OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA : 205834 (S_17)	Submission Date(s): October 07, 2016
Brand Name	Harvoni
Generic Name	Ledipasvir/Sofosbuvir
Applicant	Gilead Sciences
Submission Type	Priority
Formulation; Strength(s)	Fixed dose combination tablets; 90 mg/400 mg
Current Indication	Indicated with or without ribavirin for the treatment of chronic hepatitis C virus (HCV) genotype 1, 4, 5 or 6 infection
Proposed Indication	Extend the current indication to adolescent patients (12 to <18 years of age) with HCV infection
Review Team	Jenny Zheng, Ph.D.; Jeffry Florian, Ph.D.; Shirley Seo, Ph.D.

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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) is approved for the treatment of chronic genotype 1, 4, 5 or 6 hepatitis C virus (HCV) infection in adults. The current efficacy supplement seeks to extend the indication to include pediatric patients 12 years of age and older with chronic HCV infection (same genotypes as adults). This submission partially fulfills PREA PMRs 2780-1, 2983-1, and 2985-1: *Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ledipasvir/sofosbuvir (LDV/SOF) in pediatric subjects 3 to 17 years of age with chronic hepatitis C.* The applicant will fulfill the remaining PMRs (pediatric subjects ages 3-11 years) when data become available.

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).

This efficacy supplement contains SVR12 data from the ongoing Phase 2 study GS-US-337-1116 to support the safety and efficacy of LDV/SOF in pediatric patients aged 12 to <18 years old. Pharmacokinetic data from this study are provided to support the proposed dosing regimen.

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 pediatric patients aged 12 to <18 years old or weighing at least 35 kg.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

The dosing recommendations for adolescents are based on the results from Study GS-US-338-1116, Group 1. Study GS-US-338-1116 is a Phase 2, open-label, multi-cohort study to investigate the safety and efficacy of LDV/SOF fixed dose combination +/-ribavirin in adolescents and children with chronic genotype 1, 3 (UK only), 4, 5, or 6 HCV infection. The submission only provides the results for adolescent subjects aged 12 to <18 years of age (Group 1). The interim analysis was conducted after all subjects in Group 1 had completed the post-treatment Week 12 visit or had prematurely discontinued from the study.

The study consists of a PK lead-in phase and a treatment phase. The PK lead-in phase evaluated and confirmed the age-appropriate LDV/SOF dose by analyzing PK, safety, and antiviral activity of LDV/SOF through 10 days of dosing. Subjects were required to be treatment naive without a history of cirrhosis to participate in the PK lead-in phase. Ten subjects weighing at least 45 kg were enrolled in the PK lead-in phase in Cohort 1 to receive LDV/SOF 90/400 mg once daily for 10 days, and to undergo intensive PK evaluation on Day 10. In Group 1, approximately 100 subjects (treatment naïve with or without cirhosis (n =80) or treatment experienced without cirrhosis (n=20)) 12 to < 18 years of age with HCV genotype 1 infection, including subjects from the PK lead-in phase, received the full adult dose (LDV/SOF 90/400 mg once daily for 12 weeks). Although subjects with Genotypes 3 (UK only), 4, 5 and 6 HCV infection were eligible to in enrolled in the study, only patients with Genotype 1 were enrolled.

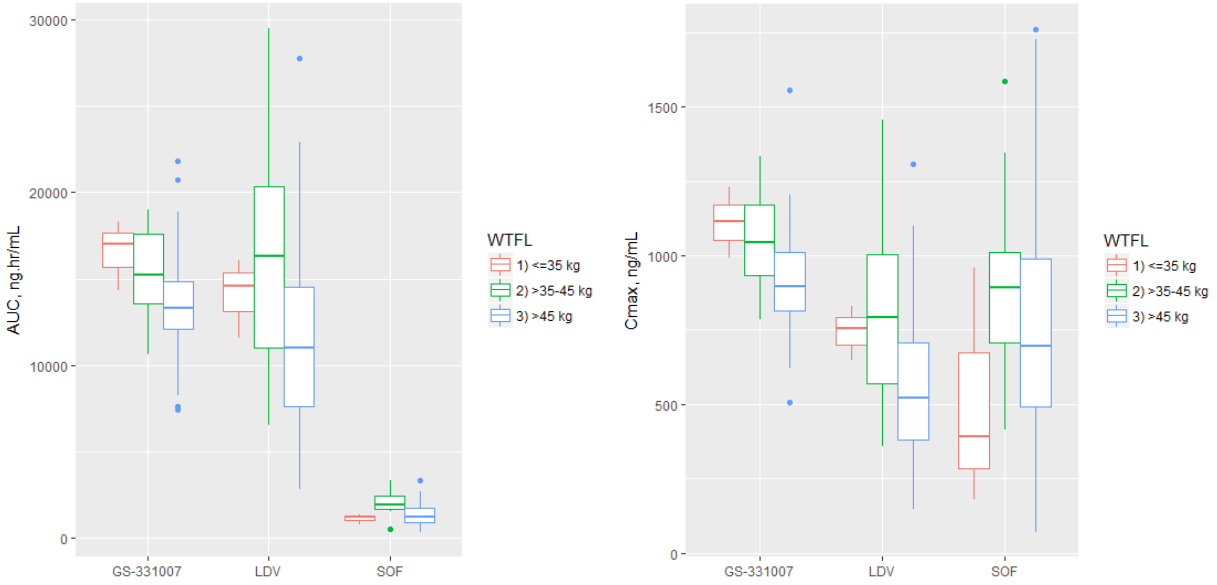
A summary of the geometric (CV%) C_{max}, AUC and Ctau for SOF, GS-331007, and LDV based on intensive PK and population PK results are shown in Table 1. Exposures were similar between intensive PK and population PK results except SOF, where AUC and Cmax were about 47% higher from intensive PK analysis. Based on the population PK analysis, exposures were typically similar between adolescents and adults with the exception of LDV, which was 50-80% higher in adolescents. These differences are not expected to be clinically significant based on the known safety profile of LDV.

Table 1 Comparisons of Mean (%CV) SOF, GS-331007, and LDV Exposures between Adolescents in Group 1 (12 to < 18 Years Old) and Adults from the LDV/SOF Phase 2/3 Population (PK Analysis Set)

PK Parameter Mean (%CV)	Adolescents Group 1 (12 to < 18 Years) (lead-in, BW ≥ 45 kg, intense PK) (n=10)	Adolescents Grp 1 (12 to < 18 Years) pop PK) (N = 100)	Adults LDV/SOF Phase 2/3 Population (N = 2113)	Adolescents vs Adults % GMR (90% CI) (pop PK)
SOF				
AUCtau (ng•h/ml)	2176 (26.6)	1494 (45.2)	1376 (34.0)	102.3 (96.5, 108.5)
Cmax (ng/ml)	1140 (57.2)	772 (51.1)	659 (34.0)	106.8 (98.7, 115.6)
GS-331007				
AUCtau (ng•h/ml)	12683 (13.7)	13888 (18.9)	12454 (29.2)	114.1 (108.8, 119.7)
Cmax (ng/ml)	1008 (21.5)	936 (17.8)	736 (28.2)	130.2 (124.2, 136.5)
LDV				
AUCtau (ng•h/ml)	10202.4 (50.9)	12414 (45.7)	8534 (60.8)	153.3 (139.6, 168.4)
Cmax (ng/ml)	564 (41.2)	608 (44.2)	364 (51.4)	170.2 (156.8, 184.7)
Ctau (ng/ml)	319.0 (71.5)	439 (48.8)	247 (59.2)	184.4 (167.6, 202.8)

The treatment phase of GS-US-337-1116 had no weight restrictions and sixteen participants who weighed less than 45 kg were enrolled including three participants who weighed <35 kg. Sparse PK data from the 15 participants with body weight 35 kg to <45 kg demonstrated that although the exposures (AUC and Cmax) for SOF, GS-331007, and LDV are 13% to 46% higher in patients with body weight of 35 kg to <45 kg as compared to patients with body weight of ≥45 kg, the exposures were generally considered similar between these two weight groups (Figure 1). The Clinical Reviewer, Dr. Sheikh, conducted an analysis to assess differences in adverse event rates (AEs) by baseline weight and observed no differences in AEs for patients <45 kg as compared to ≥45 kg.

Figure 1 Comparison of AUC and Cmax of LDV, SOF, and GS-331007 based on body weight (source: sponsor's analysis)



Based on Dr. Virginia Sheikh's Clinical Review, the efficacy and safety are acceptable from Study GS-US-337-1116 for adolescents administered the adult dose (LDV/SOF 90/400 mg once daily).

Ninety-eight percent (98%) of enrolled participants achieved the primary endpoint SVR12 (sustained virologic response 12 weeks after stopping study treatment) and no subjects experienced on-treatment virologic failure or relapse. The only participants who were counted as SVR treatment failures were the two participants who were lost-to-follow-up; however, they were not virologic failures while on treatment.

Results from GS-US-337-1116 demonstrate that LDV/SOF was safe and well-tolerated in adolescents. As mentioned above, no increased AEs were observed by patients <45 kg as compared to ≥45 kg. The review team concluded that although GS-US-337-1116 group 1 only includes patients at least 12 years of age, there are enough data to support the safety of projected higher exposures of LDV and SOF for patients younger than 12 years of age but weighing ≥35 kg administered the adult dose (LDV/SOF 90/400 mg once daily). Therefore, the indication is extended to pediatric patients 12 years of age and older **or** weighing at least 35 kg.

Although Study GS-US-337-1116 (Group 1) only includes patients with Genotype 1, the safety and efficacy of HARVONI for treatment of HCV genotypes 4, 5, or 6 infection in pediatric patients 12 years of age and older or weighing at least 35 kg without cirrhosis or with compensated cirrhosis is supported by comparable ledipasvir, sofosbuvir, and GS-331007 exposures between adults and adolescents with HCV genotype 1 and similar efficacy and exposures across HCV genotypes 1, 4, 5, and 6 in adults (see the Clinical and Clinical Pharmacology reviews for the original NDA205834).

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

At the time of this review, the following sections of the package insert were updated for Harvoni®.

- Section 1 (Indications and Usage): Indication for pediatric patients 12 years of age and older or weighing at least 35 kg with HCV genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis was added.
- Section 2 (Dosage and Administration): Treatment regimens and treatment and durations (same as adults) were added to Pediatric Patients 12 Years of Age or Older or Weighing at Least 35 kg with Genotype 1, 4, 5, or 6 HCV without Cirrhosis or with Compensated Cirrhosis.
- Section 8 (Use in Specific Populations): The study design for Study GS-US-337-1116 as well as the base of the approval was described.
- Section 12 (Clinical Pharmacology): the PK parameters for LDV, SOF and GS-331007 were provided for pediatric subjects 12 years of age and older.

4. APPENDICES

4.1 Summary of Study Design for GS-US-337-1116

GS-US-337-1116 is an ongoing phase 2, open-label, multicenter, multi-cohort trial designed to evaluate the pharmacokinetics, safety and efficacy of LDV/SOF fixed dose combination in adolescents and children with chronic HCV. Although the trial was amended to include participants with Genotypes 4,5, and 6 after LDV/SOF was approved for these genotypes in adults, this submission only includes the SVR 12 results from Group 1 (children ages ≥12 to <18 years) with Genotype 1 HCV infection.

The study consists of a PK lead-in phase and a treatment phase. The PK lead-in phase evaluated and confirmed the age-appropriate LDV/SOF dose by analyzing PK, safety, and antiviral activity of LDV/SOF through 10 days of dosing. Subjects were required to be treatment naive without a history of cirrhosis to participate in the PK lead-in phase. Ten subjects weighing at least 45 kg were enrolled in the PK lead-in phase in Cohort 1 to receive LDV/SOF 90/400 mg once daily for 10 days, and to undergo intensive PK evaluation on Day 10. In Group 1, approximately 100 subjects (treatment naïve with or without cirhosis (n =80) or treatment experienced without cirrhosis (n=20)) 12 to < 18 years of age with HCV genotype 1 infection, including subjects from the PK lead-in phase, received the full adult dose (LDV/SOF 90/400 mg once daily for 12 weeks).

For the subjects in the PK lead-in phase, intensive serial PK blood samples (were collected (predose, 0.5, 1, 2, 3, 4, 5, 8, and 12 hours postdose) at the Day 10 visit. During the treatment phase, a single PK blood sample was collected from all subjects at Weeks 1 (excluding subjects who rolled over from the PK lead-in phase), 2, 4, 8, and 12, or early termination as applicable. The PK of LDV, SOF, and SOF metabolite GS-331007 were assessed. The bioanalytical site ((b) (4)) for the study was inspected by the FDA/CDER/Office of Tanslational

Science/Office of Study Integrity and Surveillance and was determined to be acceptable. In addition, the standard curve and QC data indicated that the plasma assay methods for LDV, SOF, and GS-331007 were precise and accurate.

The PK, efficacy and safety results were summarized in the Summary of Important Clinical Pharmacology Finding. For the detailed analysis, please see Section 4.2 of this review and Dr. Virginia Sheikh's Clinical Review.

4.2 Population Pharmacokinetic Analyses

4.2.1 Sponsor's Population PK Analysis of sofosbuvir (SOF), GS-331007, and ledipasvir (LDV)

Population PK analyses (SOF, GS-331007, and LDV) have previously been developed and reviewed for SOF coadministered with LDV in adult patients with chronic hepatitis C virus infection (Clinical Pharmacology Review by Dr. Zheng on 7/10/2014). In the current submission, the sponsor used these previously developed models as the base structures for population PK analyses of SOF, GS-331007, and LDV in adolescents following administration of LDV/SOF 90/400 mg fixed dose combination (FDC) in GS-US-337-1116. In situations where the models did not adequately predict the observed data, the model was updated. Final model structures were used to estimate individual exposures of SOF, GS-331007, and LDV for comparison with adult exposures.

Study Pharmacokinetic Data

Adolescent pharmacokinetic data was obtained from GS-US-337-1116, an ongoing Phase 2 study where LDV/SOF 90/400 mg FDC (+/- RBV if indicated) was administered for a treatment duration of 12 or 24 weeks based on HCV genotype. Data included intensive PK sampling from a subset of subjects after 10-days of dosing, which were used to confirm dosing before opening up enrollment to an additional 90 subjects. For all subjects, a single PK sample was collected at all on-treatment visits (week 1, 2, 4, 8, and 12).

Model Evaluation

Diagnostic graphs were population predicted concentrations (PRED) versus observed concentrations (DV), individual predicted concentrations (IPRED) versus DV, and conditional weighted residuals (CWRES) versus PRED and time. This set of diagnostic graphs showed whether the predicted concentrations matched the observed concentrations.

A prediction corrected visual predictive check (pcVPC) based on 1000 trial replicates 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. A numerical predictive check (NPC) was also used to evaluate the final population PK model. For each subject, 1000 simulations constructed the distribution of model predictions for that subject, using subject-specific covariates and dose regimens. The percent of observed data above and below various prediction percentiles were summarized for the population.

4.2.2 Sofosbuvir Population PK Model Results

In the original PopPK model developed in adults, plasma PK of SOF after administration of LDV/SOF 90/400 mg FDC was best described with a 1-compartment model with first order absorption, first order elimination from the central compartment and an absorption lag time.

In the current analysis, the SOF dataset included 570 plasma samples from 100 subjects. A portion of the samples (301 samples) were below-LLOQ, thus were excluded from the analysis along with 17 measureable concentrations beyond 12 hours post dose. The remaining dataset included 252 measureable SOF concentrations from 70 subjects.

The full adult covariate model was utilized initially for characterizing the disposition of SOF in this population. Model estimation occurred as the initial step in the analysis and covariate exploration occurred with the new post-hoc parameter estimates and individual random-effect ETAs. Minimization was successful but the covariance between clearance and volume was found to be approaching its boundary so a shared ETA term between CL and V was used. There were no covariates showing significant trends. The final model used for the adolescent population was the original SOF full covariate model from adults with re-estimated final model parameters for SOF. Final model parameters are shown in **Table 1**.

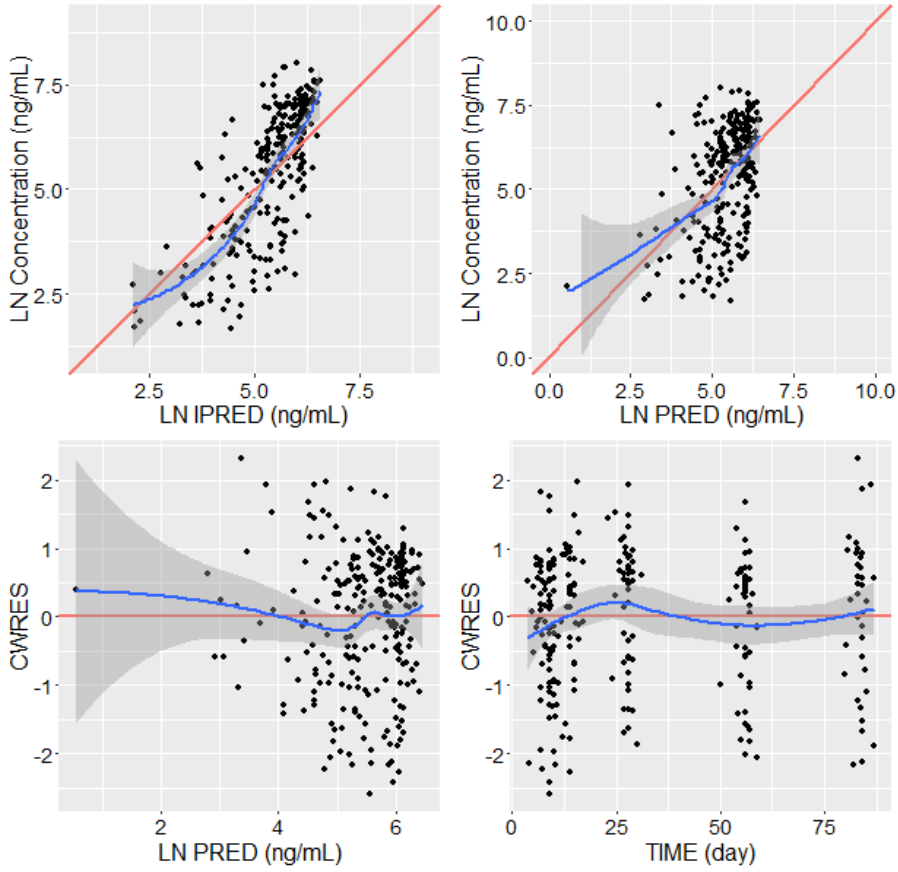
Table 1 Population PK Model Parameters for SOF

Parameter	Parameter Description	Model Estimates from Current Study	Original Model (Adult)
$exp(\theta_1)$	Apparent oral clearance, CL/F (L/hr)	257.2	304.9
	Influence of creatinine clearance on CL/F	0.73	0.22
$exp(\theta_2)$	Apparent central volume, V_c/F (L)	415.7	298.9
$exp(\theta_3)$	Absorption rate constant, K_a (1/hr, fasted)	1.94	3.49
	Influence of Food on K_a	-0.64	-0.81
$exp(\theta_4)$	Lag time, T_{lag}, (hr)	0.15	0.19
Inter-individual variability (%)	CL/F	45.4	40.2
	V_c/F	20.8	33.3
	K_a	99.5	115.8
σ^2	Residual error (%CV)	122.9	95.3

Source: Sponsor's Population pharmacokinetic report, pg 9

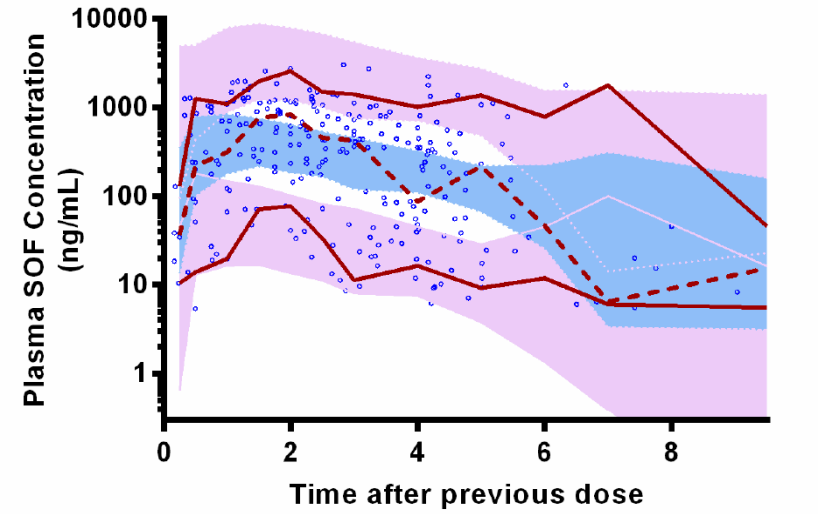
The general goodness-of-fit plots and pcVPC for SOF in this study are shown in Figure 1 and Figure 2. The goodness-of-fit plots for SOF were not centered around the line of unity. Certain parameters from the population PK analysis, such as C_{max}, should be interpreted with caution unless that data was from patients included in the PK run-in due to the timing of PK sampling and the number of samples obtained that were below the limit of quantification. The pcVPC overall showed a reasonable ability of the model to describe the time course of SOF data. The provided NPC showed no substantial bias with 31.7% of samples above the 75th percentile, 3.6% above the 95th percentile, 26.2% below the 25th percentile, and 7.5% below the 5th percentile.

Figure 1 General Goodness of Fit Plots for SOF



Source: Sponsor's Population pharmacokinetic report, pg 10

Figure 2 Prediction-Corrected VPC of SOF Plasma Concentrations



Source: Sponsor's Population pharmacokinetic report, pg 11

4.2.3 GS-331007 Population PK Model Results

In the original PopPK model developed in adults, the plasma PK of GS-331007 after administration of LDV/SOF 90/400 mg FDC was best described by a 2-compartment model with first order absorption, first order elimination from the central compartment and an absorption lag time.

In the current analysis, the GS-331007 dataset included 570 plasma samples from 100 subjects. One sample was below-LLOQ and it was excluded from the analysis. The remaining dataset included 569 measureable GS-331007 concentrations from 100 subjects.

The full adult covariate model was utilized initially for characterizing the disposition of GS-331007 in this study. Model estimation occurred as the initial step in the analysis and covariate exploration occurred with the new post-hoc parameter estimates and individual random-effect ETAs. None of the evaluated covariates showed a significant improvement on model performance. Thus, the final model used for the adolescent population was the GS-331007 full covariate model from adults with re-estimated final model parameters for GS-331007. Final model parameters are shown in **Table 2**.

Table 2 Population PK Model Parameters for GS-331007

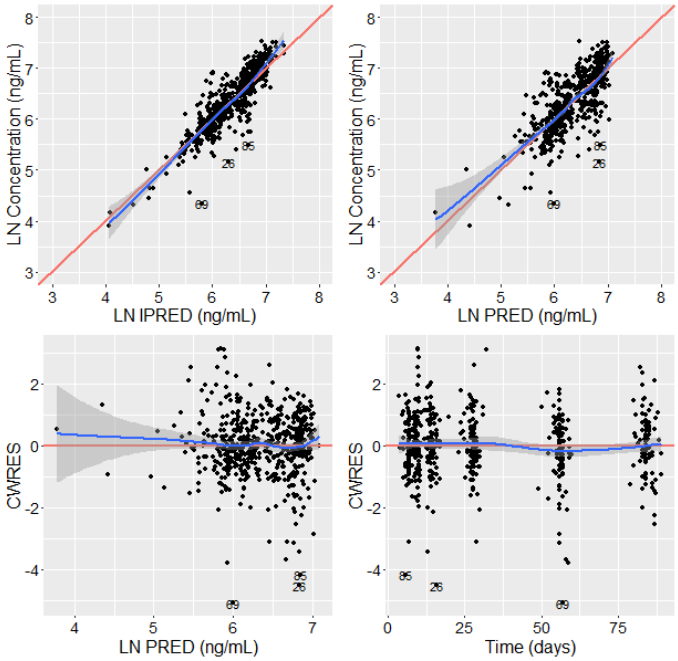
Parameter	Parameter Description	Model Estimates from Current Study	Original Model (Adult)
$exp(\theta_1)$	Apparent oral clearance, CL/F (L/hr)	29.1	31.8
	Influence of creatinine clearance on CL/F	0.35	0.47
	Influence of gender on CL/F	-0.07	-0.17
	Influence of RBV on CL/F	0.04	0.19
	Influence of RACE (white vs. non-white) on CL/F	0.28	0.12
$exp(\theta_2)$	Apparent central volume, Vc/F (L)	411.6	192.5
	Influence of RBV on Vc/F	-0.09	0.34
	Influence of CLCR on Vc/F	0.31	0.43
$exp(\theta_3)$	Apparent inter-compartmental clearance, Q/F (L/hr)	56.8	51.9
$exp(\theta_4)$	Apparent peripheral volume, Vp/F (L)	765.1	788.4
$exp(\theta_5)$	Absorption rate constant, Ka (1/hr, fasted)	0.67	0.32
	Influence of Food on Ka	0.29	-0.35
$exp(\theta_6)$	Lag time (hr)	0.92	0.27
	Influence of food on F	1.01	0.96
Inter-individual variability (%)	CL/F	17.4	22.9
	Vc/F	10.5	53.1
	Q/F	44.7	47.5
	Vp/F	28.3	32.9
	Ka	75.4	28.7
$\omega^2_{CL/F,Vc/F}$	Covariance between CL/F and Vc/F	0.018	0.020
$\omega^2_{Q/F,Vp/F}$	Covariance between Q/F and Vp/F	0.006	0.146
σ^2	Residual error (%CV)	30.1	23.3

Source: Sponsor's Population pharmacokinetic report, pg 13

The general goodness-of-fit plots and pcVPC for GS-331007 in this study are shown in Figure 3 and Figure 4. The goodness-of-fit plots showed good agreement between predicted and

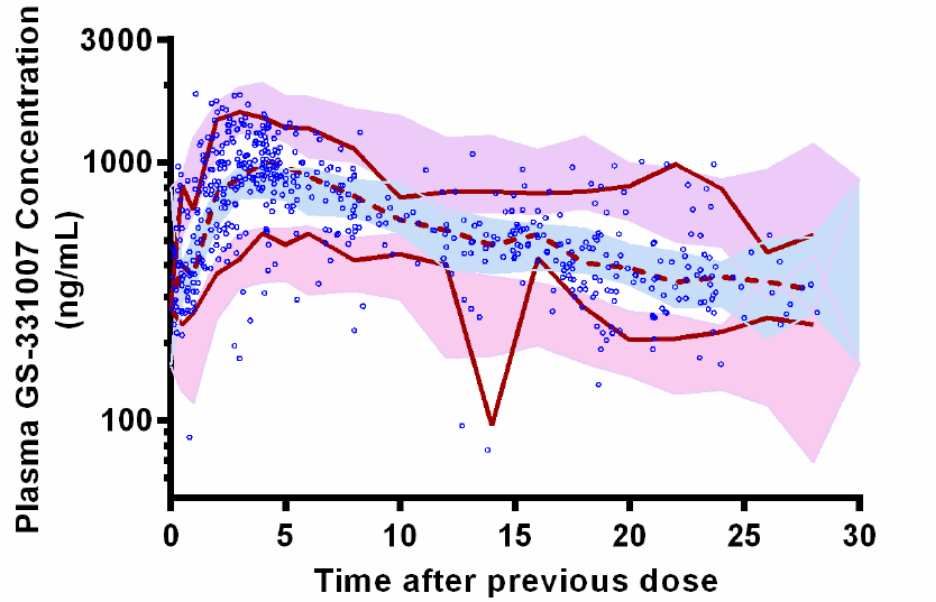
observed concentrations. The pcVPC adequately described the spread in the observed data. The provided NPC showed no substantial bias with 21.1% of samples above the 75th percentile, 2.5% above the 95th percentile, 27.2% below the 25th percentile, and 3.0% below the 5th percentile.

Figure 3 General Goodness of Fit Plots for GS-331007



Source: Sponsor's Population pharmacokinetic report, pg 14

Figure 4 Prediction-Corrected VPC of GS-331007 Plasma Concentrations



Source: Sponsor's Population pharmacokinetic report, pg 15

4.2.4 LDV Population PK Model Results

In the original PopPK model developed in adults, the plasma PK of LDV after administration of LDV/SOF 90/100 mg FDC was best described by a 2-compartment model with first order absorption, first order elimination from the central compartment and an absorption lag time.

In the current analysis, the LDV dataset included 569 plasma samples from 100 subjects. No samples were below-LLOQ and all samples were used in the analysis for LDV.

The full adult covariate model was utilized initially for characterizing the disposition of LDV in this study. Model estimation occurred as the initial step in the analysis and covariate exploration occurred with the new post-hoc parameter estimates and individual random-effect ETAs. None of the evaluated covariates showed a significant improvement on model performance. Thus, the final model used for the adolescent population was the LDV full covariate model from adults with re-estimated final model parameters for LDV. Final model parameters are shown in **Table 3**.

Table 3 Population PK Model Parameters for LDV

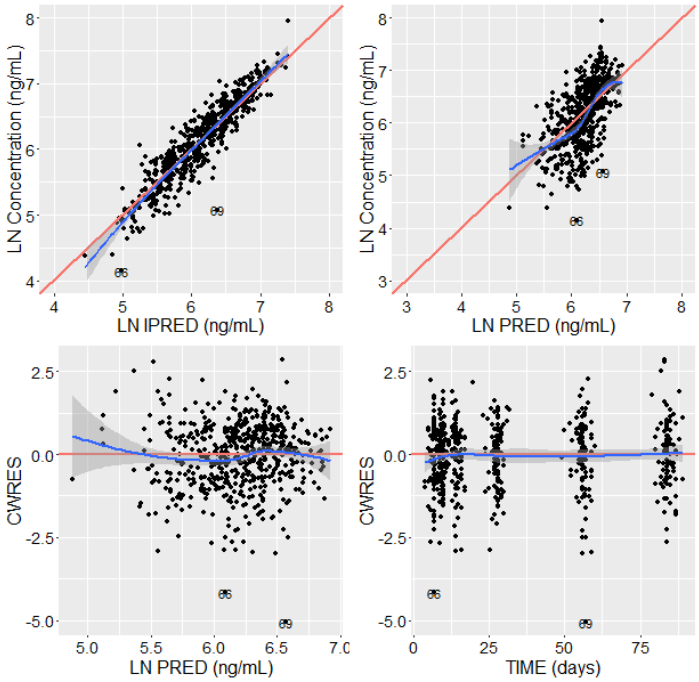
Parameter	Parameter Description	Model Estimates from Current Study	Original Model (Adult)
$exp(\theta_1)$	Apparent oral clearance, CL/F (L/hr)	8.76	13.1
	Influence of weight on CL/F	0.53	0.47
	Influence of gender on CL/F	-0.38	-0.40
	Influence of RBV on CL/F	-0.43	0.17
$exp(\theta_2)$	Apparent central volume, Vc/F (L)	175.9	399
	Influence of weight on Vc/F	1.35	1.18
$exp(\theta_3)$	Apparent inter-compartmental clearance, Q/F (L/hr)	33.1	28.5
$exp(\theta_4)$	Apparent peripheral volume, Vp/F (L)	399.4	620.2
$exp(\theta_5)$	Absorption rate constant, Ka (1/hr)	0.26	0.33
$exp(\theta_6)$	Lag time, Tlag, (hr)	0.72	0.44
	Influence of patient status on F	0.61	0.83
Inter-individual variability (%)	CL/F	39.4	47.6
	Vc/F	37.4	56.0
	Vp/F	91.9	78.0
	Ka	23.9	45.9
$\omega^2_{CL/F,Vc/F}$	Covariance between CL/F and Vc/F	0.147	0.178
$\omega^2_{CL/F,Vp/F}$	Covariance between CL/F and Vp/F	0.044	0.081
$\omega^2_{Vc/F,Vp/F}$	Covariance between Vc/F and Vp/F	0.038	0.272
σ^2	Residual error (%CV)	26.8	24.9

Source: Sponsor's Population pharmacokinetic report, pg 17

The general goodness-of-fit plots and pcVPC for LDV in this study are shown in Figure 5 and Figure 6. The goodness-of-fit plots showed good agreement between predicted and observed concentrations. The pcVPC adequately described the spread in the observed data. The

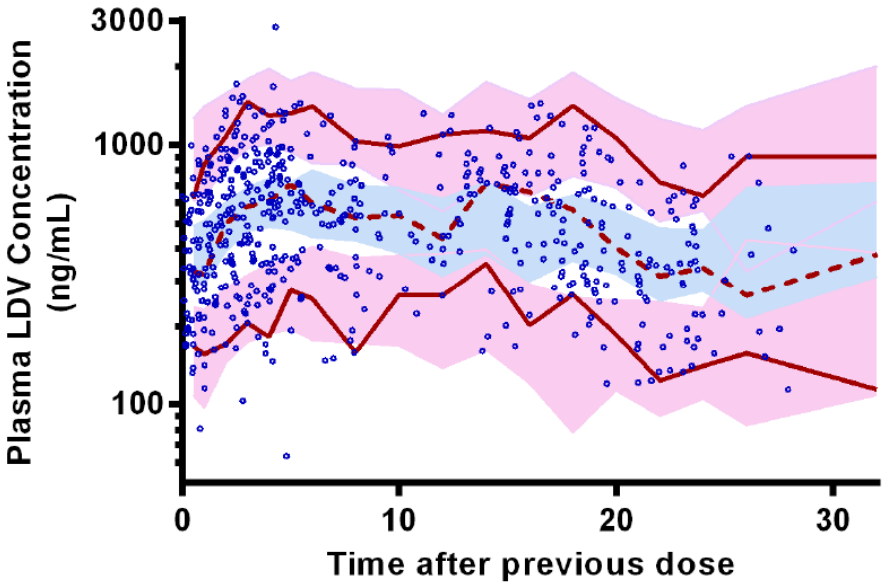
provided NPC showed no substantial bias with 25.7% of samples above the 75th percentile, 3.5% above the 95th percentile, 23.4% below the 25th percentile, and 5.1% below the 5th percentile.

Figure 5 General Goodness of Fit Plots for LDV



Source: Sponsor's Population pharmacokinetic report, pg 18

Figure 6 Prediction-Corrected VPC of LDV Plasma Concentrations



Reviewer Comments: Overall, the approaches used by the sponsor to characterize the PK for SOF, GS-331007, and LDV in adolescents were acceptable. The reviewer was able to recreate

the analyses conducted by the sponsor by taking the original adult modeling results and reestimating parameters based on the adolescent data. As shown above in Table 1, 2, and 3, when this approach was utilized, substantial changes to the original model parameters occurred. As the only purpose of this model was to characterize pediatric exposures for the three compounds based on the population PK model, these differences were considered acceptable. The review notes that the covariate values from the Applicant's analysis should not be taken to represent actual covariate effects. Rather, in this case they were degrees of freedom that permitted a best description of the adolescent data. The review conducted sensitivity analyses where all covariate and random effects were fixed. Similar overall results to those presented by the sponsor were obtained, so the reviewer concluded that no summary PK values provided by the sponsor were acceptable for comparing exposures to adults and for labeling. A summary of the geometric (CV%) C_{max} and AUC for SOF, GS-331007, and LDV based on intensive PK and population PK results are shown below. Exposures were typically similar between adolescents and adults with the exception of LDV.

		Geometric mean (CV%)		
Parameter	**Calculated from**	**SOF**	**GS-331007**	**LDV**
AUC (hr.ng/mL)	Intensive PK (n=10 for all)	2106 (27%)	12576 (14%)	9268 (47%)
	Population PK (n=78 for SOF, n=100 for others)	1348 (49%)	13638 (20%)	11173 (50%)
	Adults	1316 (29%)	12032 (29%)	7315 (61%)
Cmax (ng/mL)	Intensive PK (n=10 for all)	961 (79%)	983 (25%)	523 (43%)
	Population PK (n=78 for SOF, n=100 for others)	659 (69%)	921 (18%)	550 (48%)
	Adults	635 (36%)	711 (29%)	324 (52%)
Ctrough (ng/mL)	Intensive PK (n=0 for SOF and n=10 for others)	-	347 (20%)	270 (62%)
	Population PK (n=0 for SOF, n=100 for others)	-	371 (27%)	389 (55%)
	Adults	-	308 (44%)	224 (77%)

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