OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	204671 (S-6)
Submission Date(s)	October 27, 2016
Brand Name	SOVALDI
Generic Name	Sofosbuvir
Applicant	Gilead Sciences
Submission Type	Priority
Formulation; Strength(s)	400 mg tablets
Current Indication	Indicated in adult patients with genotype 1, 2, 3 or 4 chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis as a component of a combination antiviral treatment regimen.
Proposed Indication	Extension of the current indication to pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 2 or 3 chronic HCV infection without cirrhosis or with compensated cirrhosis in combination with ribavirin
Review Team	Jenny Zheng, Ph.D.; Jeffry Florian, Ph.D.; Shirley Seo, Ph.D.

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1. EXECUTIVE SUMMARY

Sofosbuvir (SOF) is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of genotype 1, 2, 3 or 4 chronic hepatitis C virus (HCV) infection in adults as a component of a combination antiviral treatment regimen. The approved dosage of SOF is one 400 mg tablet, taken orally, once daily with or without food. The current efficacy supplement seeks to extend the indication to include pediatric patients 12 years of age and older with chronic HCV infection genotype 2 and 3 using the same regimen as adults. The approved treatment regimen for SOF combination therapy in adults is SOF+ribavirin (RBV) for 12 weeks for genotype 2 or SOF+RBV for 24 weeks for genotype 3. This submission partially

fulfills PREA PMR 2110: *Conduct a trial to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of SOVALDI (sofosbuvir) as a component of an antiviral treatment regimen in pediatric subjects 3 through 17 years of age with chronic hepatitis C.* The applicant will fulfill the remaining portion of the PMR (pediatric subjects ages 3-11 years) when data become available.

This efficacy supplement contains SVR12 data from the ongoing Phase 2 study GS-US-337-1112 to support the safety and efficacy of SOF in pediatric patients aged 12 to <18 years old, as the primary basis in support of approval. Pharmacokinetic data from this study are provided as supportive information for the proposed dosing regimen.

1.1 Recommendation

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in this supplemental NDA to support a recommendation of approval for 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 efficacy, safety and PK results from Study GS-US-338-1112, Group 1. Study GS-US-338-1112 is a Phase 2, open-label, multicenter, multi-cohort, single-arm study to investigate the safety and efficacy of SOF + RBV in adolescents and children with genotype 2 or 3 chronic HCV infection. The current 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 SOF dose by analyzing PK, safety, and antiviral activity of SOF in combination with RBV through 7 days of dosing. Subjects were required to have HCV RNA ≥ 1000 IU/mL at enrollment and be treatment naive to participate in the PK lead-in phase. Ten subjects with HCV genotype 2 or 3 infection weighing at least 45 kg were enrolled in the PK lead-in phase in Cohort 1 to receive SOF 400 mg + RBV (weight-based) once daily for 7 days, and to undergo intensive PK evaluation on Day 7. In Group 1, approximately 50 treatment naïve or treatment experienced subjects 12 to < 18 years of age with HCV genotype 2 (n = 13) or 3 infection (n = 37), including subjects from the PK lead-in phase, received the full adult dose (SOF 400 mg + RBV) for 12 weeks (genotype 2) or 24 weeks (genotype 3).

Based on Dr. Melisse Baylor's Clinical Review, the efficacy and safety are acceptable from Study GS-US-337-1112 for adolescents administered the adult dose (SOF 400 mg once daily in combination with RBV) for 12 weeks (genotype 2) or 24 weeks (genotype 3). The SVR12 rate was 100% (13/13) in genotype 2 subjects and 97% (36/37) in genotype 3 subjects. No subject experienced on-treatment virologic failure or relapse. The only subject counted as SVR treatment failure was lost-to-follow-up; however, the subject was not a virologic failure while on treatment. The findings in this pediatric clinical trial are consistent with previously described adverse events observed with the use of sofosbuvir in adults.

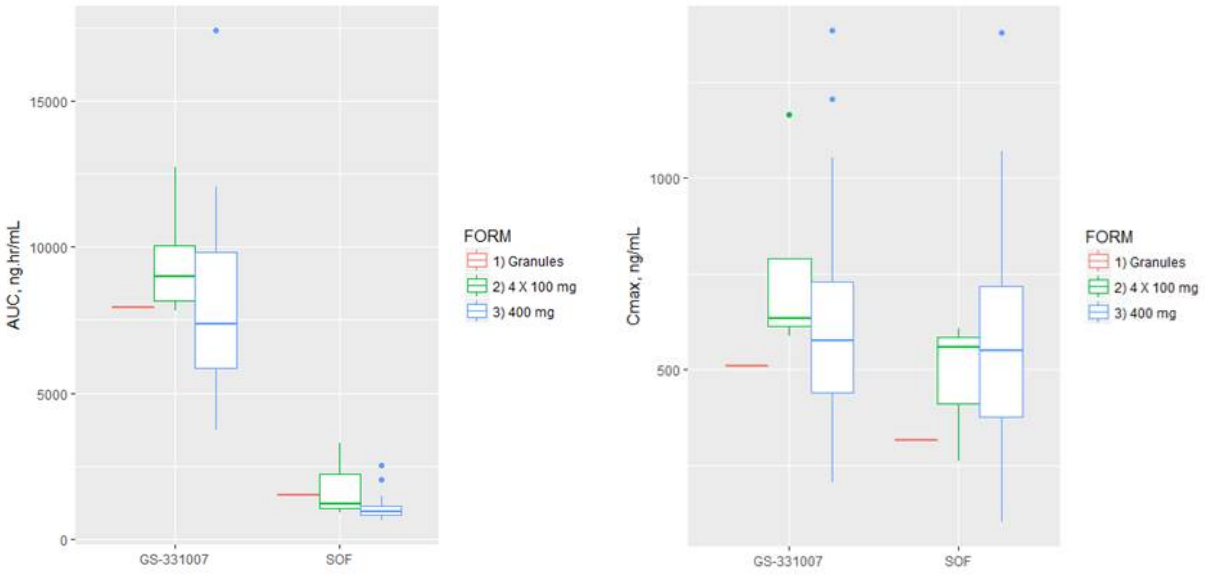
A summary of the geometric (CV%) AUC and C_{max} for SOF and GS-331007 based on intensive PK and population PK results are shown in Table 1. Exposures were similar between intensive PK and population PK results. Based on the population PK analysis, exposures were typically similar between adolescents and adults.

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

PK Parameter Mean (%CV)	Adolescents Group 1 (12 to < 18 Years) (lead-in, BW ³ 45 kg, intense PK) (n=10)	Adolescents Grp 1 (12 to < 18 Years) pop PK) (N = 50)	Adults SOF Phase 2/3 Population (N=1695)	Adolescents vs Adults % GMR (90% CI)
SOF				
AUC_{tau} (h•ng/mL)	1174.7 (67.6)	1157 (50.6)	1027 (36.5)	109.7 (98.4, 122.3)
C_{max} (ng/mL)	591.6 (84.1)	546 (53.0)	511 (32.5)	98.5 (86.7, 111.9)
GS-331007				
AUC_{tau} (h•ng/mL)	9106 (28.6)	7969 (32.8)	7123 (30.7)	111.5 (103.5, 120.1)
C_{max} (ng/mL)	980.9 (43.7)	621 (40.7)	582 (36.3)	105.5 (96.2, 115.6)

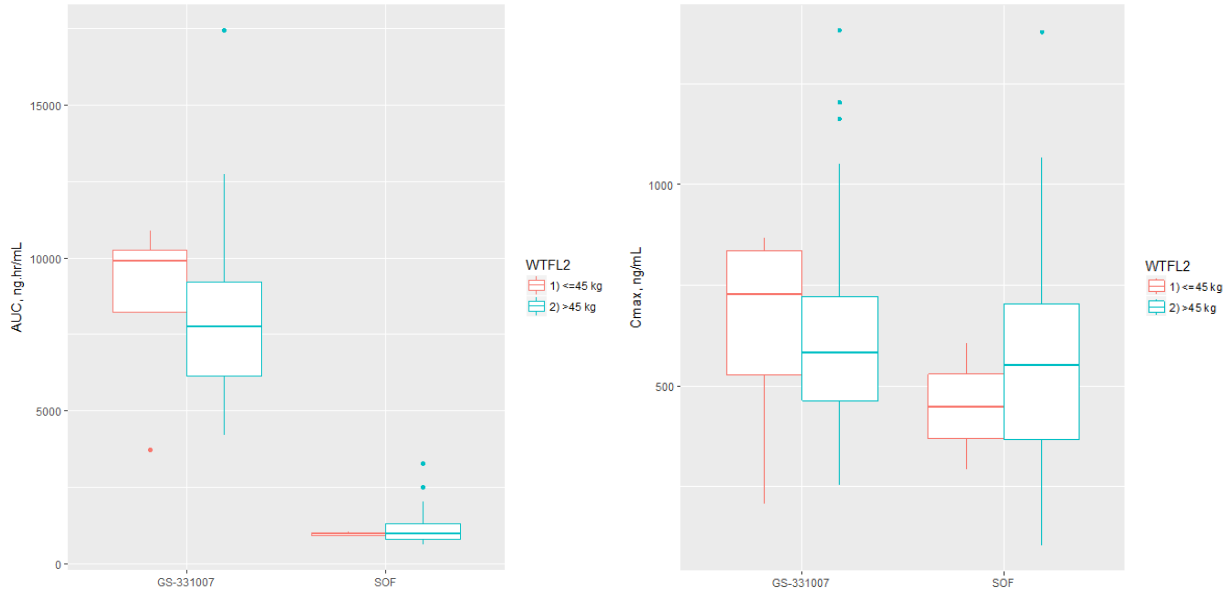
SOF was administered as a single 400 mg tablet in 44 of 50 subjects, as 4 x 100- mg tablets in 5 subjects, and as granules in water in one subject. A single 400 mg tablet is expected to be bioequivalent to four 100-mg tablets because all the ingredients are dose proportional between these two tablets and all the manufacturing processes are the same. In addition, a phase 1 study (GS-US-334-1111) was conducted to evaluate the relative bioavailability of, and effect of food on SOF oral granules in healthy adult subjects to support the use of this formulation in subjects unable to swallow the tablet formulations. The applicant stated that the preliminary results of this study indicated that the GS-331007 exposures were bioequivalent between the pediatric granules in capsules and the 400-mg tablets. Exploratory analyses of SOF and GS-566500 showed no clinically significant differences between the granule and tablet formulation administered in the fasted state, and comparable effects of food on the granule formulation as was previously observed for the tablet formulation (Study P7977-1318). Very limited data from Study GS-US-338-1112 show that the AUC with different formulations are generally comparable but Cmax is lower for the granules as compared to the 100-mg tablets and 400-mg tablets (Figure 1).

Figure 1: Comparison of AUC and Cmax of SOF and GS-331007 by Formulation



The treatment phase of GS-US-337-1112 had no weight restrictions and 4 out of 50 subjects weighing less than 45 kg were enrolled, including 1 subject who weighed <35 kg. Population PK analysis show median Cmax values for both SOF and GS-331007 were generally considered similar between subjects with body weight ≤45 kg and body weight >45 kg, while GS-331007 AUC was higher for subjects weighing ≤45 kg as compared to >45 kg(Figure 2). These differences are not considered clinically relevant.

Figure 2 Comparison of AUC and Cmax of SOF and GS-331007 by Body Weight



Although there were no subjects with documented cirrhosis in the study, the data from adult PK trials demonstrate that differences in the pharmacokinetics of SOF in subjects with compensated cirrhosis and without cirrhosis are not clinically significant and the same dose is used in adults with compensated cirrhosis or without cirrhosis. In addition, the PK of SOF is

similar between adults and adolescents. Therefore, the 400 mg daily dose is acceptable for use in adolescents with compensated cirrhosis and without cirrhosis.

Results from GS-US-337-1112 demonstrate that SOF + RBV were safe and well-tolerated in adolescents and no trend of increased AEs were observed in patients weighing <45 kg as compared to ≥45 kg. The review team concluded that although GS-US-337-1112 Group 1 only included patients at least 12 years of age, there are enough data to support the safety of projected higher exposures of SOF and GS-331007 for patients younger than 12 years of age but weighing ≥35 kg administered the adult dose (SOF 400 mg once daily). Therefore, the indication is extended to pediatric patients 12 years of age and older **or** weighing at least 35 kg.

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 Sovaldi®.

- Section 1 (Indications and Usage): Indication for pediatric patients 12 years of age and older or weighing at least 35 kg with HCV genotype 2 or 3 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 HCV genotype 2 or 3 infection without Cirrhosis or with Compensated Cirrhosis.
- Section 8 (Use in Specific Populations): The study design for Study GS-US-337-1112 as well as the base of the approval was described.
- Section 12 (Clinical Pharmacology): the PK parameters for 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-337-1112

GS-US-337-1112 is an ongoing Phase 2, open-label, multicenter, multi-cohort, single-arm study to investigate the safety and efficacy of SOF + RBV in adolescents and children with genotype 2 or 3 chronic HCV infection. This submission only includes the SVR 12 results from Group 1 (children ages ≥12 to <18 years).

The study consists of a PK lead-in phase and a treatment phase. The PK lead-in phase evaluated and confirmed the age-appropriate SOF dose by analyzing PK, safety, and antiviral activity of SOF in combination of RBV through 7 days of dosing. Subjects were required to have HCV RNA ≥ 1000 IU/mL and be treatment naive to participate in the PK lead-in phase. Ten subjects with HCV genotype 2 or 3 infection weighing at least 45 kg were enrolled in the PK lead-in phase in Cohort 1 to receive SOF 400 mg + RBV once daily for 7 days, and to undergo intensive PK evaluation on Day 7. In Group 1, approximately 50 treatment naïve or treatment

experienced subjects 12 to < 18 years of age with HCV genotype 2 (n = 13) or 3 infection (n = 37), including subjects from the PK lead-in phase, received the full adult dose (SOF 400 mg + RBV once daily) for 12 weeks (genotype 2) or 24 weeks (genotype 3).

Originally, SOF 400-mg tablets were administered. Subjects determined unable to swallow the 400-mg tablet (by SOF swallowability assessment at Day 1 or at any time during the study) were re-assigned to 4 x 100-mg tablets daily, and subjects who could not swallow the 100-mg tablets were assigned to granules.

RBV was administered orally at a total daily dose according to weight as shown below.

Body Weight kg (lb)	RBV Daily Dose	RBV Number of Capsules
< 47 (< 103)	15 mg/kg/day	Oral Solution. Divided dose in the morning and evening.
47−49 (103−108)	600 mg/day	1 × 200-mg capsules AM 2 × 200-mg capsules PM
50−65 (110–143)	800 mg/day	2 × 200-mg capsules AM 2 × 200-mg capsules PM
66−80 (145–176)	1000 mg/day	2 × 200-mg capsules AM 3 × 200-mg capsules PM
81−105 (178−231)	1200 mg/day	3 × 200-mg capsules AM 3 × 200-mg capsules PM
105 (> 231)	1400 mg/day	3 × 200-mg capsules AM 4 × 200-mg capsules PM

For the subjects in the PK lead-in phase, intensive serial PK blood samples were collected (0 (predose), 0.5, 1, 2, 3, 4, 8, and 12 hours postdose) at the Day 7 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, 12, or early termination as applicable (all subjects), and Weeks 16, 20, and 24 (24-week treatment group). The PK of 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 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. Melisse Baylor's Clinical Review.

4.2 Population Pharmacokinetic Analyses

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

Population PK analyses (SOF and GS-331007) have previously been developed and reviewed for SOF coadministered with ribavirin 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 and GS-331007 in adolescents following administration of SOF 400 mg with RBV in GS-US-334-1112. 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 and GS-331007 for comparison with adult exposures.

Study Pharmacokinetic Data

Adolescent pharmacokinetic data was obtained from GS-US-334-1112, an ongoing Phase 2 study where SOF with RBV 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 7 days of dosing, which were used to confirm dosing before opening up enrollment to an additional 40 subjects. For all subjects, a single PK sample was collected at all on-treatment visits (week 1, 2, 4, 8, and 12 and 16, 20 and 24, if applicable).

Model Evaluation

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.

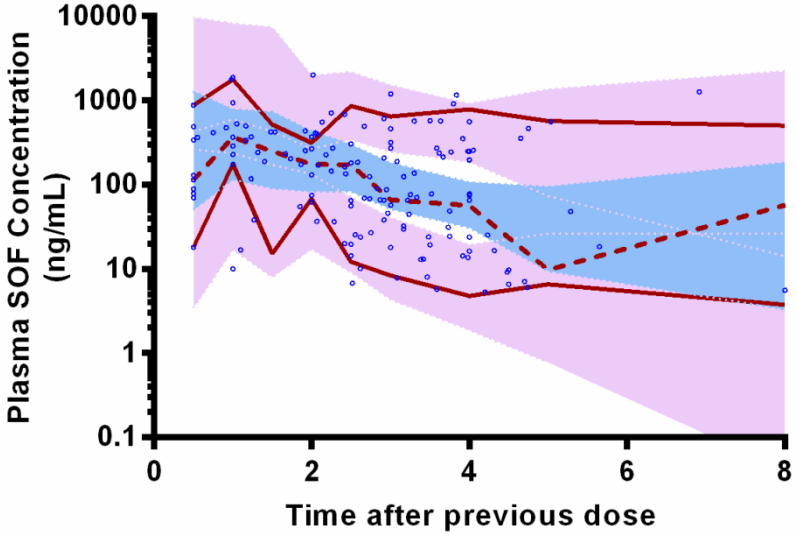
4.2.2 Sofosbuvir Population PK Model Results

In the original PopPK model developed in adults, the plasma PK of SOF after administration of SOF 400 mg 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 50 subjects with 428 plasma samples of which 151 were below the lower limit of quantitation (LLOQ). Data exploration identified 6 measurable PK samples as outliers and thus was excluded from the analysis. The remaining dataset included 145 measureable SOF concentrations from 28 subjects. The full covariate model was utilized for characterizing the disposition of SOF in this population.

The pcVPC for SOF in this study are shown in **Error! Reference source not found.**. 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 quantitation. 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 22.2% of samples above the 75th percentile, 7.6% above the 95th percentile, 32.6% below the 25th percentile, and 10.4% below the 5th percentile.

Figure 1 Prediction-Corrected VPC of SOF Plasma Concentrations



Source: Sponsor's Population pharmacokinetic report, pg 7

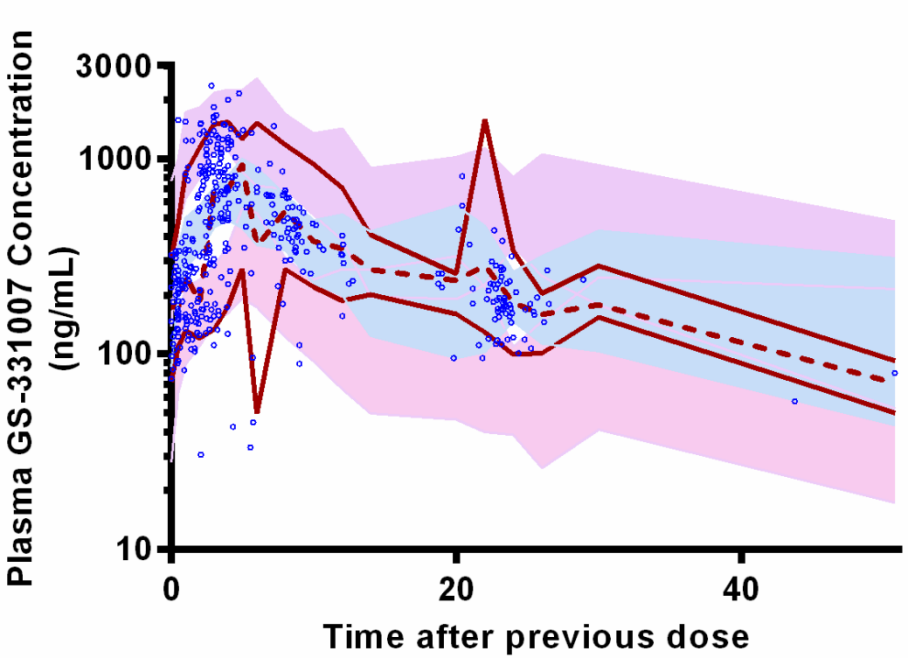
4.2.3 GS-331007 Population PK Model Results

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

In the current analysis, the GS-331007 dataset included 428 plasma samples from 50 subjects. Seven samples were below-LLOQ and data exploration identified 6 PK samples as outliers excluded from the analysis. The remaining dataset included 415 measureable GS-331007 concentrations from 50 subjects. The full covariate model was utilized for characterizing the disposition of GS-331007 in this study.

The pcVPC for GS-331007 in this study are shown in Figure 2. The pcVPC adequately described the spread in the observed data. The provided NPC showed no substantial bias with 25.1% of samples above the 75th percentile, 3.6% above the 95^{h} percentile, 29.6% below the 25th percentile, and 10.8% below the 5th percentile.

Figure 2 Prediction-Corrected VPC of GS-331007 Plasma Concentrations



Source: Sponsor's Population pharmacokinetic report, pg 15

4.2.4 Reviewer Comments:

Overall, the approaches used by the sponsor to characterize the PK for SOF and GS-331007 in adolescents were acceptable. The reviewer was able to recreate the pcVPC analyses conducted by the sponsor by taking the original adult modeling results and the provided adolescent data. As the primary purpose of this model was to characterize pediatric exposures for SOF and GS-331007 based on the population PK model, this approach was considered acceptable. The exposures from this analysis can be used for labeling or for comparison with adult exposures. A summary of the geometric (CV%) C_{max} and AUC for SOF and GS-331007 based on intensive PK and population PK results are shown below. Overall, SOF and GS-331007 exposures were comparable between adolescents and adults, though exposures were slightly higher (10-30%) in adolescents:

Parameter	Calculated from	SOF	GS-331007
AUC (hr.ng/mL)	Intensive PK (n=10 for all)	975 (70%)	8795 (28%)
	Population PK (n=28 for SOF, n=50 for others)	1062 (41%)	7573 (33%)
	Adults (Phase 2/3 Population)	814 (34%)	6864 (32%)
Cmax (ng/mL)	Intensive PK (n=10 for all)	467 (76%)	912 (41%)
	Population PK (n=28 for SOF, n=50 for others)	472 (63%)	572 (44%)
	Adults (Phase 2/3 Population)	511 (33%)	540 (42%)

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