OFFICE OF CLINICAL PHARMACOLOGY REVIEW	
NDA Numbers (SDN)	208341 (570) S-14
Link to EDR	\\CDSESUB1\evsprod\NDA208341\0123
Submission Date	09/19/2019
Submission Types	Prior Approval Efficacy Supplement
Brand Name	EPCLUSA®
Generic Name	Sofosbuvir/Velpatasvir (SOF/VEL)
Dosage Regimen	Adults: one tablet (SOF/VEL; 400/100 mg) to be taken orally once daily with or without food.
Route of Administration	Oral
Proposed Indication	Treatment of Hepatitis C Virus (HCV) infection
Applicant	Gilead Sciences, Inc.
OCP Review Team	Hazem E. Hassan, PhD, MS, RPh, FCP Jihye Ahn, PharmD, MS Justin Earp, PhD Su-Young Choi, Pharm D, PhD

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1. Executive Summary

Epclusa® tablet is a fixed-dose combination (FDC) of SOF, an HCV nucleotide analog NS5B polymerase inhibitor, and VEL, an HCV NS5A inhibitor. EPCLUSA is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection: a) without cirrhosis or with compensated cirrhosis, or b) with decompensated cirrhosis for use in combination with ribavirin. The recommended dosage in adults is one tablet (400 mg of SOF and 100 mg of VEL) taken orally once daily with or without food. The Applicant submitted a Prior Approval Efficacy Supplement to NDA 208341 in support of expanding the indication of EPCLUSA to pediatric patients 6 to <18 years. In addition, the Applicant is seeking approval for a reduced strength tablet of EPCLUSA, containing SOF/VEL 200/50mg. The proposed pediatric dosage regimens for patients 6 years or older are as follows:

Proposed Dosing for Pediatric Patients 6 Years and Older with Genotype 1, 2, 3, 4, 5, or 6 HCV

Body Weight (kg)*	Dosing of EPCLUSA	EPCLUSA Daily Dose
at least 30	one 400 mg/100 mg tablet once daily or, two 200 mg/50 mg tablets once daily	400 mg/100 mg per day
17 to less than 30	one 200 mg/50 mg tablet once daily	200 mg/50 mg per day

*The Applicant initially proposed a cut off of 35 kg. However, during the review cycle, the Applicant proposed the revised weight band. Please see Section 4.

The basis of approval of the current application is extrapolation of the efficacy from adult subjects by demonstrating comparable systemic exposures of SOF, GS-331107 (SOF major inactive metabolite), and VEL between adults and pediatric patients with HCV infection. The proposed dosage regimens were supported by PK, safety, and efficacy data from study GS-US-341-1143 in HCV infected pediatric patients. Data from Study GS-US-341-1143 was submitted as two interim clinical study reports (CSRs) organized by age groups: 12 to <18 year (Group 1, SOF/VEL 400 mg/100 mg once daily) and 6 to <12 year (Group 2 SOF/VEL 200 mg/50 mg once daily). Results from this study support the proposed dosing regimen. GS-331107 and VEL exposures in pediatric subjects were generally comparable to those observed in the adult Phase 2/3 studies. While SOF exposures were approximately 2-fold higher in pediatric patients as compared to adults, there is no new or concerning safety concerns identified in the trial.

2. Recommendations

The Office of Clinical Pharmacology has reviewed the application and determined that the submitted information supports the *approval* of this application from a clinical pharmacology perspective.

3. Labeling Recommendations

The following clinical pharmacology related information will be added in EPCLUSA® USPI:

Section 2 Dosage and Administration

Sub-Section 2.4 Recommended Dosage in Pediatric Patients 6 years of Age and Older

- Add recommended weight-based doses of EPCLUSA.
- Add recommended weight-based doses of Ribavirin (RBV) to be given in combination with EPCLUSA®.

Section 8 Specific Population

Sub-Section 8.4 (Pediatric Use)

- Add the summary of findings in study GS-US-341-1143.

Section 12 Clinical Pharmacology

Sub-Section 12.3 Pharmacokinetics

- Add PK table (under Specific Populations) to include exposure parameters of EPCLUSA® in pediatrics (6 to <18 yr and ≥17 kg) based on the findings in study GS-US-341-1143.

4. Key Review Questions

1. Are the proposed dosing regimen and weight band acceptable from a clinical pharmacology perspective?

The Applicant's proposed dosing regimen of 400/100 mg SOF/VEL for pediatric subjects weighing at least 30 kg, and 200/50 mg SOF/VEL for subjects 17 - <30 kg is acceptable from a clinical pharmacology perspective.

The Applicant initially proposed 400/100 mg SOF/VEL for subjects ≥35 kg, and 200/50 mg SOF/VEL for subjects 17 - <35 kg. At the proposed dosing regimen, higher SOF AUC_{tau} and C_{max}, but lower VEL C_{tau}, were observed in pediatric subjects weighing 17 to <35 kg in comparison to adults. For the weight band ≥35 kg, higher SOF AUC_{tau} and C_{max} were observed in comparison to adults (Table 1).

Table 1. Summary of Population Pharmacokinetic (PPK) Estimated SOF, GS-331007, and VEL Exposures in Pediatrics and Adults Stratified by Weight Bands.

Weight Band (Dose, mg)	Analyte	PK Parameter[#]	Geometric Mean[#]	Geometric Mean Ratio (90% CI) (vs. SOF/ GS-331007/VEL Exposures in Adults)
17 to <35 kg SOF/VEL (200/50) N=51	SOF	AUC_{tau}	1900	**1.60 (1.47, 1.75)**
		C_{max}	928	**1.72 (1.58, 1.87)**
	GS-331007	AUC_{tau}	10591	**0.79 (0.73, 0.84)**
		C_{max}	1021	1.22 (1.14, 1.30)
	VEL	AUC_{tau}	3246	1.23 (1.10, 1.38)
		[a]C_{max}	315	1.40 (1.23, 1.59)
		C_{tau}	28	**0.79 (0.69, 0.90)**
≥35 kg SOF/VEL (400/100) N=96	SOF	AUC_{tau}	2003	**1.69 (1.57, 1.82)**
		C_{max}	940	**1.74 (1.62, 1.89)**
	GS-331007	AUC_{tau}	12915	0.96 (0.92, 1.01)
		C_{max}	1127	1.35 (1.28, 1.41)
	VEL	AUC_{tau}	3493	1.32 (1.22, 1.44)
		[a]C_{max}	313	1.39 (1.27, 1.53)
		C_{tau}	32	0.92 (0.84, 1.02)

Source: Adapted from Applicant's submission of adhoc-tfls.pdf. Ad Hoc Table 10253.12. All values are PPK model derived values.
[#]PK parameter units: AUC_{tau}, h·ng/mL; C_{max}, ng/mL; C_{tau}, ng/mL. [a]Values derived from VEL model (run016).

The review team requested the Applicant to explore different weight bands by simulating SOF and VEL exposures to determine whether a change in weight band should be considered. Specifically, the review team's concern was low VEL C_{tau} observed in pediatric patients whose mg/kg dose is the lowest (i.e., 30 to <35 kg receiving SOF/VEL 200 mg/50 mg) (Table 2).

Table 2. VEL C_{tau} in Pediatric Subjects Weighing 30 to <35 kg

	Cohort 1 (n=4, SOF/VEL 400/100 mg)	Cohort 2 (n=8, SOF/VEL 200/50 mg)	All pediatric patients	Adult Phase 2/3 program
VEL C_{tau} (ng/mL)	51 (20%)	17 (78%)	30.1 (67%)	41.5 (65%)

*Different doses were administered based on ages per protocol. 400/100 for >12 years old and 200/50 for <12 years old regardless of weight; Values are presented as mean (CV%); PPK posthoc estimate Data source: modified from PPK CSR Data expressed as geometric mean (%CV)

Upon information request, the Applicant proposed a revised dosing regimen of 400/100 mg SOF/VEL for pediatric subjects weighing at least 30 kg, and 200/50 mg SOF/VEL for subjects weighing 17 - <30 kg (EDR Link). The Applicant stated that they proposed the revised weight band to ensure a greater proportion of subjects in the 30 - <35 kg weight range have VEL C_{tau} values within the range of those observed in the adult population. The revised weight band is expected to decrease the percentage of subjects (30 - 40 kg) with VEL C_{tau} values below the 5th percentile of adults from 14.4% to 6.5%.

The interdisciplinary review team discussed the Applicant's proposal and agreed to the Applicant's rationale. The review team acknowledged that the revised weight-band based dosing may result in an even higher SOF exposure. The Applicant's simulations indicated that the percentage of subjects (30 – 40 kg) with SOF exposures exceeding the maximum exposure value in adults would increase from 19.3% to 31.4% (AUC_{tau}) and from 34.6% to 48.9% (C_{max}) for the original and revised weight bands, respectively (*Refer to Section 7, Pharmacometrics review, for additional simulation analyses*). However, an overall benign safety profile of SOF in pediatrics and adults and the lack of any exposure-response relationship for adverse events support the use of the adult dose of SOF in pediatric patients weighing 30 to <35 kg. In addition, safety is also supported by safety data from 6 subjects in this trial who received the adult dose and whose body weight was <35 kg (subjects IDs).

Q2. What are the causes and implications of higher SOF exposures in pediatric subjects receiving EPCLUSA?

SOF exposures observed in this trial are approximately 2-fold higher than those observed in adults receiving HARVONI or EPCLUSA and pediatrics receiving HARVONI (Table 3) *(Refer to Section 7, Pharmacometrics review, for further weight-band based simulation).* The root cause of higher SOF exposure observed in this study is unknown. The Applicant indicated that there is no clear scientific explanation for the observed higher SOF exposure since there were no clear differences in the demographic and baseline characteristics in the Epclusa pediatric Study GS-US-342-1143 compared to similar age groups in the Harvoni or Sovaldi programs. The Applicant also indicated that given the favorable safety profiles observed in Study GS-US-342-1143, the observed increased SOF exposure is not clinically significant (EDR Link).

Table 3. Summary of SOF PK Parameters in Pediatrics and Adults who Received Epclusa or Harvoni.

SOF PK Parameter	Epclusa		Harvoni	
	Pediatrics[a]	Adults[b]	Pediatrics[c, d]	Adults[d]
AUC_{tau} (h*ng/mL)	2420 (78.3)	1268 (38.5)	1761 (37.6)	1380 (34.0)
C_{max} (ng/mL)	1269 (88.6)	567 (30.7)	810.6 (30.1)	659 (34.0)

All values are PPK model derived values and presented as mean (CV%); [a]Subjects 6 to <18 yr. PPK report, P. 54.; [b]From Epclusa USPI [c]Subjects 3 to <18 yr. PPK report, P. 54.; [d]From PPK report of NDA 205834 -S29 (SDN 835), Table 36, P. 75

5. Individual Study Review

Study # GS-US-341-1143*

**This review focuses only on the clinical pharmacology aspects of this trial (Please refer to clinical review regarding efficacy and safety).*

Two interim CSRs organized by age groups: Group 1: 12 to <18 yr (EDR Link) and Group 2: 6 to <12 yr (EDR Link) were submitted.

Title: A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir in Adolescents and Children with Chronic HCV Infection.

Study Period*:* 26 January 2017 - 18 April 2019 (Group 1: 12 to <18 yr). 26 January 2017 - 25 April 2019 (Group 2: 6 to <12 yr).

Objectives: Primary objectives:

a. PK lead-in phase: To evaluate the steady-state PK and confirm the dose of SOF/VEL FDC in chronic HCV infected pediatric subjects.
b. Treatment phase: To evaluate the safety and tolerability of SOF/VEL for 12 weeks in chronic HCV-infected pediatric subjects.

Trial Design: This is an ongoing Phase 2, open-label, multicohort, 2-part study to evaluate the PK, safety, and efficacy of SOF/VEL in pediatric subjects 3 to <18 yr with chronic HCV infection. This study consisted of a PK lead-in phase (Cohorts 1, 2, and 3) and a treatment phase (Groups 1 and 2) within each age group.

- Group 1 (including Cohort 1): Pediatric subjects 12 to <18 yr
- Group 2 (including Cohorts 2 and 3): Pediatric subjects 6 to <12 yr and 3 to <6 yr.
  Note: No data for pediatric subjects 3 to <6 yr were submitted in this application.

PK sampling scheme

Intensive PK lead-in Phase: blood samples were collected at Day 7 visit at pre-dose and 0.5, 1, 2, 3, 4, 6, 8, and 12 hr postdose.

Treatment Phase: a single blood sample was collected any time at Weeks 1 and 12, and 2 blood samples were collected at Weeks 4 and 8 at predose and between 15 min to 4 hr postdose.

Optional intensive PK substudy for Group 1 only: subjects who did not participate in the intensive PK lead-in phase were eligible to participate in an optional intensive PK substudy. For those subjects, blood samples were collected at Week 4 or 8 at predose and 0.5, 1, 2, 3, 4, 6, 8, and 12 hr postdose.

Main Inclusion Criteria: Males or nonpregnant females 12 to <18 yr (Group 1) or 6 to <12 yr (Group 2) with chronic HCV infection who were either HCV treatment naive or experienced.

Test Product, Dose and Mode of Administration:

Test product:

a. SOF/VEL FDC (400/100-mg tablet) (adult-strength tablet). Approved formulation.
b. SOF/VEL FDC (200/50-mg tablet) (low-dose tablet). New formulation.
c. SOF/VEL FDC (50/12.5-mg packets containing granules). New formulation*.
d. Placebo-to-match SOF/VEL FDC (400/100-mg tablet).
e. Placebo-to-match SOF/VEL FDC (200/50-mg tablet).

** The Applicant is not pursuing an approval for this formulation in this supplement.*

Dosages and formulations by age group:

1. Group 1, 12 to <18 yr: once daily oral dose of SOF/VEL 400/100 mg (as 1 × 400/100-mg FDC tablet or as 2 × 200/50-mg FDC tablets).
2. Group 2, 6 to <12 yr: once daily oral dose of SOF/VEL 200/50 mg (as 1 × 200/50-mg FDC tablet or as 4 × 50/12.5-mg packets containing granules).

Duration of Treatment: Treatment duration was 12 weeks, with 24 weeks of posttreatment follow-up.

Bioanalytical method:
All PK samples were analyzed using validated liquid chromatography-tandem mass spectroscopy (LC/MS/MS) methods. The precision and accuracy were acceptable for the calibration curve and QC runs. All samples were analyzed within the long-term storage stability duration.

Results:
Main Subject Demographics and Baseline Disease Characteristics
Group 1: 12 to <18 Years Old
One hundred and three subjects were enrolled. One subject discontinued the study due to pregnancy. Most subjects were female (51.0%), white (72.5%), and not Hispanic or Latino (81.4%), with a mean age of 15 (range: 12–17) yr. Most subjects had genotype 1 HCV infection (73.5%) or genotype 3 HCV infection (11.8 %). Most subjects were treatment naive (78.4%) and no subjects had cirrhosis. Most subjects had HCV RNA ≥ 800,000 IU/mL (57.8%) with a mean (SD) baseline HCV RNA value of 6.1 (0.59) $\log_{10}$ IU/mL. The mean (SD) baseline ALT value was 44 (35.7) U/L, and 19.6% of subjects had baseline ALT values >1.5 × upper limit of normal. The mean (SD) baseline estimated glomerular filtration rate using the Schwartz formula was 163.3 (30.05) mL/min/1.73 m^2.

Group 2: 6 to <12 Years Old
Seventy-three subjects were enrolled. Most subjects (94.5%) completed study treatment. The reasons for premature discontinuation of study treatment were AEs (2.7%, 2 subjects), investigator's discretion (1.4%, 1 subject) and lack of efficacy (1.4%, 1 subject). Most subjects were female (52.1%), white (90.4%), and not Hispanic or Latino (87.7%), with a mean age of 8 (range: 6–11) yr. Most subjects had genotype 1 HCV infection (76.7%) or genotype 3 HCV infection (15.1%). Most subjects were treatment naive (94.5%) and no subjects had cirrhosis. Most subjects had HCV RNA ≥ 800,000 IU/mL (52.1%), with a mean (SD) baseline HCV RNA value of 5.9 (0.69) $\log_{10}$ IU/mL. The mean (SD) baseline ALT value was 62 (54.7) U/L, and 35.6% of subjects had baseline ALT values >1.5 × upper limit of normal. The mean (SD) baseline estimated glomerular filtration rate using the Schwartz formula was 158.7 (24.51) mL/min/1.73 m^2.

Pharmacokinetics
Exposures of SOF, GS-331007, and VEL in the PK lead-in phases (Groups 1 and 2) were compared with PPK-derived exposure data from adult Phase 2/3 studies (Tables 4 and 5). For Group 1, higher SOF and VEL exposures (AUC_{tau} and C_{max}) were observed in comparison to adults. For Group 2, higher SOF AUC_{tau} and C_{max}, lower GS-331007 AUC_{tau}, higher VEL C_{max} and lower VEL C_{tau} were observed in comparison to adults.

Table 4. Summary of PK Lead-in Phase SOF, GS-331007, and VEL Exposures in Subjects 12 to <18 yr (Group 1) Compared with PPK-Based Exposures in the Adult Phase 2/3 Population.

Analyte	PK Parameter	(Mean [%CV])		GMR (90%CI)
		Adolescent Subjects 12 to < 18 Years Old SOF/VEL 400/100 mg (N = 16)[a]	Adult Phase 2/3 Population SOF/VEL 400/100 mg (N = 982)[b]	Adolescent Subjects/Adults Subjects
SOF	AUC_{tau} (h•ng/mL)	3020.1 (38.5)	1261.6 (37.2)	234.99 (202.93, 272.12)
	C_{max} (ng/mL)	1595.2 (48.2)	566.3 (31.4)	265.52(232.43, 303.31)
GS-331007	AUC_{tau} (h•ng/mL)	13852.9 (25.7)	13966.7 (28.0)	99.56 (89.03, 111.34)
	C_{max} (ng/mL)	1128.5 (32.3)	868.2 (27.6)	129.32 (115.37, 144.97)
VEL	AUC_{tau} (h•ng/mL)	4479.3 (47.0)	2967.3 (50.2)	150.07 (122.35, 184.07)
	C_{max} (ng/mL)	629.9 (48.3)	259.0 (53.9)	244.93 (195.31, 307.16)
	C_{tau} (ng/mL)	46.5 (48.2)	41.5 (65.0)	118.49 (93.57, 150.04)

CV = coefficient of variation; GMR (90% CI) = geometric mean ratio (90% confidence interval); PK = pharmacokinetic; SOF = sofosbuvir; VEL = velpatasvir

a Seventeen subjects were enrolled in the PK lead-in phase. One had an incident of vomiting and was excluded from the noncompartmental analysis. The exposure in this subject will be evaluated using the population PK modeling approach.

b For GS-331007 and VEL, n = 1428 and 1425, respectively.

Source: Table 15.10.1.9

Source: Interim Clinical Study Report (Group 1: 12 to <18 yr), P. 89

Table 5. Summary of PK Lead-in Phase SOF, GS-331007, and VEL Exposures in Subjects 6 to <12 yr (Group 2) Compared with PPK-Based Exposures in the Adult Phase 2/3 Population.

Analyte	PK Parameter	Mean (%CV)		GMR (90% CI)
		Pediatric Subjects 6 to < 12 Years Old SOF/VEL 200/50 mg N = 17[a]	Adult Phase 2/3 Population SOF/VEL 400/100 mg N = 982[b]	Pediatric Subjects vs Adult Phase 2/3 Population
SOF	AUC_{tau} (h•ng/mL)	1764.5 (39.1)	1261.6 (37.2)	136.93 (118.75, 157.89)
	C_{max} (ng/mL)	1330.1 (52.1)	566.3 (31.4)	218.92 (192.33, 249.19)
GS-331007	AUC_{tau} (h•ng/mL)	9913.8 (31.0)	13,966.7 (28.0)	70.98 (63.68, 79.11)
	C_{max} (ng/mL)	992.1 (28.0)	868.2 (27.6)	114.57(102.56, 127.98)
VEL	AUC_{tau} (h•ng/mL)	3697.5 (44.7)	2967.3 (50.2)	121.21 (99.35, 147.88)
	C_{max} (ng/mL)	560.1 (48.5)	259.0 (53.9)	214.85(172.42, 267.72)
	C_{tau} (ng/mL)	30.6 (66.0)	41.5 (65.0)	70.90 (56.34, 89.23)

%CV = percentage coefficient of variation; GMR = geometric mean ratio; PK = pharmacokinetic(s); SOF = sofosbuvir; VEL = velpatasvir

a Twenty subjects were enrolled in the PK lead-in phase. Three subjects erroneously received SOF/VEL 400/100 mg and were excluded from the noncompartmental analysis; the exposures in these subjects will be evaluated using the population PK modeling approach.

b For GS-331007 and VEL, N = 1428 and 1425, respectively

Source: Table 15.10.1.9

Source: Interim Clinical Study Report (Group 2: 6 to <12 yr), P. 88

- Exposures of SOF, GS331007, and VEL in subject who did not achieve sustained virological response by week 12 (SVR12).

  Subject (b) (6) did not achieve SVR12 and was considered a virologic failure (non-response) with a treatment-emergent NS5A L31V substitution. The subject was a 10 yr old white treatment-naïve female weighing 35.1 kg and received the SOF/VEL 200/50 mg dosage regimen. Subject adherence to the SOF/VEL dosage regimen was 100%. The observed VEL C_{tau} values in this subject at Weeks 4 and 8 were below the limit of quantitation. The PPK model predicted steady-state VEL C_{tau} value was noticeably lower than the respective typical population exposures (Table 6). Lower VEL C_{tau} values could possibly explain the observed virologic failure in this subject. However, it is worth mentioning that the majority of patients who had similar exposures achieved SVR12 in pediatrics and adults.

Table 6. PK Parameters of SOF, GS-331007 and VEL in Subject (b) (6)

	SOF		GS-331007		VEL		
	AUC_{tau}	C_{max}	AUC_{tau}	C_{max}	AUC_{tau}	C_{max}	C_{tau}
ID= (b) (6)	1197	1021	9049	824	1658	211	9.3
Population mean (CV%)	2420 (78.3)	1269 (88.6)	12297 (30.7)	1106.4 (28.4)	3673 (43)	334.7 (39.1)	34.9 (58.4)

PPK model derived values. Units: AUC_{tau}, h·ng/mL; C_{max}, ng/mL; C_{tau}, ng/mL
Source: PPK report, P. 54 (population mean) and P. 385 (ID= (b) (6)).

Conclusions

- Exposures of SOF, GS-331007, and VEL in the PK lead-in phases (aged based dosing) were compared with PPK-derived exposure data from adult Phase 2/3 studies. For Group 1 (12 to <18 years old, 400 mg/100 mg SOF/VEL, higher SOF and VEL exposures (AUC_{tau} and C_{max}) were observed in comparison to adults. For Group 2 (6 to <12 years old, 200 mg/50 mg SOF/VEL), higher SOF AUC_{tau} and C_{max}, lower GS-331007 AUC_{tau}, higher VEL C_{max} and lower VEL C_{tau} were observed in comparison to adults.
- The review team re-analyzed data by body weight using PPK approach (See Sections 4 and 7) and concluded that the study results support the proposed dosing regimen.

6. Data Integrity-Related Consults (OSIS Inspections)

Analytical site inspection for Study GS-US-342-1143 was not conducted by the Office of Study Integrity and Surveillance (OSIS) because inspection was conducted in January 2019, which falls within the surveillance interval. The final classification for the inspections was No Action Indicated (NAI). (Refer to Dr. Ting Wang's memorandum for details).

7. Pharmacometrics Review

The Applicant conducted population PK analysis (PPK) for sofobusvir (SOF) and velpatasvir (VEL) in pediatric subjects with HCV infection to support the proposed weight-band dosing regimen. Summaries of the dosing regimen and PK sampling for the studies included in PPK analyses are presented in Table 7. The Applicant used R (Version 3.2.3 or later) for all exploratory data analysis and NONMEM (Version 7.3.0 or later), Perl-Speaks-NONMEM (PSN), and R (version 3.2.3 or later) for the PPK analysis. The reviewer used R (Version 3.5.2) and NONMEM (Version 7.4.3). This section of review is primarily focused on the adequacy of pediatric PPK models for SOF and VEL, the acceptability of proposed dosing regimen, and evaluation of the exposure-response relationships for efficacy and safety.

Table 7. Summary of Studies Included in PK Dataset

Study	Age (years)	Dosing Regimen (mg)	Subjects with PK sampling
GS-US-334-1112	12 to < 18	**400** SOF	N=10 (PK lead-in); N=42 (sparse only)
	6 to < 12	**200** SOF	N=12 (PK lead-in); N=29 (sparse only)
	3 to < 6	**200** SOF (> 17 kg) **150** SOF (≤ 17 kg)	N=11 (PK lead-in); N=1 (sparse only)
GS-US-337-1116	12 to < 18	90/**400** LDV/SOF	N=10 (PK lead-in); N=90 (sparse only)
	6 to < 12	45/**200** LDV/SOF	N=12 (PK lead-in); N=80 (sparse only)
	3 to < 6	45/**200** LDV/SOF (>17 kg) 33.75/**150** LDV/SOF (≤17 kg)	N=14 (PK lead-in); N=8 (sparse only), N=12(Intense + sparse)
GS-US-342-1143	12 to < 18	**400**/100 SOF/VEL	N=17 (PK lead-in); N=85 (sparse only)
	6 to < 12	**200**/50 SOF/VEL	N=20 (PK lead-in); N=51 (sparse only)
Source: Applicant's Table in Synopsis, pg. 9, Report CTRA-2019-1038 EPC Peds PPK			

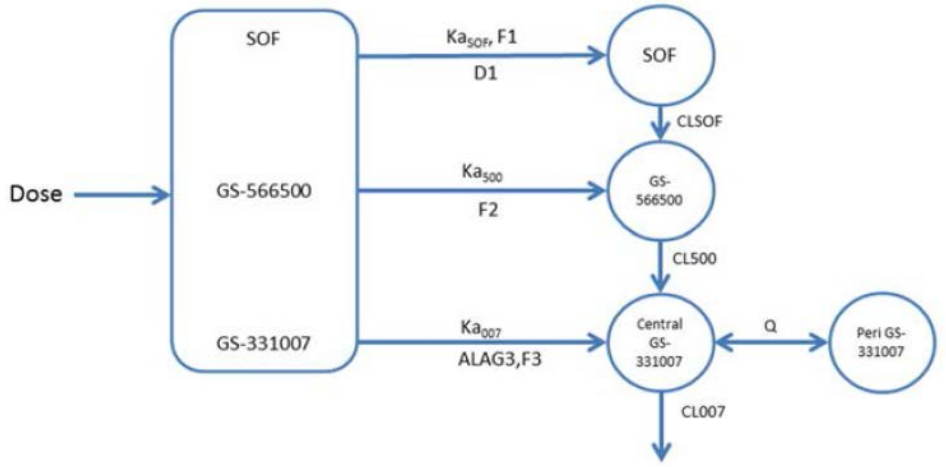
SOF Population PK Analysis in Pediatric Subjects

Population PK model for SOF and GS-331007

Previously, to support the pediatric dosing regimen for Harvoni™ (NDA205834-S29, NDA212477), the Applicant developed a parent-metabolite joint PPK model to describe the PK of SOF, and its major metabolites, GS-566500, and GS-331007, in pediatric subjects with chronic HCV infection using the data from two phase 2 studies, Study GS-US-334-1112 (SOF+RBV) and Study GS-US-337-1116 (LDV/SOF ± RBV). The Division of Pharmacometrics has previously reviewed the PPK model and found it to be acceptable. With the current submission, the Applicant further refined the PPK model and updated the PK dataset to include the PK data from the phase 2 pediatric study GS-US-342-1143 (SOF/VEL).

The structural model of the Applicant's PPK model (Figure 1) depicts that the orally administered SOF dose undergoes pre-systemic metabolism to GS-566500 (the intermediate metabolite), and subsequent metabolism to GS-331007 (the major inactive metabolite). The relative absorption for SOF, GS-566500, and GS-331007 are parametrized as to the relative absorption fraction F1, F2, and F3, respectively. A one-compartment model for SOF and GS-566500, a two-compartment model for GS-331007, and three parallel absorption compartments are incorporated. Each analyte is absorbed to the respective compartment with first-order absorption with an additional zero-order input for SOF and an absorption lag time (ALAG) for both SOF and GS-331007, followed by first-order elimination.

Figure 1. PPK Model Diagram for SOF and Covariates Included



Covariates	
Weight	CL_{SOF}, V_{SOF}, CL_{500}, V_{500}, CL_{007}, V_{007}
Age	CL_{500}, CL_{007}
Sex	CL_{007}
LDV	F1
VEL	F1
RBV	CL_{500}, CL_{007}

ALAG = absorption lag time; CL_{007} = clearance of GS-331007; CL_{500} = clearance of GS-566500; CL_{SOF} = clearance of SOF; D1 = duration of zero order input; F1 = relative fraction absorbed; Ka_{007} = first-order absorption rate constant of GS-331007; Ka_{500} = first-order absorption rate constant of GS-566500; Ka_{SOF} = first-order absorption rate constant of SOF
Source: Adapted from the applicant's Figure 1, pg. 17, Report CTRA-2019-1038 EPC Peds PPK

The apparent clearances and apparent central volumes for SOF (CL_{SOF}, V_{SOF}), GS-566500 (CL_{500}, V_{500}), and GS-331007 (CL_{007}, V_{007}) were scaled based on body weight with the allometric exponents fixed to 0.75 and 1, for clearances and volumes, respectively. Inter-individual variability (IIV) was included on CL_{SOF}, V_{SOF}, CL_{500} and CL_{007}. The applicant noted that >15% PK samples for SOF and GS-566500 were below the limit of quantification (BLQ) and as such, the M4 method in NONMEM was utilized to handle BLQ data for SOF and GS-566500 using a single importance sampling estimation approach. Final parameter estimates from the PPK model and bootstrap resampling analysis results are provided in Table 8.

Table 8. Final Model Estimates and Bootstrap Results

Parameter	Parameter Description	Estimate [RSE[a]]	Bootstrap Estimate Median [2.5th, 97.5th Percentiles]	SIR Median [2.5th, 97.5th Percentiles]
$\exp(\theta_1)$	Absorption rate for SOF (1/hr)	1.25 [2]	1.27 [1.14;1.4]	1.25 [1.19;1.3]
$\exp(\theta_2)$	Absorption rate for GS-566500 (1/hr)	0.292 [3]	0.291 [0.274;0.313]	0.292 [0.281;0.304]
$\exp(\theta_3)$	Absorption rate for GS-331007 (1/hr)	0.0225 [7]	0.023 [0.0201;0.0264]	0.0229 [0.0202;0.0268]
$\exp(\theta_4)$	Apparent oral clearance of SOF (L/hr)	304 [6]	302 [268;341]	305 [276;339]
$\exp(\theta_5)$	Apparent central volume of SOF (L)	148 [15]	154 [110;203]	156 [120;196]
$\exp(\theta_6)$	Apparent oral clearance of GS-566500 (L/hr)	811 [3]	811 [766;855]	822 [772;871]
$\exp(\theta_7)$	Apparent central volume of GS-566500 (L)	1190 [4]	1180 [1010;1370]	1180 [1110;1270]
$\exp(\theta_8)$	Apparent oral clearance of GS-331007 (L/hr)	169 [2]	167 [160;174]	166 [160;173]
$\exp(\theta_9)$	Apparent central volume of GS-331007 (L)	212 [5]	212 [180;285]	213 [190;232]
$\exp(\theta_{10})$	Apparent intercompartmental clearance of GS-331007 (L/hr)	47.6 [9]	52.2 [39.6;74.8]	49.4 [42.4;57]
$\exp(\theta_{11})$	Apparent peripheral volume of GS-331007 (L)	1030 [21]	1100 [172;1840]	1090 [707;1540]
$\exp(\theta_{12})$	Absorption duration for SOF (hr)	0.609 [7]	0.61 [0.482;0.8]	0.597 [0.507;0.688]
	F1 for SOF	1 [Fixed]	--	--
θ_{13}	F1 for GS-331007	7.18 [Fixed]	7.18 [7.18;7.18]	--
θ_{14}	Ledipasvir on F1 for SOF	0.769 [Fixed]	0.769 [0.769;0.769]	--
θ_{15}	F1 for GS-566500	5.32 [Fixed]	5.32 [5.32;5.32]	--
θ_{16}	Proportional error SD for GS-566500	0.603 [2]	0.602 [0.577;0.628]	0.602 [0.585;0.625]
θ_{17}	Proportional error SD for GS-331007	0.306 [1]	0.305 [0.292;0.317]	0.305 [0.296;0.313]
$\exp(\theta_{18})$	Absorption lag time for GS-331007	3 [2]	3 [0.5;11.5]	3.01 [2.91;3.12]
θ19	Proportional error SD for SOF	0.93 [3]	0.927 [0.888;0.968]	0.934 [0.873;0.979]
$\exp(\theta_{20})$	Oral clearance of GS-566500+RBV (L/hr)	1240 [4]	1260 [1170;1350]	1240 [1160;1360]
$\exp(\theta_{21})$	Oral clearance of GS-331007+RBV (L/hr)	188 [3]	186 [174;197]	186 [175;197]
$\exp(\theta_{22})$	Absorption lag time for SOF (hr)	0.0821 [Fixed]	0.0821 [0.0821;0.0821]	--
θ_{23}	Velpatasvir on F for SOF	1.4 [9]	1.41 [1.05;1.79]	1.42 [1.17;1.61]
θ_{24}	Age effect on clearance of GS-331007	-0.17 [19]	-0.184 [-0.24;-0.123]	-0.181 [-0.249;-0.115]
θ_{25}	Sex effect on clearance of GS-331007	0.101 [31]	0.105 [0.0521;0.16]	0.0998 [0.0417;0.163]
θ_{26}	Age effect on clearance of GS-566500	-0.239 [20]	-0.241 [-0.332;-0.163]	-0.255 [-0.341;-0.192]
ω^2_{11}	Between subject variance on clearance of SOF	80% [11]	76.7 [64.9;87.4]	80 [69.5;91.1]
ω^2_{22}	Between subject variance on volume of SOF	224% [13]	204 [151;337]	212 [190;237]
$\omega^2_{12.12}$	Between subject variance on clearance of GS-566500	32% [22]	32.3 [27.9;40.3]	33.7 [29.5;37.7]
$\omega^2_{13.13}$	Between subject variance on clearance of GS-331007	27% [9]	27.2 [25.2;29.3]	27.7 [25;29.3]

F1 = relative fraction absorbed; RBV = ribavirin; RSE = residual standard error; SD = standard deviation; SE = standard error; SIR = sampling importance resampling; SOF = sofosbuvir.

[a] RSE is defined as the SE divided by the absolute value of the estimate ($|\theta|$) × 100% for nontransformed parameters and as SE × 100% for log-transformed parameters.

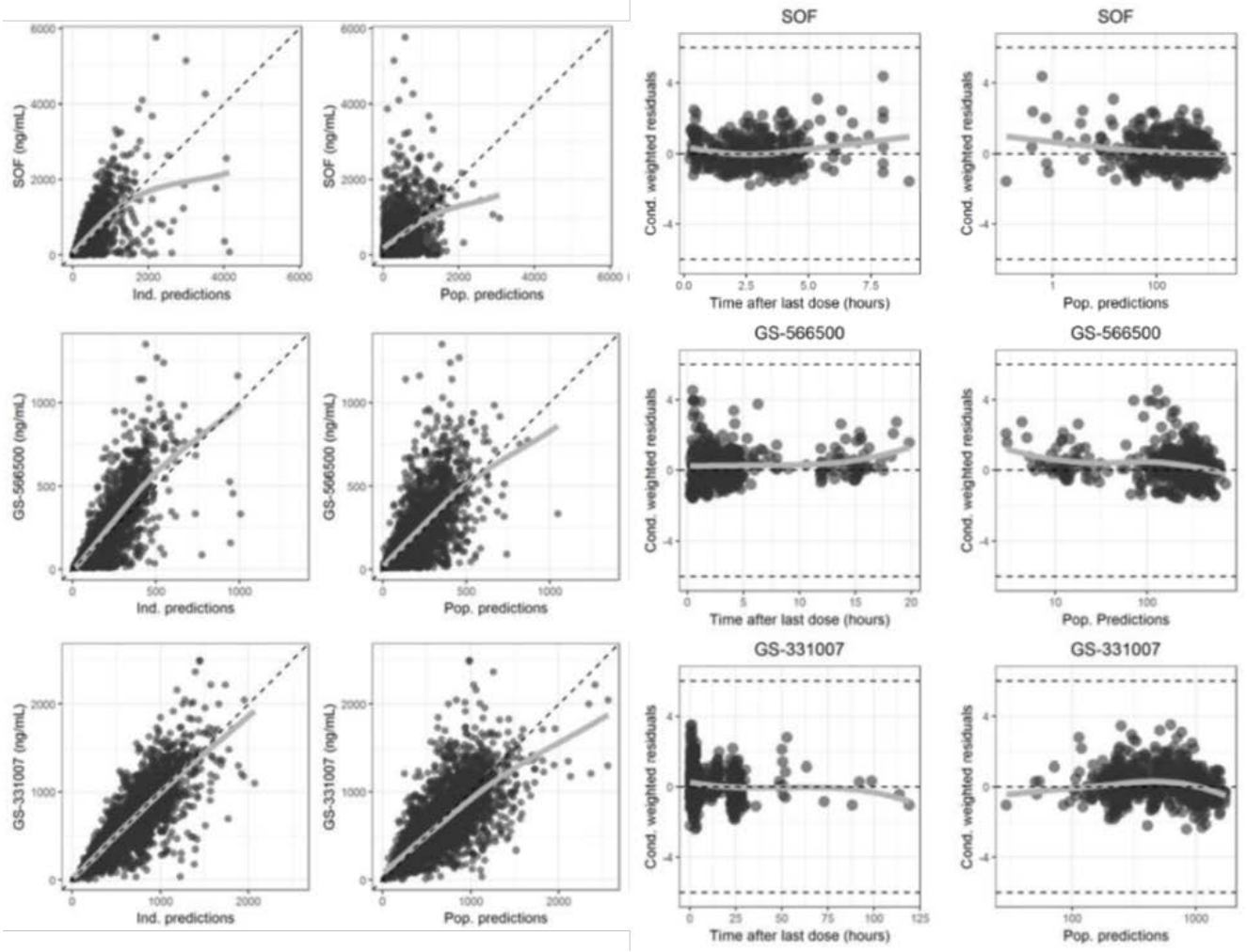
Source: Applicant's Table 15 pg. 36 in Report CTRA-2019-1038 EPC Peds PPK

Adequacy of the Applicant's model describing PK of SOF/GS-331007 in pediatric patients

The reviewer was able to reproduce the model estimation only after removing the PK data from one subject which had repeatedly caused unexpected exit from NONMEM execution. The final estimates from the reviewer's

run were consistent with the Sponsor's analysis and the removed PK data does not affect the final estimates. The reviewer found that the PPK model describes the PK of SOF, GS-566500, and GS-331007 and is acceptable for simulations to predict exposure in pediatric subjects. The parameters were estimated with acceptable precision. Biases or trends were not identified in GOF plots for SOF, GS-566500, and GS-331007 (Figure 2). Shrinkage for IIVs were <30%. The interindividual variability in PK parameters were 80%, 224%, 32%, and 27% CV for CLSOF, VSOF, CL500, and CL007, respectively.

Figure 2. Goodness of Fit Plots for Applicant's Final Model for SOF, GS-566500, and GS-331007



Source: Applicant's Table 6 and Table 7, pg. 30-31 in Report CTRA-2019-1038 EPC Peds PPK

SOF and GS-331007 Exposure and Covariates

The Applicant's sensitivity analyses suggested that WT was the most influential covariate on SOF and GS-331007 exposures. The steady state AUC for both SOF and GS-331007 ranged from + 101% to -38% for the subjects with extreme body weights, 18.1 kg and 87.6 kg, compared to a typical subject with a body weight of 46 kg. SOF exposure is estimated to be 140% higher when administered as SOF/VEL compared to when administered as SOF alone in pediatric subjects. Also, SOF exposure administered as SOF/VEL is higher compared to when administered as SOF/LDV. The comparison of SOF exposures across the different programs for SOF containing products is summarized in Section 4 of this review.

VEL Population PK Analysis for Pediatric Subjects

Population PK model for VEL

The Applicant initially submitted a pediatric PPK model (run016) for VEL based on the PK data from HCV-infected pediatric subjects (n=153) in a phase 2 study, GS-US-342-1143.In examining the GOF plots (refer to PPK report, Figure13, page 48), the reviewer noted the model tends to underpredict the plasma VEL concentrations at higher concentration values, while the model adequately described the observed data at lower concentration levels. The reviewer examined the individual concentration-time profile overlaying the observed and the predicted concentration and noted the Applicant's final model (run016) does not adequately capture the observed C_{max} values from the intense PK sampling data. The mean values for C_{max} derived from the model (314 ng/mL) was about 40% lower than those derived from the subjects from the PK-lead in phase (529 ng/mL).

The review team issued an IR for the Applicant to re-evaluate the performance of the final model (run016). The Applicant responded by submitting the updated VEL PPK model (run103) (Refer to "Response to FDA Clin Pharm Request on S-014 dated 11/5/2019). The final updated model was a 2-compartment model with a sequential zero/first-order absorption model and used untransformed data. The final parameter estimates (run103) are listed in Table 9.

Table 9. Model of VEL (Run103), Parameter Estimates, Bootstrap Resampling Results

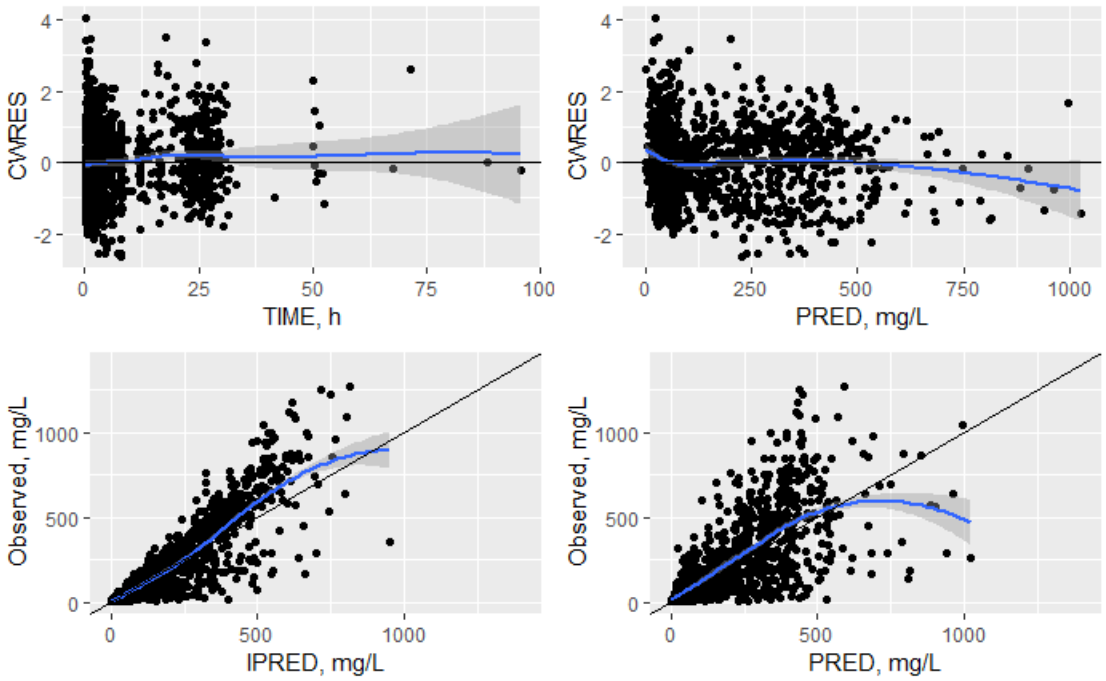
	Model Estimates	Bootstrap Estimates	
		Median [95% CI]	IIV (CV%)
CL/F (L/h)	22.9	22.7 [20.6-25.7]	38%
Vc/F (L)	113	114 [85.2-141]	40%
Q/F (L/h)	6.4	6.5 [3.36-9.63]	-
Vp/F (L)	80.6	85.2 [55.4-406]	-
Ka (1/h)	0.82	0.83 [0.57-1.06]	91%
D1 (h)	2.06	2.06 [1.78-2.35]	-
prop err	0.48	0.48 [0.44-0.51]	-
add err	5.72	5.50 [0.27-8.43]	-

Source: Reviewer's analysis. Bootstrap estimates were based on only the successful runs (n=390) from a nonparametric bootstrap (n=500)

Adequacy of the final model (run103) describing VEL PK in pediatric patients

Most parameters for the updated model (run103) were estimated with acceptable precision. RSE (%) of the Ka estimates were relatively high (~62%). IIV for Ka was as high as 91% which was anticipated as incorporating a zero/first order absorption to fit the C_{max} provided more flexibility within the absorption phase. The reviewer's bootstrap estimates of median values were consistent with the model estimates (Table 9). GOF plots (Figure 2) did not show an obvious bias in model predictions, except that the model tends to slightly underpredict the higher concentrations. The updated model (run103) estimated C_{max} values closer to the observed values compared to the initial model (run016).

Figure 3. Goodness of Fit Plots for Applicant's Final Model (Run103)



Source: Reviewer's analysis.

The reviewer recognized that the underprediction of C_{max} from both models may not be due to the PPK model structure but due to the high intra-individual variability of concentrations which were measured from intense or sparse PK sampling. Within the same subjects, the concentration values are highly variable, especially at 0-5 hours post dose, and the model predictions lay in general between those two measurements. Therefore, the reviewer opines that both models (run016 and run103) still can be used to derive PK parameters, AUC_{tau} and C_{tau}. For the simulations and deriving model predicted PK parameters for the labeling, the updated model (run103) will be used as the model predictions are closer to the intense PK sampling data.

VEL Exposure-Covariates

The Applicant's sensitivity analyses identified baseline body weight (WT) as the only influential covariate on VEL exposures: the steady state AUC ranged from -40% to +75%, and the steady state C_{tau} ranged from -41% to 81% for the subjects with extreme body weights, 87.6 kg and 18.1 kg, compared to a typical subject with a body weight of 46 kg.

Exposure-Response

Exposure - Efficacy

The Applicant did not perform the E-R analysis for efficacy due to high response rate. The key efficacy endpoint was SVR12, defined as HCV RNA < LLOQ at 12 weeks after discontinuation of study drug. Among the pediatric subjects 6 to < 18 years old who enrolled in the Study, a total of 10 subjects out of 173 subjects did not achieve SVR12, among whom only 1 subject had on-treatment virologic failure (nonresponse). Any inference for exposure-efficacy relationship is not feasible.

Exposure - Safety

The Applicant compared SOF and VEL exposures by the presence or absence of most commonly reported adverse events (AEs) for each age group. Evaluated AEs included headache, fatigue, and nausea for the age group 12 to <18 years old, and vomiting, cough, and headache for the age group 6 to <12 years old. The Applicant's summary suggested the exposures were similar between subjects with the presence or absence of the evaluated AEs. The reviewer performed univariate logistic regressions for the AEs with the exposure metrics AUCss and C_{max} for SOF, GS0331997, and VEL. No apparent relationships between exposure and the AEs above were noted.

Pediatric SOF/VEL Exposure with the Proposed Dosing Regimen

The reviewer conducted a series of simulations to evaluate the newly proposed dose with weight band with 30 kg cutoff would provide comparable exposure of SOF and VEL to those in adults using the Applicant's PPK model for SOF, and Monte Carlo simulation. A pediatric population (50 males and 51 females) was generated by sampling from NHANE (2015-2016) data, so that the age of the generated population ranged from 5 to <18 years old and the body weight of the population ranged from 16.7 kg to 125 kg. PK profiles for the generated population (n=10100) were simulated following administration of SOF/VEL per the proposed weight-band dosing regimen. The simulation results are presented (*Figure 3*, *Figure 4*, *Figure 5*) with a summary of the PK parameters for the weight groups.

SOF exposure is highly variable in pediatric subjects as anticipated based on PPK analysis for SOF, hence it is presented in log scale (Figure 3). SOF exposure is estimated to be overall higher in pediatric subjects receiving the proposed dose compared to those in adults. The higher SOF exposures are more pronounced in the subjects with body weight approaching but greater than 30 kg receiving 400/100 mg. More than 25% of subjects in the weight groups (30 to < 35 kg) and (35 to <45 kg) are expected to have higher AUCss than the maximum AUCss value observed in adults. C_{max} of SOF in pediatric subjects is overall higher than those observed in the adult population. Across the all weight groups, more than 25% of subjects in each weight group are likely to have higher C_{max} than the maximum observed in adults. In the weight group (30 to <35 kg), nearly 50% of subjects are likely to have C_{max} greater than the maximum observed C_{max} in adults.

GS-331007 exposure is highly variable in pediatric subjects, hence the values in graphs are presented in log scale (Figure 4). With the proposed dosing regimen, the simulated AUC_{ss} values are contained within those observed in the adult population. The simulated C_{max} values are generally higher in pediatric subjects across the evaluated weight range.

VEL exposure AUC_{ss} and C_{max} in pediatric patients across the weight range (15 to 50 kg) are expected to be higher than those observed in adults (Figure 5). However, the simulated AUC_{ss}, C_{max}, C_{tau} values are mostly contained within those observed in the adult population. The subjects in the weight group (25 to < 30 kg) are expected to have the lowest VEL exposure compared to other weight groups. The simulation suggests that the proposed dosing regimen would provide similar C_{tau} in this weight group as those observed in adults.

Figure 4. Simulated SOF Exposure by Weight Groups (log scale)

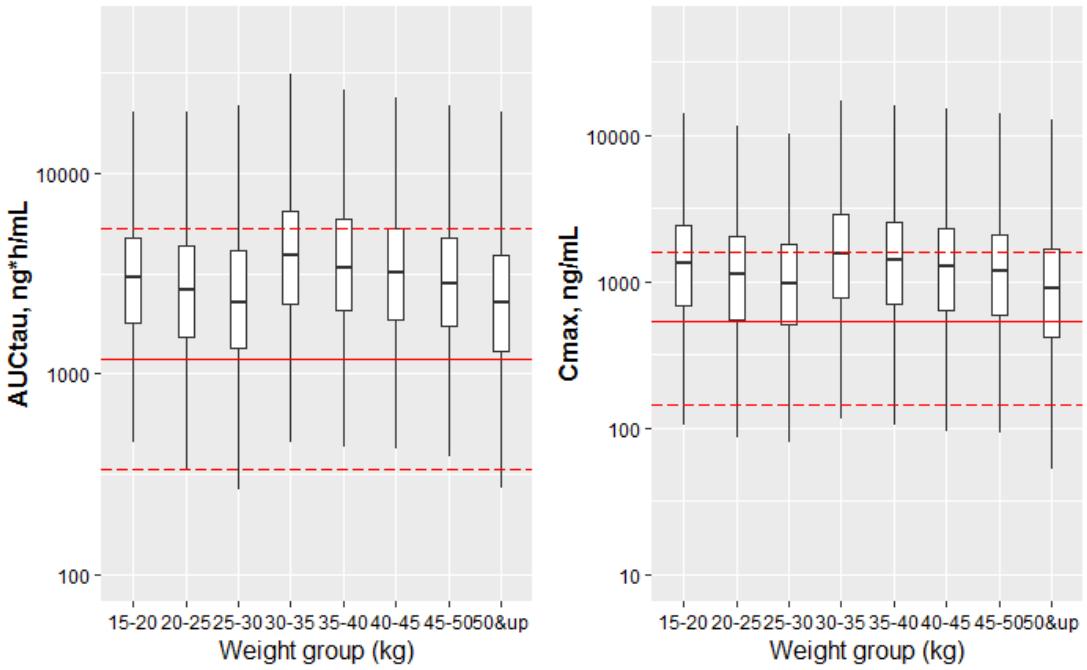


Figure 5. Simulated GS-331007 Exposure by Weight Groups (logscale)

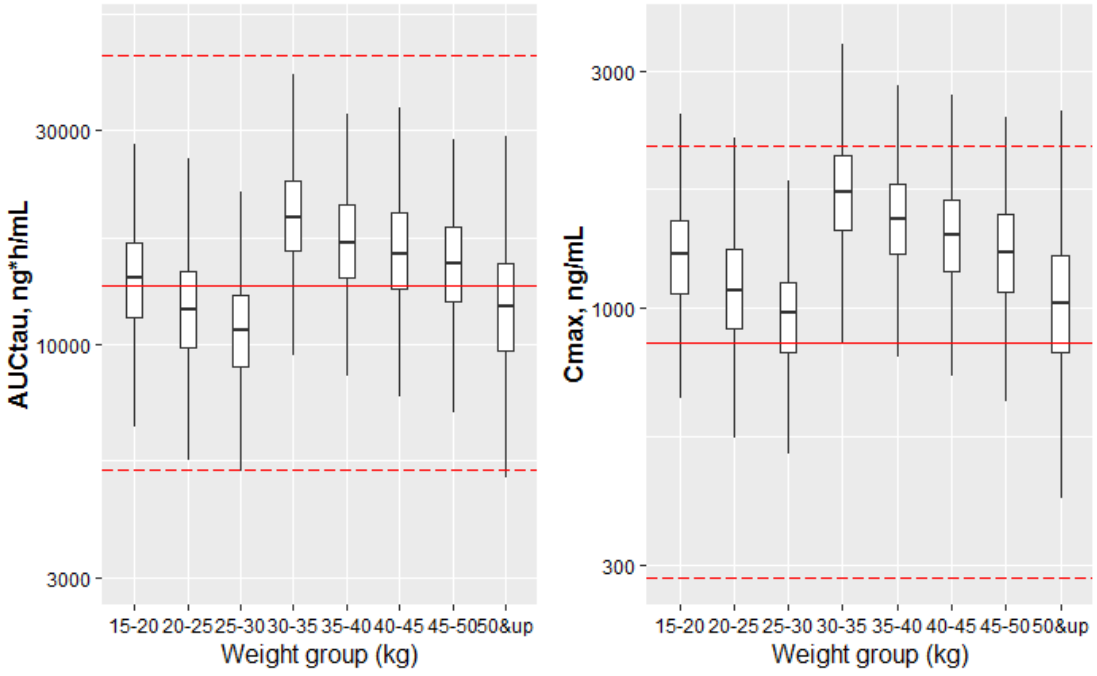
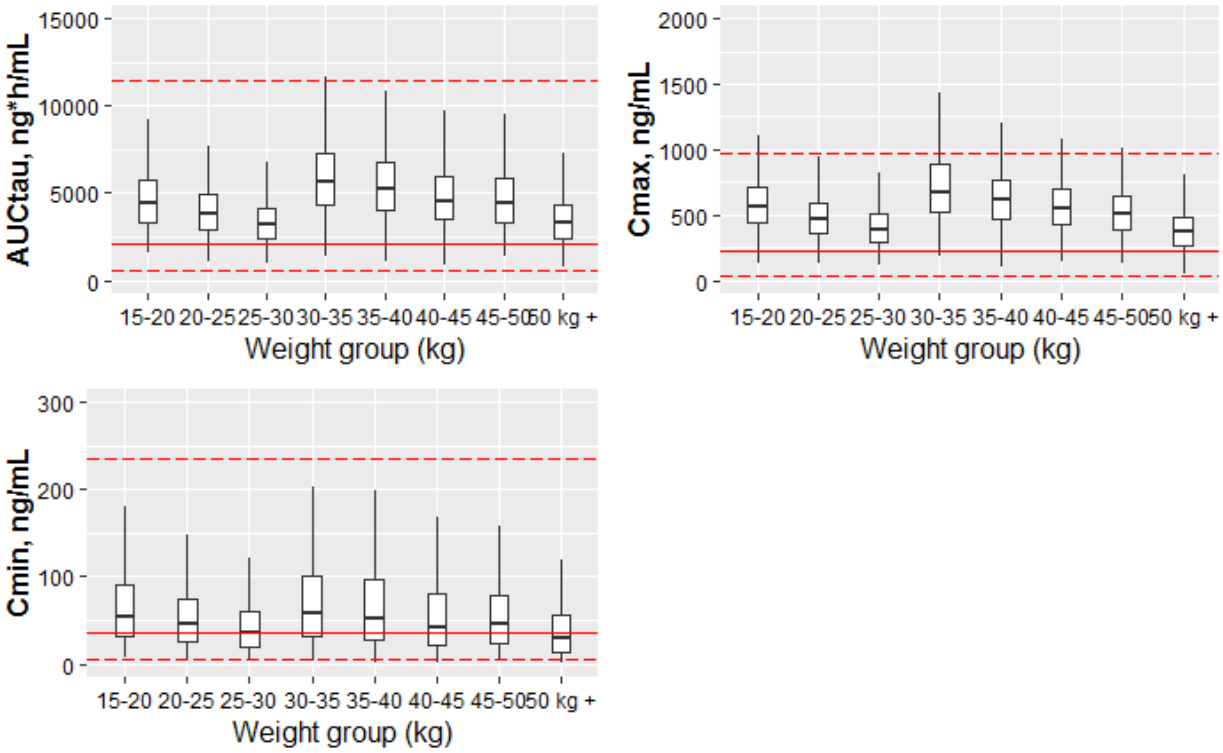


Figure 6. Simulated VEL Exposure by Weight Groups (Note: linear scale)



Source: Reviewer's analysis. For each box, the bottom and top edges represent the 25th and 75th percentiles, respectively. Red solid lines represent median values for each metric (AUC or C_{max}) estimated for adults in Epclusa program. Red dotted lines represent maximum, minimum values for each metric estimated for adults in Epclusa program.

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/s/

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