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APPLICATION NUMBER:

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**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA : 205834 (S-7, S-8, S-9)	Submission Date(s): August 26, 2015
Brand Name	Harvoni
Generic Name	Ledipasvir/Sofosbuvir
Clinical Pharmacology Reviewers	Jeffrey Florian, Ph. D., Jenny H. Zheng, Ph.D.
Secondary Reviewer	Shirley K. Seo, Ph.D.
OCP Division	Division 4
OND division	DAVP
Applicant	Gilead Sciences
Relevant IND(s) and NDA(s)	INDs 106739, (b) (4), 115268 and NDA 204671
Submission Type	Priority
Formulation; Strength(s)	Fixed dose combination tablets; 90 mg/400 mg
Current Indication	Treatment of chronic hepatitis C (CHC) genotype 1 infection in adults
Proposed Indication	Extend the current indication to patients with decompensated cirrhosis or liver transplant recipients

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1. EXECUTIVE SUMMARY

Ledipasvir (LDV, GS-5885) and sofosbuvir (SOF, GS-7977) oral fixed-dose combination (Harvoni, LDV/SOF 90 mg/400 mg FDC tablet) was originally approved for the treatment of chronic genotype 1 hepatitis C virus (HCV) infection. Efficacy supplements extending the indication to include patients with HCV/human immunodeficiency virus (HIV-1) coinfection and genotype 4, 5, and 6 HCV were approved on 11/23/2015. The current efficacy supplement seeks to extend the indication to include patients with decompensated cirrhosis or liver transplant recipients with ongoing HCV infection.

LDV is a novel HCV NS5A inhibitor that inhibits both RNA replication and the assembly of HCV virions. SOF is a novel nucleotide NS5B polymerase inhibitor that inhibits HCV RNA replication and has been approved for use in combination with other agents for the treatment of chronic HCV infection in adults (Sovaldi®; NDA 204671).

The submission includes the efficacy and safety data of LDV/SOF in patients with decompensated cirrhosis and liver transplant studies from two studies: GS-US-337-0123 (U.S., SOLAR-1) and GS-US-337-0124 (non-U.S., SOLAR-2). Updated population PK analyses were submitted to support labeling that no clinically relevant differences in SOF, LDV, and GS-331007 PK were observed in patients with decompensated cirrhosis.

1.1 Recommendation

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in this supplement NDA to support a recommendation of approval of LDV/SOF in patients with decompensated cirrhosis and patients who have received a liver transplant.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

LDV/SOF with ribavirin (RBV) was evaluated for 12- or 24-weeks in two studies (GS-US-337-0123 [SOLAR-1] and GS-US-337-0124 [SOLAR-2]) in subjects with genotype 1 or 4 HCV infection with decompensated cirrhosis or who were posttransplantation with compensated liver disease. The dose of LDV/SOF was 90/400 mg once daily. RBV starting dose was 600 mg/day in subjects with decompensated cirrhosis and 1000 or 1200 mg/day (<75 kg and ≥75 kg) for all other subjects. The trials were similar in study design and eligibility criteria with the exception that GS-US-337-0123 included only in U.S. subjects while GS-US-337-0124 included only non-U.S. (Europe, Canada, Australia, and New Zealand) subjects. For the purpose of all discussions below, results and PK data from the two trials were pooled. The trials consisted of seven groups of patients:

- Group 1 - pretransplantation with cirrhosis and moderate hepatic impairment (Child Pugh [CPT] B)
- Group 2 - pretransplantation with cirrhosis and severe hepatic impairment (CPT C)
- Group 3 - posttransplantation without cirrhosis (fibrosis stage F0-F3)
- Group 4 - posttransplantation with cirrhosis and mild hepatic impairment (CPT A)
- Group 5 - posttransplantation with cirrhosis and moderate hepatic impairment (CPT B)
- Group 6 - posttransplantation with cirrhosis and severe hepatic impairment (CPT C)
- Group 7 - posttransplantation with fibrosing cholestatic hepatitis (FCH)

PK for LDV, SOF, and the predominant circulating metabolite of SOF (GS-331007) were evaluated in subjects with decompensated cirrhosis and posttransplantation subjects with or without compensated liver disease. No difference in PK was observed based on liver transplantation status, but differences were observed based on degree of hepatic impairment. Consequently, PK comparisons are presented using pooled results for Group 1 and 5 (CPT B) and Group 2 and 6 (CPT C). All Groups from the current trials are compared with observations

from the original LDV/SOF NDA submission (treatment naïve and treatment-experienced genotype 1 HCV patients with or without compensated cirrhosis). Based on population PK analyses SOF AUC_T was increased by 100%, 105%, 97%, and 121% in subjects without cirrhosis (Group 3), and mild, moderate, and severe hepatic impairment, respectively. GS-331007 exposures were increased 51%, 52%, 23%, and 25% in subjects without cirrhosis, and mild, moderate, and severe hepatic impairment, respectively. LDV exposures were decreased 6%, 6%, 13%, and 14% in subjects without cirrhosis, and mild, moderate, and severe hepatic impairment, respectively. The increases in SOF and GS-331007 exposure for moderate and severe hepatic impairment are similar to the effects observed in the dedicated hepatic impairment study. However, the increase in SOF and GS-331007 exposure in subjects without cirrhosis or with mild hepatic impairment could not be explained, though the exposures were similar to that observed in other subjects (CPT B and CPT C) from the two trials. These changes in LDV, SOF, and GS-331007 exposure are not considered clinically relevant and no dose adjustments are recommended.

SOF AUC_T was increased by 77%, GS-331007 AUC_T was increased by 15%, and LDV AUC_T was decreased by 22% in subjects with FCH relative to exposures in subjects from the original NDA submission. These changes in LDV, SOF, and GS-331007 exposure are not considered clinically relevant and no dose adjustments are recommended.

In posttransplantation patients on cyclosporine-containing immunosuppressant regimens, SOF, GS-331007, and LDV AUC_T were increased 13%, 10%, and 45%, respectively, relative to posttransplantation patients not on a cyclosporine regimen. No dose adjustments are recommended in posttransplantation patients on a cyclosporine containing regimen.

Decreased SOF, GS-331007, and LDV AUC_T were observed (15-40%) in subjects who relapsed compared to those subjects achieving sustained virologic response (SVR). However, exposures of SOF, GS-331007, and LDV were not significant predictors of response from multivariate analyses. No dose adjustments are proposed based on this observation.

2. QUESTION BASED REVIEW

See the Clinical Pharmacology review from the original NDA 205834 (7/10/2014) and the above Summary of Important Clinical Pharmacology Findings.

3. LABELING RECOMMENDATIONS

Section/heading	Acceptable to OCP?			Comment
	A	AWE	NA	
12.3/specific populations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The specific populations subsections was revised to include information regarding decompensated cirrhosis on sofosbuvir, ledipasvir, and GS-331007 from the pop-PK analysis.

A = Acceptable; AWE=Acceptable with minor edits; NA=not acceptable/substantive disagreement (must provide comment)

4. APPENDICES

4.1 Individual Study Review

4.1.1 External Model Validation of the Population Pharmacokinetics for LDV/SOF Fixed Dose Combination

All tables and figures obtained from the above listed population PK report unless explicitly noted.

Objectives:

- Perform external model validation of the population PK models of SOF, GS-331007, and LDV
- Predict SOF, GS-331007, and LDV PK based on data from GS-US-337-0123 and GS-US-337-0124 and previously developed population PK models
- If the previously developed population PK models are inadequate to characterize data from these studies, updated population models will be developed for that compound based on data from these two studies

Data Sets: Pharmacokinetic data from the Phase 2 studies GS-US-337-0123 and GS-US-337-0124 were used for external validation.

A single PK blood sample was collected at all on treatment subject visits (except week 6). An intensive PK substudy was performed at Week 2 or Week 4 in a subset of subjects who provided separate consent (up to N = 15 per group). The PK of SOF (and its metabolite GS-331007), and LDV were assessed.

The SOF validation dataset included 4527 PK samples from 660 subjects. A large portion of the PK samples were below-LLOQ (2203 samples), incorrect sampling time (132 samples), or outliers (20 samples) and excluded from the analysis. The remaining dataset included 2172 samples from 469 subjects. The GS-331007 validation dataset included 4565 PK samples from 660 subjects. Seventy-four samples were excluded for the above reasons leaving 4491 PK samples from 659 subjects. The LDV validation dataset included 4624 PK samples from 668 subjects. Seventy-nine samples were excluded for the above reasons leaving 4545 PK samples from 668 subjects.

Reviewer's comment: PK comparisons focus on AUC_t rather than C_{max}. Given the sampling scheme used for patients from these two studies the external validation approach may result in biased C_{max} predictions in all patients except those that participated in the intensive PK substudy.

Methods: Predicted SOF, GS-331007, and LDV plasma concentrations for validation subjects were obtained by fixing the parameters in the structural and variance model to the parameter estimates in the final model using post-hoc Bayesian forecasting with NONMEM 7. The \$ESTIMATION command was set as MAXEVAL=0. The predicted SOF, GS-331007 and LDV concentrations (PRED) were compared with the corresponding observed SOF, GS-331007, and LDV concentrations (DV).

Diagnostic graphs were population predicted concentrations (PRED) versus observed concentrations (DV), individual predicted concentrations (IPRED) versus DV, and individual weighted residuals (IWRES) or conditional weighted residuals (CWRES) versus PRED or time.

A prediction corrected visual predictive check (pcVPC) was created to show the time course of the predicted mean and spread of concentrations (5th to 95th percentile) versus the observed data for each arm of each trial (7, 8). A total of 1000 trial replicates were simulated using the observed covariates and dose regimens for each subject, the final model parameter estimates, and simulated subject-specific random effects and residual errors. A numeric predictive check (NPC) was also conducted to evaluate the predictions.

Results:

Diagnostic plots, VPC, and NPC results for GS-331007 and LDV were in good agreement and supported that the post-hoc predictions for these compounds could be used for comparisons between groups and with previous SOF/LDV trial results.

Bias was observed between post-hoc predicted and observed SOF exposures, most notably in those subjects from the PK substudy. Specifically, the external validation for SOF indicated that the final model was underpredicting SOF concentrations. As such, population PK parameters were re-estimated for SOF based on data from the two studies. SOF population PK parameters are shown below in Table 1.

Parameter	Parameter Description	Estimated (%SE)
$exp(\theta_1)$	Apparent oral clearance, CL/F (L/hr, HCV-infected subject)	170.0 (1.05%)
$\square\square$	Influence of creatinine clearance on CL/F	0.330 (25.5%)
$exp(\theta_2)$	Apparent central volume, Vc/F (L)	254.7 (1.03%)
$exp(\theta_3)$	Absorption rate constant, Ka (1/hr, fasted)	3.238 (35.9%)
θ_5	Influence of Food on Ka	-0.339 (118.0%)
$exp(\theta_4)$	Lag time (hr)	0.172 (5.0%)
Inter-individual variability (%)	CL/F	52.7 (16.1%)
	Vc/F	37.5 (53.1%)
	Ka	115.8 (26.2%)
$\omega^2_{CL/F, Vc/F}$	Covariance between CL/F and Vc/F	0.085 (55.8%)
σ^2	Residual error (%CV)	103.3 (3.68%)

Comparison of SOF, GS-331007, and LDV Exposures Based on Hepatic Function

SOF, GS-331007, and LDV AUC_T from GS-US-337-0123 and GS-US-337-0124 were compared with exposures from the original LDV/SOF NDA submission. Exposures from the current submission were pooled by study. Results were further pooled based on hepatic function status as liver transplantation status (pretransplantation versus posttransplantation) was not observed to impact exposures. Only PK exposures from treatment arms including ribavirin were included from the original NDA submission as differences in LDV and GS-331007 PK were noted in the presence or absence of ribavirin. Table 2 provides a comparison to subjects without cirrhosis or with mild hepatic impairment. Table 3 provides a comparison to subjects with moderate or severe hepatic impairment or with fibrosing cholestatic hepatitis (FCH).

SOF AUC_T exposures were increased 100%, 105%, 97%, and 121% in subjects without cirrhosis, and with mild, moderate, and severe hepatic impairment compared to subjects from the original NDA submission. GS-331007 AUC_T exposures were increased 51%, 52%, 23%, and 25% in subjects without cirrhosis, and with mild, moderate, and severe hepatic impairment compared to subjects from the original NDA submission. LDV AUC_T exposures were decreased 6%, 6%, 13%, and 14% in subjects without cirrhosis, and with mild, moderate, and severe hepatic impairment compared to subjects from the original NDA submission. The increased

SOF and GS-331007 AUC_T in subjects with moderate and severe hepatic impairment are in agreement with previous observations from a dedicated hepatic impairment study. The increased SOF and GS-331007 AUC_T cannot be explained based on the available data, but the exposures do not exceed the exposures from subjects with moderate or severe hepatic impairment in the current study. The difference in SOF, GS-331007, and LDV AUC_T are not considered clinically relevant and no dose adjustments are recommended.

SOF and GS-331007 AUC_T were increased by 77% and 15% and LDV AUC_T was decreased by 22% in subjects with FCH compared to exposures in the original NDA submission. These changes in exposure were similar to that observed from subjects without cirrhosis or with various degrees of hepatic impairment from the current submission. While there are few subjects with FCH in this assessment (n=10), the results do not suggest substantially different exposures in this population. No dose adjustments are recommended for patients with FCH.

Table 2: Comparison of SOF, GS-331007, and LDV AUC_T Based on Hepatic Function from the Current Submission to Exposures from the Original NDA Submission (Includes Fibrosis Stage 0-3 and CPT A)

PK Parameter		Original NDA (n=868)	F0-3 (Group 3) (n=211)	CPT A (Group 4) (n=118)
SOF AUC _T (h·ng/mL)	Geometric Mean	1320	2640	2702
	Median (IQR)	1312 (1099; 1553)	2704 (2271; 3112)	2711 (2272; 3231)
	Ratio to Original	-	2.00	2.05
GS-331007 AUC _T (h·ng/mL)	Geometric Mean	10769	16310	16392
	Median (IQR)	10839 (8902; 13010)	16267 (13332, 20128)	16047 (13596; 20426)
	Ratio to Original	-	1.51	1.52
LDV AUC _T (h·ng/mL)	Geometric Mean	6775	6351	6343
	Median (IQR)	6694 (4640; 10079)	6447 (4266; 9294)	6324 (3713; 10030)
	Ratio to Original	-	0.94	0.94

Note: n=659, 211, and 118 for SOF

Table 3: Comparison of SOF, GS-331007, and LDV AUC_T Based on Hepatic Function from the Current Submission to Exposures from the Original NDA Submission (Includes CPT B, CPT C, and FCH)

PK Parameter		Original NDA (n=868)	CPT B (Group 1 and 5) (n=208)	CPT C (Group 2 and 6) (n=117)	FCH (Group 7) (n=10)
SOF AUC _T (h·ng/mL)	Geometric Mean	1320	2597	2907	2335
	Median (IQR)	1312 (1099; 1553)	2686 (2069; 3157)	2907 (2403; 3391)	2477 (2285; 2677)
	Ratio to Original	-	1.97	2.21	1.77
GS-331007 AUC _T (h·ng/mL)	Geometric Mean	10769	13244	13427	12436
	Median (IQR)	10839 (8902; 13010)	12931 (9573; 17610)	12561 (9770; 17699)	16267 (13332; 20128)
	Ratio to Original	-	1.23	1.25	1.15
LDV AUC _T (h·ng/mL)	Geometric Mean	6775	5909	5849	5287
	Median (IQR)	6694 (4640; 10079)	5790 (3931; 8718)	5925 (4100; 8389)	5858 (4254; 6423)
	Ratio to Original	-	0.87	0.86	0.78

Note: n=659, 208, 113, and 10 for SOF

Comparison of SOF, GS-331007, and LDV Exposures in Posttransplantation Subjects on Cyclosporine-Containing Regimens

A common immunosuppressant used in patients undergoing liver transplantation is cyclosporine, which is also a known inhibitor of transporters such as P-glycoprotein (PGP) and breast cancer resistance protein (BCRP). As SOF and LDV and both PGP and BCRP substrates, a comparison of PK exposures was performed between those subjects on a cyclosporine containing immunosuppressant regimen (wCsA) and those subjects not on a cyclosporine containing immunosuppressant regimen (non-CsA). SOF, GS-331007, and LDV AUC_T were slightly increased 13%, 10%, 45% in wCsA compared to non-CsA subjects (Table 4). These increases in exposure are not considered to be clinically relevant, and no dose adjustments are proposed based on this interaction.

Table 4: Comparison of SOF, GS-331007, and LDV AUC_t Based on Background Immunosuppressant Regimen (With or Without Cyclosporine)

PK Parameter		Subjects not on cyclosporine-containing regimens (n=351)	Subjects on cyclosporine-containing regimens (n=94)
SOF AUC _t (h·ng/mL)	Geometric Mean	2663	3011
	Median (IQR)	2702 (2266; 3200)	2985 (2650; 3535)
	Ratio	-	1.13
GS-331007 AUC _t (h·ng/mL)	Geometric Mean	15920	17467
	Median (IQR)	15716 (12331; 20431)	16801 (14171; 21709)
	Ratio	-	1.10
LDV AUC _t (h·ng/mL)	Geometric Mean	5642	8172
	Median (IQR)	5682 (3715; 8513)	8745 (5385; 12908)
	Ratio	-	1.45

Comparison of SOF, GS-331007, and LDV Exposures in Subjects That Relapses

Exploratory evaluation of the role of SOF, GS-331007, and LDV exposure on relapse was conducted based on results from GS-US-337-0123 and GS-US-337-0124 (Table 5). In all, there were 23 subjects who relapsed (20 genotype 1 and 3 genotype 4), 10 with CPT B (N=212), 10 with CPT C (N=117), and 3 without cirrhosis (N=212). No subject with CPT A (N=118) or FCH (N=11) relapsed. Typically, lower exposures were observed in those patients who relapses compared to those that achieved SVR. However, univariate and multivariate logistic regression analyses did not identify exposure as a signification predictor of treatment outcome. Also, the exposures in subjects that relapsed, while trending lower, were around the 25th percentile of overall exposures (Table 2 and 3). Altogether, while lower exposures were observed in those subjects that relapsed, these subjects cannot be identified prior to treatment and no dose adjustments are recommended based on this observation.

Table 5: Comparison of SOF, GS-331007, and LDV AUC_t Exposures in Those Subjects That Achieved SVR and Those That Relapsed

PK Parameter		Group 3		Group 1 and 5		Group 2 and 6	
		SVR	Relapse	SVR	Relapse	SVR	Relapse
SOF AUC _t (h·ng/mL)	Geometric Mean	2636	2969	2652	2045	2942	2547
	Ratio	-	1.13	-	0.77	-	0.87
GS-331007 AUC _t (h·ng/mL)	Geometric Mean	16335	14662	13561	7999	13644	9641
	Ratio	-	0.90	-	0.59	-	0.71
LDV AUC _t (h·ng/mL)	Geometric Mean	6386	4314	5976	4297	6108	3633
	Ratio	-	0.68	-	0.72	-	0.59

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