OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW

NDAs(Supplement Number)	214187(original), 208341(S-17)
Link to EDR	NDA214187 - (0001), NDA208341 - (0156)
Submission Date	12/15/2020
Submission Type	Priority
Brand Name	Epclusa
Generic Name	Sofosbuvir/Velpatasvir
Dosage Form and Strength	Oral Pellets; 200/50 mg & 150/37.5 mg
Proposed Indication	Treatment of chronic hepatitis C in pediatrics.
Applicant	Gilead Sciences, Inc.
Associated INDs	IND118605, IND115670, IND106739
OCP Review Team	Abhay Joshi, Elyes Dahmane, Jihye Ahn, Jenny Zheng

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1. EXECUTIVE SUMMARY

This submission is an original NDA for a new oral EPCLUSA® pellets (also referred as granules) proposed to be used for the treatment of hepatitis C virus (HCV) infection in pediatric patients (HCV patients). EPCLUSA® is a fixed combination drug product for sofosbuvir (SOF) and velpatasvir (VEL). SOF is a HCV nonstructural protein 5B (NS5B) polymerase inhibitor and VEL is an HCV NS5A inhibitor. Two SOF/VEL fixed dose combination tablet formulations (400 mg/100 mg and 200 mg/50 mg tablets) are currently approved by the FDA for the treatment of adults and pediatrics 6 years of age and older or weighing at least 17 kg with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis, with compensated cirrhosis, or with decompensated cirrhosis. For patients with decompensated cirrhosis, EPCLUSA's use is recommended in combination with ribavirin.

This submission is also in accordance to a Post Marketing Requirement (PMR 3092-2) under the Pediatric Research Equity Act (PREA) for NDA 208341 (EPCLUSA, SOF/VEL tablets). The PMR was to conduct a study to evaluate the pharmacokinetics, safety, and treatment response (using sustained virologic response) of SOF/VEL in pediatrics 3 years to 12 years with chronic HCV infection.

With this submission, the Applicant proposes to extend the indication for EPCLUSA for pediatric HCV patients down to 3 years of age and proposes revisions to the currently recommended pediatric dosing regimen as summarized in **Table 1**. The Applicant also proposes revisions to pharmacokinetic information included in the clinical pharmacology sections of EPCLUSA labeling. The Applicant's proposals are being supported based on the findings from:

- A Phase 2 study (Study GS-US-342-1143) that evaluated the safety and efficacy of the currently approved SOF/VEL tablet formulations and the to-be-marketed pellet formulation in adolescents and children with chronic HCV
- A Phase 1 relative bioavailability study (Study GS-US-342-1142) that compared the to-be-marketed SOF/VEL pellet formulation (at the 400/100 mg dose; under fasted and fed conditions) to the approved 400 mg/100 mg tablet formulation in healthy adults
- An updated population PK (POP-PK) analysis (Report CTRA-2020-1044) that characterized and estimated individual exposures of SOF, SOF metabolites (GS-331007, GS-566500), and VEL in the pediatrics.

Table 1: The Approved Dosage and the Applicant's Proposed Changes (in red) for Pediatrics

Dosing for Pediatric Patients 3~~6~~ Years and Older ~~or Weighing at Least 17 kg~~ with Genotype 1, 2, 3, 4, 5, or 6 HCV Using EPCLUSA Oral Pellets or Tablets

Body Weight (kg)	EPCLUSA Daily Dose	Dosing of EPCLUSA Oral Pellets	Dosing of EPCLUSA Tablet
less than 17	150 mg/37.5 mg per day	one 150 mg/37.5 mg packet of pellets once daily	N/A
17 to less than 30	200 mg/50 mg per day	one 200 mg/50 mg packet of pellets once daily	one 200 mg/50 mg tablet once daily

Body Weight (kg)	EPCLUSA Daily Dose	Dosing of EPCLUSA Oral Pellets	Dosing of EPCLUSA Tablet
at least 30	400 mg/100 mg per day	two 200 mg/50 mg packets of pellets once daily	one 400 mg/100 mg tablet once daily[a] ~~or~~ ~~two 200 mg/50 mg tablets once daily~~

N/A: Not applicable.

a. Two 200 mg/50 mg tablets once daily can be used for patients who cannot swallow the 400 mg/100 mg tablet.

Source: Adapted from the annotated draft label submitted by the Applicant

The key clinical pharmacology review issues are listed below:

(1) Interchangeability between tablets and pellets
(2) SOF/VEL dosing regimen for pediatric HCV patients ≥ 3 years
(3) Labeling revisions to the clinical pharmacology sections

1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information provided by the Applicant in NDA214187 as well as NDA208341 and recommends approval for the new EPCLUSA oral pellet formulation.

1.1. Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1. Interchangeability Between Tablets and Pellets

The Applicant proposes interchangeable use of tablets and pellets and this proposal is primarily supported by the findings from a Phase 1 relative bioavailability study (Study GS-US-342-1142). The Phase 1 study compared the to-be-marketed SOF/VEL pellet formulation to the currently approved SOF/VEL tablet formulation (400/100 mg) in healthy adults. The findings from Study GS-US-342-1142 show that the exposures to SOF, GS-566500, GS-331007, and VEL from the to-be-marketed SOF/VEL pellet formulation was comparable to the SOF/VEL tablet formulation under fasted conditions. The comparison of exposures was based on the determination if geometric least-squares mean (GLSM) and associated 90% confidence intervals (CI) for drug exposure parameter estimates (AUC and Cmax) contained within the traditionally used boundaries of 80% to 125% for bioequivalence studies. The AUC estimates for SOF were also comparable between the SOF/VEL pellet and tablet formulations, however, the mean of SOF Cmax estimate from the SOF/VEL pellet formulation was approximately 20% lower compared to the tablet formulation (GLSM ratio: 0.8, 90% CI: 0.72-0.9). The reduced SOF Cmax from the new pellet formulation is not expected to be clinically relevant for the pediatric patients ≥ 3-6 years of age. The Applicant proposes that the SOF/VEL pellet formulation can be administered without regard to

food. The Applicant's proposal is based on the findings from Study GS-US-342-1142 that assessed the effect of food on the systemic exposure to SOF, GS-331007, GS-566500, and VEL following the administration of a single SOF/VEL dose of 400/100 mg after a high fat meal in healthy adult subjects. Given that the currently approved tablet formulations are recommended to be taken with or without food, the findings reported on food-effect for pellet formulation from Study GS-US-342-1142 were compared against the reported findings on food-effect for tablet formulation in the Clinical Pharmacology Biopharmaceutics Review (**Link**). The comparison shows that the food-effect on the PK of SOF/VEL is comparable between the new pellet formulation and the approved tablet formulation (**Table 6**). Therefore, the Applicant's proposal that the to-be-marketed SOF/VEL pellet formulation can be administered without regard to food is acceptable. It is noteworthy that in Study GS-US-342-1143, which evaluated the safety and efficacy of the new pellet formulation, SOF/VEL doses were administered in pediatric patients without regard to food. Please refer to **Section 3.2** for additional details on Study GS-US-342-1142 findings.

An inspection for the bioanalytical sites was also requested for Study GS-US-342-1142 and Study GS-US-342-1143. The Office of Study Integrity and Surveillance (OSIS) concluded that an inspection of the analytical site is not warranted at this time (OSIS review, Non Responsive dated (b) (4)). The bioanalytical site (b) (4) for Studies GS-US-342-1142 and GS-US-342-1143 was inspected in (b) (4) (OSIS review, Non Responsive) and the final classification was NAI. The OSIS reviewer concluded "…the data from the audited studies are reliable to support a regulatory decision." Therefore, we determined that the favorable inspection results at the bioanalytical site under Non Responsive can be applied to this submission and we accept PK results from the abovementioned studies.

2.2. SOF/VEL Dosing Regimen for Pediatric Patients ≥ 3 Years

The results from the Applicant's population PK analysis and simulations suggest that the proposed weight band-based dosing regimen of 150 mg/37.5 mg once daily for SOF/VEL in pediatric patients with body weight < 17 kg is appropriate. The proposed regimen provides exposure comparable to the exposure expected from the already approved dosing in pediatric patients with body weight ≥17 kg and within the range of the observed exposures in adults. Please see **Section 3.4** for additional details.

2.3. Proposed Labeling Changes

The Applicant proposed labeling changes related to clinical pharmacology aspects are summarized in **Table 2** below along with the clinical pharmacology assessments.

Table 2: Prescription Drug Labeling Changes (Selected)

Summary of Significant Labeling Changes		
Section	**Applicant Proposed Changes**	**Clinical Pharmacology Assessment**
INDICATIONS AND USAGE	- Lower the minimum age for treatment eligibility from 6 years to 3 years and remove lower weight cutoff of at least 17 kg	The proposed changes are acceptable. See **Section 2.2** for additional details.
DOSAGE AND	- Corresponding changes to align with INDICATIONS	The proposed changes

ADMINISTRATION	AND USAGE - Proposed a new dosing regimen (to-be-administered with the pellet formulation) for patients weighing less than 17 kg - Proposed interchangeable use of pellets with tablets for patients weighing 17 kg or greater	are acceptable. See **Sections 2.1 and 2.2** for additional details.
CLINICAL PHARMACOLOGY	- Inserted new pharmacokinetic information for the EPCLUSA components in pediatric patients weighing less than 17 kg - Proposed revisions to pharmacokinetic information for the EPCLUSA components in pediatric patients weighing 17 kg or greater	The proposed changes are acceptable. See **Section 2.2** for additional details.

3. APPENDICES[1]

Note: The following is the summary of individual study reports that support the OCP review. The conclusions drawn by the Applicant are listed at the end of individual study summary. The Applicant's conclusions are found to be reasonable by the Reviewer unless noted otherwise in a Reviewer's Assessment section.

3.1. Summary of Bioanalytical Method Validation and Performance

Table 3: Summary of Bioanalytical Method Validation and Performance

Method/Report	**Findings**	
Study: GS-US-342-1142		
Analyte/assessment	SOF, GS-566500, GS-331007, and VEL	
Method	LC-MS/MS	
Matrix	Human plasma (K_2EDTA)	
Validation reports	Validation report provided Report (b) (4) 60-1323 (b) (4) for SOF, GS-566500, GS-331007 Report (b) (4) 60-1393 (b) (4) for VEL	☒ Yes ☐ No
	Validation report acceptable *Note: Report (b) (4) 60-1323 Amendment 5 and prior amendments of the Report (b) (4) 60-1393 were reviewed during* Non Responsive *deemed these reports acceptable. Report (b) (4) 60-1393 (b) (4) was reviewed from a clinical pharmacology perspective.*	☒ Yes ☐ No

[1]The new SOF/VEL oral pellets formulation is noted as the granule formulation interchangeably throughout the NDA submission. Therefore, for the purpose of this review, pellets and granules terms are used interchangeably.

Performance reports	Performance reports provided (b) (4) 60-1708A for SOF (GS-7977), GS-566500, GS-331007 (b) (4) 60-1708B for VEL	☒ Yes ☐ No
	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
Inspection	Will an inspection for bioanalytical site be requested?	☒ Yes ☐ No
Study: GS-US-342-1143		
Analyte/assessment	SOF, GS-566500, GS-331007, and VEL	
Method	LC-MS/MS	
Matrix	Human plasma (K_2EDTA)	
Validation reports	Same as Study: GS-US-342-1142	
Performance reports	Performance reports provided (b) (4) 60-1672A for SOF (GS-7977), GS-566500, GS-331007 (b) (4) 60-1672B for VEL	☒ Yes ☐ No
	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
Inspection	Will an inspection for bioanalytical site be requested?	☒ Yes ☐ No
Source: Compiled by the Reviewer		

[#]Note: A request for biopharmaceutical inspections was sent to the Office of Study Integrity and Surveillance (OSIS). OSIS determined that inspections are not warranted because the sites pertaining to these studies were inspected by OSIS in (b) (4) *which falls within the surveillance interval. The final classification for the inspections in* (b) (4) *was No Action Indicated (NAI).*

3.2. GS-US-342-1142

Overview:

This was a Phase 1 pharmacokinetic study that assessed the relative bioavailability (BA) of sofosbuvir (SOF), SOF metabolites (GS-331007 and GS-566500), and velpatasvir (VEL) from the to-be-marketed granule formulation and compared to the tablet formulation following administration of a single SOF/VEL dose of 400/100 mg in healthy adult subjects under fasted conditions. The study also assessed the effect of food on the systemic exposure to SOF, GS-331007, GS-566500, and VEL following administration of a single SOF/VEL dose of 400/100 mg granule formulation after a high fat meal in healthy adult subjects.

The study evaluated the following treatments in a cross-over manner separated by 9-10 days:

Treatment A: Single dose of SOF/VEL tablet 400/100 mg (1 X 400/100 mg tablet) administered under fasted conditions

Treatment C: Single dose of SOF/VEL granules 400/100 mg (8 X 50/12.5 mg packets) administered under fasted conditions

Treatment G: Single dose of SOF/VEL granules 400/100 mg (8 X 50/12.5 mg packets) administered under fed conditions (high-fat meal)

Prior to administering each treatment, subjects fasted overnight for a minimum of 10 hours except for Treatment G. For Treatment G, subjects started the standardized meal approximately 30 minutes prior to drug administration and complete it within
5 minutes of dosing. The composition of meal contained total 1000 calories (~50% from fat).

In total, 56 subjects were randomized and 38 (68%) were male, 35 (63%) were white, and 42 (75%) were Hispanic or Latino. All subjects completed the study and were included in the safety as well as PK analysis. The age and weight of enrolled patients ranged between 19 to 45 years and between 49 to 97 kg.

The patients remained at the study center up to Day 24 post-dose. For PK assessments, 17 blood samples were collected between pre-dose to 120 hours post-dose. SOF, GS-566500, GS-331007, and VEL concentrations in plasma were measured using validated LC-MS/MS methods.

Pharmacokinetic Results:
Plasma concentrations of all four analytes were analyzed using noncompartmental analysis to derive PK parameter estimates reported in **Table 4.** Exposure parameter estimates (Cmax and AUC) for all analytes from Treatment C (granules 400/100 mg fasted) were compared against the estimates from Treatment A (tablet 400/100 mg fasted) (**Table 5**). In addition, exposure parameter estimates (Cmax and AUC) for all analytes from Treatment G (granules 400/100 mg fed) were compared against the estimates from Treatment C (granules 400/100 mg fasted) (**Table 5**). Comparison between administration of tablet and granule formulation under fasting conditions showed that Cmax and AUC estimates following a single 400/100 mg dose were comparable for all analytes except for SOF, which had approximately 20% lower Cmax with the lower bound of 90% confidence interval (CI) at 72% (**Table 5**). When granules formulation was administered with high-fat meal, Tmax was delayed by approximately one hour (**Table 4**) for all analytes. The mean estimates for Cmax for SOF, GS-566500, GS-331007, and VEL under fed condition were 105%, 119%, 64%, and 101%, respectively, compared to estimates under fasted condition (**Table 5**). The mean estimates for AUC_{last} for SOF, GS-566500, GS-331007, and VEL under fed condition were 168%, 154%, 104%, and 122%, respectively, compared to estimates under fasted condition (**Table 5**).

Table 4: Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for SOF, GS-566500, GS-331007, and VEL (N=56)

Treatment (Formulation-Meal condition)	$AUC_{0\text{-}t.last}$ (ng·h/mL)	C_{max} (ng/mL)	$T_{max}^{a,b}$(h)	$T_{1/2}^{b}$(h)
SOF				
A (Table-Fasting)	1730.4 (54.5)	1474.6 (49.9)	0.75 (0.5-4)	0.49 (32,n=49)
C (Granules-Fasting)	1598.3 (45.6)	1171.8 (44.8)	1 (0.5-3)	0.53 (60,n=47)
G (Granules-Fed)	2494.5 (36.1)	1194.1 (43.0)	2 (0.5-4)	0.65 (29, n=42)
GS-566500				
A (Table-Fasting)	1912.3 (37.2)	491.8 (39.1)	2 (1-4)	2.09 (11)

Treatment (Formulation-Meal condition)	$AUC_{0\text{-}t.last}$ (ng·h/mL)	C_{max} (ng/mL)	$T_{max}^{a,b}$(h)	$T_{1/2}^{b}$(h)
C (Granules-Fasting)	1868.2 (35.4)	468.8 (35.5)	2 (1-4)	2.05 (9)
G (Granules-Fed)	2719.5 (19.0)	530.1 (21.2)	3 (1.5-6)	2.38 (11)
GS-331007				
A (Table-Fasting)	11077.1 (25.6)	910.3 (29.2)	3 (1-6)	28.49 (18)
C (Granules-Fasting)	11315.9 (23.9)	988.2 (24.4)	2.5 (1-4)	27.78 (28)
G (Granules-Fed)	11678.3 (22.0)	621.9 (20.3)	4 (2-6)	28.88 (13)
VEL				
A (Table-Fasting)	4068.8 (62.4)	497.3 (57.9)	3 (1.5-6)	17.16 (26)
C (Granules-Fasting)	3740.3 (56.5)	476.5 (51.9)	3 (1.5-4)	16.44 (25)
G (Granules-Fed)	3906.8 (44.0)	407.1 (32.8)	4 (1.5-6)	17.83 (26)

a: Median [Range], b: From Reviewer's analysis, h: Hours
Source: Adapted from Study GS-US-342-1142 report

Table 5: Summary of the Bioavailability Assessment

Parameters	% Point Estimates (90% Confidence Interval)	
	C (Granules-Fasting)/A (Tablet-Fasting)	G (Granules-Fed)/C (Granules-Fasting)
SOF		
AUC_{last}	94 (86 - 102)	168 (151 - 187)
C_{max}	80 (72 - 90)	105 (91-121)
GS-566500		
AUC_{last}	97 (92-103)	154 (142-167)
C_{max}	96 (89-102)	119 (109-129)
GS-331007		
AUC_{last}	102 (100-105)	104 (100-108)
C_{max}	109 (104-115)	64 (61-67)
VEL		
AUC_{last}	94 (82-107)	122 (101-148)
C_{max}	97 (86-110)	101 (85-120)

Source: Adapted from Study GS-US-342-1142 report

Applicant's Conclusions:

- Systemic exposure to VEL and GS-331007 were similar/comparable after administration of the SOF/VEL granule and tablet formulations.
- SOF and GS-566500 exposures were also comparable between the granule formulation and the tablet formulation.
- The effect of food on the PK of the SOF/VEL granule formulation is similar to that observed with the approved tablet formulation (EPCLUSA®), *hence, SOF/VEL granules can be administered without regard to food.*

Reviewer's Assessments:

- *The Applicant concludes that SOF exposures were comparable between the granule formulation and the tablet formulation. On average, SOF had approximately 20% lower Cmax with the lower bound of 90% confidence interval (CI) at 72% and the observed 20% lower Cmax is not expected to be clinically relevant.*
- *The study report notes that the meal contained total 1000 calories with ~50% calories from fat, however, the report did not include information on the meal's proteins or carbohydrates contents.*
- *The Applicant concludes that the food-effect on the PK of the SOF/VEL granule formulation is similar to that observed with the approved tablet formulation (EPCLUSA® 2017). This conclusion is reasonable based on the comparison of (A) the observed food-effect for the new granule formulation in this study and (B) the reported food-effect for EPCLUSA tablet formulation in the Clinical Pharmacology Biopharmaceutics Review of NDA208341 (Pages 39-40,* ***Link****) (****Table 6****).*
- *The Applicant proposes to administer the new granule formulation without regard to food. The Applicant's proposal is reasonable based on the abovementioned comparison as well as the efficacy and safety findings from Study GS-US-342-1143 that administered granule formulation without regard to food in pediatrics 3 to < 6 years old.*

Table 6: Comparison of Food Effect Between EPCLUSA Tablet Formulation and the Proposed Granule Formulation

Parameters	% Point Estimates (90% Confidence Interval)	
	Tablet-Fed/Tablet-Fasted	Granules-Fed/ Granules-Fasted
SOF		
AUC_{last}	178 (157-201)	168 (151 - 187)
C_{max}	89 (75-105)	105 (91-121)
GS-566500		
AUC_{last}	182 (163-203)	154 (142-167)
C_{max}	137 (124-151)	119 (109-129)
GS-331007		
AUC_{last}	99 (94-103)	104 (100-108)
C_{max}	63 (58-68)	64 (61-67)
VEL		
AUC_{last}	122 (99-149)	122 (101-148)
C_{max}	105 (87-127)	101 (85-120)

Source: Adapted from Study GS-US-342-1142 report and EPCLUSA original Clinical Pharmacology Biopharmaceutics Review

3.3. GS-US-342-1143

Overview:

This was an open-label Phase 2 study that evaluated safety and efficacy of SOF/VEL tablets and the to-be-marketed pellets in adolescents and children with chronic HCV infection.

The study design included three cohorts across two age-based groups and the enrolled patients received SOF/VEL dosing (once a day with or without food) for 12 weeks as described below:

Group 1:

- **Cohort 1** (12 to < 18 years old): SOF/VEL 400/100 mg (total daily dose)

Group 2:

- **Cohort 2** (6 to < 12 years old): SOF/VEL 200/50 mg (total daily dose)
- **Cohort 3** (3 to < 6 years old):
    - Patients with ≥ 17 kg weight: SOF/VEL 200/50 mg (total daily dose)
    - Patients with < 17 kg weight: SOF/VEL 150/37.5 mg (total daily dose)

The PK data from Cohorts 1 and 2 have been reviewed in the Clinical Pharmacology Review dated 02/25/2020 (**Link**). The distribution of patients from Cohort 3 is summarized in the table below.

Table 7: Patients' Distribution

	Group 2: Cohort 3
	3 to < 6 Years Old
Full Analysis Set (FAS)	41
Safety Analysis Set	41
Lead-in Phase PK Analysis Set	19 (Cohort 3)
Population PK Analysis Set	36
PK Analysis Set	36

Source: Adapted from Study GS-US-342-1143 report

The study collected intensive PK samples predose and up to 12 hours postdose on Day 7 in a lead-in phase and sparse samples during treatment phase to assess systemic exposure to sofosbuvir (SOF), SOF metabolites (GS-331007 and GS-566500), and velpatasvir (VEL) for the to-be-marketed pellet formulation. A population-PK (POP-PK) approach was used to analyze the PK data collected from the lead-in phase and the treatment phase as well as other pediatric studies. Please refer to the Pharmacometrics Review section for discussion of findings from POP-PK analysis.

Please refer to the clinical review for the safety and efficacy findings. Pharmacokinetic results from the lead-in phase is summarized below.

Pharmacokinetic Results from the Lead-In Phase:

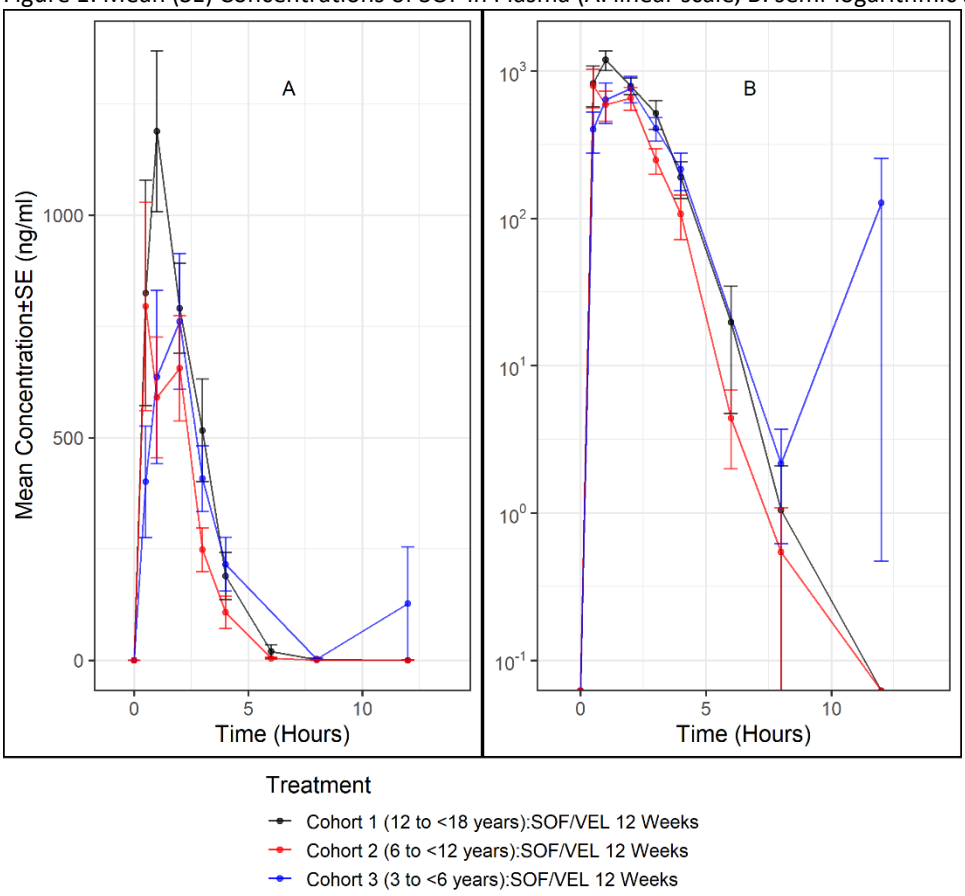
In total, 18 patients from Cohort 3 completed the lead-in PK phase and underwent an intensive PK evaluation. Selected demographic information of patients in the lead-in PK phase is summarized in **Table 8** below.

Table 8: Demographic Information Summary for Patients in Lead-in PK Phase

Planned Treatment Groups	**N**	**Weight Range (kg)**	**Age Range (Years)**	**Race**
3 to <6 years	18	12.9-24.9	3-5	White-13 Black/African American-1 Other-4
Source: Compiled by the Reviewer from Study GS-US-342-1143 report				

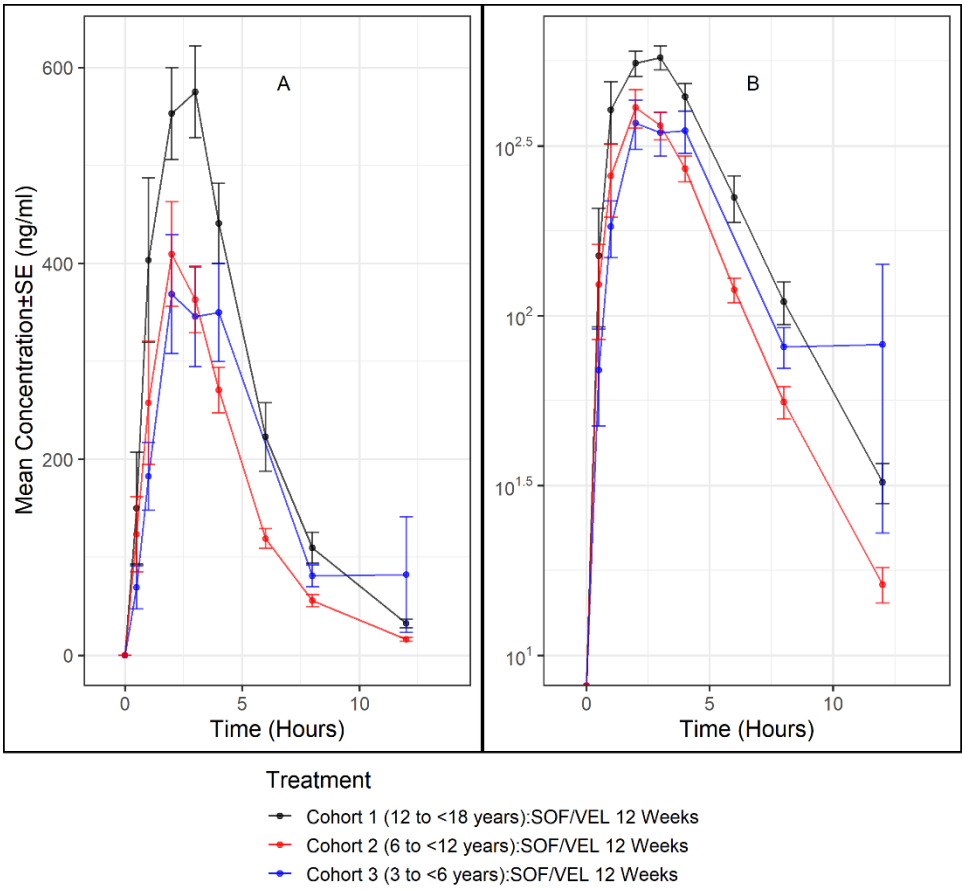
The reported mean plasma concentration-time profiles for SOF, GS-566500, GS-331007, and VEL from Cohort 3 (3 to < 6 years old) are presented in **Figure 1**, **Figure 2**, **Figure 3**, and **Figure 4**, respectively, along with the concentration-time profiles from other two cohorts, i.e., Cohort 1 (12 to < 18 years old) and Cohort 2 (6 to < 12 years old). Plasma concentrations (from Cohort 3) of all four analytes were subjected to noncompartmental analysis to derive PK parameter estimates reported in **Table 9**. These estimates from pediatric patients were also compared to the estimates for adults patients, which were derived by the Applicant using a POP-PK analysis approach (**Table 10**).

Figure 1: Mean (SE) Concentrations of SOF in Plasma (A: linear scale, B: semi-logarithmic scale)



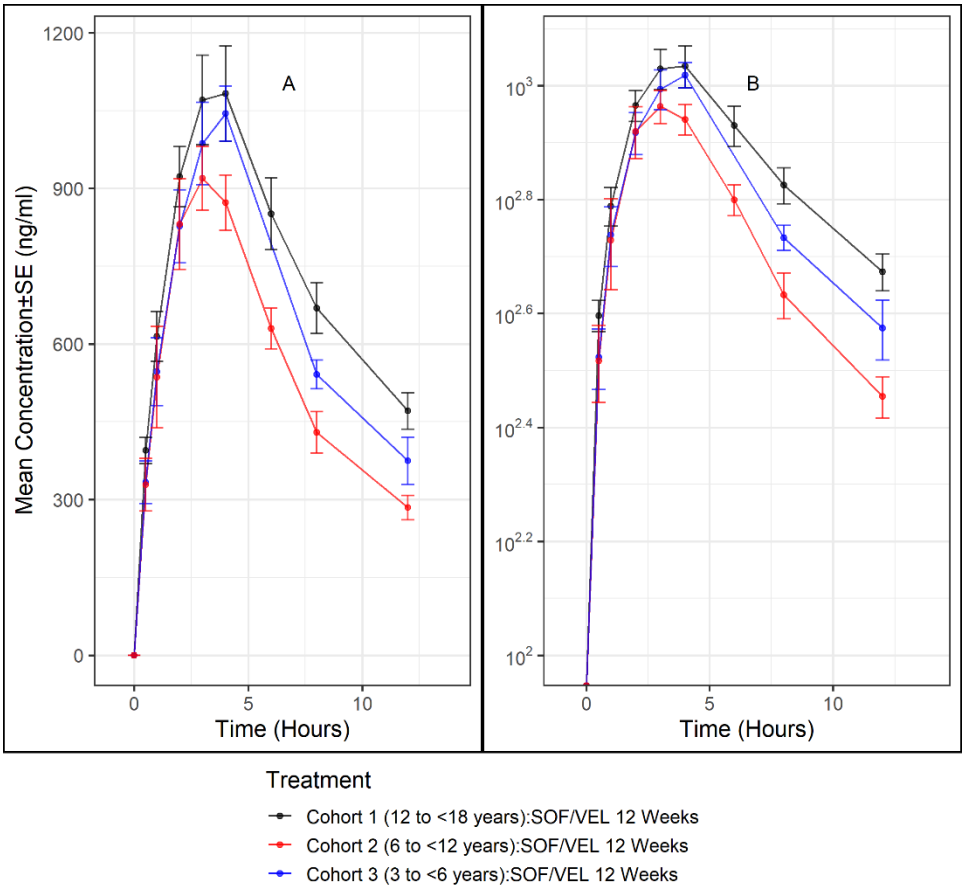
Source: Reviewer's Analysis

Figure 2: Mean (SE) Concentrations of GS-566500 in Plasma (A: linear scale, B: semi-logarithmic scale)



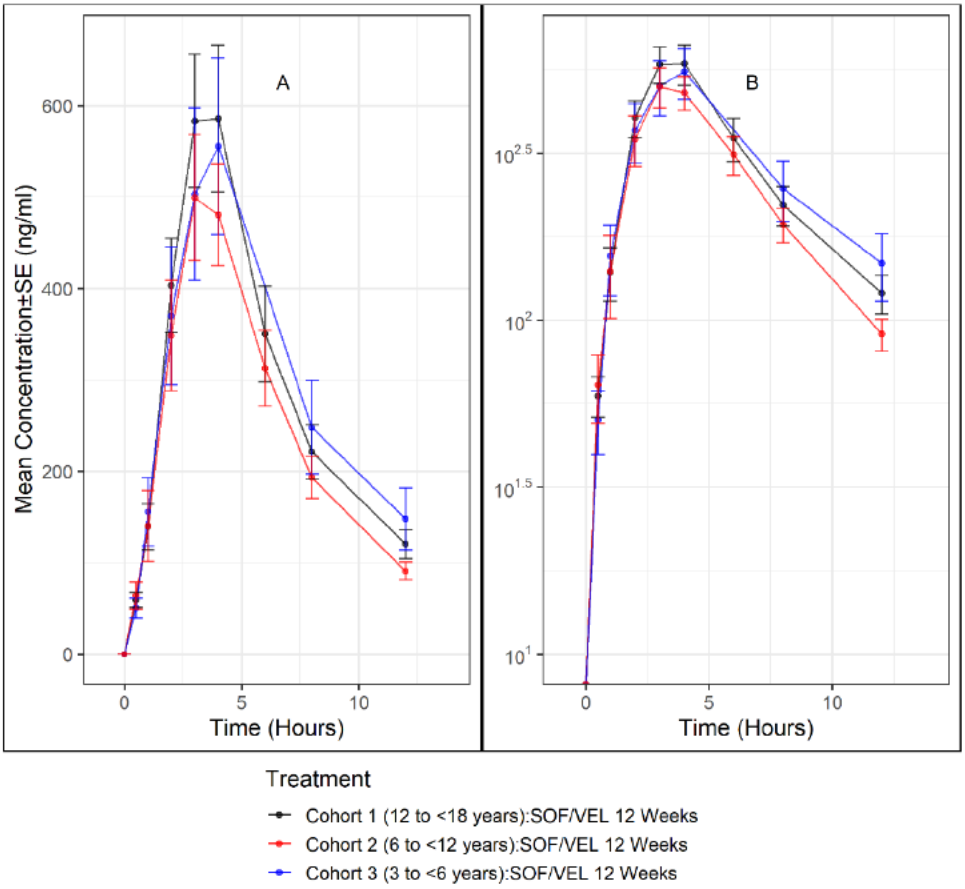
Source: Reviewer's Analysis

Figure 3: Mean (SE) Concentrations of GS- 331007 in Plasma (A: linear scale, B: semi-logarithmic scale)



Source: Reviewer's Analysis

Figure 4: Mean (SE) Concentrations of VEL in Plasma (A: linear scale, B: semi-logarithmic scale)



Source: Reviewer's Analysis

Table 9: Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for SOF, GS-566500, GS-331007, and VEL

Age Group (n)	AUC^{a}_{0-12} (ng·h/mL)	$AUC^{a,b}_{0-24}$ (ng·h/mL)	C_{max} (ng/mL)	C_{tau} (ng/mL)	$T^{a,c}_{max}$(h)	$T^{a}_{1/2}$(h)
SOF						
3 to <6 yr (18)	2348.6 (93)	3306.2 (105.8)	1207.8 (65.5)	-	2 (0.5-12)	1 (48,n=7)
Adults (>982)	-	1261.6 (37.2)	566.3 (31.4)	-	-	-
GS-566500[a]						
3 to <6 yr (18)	2023.6 (52)	2083.9 (56)	466.6 (55)	-	2.5 (1-12)	2 (13, n=12)
Adults (>982)	-	-	-	-	-	-
GS-331007						
3 to <6 yr (18)	7524.7 (16)	11604.0 (23.5)	1105.5 (23.0)	-	3.5 (1-4)	5.1 (27, n=8)
Adults (>982)	-	13966.7 (28.0)	868.2 (27.6)	-	-	-
VEL						
3 to <6 yr (18)	3464.8 (76)	4450.3 (73.8)	587.7 (66.3)	39.7 (74.0)	3 (1-8)	3.8 (25, n=8)
Adults (>982)	-	2967.3 (50.2)	259.0 (53.9)	41.5 (65.0)	-	-

a: From Reviewer's analysis, b: AUC_{0-24} calculated using pre-dose sample as 24 hr sample, c: Median [Range], h: Hours, yr: years, Parameter estimates for adults derived based on a POP-PK analysis approach.
Source: Adapted from Study GS-US-342-1143 report

Table 10: Comparison of SOF, GS-566500, GS-331007, and VEL Exposures Between Adults and Pediatrics 3 to less than 6 years of age

	% Point Estimates (90% Confidence Interval) for 3 to <6 years /Adults		
Analyte	**SOF**	**GS-331007**	**VEL**
Parameters			
AUC_{0-24}	192 (166, 222)	84 (76, 94)	123 (101, 149)
C_{max}	190 (168, 216)	129 (116, 144)	199 (160, 246)
C_{tau}	-	-	82 (66, 103)
Source: From Study GS-US-342-1143 report			

Applicant's Conclusions:

- Intensive PK analyses in the PK lead-in phase indicated that the PK of SOF, GS-331007, and VEL in adolescent and pediatric subjects were as expected and similar to those observed in the adult population.
- These findings confirm the appropriateness of the dose evaluated in the treatment phase.

Reviewer's Assessments:

- *This Phase 2 study enrolled pediatric patients across three different cohorts based on a patient's age and consequently, the study report included PK parameter summary from the lead-in PK phase based on the age-based groups (reported above). The recommended SOF/VEL dosing regimen is based on a patient's weight and therefore, additional non-compartmental analysis (NCA) was done by the Reviewer to summarize the lead-in PK phase data using the weight-based groups. The weight-based groups used in this additional NCA were kept same as the Applicant proposed dosing regimen (**Table 11-Table 13**).*

- *The currently approved EPCLUSA label include PK parameter estimates for two weight-based groups: ≥30 kg and 17 to <30 kg. These estimates were derived using a POP-PK analysis approach. With this submission, the Applicant is proposing to update the currently listed PK estimates as well as proposing to add POP-PK derived estimates for patients <17 kg weight. Therefore, the Applicant's parameter estimates from POP-PK analysis were also compared against the NCA parameter estimates derived from the lead-in PK phase (**Table 11-Table 13**). The comparison of estimates from these two different analyses methods show that in general, AUC estimates were comparable (<±30% difference). The cutoff of ±30% difference is an arbitrary cutoff selected by the Reviewer for the purposes of this review only. SOF and VEL Cmax estimates derived from POP-PK analysis tended to be lower than NCA estimates. The observed difference in Cmax estimates could be due to (A) differences in methodology and (B) sampling schedule differences between POP-PK analysis conducted using lead-in phase as well as treatment phase data and NCA analysis conducted using lead-in phase PK data. It is noteworthy that Cmax estimates for GS-331007 (major inactive circulatory metabolite) and Ctau estimates for VEL were comparable.*

Table 11: Comparison of Exposure Parameter Estimates for SOF from NCA and POP-PK Analyses Across Different Cohorts

Age Group (n)	Weight Group (n)	Dose (mg) (SOF/VEL)	Parameter	NCA (%CV)	POP-PK[b] (%CV, n)
3 to <6 yr (18)	17-30 kg (9)	200/50	AUC^{a}_{tau} (ng·h/mL)	1672 (49%)	2030 (57%, 66)
			C_{max} (ng/mL)	938 (41%)	952 (71%, 66)
	<17 kg (9)	150/37.5	AUC^{a}_{tau} (ng·h/mL)	3025 (96%)	2410 (64%, 11)
			C_{max} (ng/mL)	1478 (68%)	1270 (65%)
6 to <12 yr (17)	≥30 kg (6)	200/50	AUC^{a}_{tau} (ng·h/mL)	1336 (39%)	-
			C_{max} (ng/mL)	1089 (17%)	-
	17-30 kg (11)		AUC^{a}_{tau} (ng·h/mL)	1954 (36%)	2030 (57%, 66)
			C_{max} (ng/mL)	**1462 (57%)**	**952 (71%, 66)**
12 to <18 yr (16)	≥30 kg (15)	400/100	AUC^{a}_{tau} (ng·h/mL)	2644 (93%)	2010 (82%, 89)
			C_{max} (ng/mL)	**1598 (50%)**	**928 (91%, 89)**
	17-30 kg (1)		AUC^{a}_{tau} (ng·h/mL)	3753.5 (NA)	-
			C_{max} (ng/mL)	1560 (NA)	-

*a: From Reviewer's analysis $AUC_{0\text{-}tau}$ calculated using pre-dose sample as 24 hr sample, b: The Applicant proposed estimates derived from a POP-PK analysis for labeling, h: Hours, yr: years, Numbers marked in **Bold Red** are when percent ratio (PR) > ±30% calculated as PR=100*(POP-PK estimate-NCA estimate)/ NCA estimate.*
Source: Reviewer's analysis and from the Applicant's POP-PK report

Table 12: Comparison of Exposure Parameter Estimates for GS-331007 from NCA and POP-PK Analyses Across Different Cohorts

Age Group (n)	Weight Group (n)	Dose (mg) (SOF/VEL)	Parameter	NCA (%CV)	POP-PK[b] (%CV, n)
3 to <6 yr (18)	17-30 kg (9)	200/50	AUC^{a}_{tau} (ng·h/mL)	9973 (11%)	11100 (43%, 68)
			C_{max} (ng/mL)	980 (14%)	1070 (31%, 68)
	<17 kg (9)	150/37.5	AUC^{a}_{tau} (ng·h/mL)	13109 (23%)	11700 (20%, 11)
			C_{max} (ng/mL)	1231 (23%)	1080 (17%, 11)
6 to <12 yr (17)	≥30 kg (6)	200/50	AUC^{a}_{tau} (ng·h/mL)	8447 (16%)	-
			C_{max} (ng/mL)	792 (15%)	-
	17-30 kg (11)		AUC^{a}_{tau} (ng·h/mL)	10614 (33%)	11100 (43%, 68)
			C_{max} (ng/mL)	1102 (26%)	1070 (31%, 68)
12 to <18 yr (16)	≥30 kg (15)	400/100	AUC^{a}_{tau} (ng·h/mL)	13398 (25%)	13200 (27%, 100)
			C_{max} (ng/mL)	1056 (22%)	1150 (25%, 100)
	17-30 kg (1)		AUC^{a}_{tau} (ng·h/mL)	19265 (NA)	-
			C_{max} (ng/mL)	2220 (NA)	-

a: From Reviewer's analysis $AUC_{0\text{-}tau}$ calculated using pre-dose sample as 24 hr sample, b: The Applicant proposed estimates derived from POP-PK analysis for labeling, h: Hours, yr: years, No percent ratio (PR) > ±30% identified when calculated as PR = 100(POP-PK estimate-NCA estimate)/ NCA estimate.*
Source: Reviewer's analysis and from the Applicant's POP-PK report

Table 13: Comparison of Exposure Parameter Estimates for VEL from NCA and POP-PK Analyses Across Different Cohorts

Age Group (n)	Weight Group (n)	Dose (mg) (SOF/VEL)	Parameter	NCA (%CV)	POP-PK (%CV, n)
3 to <6 yr (18)	17-30 kg (9)	200/50	AUC^{a}_{tau} (ng·h/mL)	3658 (86%)	3860 (38%, 68)
			C_{max} (ng/mL)	486 (89%)	451 (39%, 68)
			C_{tau} (ng/mL)	**26 (73%)**	**36 (65%, 68)**
	<17 kg (9)	150/37.5	AUC^{a}_{tau} (ng·h/mL)	5233 (65%)	3860 (53%, 11)
			C_{max} (ng/mL)	**690 (48%)**	**431 (47%, 11)**
			C_{tau} (ng/mL)	53 (61%)	40 (83%, 11)

Age Group (n)	Weight Group (n)	Dose (mg) (SOF/VEL)	Parameter	NCA (%CV)	POP-PK (%CV, n)
6 to <12 yr (17)	≥30 kg (6)	200/50	AUC^{a}_{tau} (ng·h/mL)	2948 (62%)	-
			C_{max} (ng/mL)	413 (56%)	-
			C_{tau} (ng/mL)	25 (78%)	-
	17-30 kg (11)		AUC^{a}_{tau} (ng·h/mL)	4094 (36%)	3860 (38%, 68)
			C_{max} (ng/mL)	**640 (42%)**	**451 (39%, 68)**
			C_{tau} (ng/mL)	34 (62%)	36 (65%, 68)
12 to <18 yr (16)	≥30 kg (15)	400/100	AUC^{a}_{tau} (ng·h/mL)	4599 (46%)	3860 (46%, 100)
			C_{max} (ng/mL)	**653 (46%)**	**402 (56%, 100)**
			C_{tau} (ng/mL)	46 (50%)	36 (67%, 100)
	17-30 kg (1)		AUC^{a}_{tau} (ng·h/mL)	2384 (NA)	-
			C_{max} (ng/mL)	289 (NA)	-
			C_{tau} (ng/mL)	53 (NA)	-

*a: From Reviewer's analysis $AUC_{0\text{-}tau}$ calculated using pre-dose sample as 24 hr sample, b: The Applicant proposed estimates derived from POP-PK analysis for labeling, h: Hours, yr: years, Numbers marked in **Bold Red** are when percent ratio (PR) > ±30% calculated as PR = 100*(POP-PK estimate-NCA estimate)/ NCA estimate.*
Source: Reviewer's analysis and from the Applicant's POP-PK report

- *We do not agree with the Applicant's first conclusion above, i.e., the observed PK of SOF and VEL in adolescent and pediatric subjects were similar to those observed in the adult population. The ratios (as percent point estimates) of Cmax and AUC estimates for both SOF and VEL between the 3 to <6 years pediatric patient subgroup and adults were greater than 100% with lower bound of 90% CI was ≥100% and upper bound of 90% CI ranging from 149% to 246% (**Table 10**). The AUC estimates for GS-331007, the predominant circulatory inactive SOF metabolite, in the 3 to <6 years pediatric patient subgroup were 84% (76%-94%) compared to adults (**Table 10**). However, from a clinical pharmacology perspective, the observed differences in SOF and VEL exposures in the 3 to < 6 years pediatric patients group and adults noted in **Table 10)** are not clinically significant because as discussed below, (A) the extent of differences from adult patients (measured as mean % point estimates of ratios) in 3 to <6 years patients were mostly between the differences reported for 6 to <12 years and 12 to <18 years patients, except for VEL C_{max} and (B) the safety and efficacy findings from this study support the appropriateness of the proposed dosing regimen for pediatric patients 3 to <6 years.*

  Note: In the Applicant's comparison, PK information sources and analysis approaches are different between adults and pediatrics. The pediatric exposure parameter estimates for the lead-in PK phase of this study were derived using a non-compartmental analysis approach, whereas, the adult patients' exposure parameter estimates were derived using a POP-PK analysis approach. Therefore, further comparison of SOF, GS-566500, GS-331007, and VEL exposures between adult and pediatric patients were pursued using a POP-PK analysis approach. Refer to the Pharmacometrics Review section for additional details and findings.

- *The Applicant's second conclusion, i.e., the findings from this study confirm the appropriateness of the dose evaluated in the treatment phase, is reasonable based on the PK findings from lead-in phase for pediatric patients 3 to <6 years. The Applicant proposed weight-based doses for patients 3 to <6 years using the new pellet formulation is same as the doses (and formulation) that were evaluated in pediatric patients 3 to <6 years in this study. The observed exposure/PK parameter estimates for 3 to <6 years from the lead-in phase were between the estimates for 6*

to <12 years and 12 to <18 years patients[2]. Accordingly, the extent of differences from adult patients (measured as mean % point estimates of ratios) in 3 to <6 years patients were mostly between the differences reported for 6 to <12 years and 12 to <18 years patients, except for VEL C_{max}[2]. In addition, the safety and efficacy findings from this study support the appropriateness of the proposed dosing regimen for pediatric patients 3 to <6 years. Please see the review from Medical Officer for more details.

[2] Data comparison not shown in this Review.

3.4. Pharmacometrics Review

The Applicant updated the previously developed population PK model (PPK) for sofosbuvir (SOF) and velpatasvir (VEL) in pediatric subjects (6 to < 18 years old) with HCV infection by including additional pediatric PK data from study GS-US-342-1143 (patients 3 to < 6 years old receiving the weight-based fixed-dose combination (FDC) of SOF/VEL) and new data from study GS-US-367-1175 (patients 12 to < 18 years old receiving FDC of SOF/VEL/voxilaprevir (VOX) [400/100/100 mg]. PK simulations were then performed in order to support the newly proposed weight-band dosing regimen for SOF/VEL in patients less than 17 kg, and demonstrate that the expected steady-state exposure metrics (AUCtau,ss, Cmax,ss and Ctau,ss) for SOF, its metabolites and VEL are comparable across body weight groups in pediatric patients and largely contained within the range of exposure observed in the adult Phase 2/3 population. This section of review is primarily focused on the adequacy of the Applicant's pediatric PPK models for SOF and VEL, and the appropriateness of the newly proposed dosing in pediatric patients with body weight less than 17 kg and age down to 3 years old.

3.4.1. Applicant's SOF Population PK Analysis in Pediatric Subjects

Population PK model for SOF and its metabolites GS-566500 and GS-331007

Previously, in order to support the pediatric dosing regimen for EPCLUSA® (NDA208341) in patients 6 years of age and older, the Applicant developed a joint parent-metabolite PPK model to describe the PK of SOF, and its metabolites (GS-566500 and GS-331007) in pediatric subjects with chronic HCV infection using PK data from three Phase 2 studies: study GS-US-334-1112 (patients 3 to < 18 years old), GS-US-337-1116 (patients 3 to < 18 years old), and GS-US-342-1143 (patients 6 to < 18 years old). 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 additional PK data collected from 1) Cohort 3 (patients 3 to < 6 years of age) in study GS-US-342-1143 (SOF/VEL) and 2) study GS-US-367-1175 that evaluated the FDC SOF/VEL/VOX in patients 12 to < 18 years old. Summaries of the dosing regimen and PK sampling for the studies included in the PPK analysis are presented in Table 14.

The structural PK model for SOF and its metabolites is similar to the previous pediatric PPK model and is described by a zero-order input of SOF into the gastro-intestinal (GI) compartment, and pre-systemic metabolism of SOF dose to GS-566500, as well as GS-331007. SOF, GS-566500 and GS-331007 are absorbed from the GI compartment following a first-order absorption process with lag time for SOF and GS-331007, with relative absorption fractions F1, F2, and F3, respectively. SOF, GS-566500, and GS-331007 disposition was described by a 1-compartment disposition model for SOF and GS-566500 and a 2-compartment disposition model for GS-331007, with conversion of SOF to GS-566500 (intermediate metabolite) and conversion of GS-566500 to GS-331007 (major circulating inactive metabolite) following a first-order process, followed by a first-order elimination of GS-331007 from the central compartment.

Table 14. Summary of Studies Included in Population PK Analysis

Study Number; Study Drug	Age Group (years)	Study Phase	Subjects with PK Sampling[a]	Dose Regimen (mg)[b]
GS-US-334-1112; SOF + RBV[c]	12 to < 18	PK lead-in	N = 10 (Int + Sparse)	400 SOF
		Treatment	N = 42 (Sparse only)	
	6 to < 12	PK lead-in	N = 12 (Int + Sparse)	200 SOF
		Treatment	N = 29 (Sparse only)	
	3 to < 6	PK lead-in	N = 11 (Int + Sparse)	> 17 kg: 200 SOF ≤ 17 kg: 150 SOF
		Treatment	N = 1 (Sparse only)	
GS-US-337-1116; LDV/SOF ± RBV[d]	12 to < 18	PK lead-in	N = 10 (Int + Sparse)	90/400 LDV/SOF
		Treatment	N = 90 (Sparse only)	
	6 to < 12	PK lead-in	N = 12 (Int + Sparse)	45/200 LDV/SOF
		Treatment	N = 80 (Sparse only)	
	3 to < 6	PK lead-in	N = 14 (Int + Sparse)	> 17 kg: 45/200 LDV/SOF ≤ 17 kg: 33.75/150 LDV/SOF
		Treatment	N = 8 (Sparse only) N = 12[e] (Int + Sparse)	
GS-US-342-1143; SOF/VEL[f]	12 to < 18	PK lead-in	N = 17 (Int + Sparse)	400/100 SOF/VEL
		Treatment	N = 85 (Sparse only)	
	6 to < 12	PK lead-in	N = 20 (Int + Sparse)	200/50 SOF/VEL
		Treatment	N = 51 (Sparse only)	
	3 to < 6	PK lead-in	N = 19 (Int + Sparse)	≥ 17 kg: 200/50 SOF/VEL < 17 kg: 150/37.5 SOF/VEL
		Treatment	N = 17 (Sparse only)	
GS-US-367-1175; SOF/VEL/VOX[g]	12 to < 18	Treatment	N = 14 (Int + Sparse) N = 7 (Sparse only)	400/100/100 SOF/VEL/VOX

Int = intensive; LDV = ledipasvir; N = number of subjects; PK = pharmacokinetic; RBV = ribavirin; SOF = sofosbuvir; VEL = velpatasvir; VOX = voxilaprevir; WT = baseline body weight.

a For sparse PK sampling, single blood samples were collected at all on-treatment study visits.
b Protocol-defined dose regimen based on defined age and WT cutoff. All listed regimens were given once daily.
c Intensive PK sampling included 8 time points for pediatric subjects 6 to < 18 years old and 5 time points for pediatric subjects 3 to < 6 years old.
d Intensive PK sampling included 9 time points for pediatric subjects 6 to < 18 years old and 6 time points for pediatric subjects 3 to < 6 years old. Pediatric subjects 3 to < 6 years old could have participated in an optional intensive PK substudy that included 9 time points at Week 4 or 8 of treatment.
e One subject participated in both the PK lead-in phase and the intensive PK substudy during the treatment phase.
f Intensive PK sampling included 9 time points for pediatric subjects 6 to < 18 years old and 8 time points for pediatric subjects 3 to < 6 years old.
g Intensive PK sampling included 9 time points for pediatric subjects 12 to < 18 years old.

Source: Applicant's PPK Report (CTRA-2020-1044 EPC-VSV Peds PopPK), page 158.

The PPK model was parameterized in terms of apparent clearance (CL/F), apparent inter-compartment clearance (Q/F), apparent central and peripheral volume of distribution (Vc/F and Vp/F), infusion duration for the SOF zero-order input into the GI, absorption rate constants (Ka) and absorption lag-times (ALAG). The Applicant noted that >15% PK samples for SOF and GS-566500 were below the limit of quantification (BLQ) and the M4 censored-data likelihood method in NONMEM was used to handle BLQ data for SOF and GS-566500.

Table 15 shows the PK parameter estimates from the updated final PPK model, bootstrap analysis, and the Sampling-Importance Resampling (SIR) analysis. The apparent clearance and apparent central volume of distribution for SOF (CLSOF, VSOF), GS-566500 (CL500, V500), and GS-331007 (CL007, V007) were estimated for a typical subject with a body weight (WT) of 42 kg using a power function with a fixed theoretical allometric exponents of 0.75 and 1, for CL/F and Vc/F, respectively. In addition to WT, the typical (population mean) CL was standardized to a 12 years old subject for CL500 (estimated power exponent of -0.175) and to a 12 years old female subject for CL007 (estimated power exponent of -0.185), as age was found to be a statistically significant covariate on CL500 and CL007, and gender was a statistically significant covariate on CL007. However, age and sex were not considered to have a clinically relevant effect compared to WT.

The inter-individual variability (IIV) was included on CLSOF, VSOF, CL500, and CL007, with an interindividual random effect (ETA) shrinkage of 21.5%, 20.5%, 22.4%, and 8.9%, respectively. The residual error (Epsilon) shrinkage was 9.4%.

SOF and GS-331007 Exposure and Covariates Effects

The Applicant's analyses identified WT as the most influential covariate on SOF and GS-331007 exposures. The percent change in steady-state exposure (AUCtau,ss) for both SOF and GS-331007 was -38% and +112% for subjects with WT 87.1 kg and 16.9 kg (i.e., 95^{th} and 5^{th} WT percentile, respectively), compared to a typical subject with a body weight of 42 kg, when SOF is administered without WT-based adjustment (i.e., all subject receiving 400 mg of SOF).

SOF exposure is estimated to be 152% higher when administered as SOF/VEL combination compared to when administered as SOF alone in pediatric subjects. The combined effects of WT and VEL on SOF and exposures accounted for the majority of the observed PK variability, with approximately +38% to +435% change in AUCtau,ss for subjects with WT 87.1 kg and 16.9 kg, compared to a typical subject with a body weight of 42 kg (receiving 400 mg of SOF without VEL).

The effect of age on GS-331007 exposure resulted in an -18% and +7% change in AUCtau,ss for subjects 4 and 17 years old, respectively. The covariate effect of sex resulted in approximately 10% increase in GS-331007 AUCtau,ss in female subjects. The combination of WT, age, and sex effect on GS-331007 exposures accounted for the majority of the observed PK variability, with approximately -49% to +162% change in AUCtau for subjects with extreme covariate values relative to a typical 12 years-old male subject with a body weight of 42 kg, when SOF is administered without WT-based adjustment.

Table 15. Final Population PK Model Parameters Estimates and Bootstrap Results for Sofosbuvir and its Metabolites in Pediatrics

Parameter	Parameter Description	Final Model Estimate [RSE][a]	Bootstrap Estimate Median [2.5th; 97.5th Percentiles]	SIR Estimate Median [2.5th; 97.5th Percentiles]
$\exp(\theta_1)$	Absorption rate for SOF (1/h)	1.22 [2]	1.27 [1.11; 1.42]	1.22 [1.17; 1.29]
$\exp(\theta_2)$	Absorption rate for GS-566500 (1/h)	0.286 [2]	0.285 [0.263; 0.311]	0.286 [0.272; 0.3]
$\exp(\theta_3)$	Absorption rate for GS-331007 (1/h)	0.022 [8]	0.0252 [0.0197; 0.034]	0.0219 [0.0192; 0.0255]
$\exp(\theta_4)$	Apparent oral clearance of SOF (L/h)	318 [6]	305 [268; 359]	317 [284; 355]
$\exp(\theta_5)$	Apparent central volume of SOF (L)	161 [15]	161 [102; 227]	162 [125; 209]
$\exp(\theta_6)$	Apparent oral clearance of GS-566500 (L/h)	841 [2]	831 [770; 879]	839 [798; 869]
$\exp(\theta_7)$	Apparent central volume of GS-566500 (L)	1170 [4]	1160 [988; 1390]	1160 [1090; 1270]
$\exp(\theta_8)$	Apparent oral clearance of GS-331007 (L/h)	167 [2]	167 [159; 175]	167 [160; 175]
$\exp(\theta_9)$	Apparent central volume of GS-331007 (L)	220 [5]	214 [172; 274]	219 [202; 238]
$\exp(\theta_{10})$	Apparent intercompartmental clearance of GS-331007 (L/h)	49 [8]	50.6 [40.4; 153]	48.5 [42.1; 58.1]
$\exp(\theta_{11})$	Apparent peripheral volume of GS-331007 (L)	1000 [23]	1610 [114; 4130]	962 [637; 1520]
$\exp(\theta_{12})$	Duration of zero-order absorption for SOF (h)	0.562 [7]	0.568 [0.401; 0.922]	0.569 [0.486; 0.645]
	Relative fraction absorbed for SOF	1 [Fixed]	--	--
θ_{13}	Relative fraction absorbed for GS-331007	7.18 [Fixed]	7.18 [7.18; 7.18]	--
θ_{14}	Ledipasvir on relative fraction absorbed for SOF	0.769 [Fixed]	0.769 [0.769; 0.769]	--
θ_{15}	Relative fraction absorbed for GS-566500	5.32 [Fixed]	5.32 [5.32; 5.32]	--
θ_{16}	Proportional error SD for GS-566500	0.614 [2]	0.615 [0.585; 0.648]	0.617 [0.588; 0.637]
θ_{17}	Proportional error SD for GS-331007	0.304 [1]	0.302 [0.287; 0.319]	0.304 [0.297; 0.312]
$\exp(\theta_{18})$	Absorption lag time for GS-331007	3 [2]	2.98 [1.43; 11.7]	3 [2.85; 3.13]
θ_{19}	Proportional error SD for SOF	0.927 [3]	0.927 [0.877; 0.981]	0.933 [0.884; 0.98]
$\exp(\theta_{20})$	Apparent oral clearance of GS-566500 + RBV (L/h)	1350 [4]	1340 [1290; 1460]	1340 [1240; 1480]
$\exp(\theta_{21})$	Apparent oral clearance of GS-331007 + RBV (L/h)	181 [4]	183 [170; 201]	182 [172; 192]

Parameter	Parameter Description	Final Model Estimate [RSE][a]	Bootstrap Estimate Median [2.5th; 97.5th Percentiles]	SIR Estimate Median [2.5th; 97.5th Percentiles]
$\exp(\theta_{22})$	Absorption lag time for SOF (h)	0.0821 [Fixed]	0.0821 [0.0821; 0.0821]	--
θ_{23}	Velpatasvir on relative fraction absorbed for SOF	1.52 [7]	1.45 [1.07; 1.84]	1.51 [1.29; 1.75]
θ_{24}	Age effect on apparent oral clearance of GS-331007	-0.185 [17]	-0.188 [-0.257; -0.116]	-0.186 [-0.255; -0.126]
θ_{25}	Sex effect on apparent oral clearance of GS-331007	0.101 [31]	0.101 [0.0438; 0.155]	0.103 [0.0505; 0.164]
θ_{26}	Age effect on apparent oral clearance of GS-566500	-0.175 [24]	-0.172 [-0.28; -0.121]	-0.182 [-0.251; -0.101]
ω^2_{11}	Between-subject variability on clearance of SOF (%)	81 [12]	75.4 [63.6; 90.1]	81.9 [72.1; 89.7]
ω^2_{22}	Between-subject variability on volume of SOF (%)	210 [22]	193 [139; 355]	212 [181; 252]
$\omega^2_{12.12}$	Between-subject variability on apparent oral clearance of GS-566500 (%)	32 [39]	32.5 [26.2; 38.7]	32.4 [28.6; 37]
$\omega^2_{13.13}$	Between-subject variability on apparent oral clearance of GS-331007 (%)	28 [9]	27.8 [25.4; 30.5]	27.8 [25.6; 29.9]

θ = absolute value of the estimate; ω = standard deviation of between-subject variability; PopPK = population pharmacokinetic; RBV = ribavirin; RSE = relative standard error; SD = standard deviation; SE = standard error; SIR = sampling-importance resampling; SOF = sofosbuvir.

a RSE is defined as the SE divided by the θ × 100% for nontransformed parameters and as SE × 100% for log-transformed parameters.

Source: sof-run046-gof-final-20200413.R

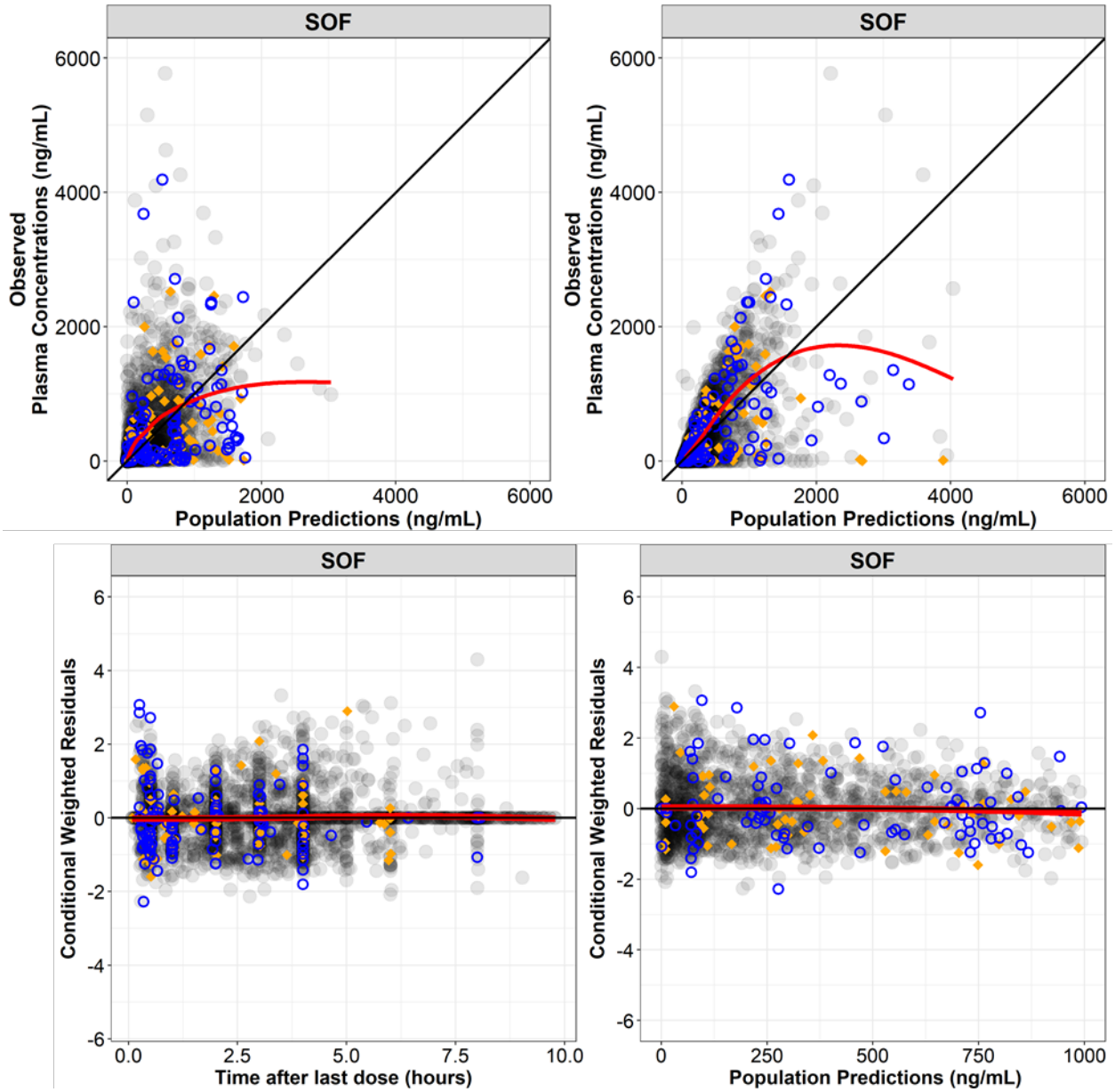
Source: Applicant's PPK Report (CTRA-2020-1044 EPC-VSV Peds PopPK), Table 14, page 66 to 67.

Reviewer's assessment of the SOF and metabolites PK model for pediatric patients

The updated PPK model reasonably describes the PK of SOF, GS-566500, and GS-331007 in pediatric patients with HCV infection and is acceptable to be used for simulations to predict SOF and its metabolites exposures in pediatric subjects (3 years old and older).

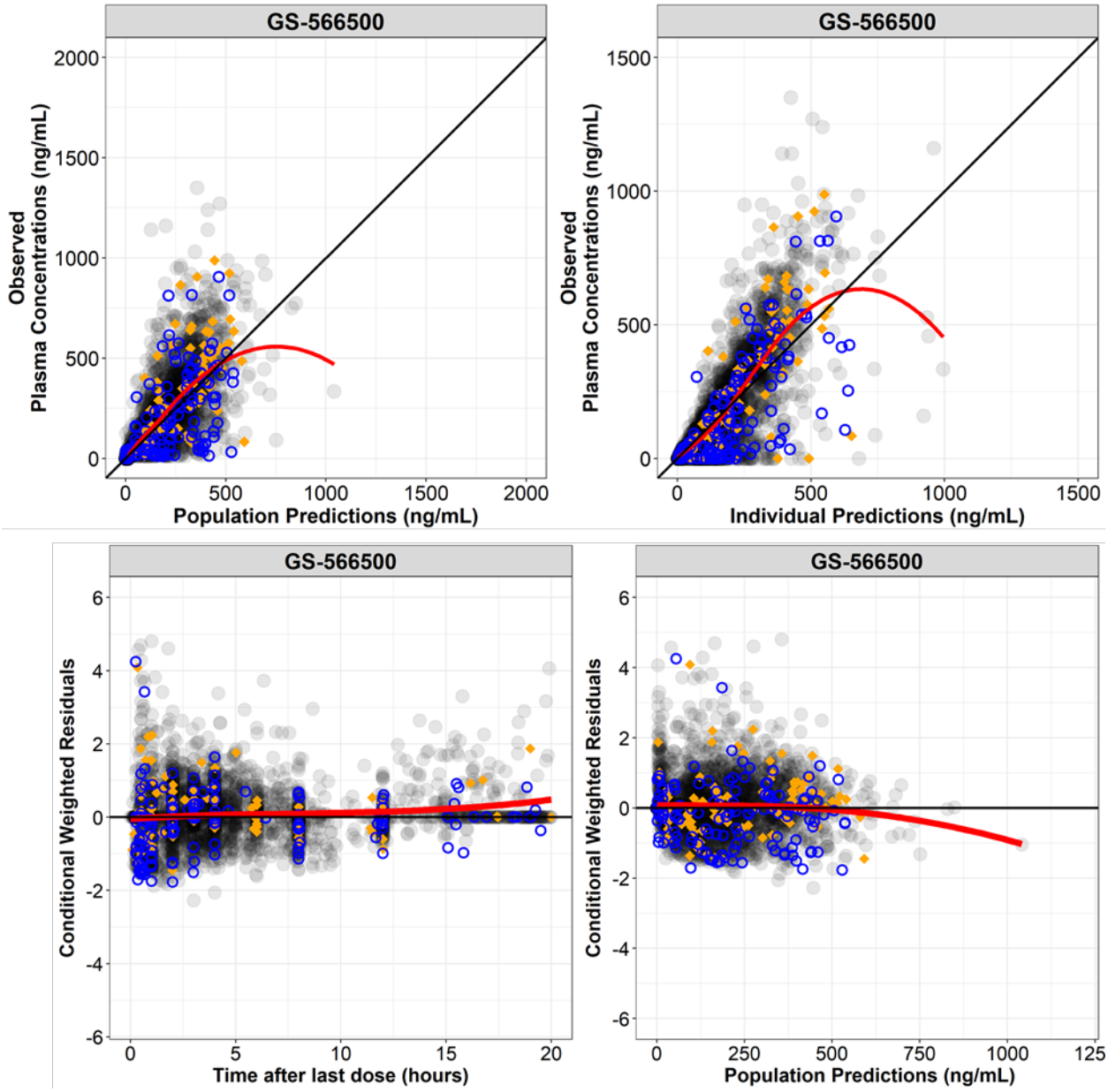
- The reviewer was able to replicate the updated PPK model parameter estimates. The PK model parameter estimates, and the magnitude of covariate effects were similar to those reported from the previously developed model in pediatric patients 6 years old and older. WT was the most clinically relevant covariate on SOF and GS-331007 exposures when the drug is administered as a FDC of SOF/VEL.
- The effect of formulation (tablet and pellets) for the SOF/VEL FDC was not evaluated in the population PK analysis, as the both formulations were considered interchangeable based on the findings from a Phase 1 relative bioavailability study (Study GS-US-342-1142).
- The PK parameters were estimated with acceptable precision with a relative standard error (%RSE) below 24%, except for the gender effect on CL007 with an RSE of 31%.
- Among the PK parameters evaluated for covariates effects, the ETA shrinkage was low (< 30%) indicating reliable assessment of covariate effects.
- The Epsilon shrinkage was low indicating the informativeness of the goodness of fit (GOF) plots to diagnose structural and residual error model misspecifications. The GOF plots (Figure 5 to Figure 7) were comparable to the previously developed model in pediatric patients 6 years old and older. The GOF plots for SOF, GS-566500, and GS-331007 showed no systematic bias in the model predicted concentrations or in the conditional weighted residual, and the residuals were normally distributed with no specific pattern particularly for the newly added pediatric data, indicating the adequacy of the structural and residual errors models.
- The estimated typical values of PK parameter from the final PK model were in good agreement with the medians values estimated from SIR (sampling-importance resampling) and from bootstrapping, and all parameters estimates were within the 95% CI obtained from SIR and bootstrapping, indicating the robustness of the PK model and the reliability of the PK parameter estimates.

Figure 5. Goodness of Fit Plots of the updated Final Population PK Model for SOF in Pediatrics



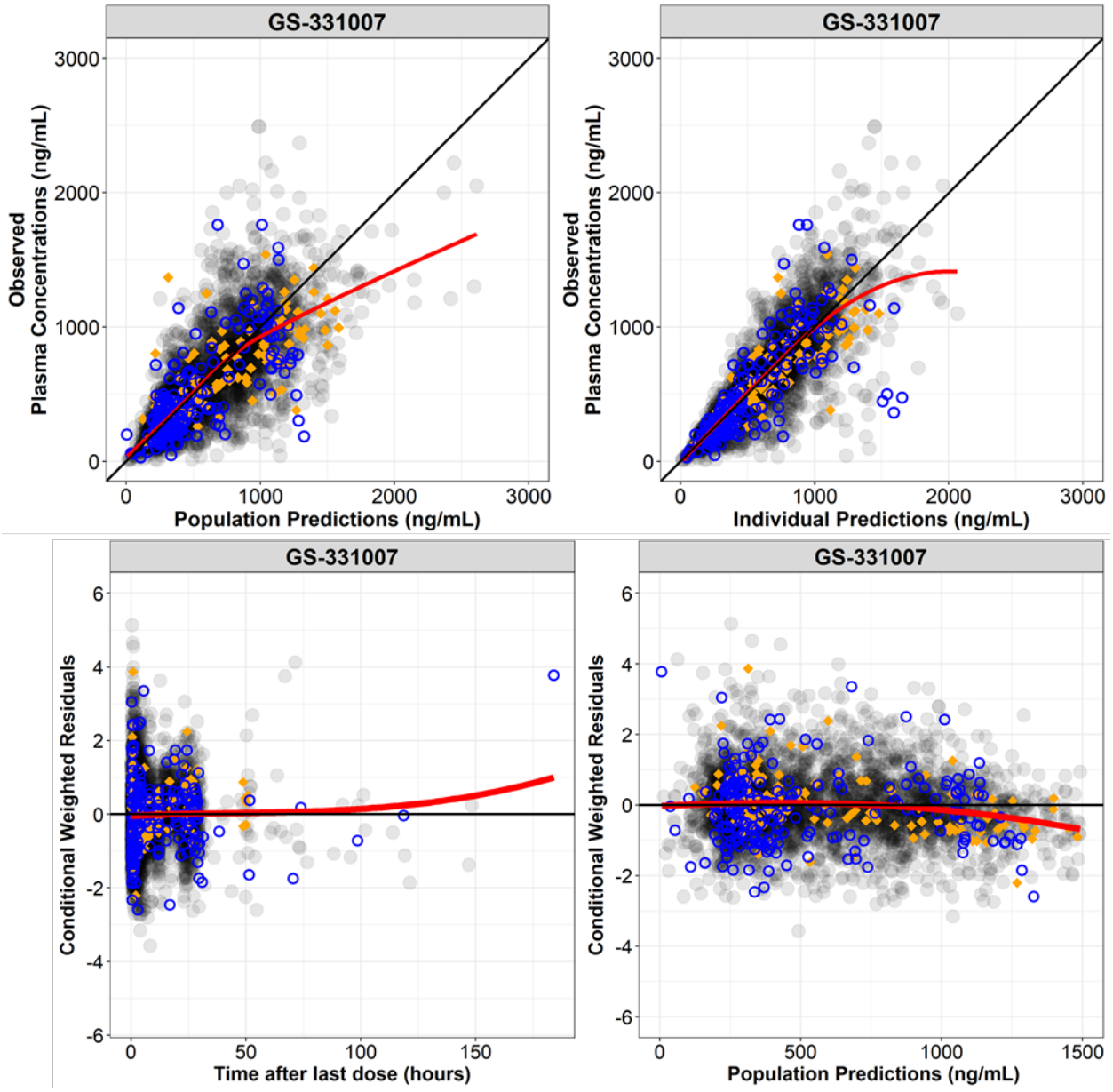
Note: the black circles represent the observations and residuals from the previous pediatric Phase 2 studies data. The orange diamonds represent the observations and residuals from study GS-US-367-1175. The blue open circles represent the observations and residuals from study GS-US-342-1143 in patients 3 to < 6 years old.

Figure 6. Goodness of Fit Plots of the updated Final Population PK Model for GS-566500 in Pediatrics



Note: the black circles represent the observations and residuals from the previous pediatric Phase 2 studies data. The orange diamonds represent the observations and residuals from study GS-US-367-1175. The blue open circles represent the observations and residuals from study GS-US-342-1143 in patients 3 to < 6 years old.

Figure 7. Goodness of Fit Plots of the updated Final Population PK Model for GS-331007 in Pediatrics



Note: the black circles represent the observations and residuals from the previous pediatric Phase 2 studies data. The orange diamonds represent the observations and residuals from study GS-US-367-1175. The blue open circles represent the observations and residuals from study GS-US-342-1143 in patients 3 to < 6 years old.

3.4.2. Applicant's VEL Population PK Analysis in Pediatric Subjects

Population PK model for VEL

The previously developed pediatric PPK model for VEL in patients 6 to <18 years old with chronic HCV infection (study GS-US-342-1143), consisted of a 2-compartment disposition model including a first-order absorption process with zero-order input of VEL into the GI compartment, and first-order elimination of VEL from the central compartment. The Division has previously reviewed the PPK model and found it to be acceptable. With the current submission, the Applicant updated the PK dataset to include new PK data collected from two Phase 2 pediatric studies, with an additional cohort of patients 3 to < 6 years of age in study GS-US-342-1143 (SOF/VEL) and a new study GS-US-367-1175 that evaluated the FDC SOF/VEL/VOX in patients 12 to < 18 years old (Table 14). The structural PK model for VEL is similar to the previously developed pediatric PPK model and the final parameter estimates of the updated PPK model are listed in Table 16.

Table 16. Final Population PK Model Parameters Estimates and Bootstrap Results for Velpatasvir

Parameter	Parameter Description	Final Model Estimate [RSE][a]	Bootstrap Estimate Median [2.5th; 97.5th Percentiles]	SIR Estimate Median [2.5th; 97.5th Percentiles]
$\exp(\theta_1)$	Apparent oral clearance, CL/F (L/h)	22.1 [5]	22.1 [20; 24.4]	22.2 [20.4; 24]
$\exp(\theta_2)$	Apparent central volume, V_c/F (L)	147 [9]	145 [115; 175]	146 [127; 171]
$\exp(\theta_3)$	Intercompartmental clearance, Q/F (L/h)	5.26 [23]	5.23 [2.61; 7.82]	5.31 [3.49; 7.68]
$\exp(\theta_4)$	Apparent peripheral volume, V_p/F (L)	36.9 [22]	38.7 [24.8; 71.2]	37.6 [26.9; 51.1]
$\exp(\theta_5)$	First-order absorption rate constant, k_a (1/h)	1.08 [8]	1.07 [0.88; 1.27]	1.08 [0.923; 1.27]
$\exp(\theta_6)$	Duration of zero-order absorption, D1 (h)	2.11 [6]	2.1 [1.84; 2.35]	2.11 [1.88; 2.34]
θ_9	VOX effect on CL/F	-0.244 [23]	-0.243 [-0.353; -0.135]	0.248 [-0.353; -0.132]
$\text{sqrt}(\theta_7)$	Residual proportional error (%)	68 [2]	68.5 [66.3; 70.9]	68.5 [66.7; 70.3]
θ_8	Residual additive	6.65 [24]	6.42 [0.626; 9.47]	6.74 [5.21; 8.84]
$\omega 11$	IIV on CL/F (%)	47 [21]	46.9 [38; 57.5]	47.6 [41.3; 54.8]
$\omega 21$	Correlation CL/F-V_c/F	0.266 [26]	0.257 [0.145; 0.406]	0.266 [0.18; 0.371]
$\omega 22$	IIV of V_c/F (%)	66 [30]	64.2 [43.8; 84.8]	66.4 [52.6; 81.7]
$\omega 33$	IIV of ka (%)	84 [23]	84.8 [62.6; 103]	84.8 [66.3; 101]

Source: Applicant's PPK Report, Table 39, page 91.

Reviewer's comment: The Applicant's reported proportional residual error (%) is the square root of the estimated value. The correct proportional residual error (%) is 47%. The reported ω21 is the covariance value. The correct random effects correlation CL/F-Vc/F is 84.7%.

VEL Exposure and Covariate effects

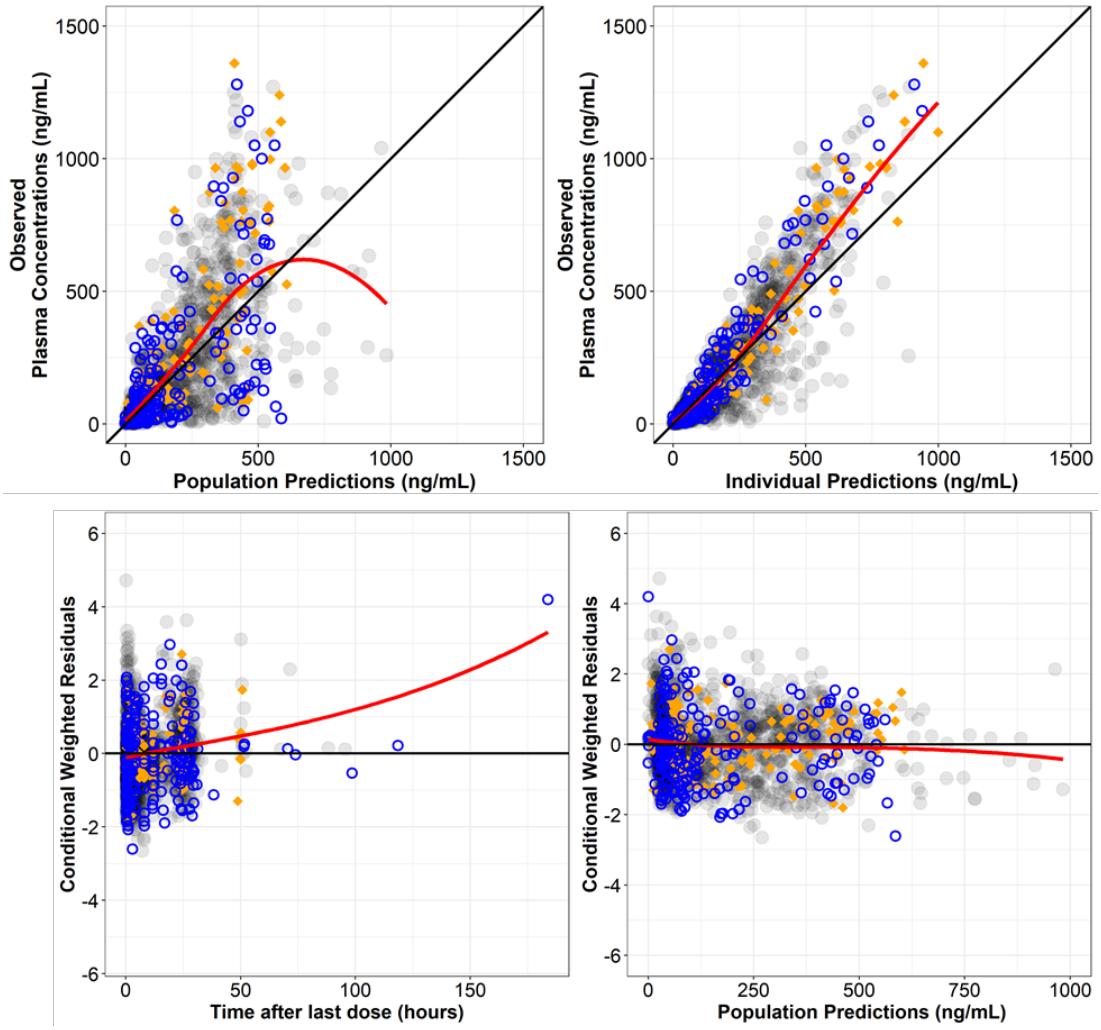
The Applicant's analyses identified WT as the only influential covariate on VEL exposure metrics when the drug is administered as a FDC of SOF/VEL. WT was introduced in the model as standardized covariate to the median WT of 46 kg using a power function with a fixed theoretical allometric exponents of 0.75 and 1 for CL/F and Vc/F, respectively. The AUCtau,ss ranged from -39% to +102%, and the Ctau,ss ranged from -32% to 120% for the subjects with extreme body weights, 88 kg and 18 kg, compared to a typical subject with a body weight of 46 kg, when VEL is administered without WT-based adjustment (i.e., all subject receiving 200 mg of VEL).

Reviewer's assessment of the VEL PK model in pediatrics

The updated PPK model description of the PK of VEL is acceptable and the model can be used for simulations to predict exposure in pediatric subjects 3 years old and older.

- The PK model parameters' estimates were similar to those reported from the previously developed model in pediatric patients 6 years old and older, except for Vc/F which is in the upper range and Vp/F which is in the lower range of the previously estimated PK parameters (typical Vc/F was 85 - 141 L and typical Vp/F was 55.4-406 L). WT was the most clinically relevant covariate on VEL exposure when the drug is administered as a FDC of SOF/VEL.
- The effect of formulation (tablet and pellets) for the SOF/VEL FDC was not evaluated in the population PK analysis, as the both formulations were considered interchangeable based on the findings from a Phase 1 relative bioavailability study (Study GS-US-342-1142).
- The PK parameters were estimated with acceptable precision with a relative standard error (%RSE) below 24% for the fixed effects parameters.
- Among the PK parameters evaluated for covariates effects, the ETA shrinkage was low (< 20%) indicating reliable assessment of covariate effects.
- The Epsilon shrinkage was low (8%) indicating the informativeness of the goodness of fit (GOF) plots to diagnose structural and residual error model misspecifications. The GOF plots (Figure 8) were comparable to the previously developed PPK model in patients 6 years old and older. The GOF plots showed no systematic bias in the model predicted concentrations (other than a slight underprediction of the highest observed concentrations) or in the conditional weighted residual, and the residuals were normally distributed with no specific pattern particularly for the newly added pediatric data, indicating the adequacy of the structural and residual errors models.
- The estimated PK parameters from the final PK model were in good agreement with the medians values and 95% CI estimated from SIR and bootstrapping, indicating the robustness and reliability of the PK model and PK parameters estimates.

Figure 8. Goodness of Fit Plots of the updated Final Population PK Model for VEL in Pediatrics



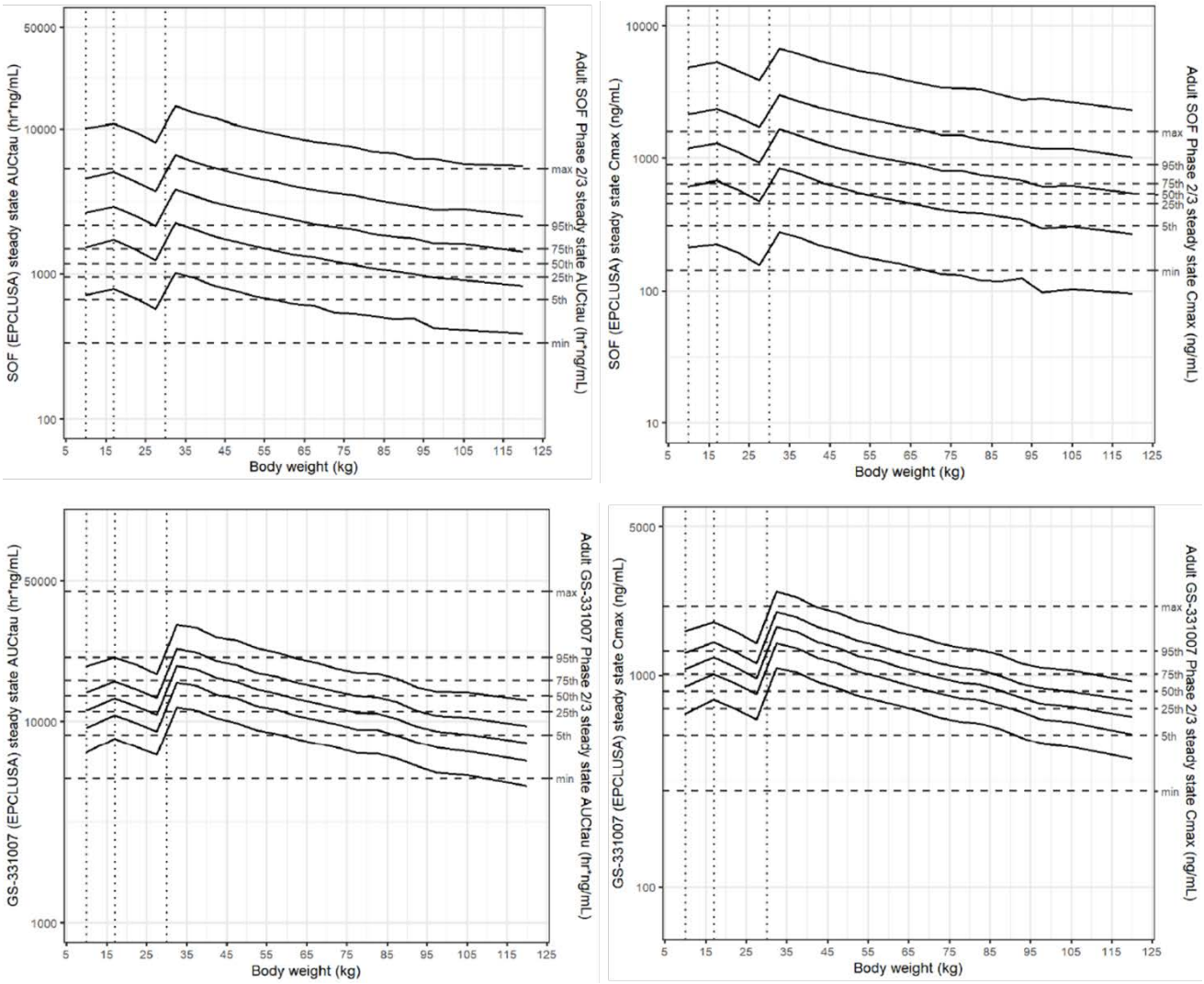
Note: the black circles represent the observations and residuals from the previous pediatric Phase 2 studies data. The orange diamonds represent the observations and residuals from study GS-US-367-1175. The blue open circles represent the observations and residuals from study GS-US-342-1143 in patients 3 to < 6 years old.

3.4.3. Assessment of SOF/VEL Exposures with the Proposed Weight Band-Based Dosing in Pediatrics

The Applicant performed population PK simulations using the updated PPK model to confirm the appropriateness of the additional proposed dosing in younger patients with WT < 17 kg and ensure that SOF, GS-331007, and VEL exposures were comparable to the those observed in pediatrics (>17 kg) and in adults receiving the approved SOF/VEL pediatric and adults dosing regimens (Figure 9 and Figure 10). A dataset for simulations was constructed based on the model development dataset, including number of subjects, actual demographic data, and study information. Monte-Carlo simulations were conducted with 500 repetitions for each subject. The AUCtau,ss, Cmax,ss (SOF, GS-331007, VEL), and Ctau,ss (VEL) were calculated using the simulated individual PK profiles.

Figure 9 and Figure 10 shows that the proposed SOF/VEL FDC of 150 mg/37.5 mg QD in younger pediatric patients < 17 kg is expected to provide comparable SOF, GS-331007, and VEL exposures to those observed in pediatric patients receiving the already approved dosing regimen of 200 mg/50 mg in patient 17 to < 30 kg and 400/100 mg in patients ≥ 30 kg. The simulated exposures in pediatric subjects following the proposed WT band–based dosing regimen were also largely contained within the range observed in the adult Phase 2/3 population, except for SOF with more than 25% and 40% of patients with WT 10 to 45 kg are expected to have AUCtau,ss and Cmax,ss, respectively, above of the maximum exposure observed in adults.

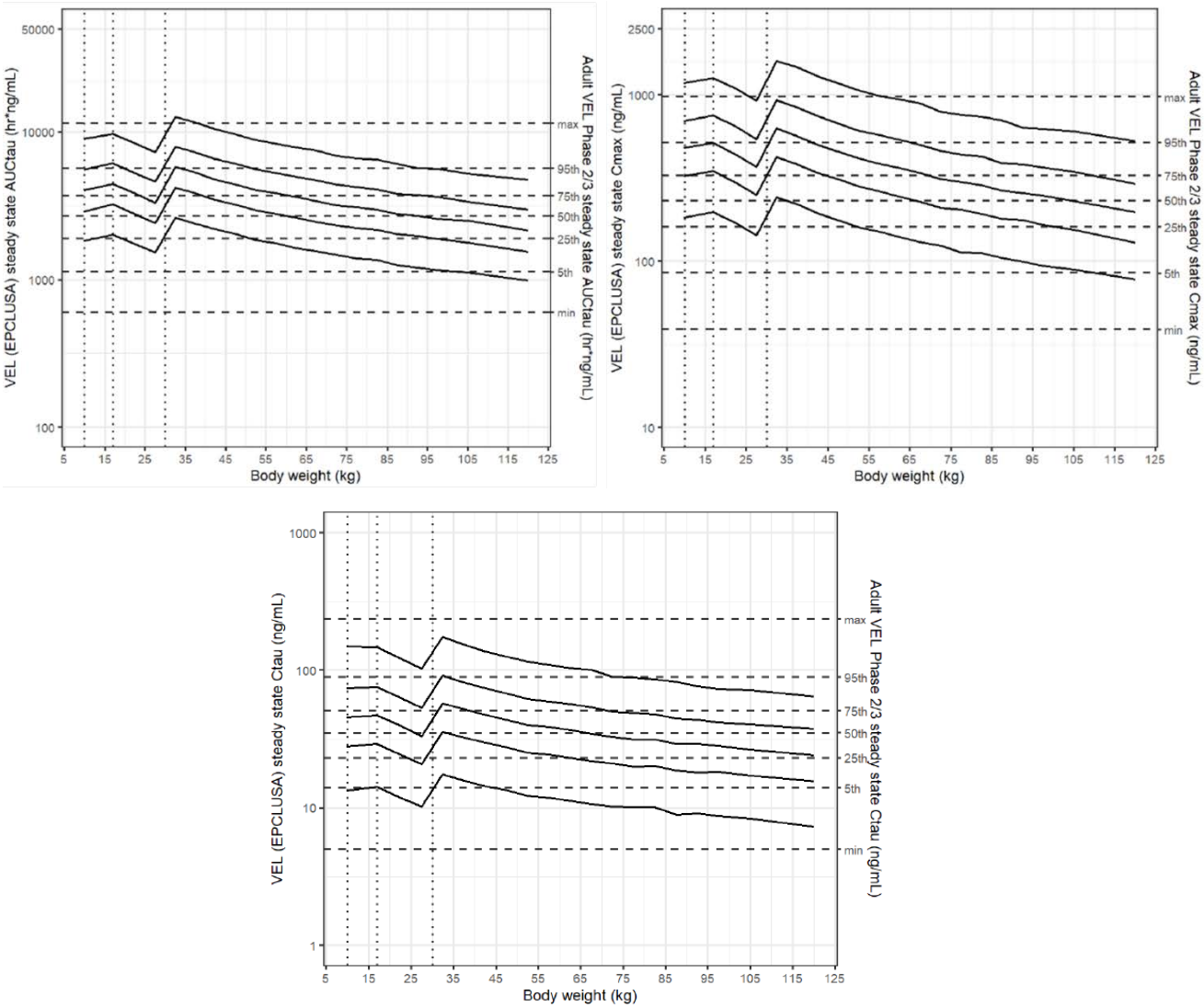
Figure 9. Simulated Steady-State AUCtau and Cmax for Sofosbuvir and GS-331007 Following the Proposed Weight-based Dosing in Pediatric Subjects



AUC_{tau} = area under the concentration-time curve over the dosing interval; C_{max} = maximum concentration; PopPK = population pharmacokinetic; SOF = sofosbuvir; VEL = velpatasvir; WT = baseline body weight.
Solid lines represent 5th, 25th, 50th, 75th, and 95th percentiles of simulated pediatric exposures; horizontal dashed lines represent distribution of adult exposures; vertical dashed lines indicate 10-, 17-, and 30-kg cutoffs. Adult exposures are the PopPK-predicted exposures from SOF/VEL (Epclusa) Phase 2/3 studies (Report# QP 15-0002 Sofosbuvir PopPK); minimum, 5th, 25th, 50th, 75th, and 95th percentiles, and maximum are shown. Top and bottom panels show SOF and GS-331007 data, respectively. Left and right panels show AUC_{tau} and C_{max}, respectively.

Source: Applicant's PPK Report, Figure 26, page 118.

Figure 10. Simulated Steady-State AUCtau, Cmax and Ctau for Velpatasvir Following the Proposed Weight-based Dosing in Pediatric Subjects



AUC_{tau} = area under the concentration-time curve over the dosing interval; C_{max} = maximum concentration; C_{tau} = concentration at the end of the dosing interval; PopPK = population pharmacokinetic; SOF = sofosbuvir; VEL = velpatasvir; WT = baseline body weight.
Solid lines represent 5th, 25th, 50th, 75th, and 95th percentiles of simulated pediatric exposures; horizontal dashed lines represent distribution of adult exposures; vertical dashed lines indicate 10-, 17-, and 30-kg cutoffs. Adult exposures are the PopPK-predicted exposures from SOF/VEL (Epclusa) Phase 2/3 studies (Report# QP 15-0001 GS-5816 PopPK); minimum, 5th, 25th, 50th, 75th, and 95th percentiles, and maximum are shown. Top left, top right, and bottom panels show AUC_{tau}, C_{max}, and C_{tau}, respectively.
Source: vel-pk-sim-20200515-epclusa-wtband.R

Source: Applicant's PPK Report, Figure 30, page 123.

Reviewer's assessment of SOF/VEL Weight based dosing in pediatrics

The reviewer conducted independent Monte-Carlo simulations to predict exposures in pediatric patients receiving the proposed WT-based dosing using the Applicant's updated pediatric PK models and a virtual pediatric population (age = 3 to <18 years old, male and female=1:1 ratio, n=3240) derived from the CDC growth chart (range: 11.3 to 96.8 kg). The AUCtau,ss, Cmax,ss (SOF, GS-331007, VEL), and Ctau,ss (VEL) were calculated using the simulated individual PK profiles and summarized by WT groups in Figure 11 (for SOF and GS331007) and Figure 12 (for VEL). The reviewer's simulations were concordant with the Applicant's simulations.

Figure 11 shows that, following the proposed dosing regimen, the expected SOF exposure metrics are comparable across WT groups (i.e. < 17kg, 17 to < 30 kg and ≥ 30 kg) in pediatric patients ages 3 to <18 years old. Median SOF exposures in pediatric patients are largely higher than the median observed exposures in adult patients.

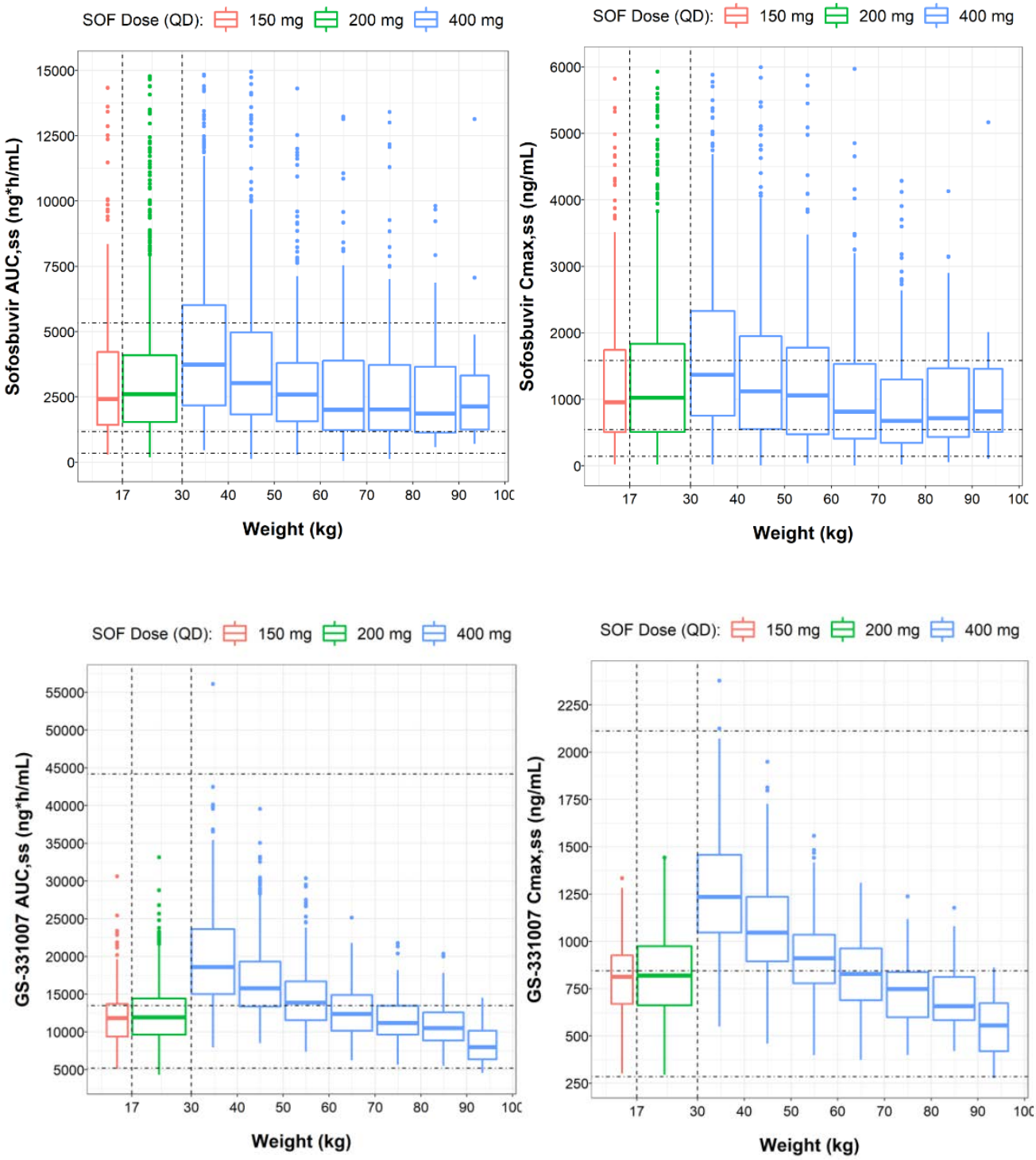
The estimated exposures for the major systemic inactive metabolite (GS-331007) are variable across WT groups. For body WT between 30 and 60 kg, the median values for AUCtau,ss, and Cmax,ss are higher than those observed in adult patients. However, for the lower WT groups (< 17 kg and 17 to < 30 kg), GS-331007 exposures are comparable to the median exposures and largely within the exposure range observed in adults.

Figure 12 shows that VEL exposure metrics (AUCtau,ss, Cmax,ss and Ctau,ss) are comparable across WT groups in pediatric patients. The expected VEL median Ctau,ss values are comparable to the observed values in adults. However, VEL AUCtau,ss, Cmax,ss median values are above those observed in adults.

Although SOF and VEL exposure metrics (AUCtau,ss, and Cmax,ss) are predicted to be higher than those observed in adults, they are largely contained within the range of exposure observed in adults and supported by the safety findings and SOF/VEL exposures observed in pediatric patients 6 to < 18 years old with WT > 17kg from study GS-US-342-1143.

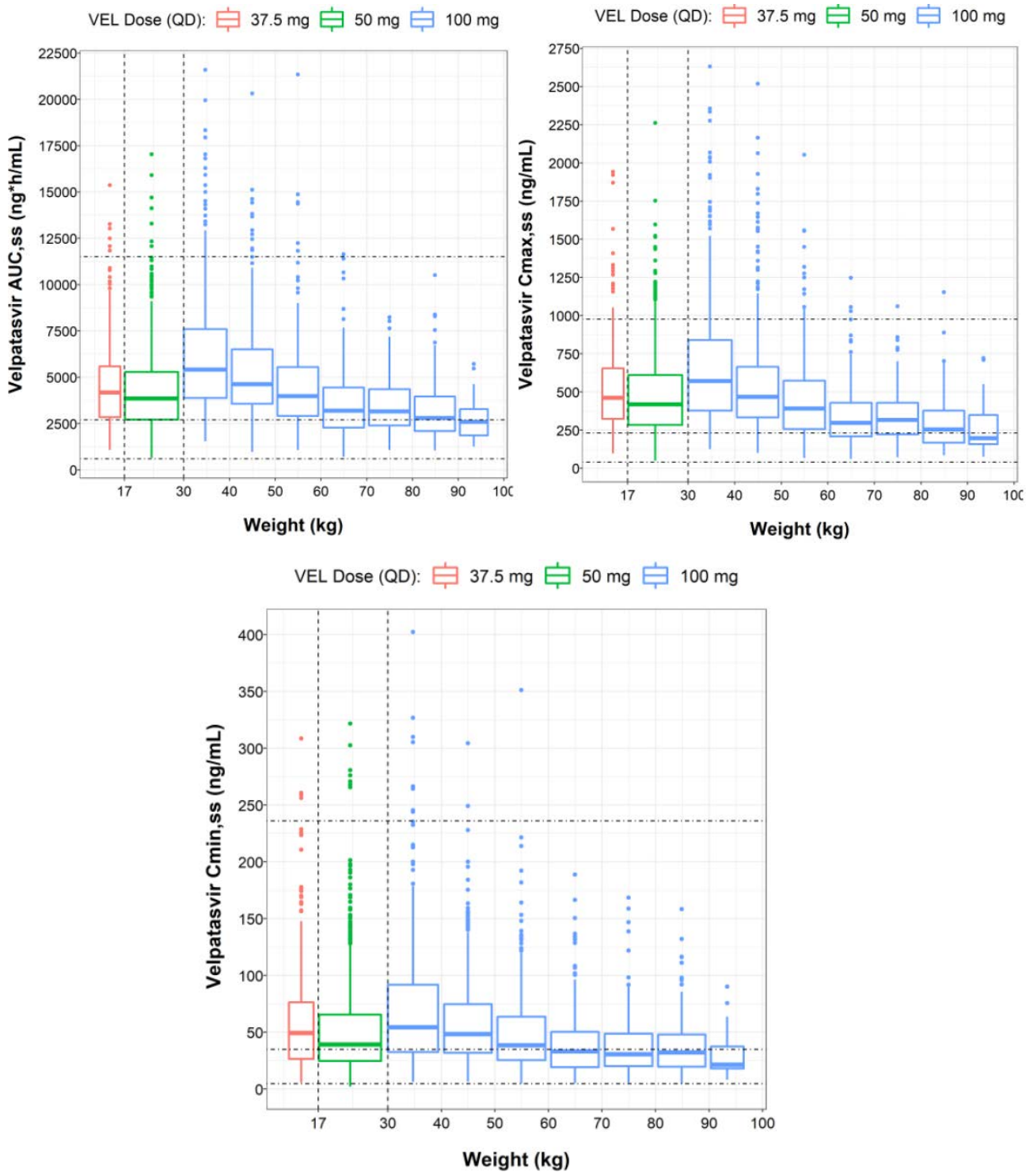
The results from the Applicant's and the reviewer's simulations suggest that the Applicant's proposed weight band-based dosing regimen for SOF/VEL in younger pediatric patients (< 17 kg) is appropriate and provides comparable exposure to the already approved dosing in older pediatric patients weighing ≥ 17 kg.

Figure 11. Simulated Sofosbuvir and GS-331007 Pediatric Exposures Following the Proposed Weight-based Dosing



Note: the black dotted lines represent the maximum, median, and minimum values for each metric from adults in Epclusa® development program (Phase 2/3 studies)

Figure 12. Simulated Velpatasvir Pediatric Exposures Following the Proposed Weight-based Dosing



Note: the black dotted lines represent the maximum, median and minimum values for each metric from adults in Epclusa® development program (Phase 2/3 studies)

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