)**; Y. Gao:** Quantitative Solutions (Consultant to Gilead)

Presented at PAGE 2015, June 2–5, 2015, Hersonissos, Crete, Greece