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*APPLICATION NUMBER:*

**212477Orig1s000**

**CLINICAL PHARMACOLOGY**  
**REVIEW(S)**

## OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA Numbers (SDN)	205834 (835) S-29 212477 (1)
Link to EDR	<a href="#">\\CDSESUB1\evsprod\NDA205834\205834.enx</a> <a href="#">\\CDSESUB1\evsprod\NDA212477\212477.enx</a>
Submission Date	02/28/2019
Submission Types	Prior Approval Efficacy Supplement (NDA 205834) Original NDA (NDA 212477)
Brand Name	HARVONI®
Generic Name	Ledipasvir/Sofosbuvir (LDV/SOF)
Dosage Regimen	<ul style="list-style-type: none"> <li>Adults and pediatric patients 12 years and older: One tablet (90 mg of LDV and 400 mg of SOF) taken orally QD with or without food.</li> <li>Pediatric patients 3 years <span style="background-color: #cccccc; padding: 0 5px;">(b) (4)</span> 33.75/150 mg to 90/400 mg LDV/SOF tablet or oral granules per day with or without food.</li> </ul>
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, RCDS Ruoqing Li, PhD Chao Liu, PhD Su-Young Choi, Pharm D, PhD

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## 1. Executive summary

Harvoni® tablet is a fixed-dose combination (FDC) of LDV, an HCV NS5A inhibitor, and SOF, an HCV nucleotide analog NS5B polymerase inhibitor. HARVONI® is indicated for the treatment of HCV in adults and pediatrics (12 years of age and older or weighing at least 35 kg). The recommended dosage in adults and pediatric patients 12 years and older is one tablet (90 mg of LDV and 400 mg of SOF) taken orally once daily with or without food.

The Applicant submitted a Prior Approval Efficacy Supplement (NDA 205834) and an original NDA (212477) in support of expanding the indication of HARVONI® to pediatric patients 3 to < 12 years. The proposed pediatric dosages for patients 3 years or older are as follows:

Proposed Dosing for Pediatric Patients 3 Years and Older Using HARVONI Tablets or Oral Granules

Body Weight (kg)	Dosing of HARVONI Tablets or Oral Granules	HARVONI Daily Dose
at least 35	one 90 mg/400 mg tablet once daily or two 45 mg/200 mg tablets once daily or two 45 mg/200 mg packets of granules once daily	90 mg/400 mg per day
17 to less than 35	one 45 mg/200 mg tablet once daily or one 45 mg/200 mg packet of granules once daily	45 mg/200 mg per day
less than 17	one 33.75 mg/150 mg packet of granules once daily	33.75 mg/150 mg per day

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 LDV between adults and pediatric patients with HCV infection. The proposed dosage regimens were supported by PK, safety and efficacy data from study GS-US-337-1116 in HCV infected pediatric patients. The LDV/SOF FDC doses employed in this study targeted systemic exposures similar to those observed in adults at the approved dose (LDV/SOF 90/400 mg). Results from this study indicated that there were no clinically relevant differences between SOF, GS-331107 and LDV exposures ( $AUC_{tau}$  or  $C_{max}$ ) in pediatric subjects and exposures observed in the adult Phase 2/3 studies. Population PK analyses and simulations were conducted to evaluate SOF, GS-331107 and LDV exposures based on proposed weight band-based dosing regimens. The simulation analyses indicated that exposures in pediatrics 3 to < 12 years are comparable to those in adults.

The applicant developed and evaluated two pediatric formulations, a low strength HARVONI tablet (45/200 mg) and oral granules (SOF/LDV 45/200 mg and 33.75/150 mg). The applicant requested a biowaiver for the low strength HARVONI® 45/200-mg tablet and conducted study GS-US-337-2091 to evaluate the bioavailability (BA) of the granules relative to the approved tablet formulation, and the food effect on the granules. Overall, there were no clinically significant differences in the exposures of SOF, GS-331107 and LDV following a) administration of granules and tablets under fasted condition and b) administration of granules under fed and fasted conditions.

## 2. Recommendations

The Office of Clinical Pharmacology has reviewed the application and determined that the proposed weight-based dosage regimens in pediatrics are acceptable. This original NDA and pediatric efficacy supplement are *approvable* from a clinical pharmacology perspective.

## 3. Labeling Recommendations

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

### Section 2 Dosage and Administration

#### Sub-Section 2.4 Recommended Dosage in Pediatric Patients 3 years of Age and Older

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

### Section 8 Specific Population

#### Sub-Section 8.4 (Pediatric Use)

- Add the summary of findings in study GS-US-337-1116.

### Section 12 Clinical Pharmacology

#### Sub-Section 12.3 Pharmacokinetics

- Update the PK table to include exposure parameters of HARVONI® in pediatrics 3 years of age and older based on the findings in study GS-US-337-1116.

## 4. Summary of Important Clinical Pharmacology Findings

### Study GS-US-337-1116:

- Comparison of SOF, GS-331007, and LDV exposures between pediatric subjects 3 to < 12 years old and adults indicated that there were no clinically significant differences in exposures between pediatrics and adults. The proposed weight band based dosing is acceptable.

- Subjects weighing  $\geq 35$  to  $< 45$  kg experienced lower SOF, GS-331007, and LDV exposures relative to subjects in other weight band groups ( $< 17$  kg or  $\geq 17$  to  $< 35$  kg). This is not a concern because these subjects received, per-protocol, only half of the currently approved dose (i.e., they received LDV/SOF; 45/200 mg).
- Subjects who received tablets tend to have lower exposures of SOF ( $AUC_{tau}$ ) and GS-331007 ( $AUC_{tau}$  and  $C_{max}$ ) than those who received packets (granules). This is likely due to the fact that subjects with higher body weight within a weight band tended to receive tablets rather than granules.

#### Study GS-US-337-2091:

- Assessment of a) relative bioavailability between LDV/SOF oral granules and LDV/SOF FDC tablet and b) food effect on LDV/SOF oral granules indicated that there were no clinically significant differences in exposures of LDV/SOF after administration of oral granules relative to LDV/SOF tablet, and that LDV/SOF oral granules can be administered without regard to food.

## 5. Individual Study Review

### Study # 1: GS-US-337-1116 ([EDR Link](#))\*

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

Title:

A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination +/- Ribavirin in Adolescents and Children with Chronic HCV- Infection.

Study Period: 05 November 2014 - 15 June 2018

Objectives:

Primary objectives:

- PK lead-in phase: To evaluate the steady-state PK and confirm the dose of LDV/SOF FDC in chronic HCV infected pediatric subjects.
- Treatment phase: To evaluate the safety and tolerability of LDV/SOF FDC  $\pm$  RBV for 12 or 24 weeks in chronic HCV-infected pediatric subjects.

### Trial Design:

This was an open-label, multicohort, 2-part study [a PK lead-in phase (Part 1) and a treatment phase (Part 2)] that evaluated the PK, safety, and efficacy of LDV/SOF±RBV in pediatric subjects aged 3 to < 18 years with chronic genotype 1, 3, 4, 5, or 6 HCV infection. Both treatment naive or treatment experienced were enrolled. *Note: Data from subjects aged 12 to < 18 years were previously submitted and reviewed.*

### PK sampling scheme

*Intensive PK Phase:* Blood samples were collected for cohort 2 (6 to <12 years old) pre-dose and 0.5, 1, 2, 3, 4, 5, 8, and 12 hours post-dose and for cohort 3 (3 to <6 years old) predose and 0.5, 2, 4, 8, and 12 hours post-dose.

*Treatment Phase:* a single PK blood sample was collected at Weeks 1, 2, 4, 8, 12, 16, 20 and 24.

### Main Inclusion Criteria:

Males or nonpregnant/nonlactating females 3 to < 18 years of age, with chronic HCV genotype 1, 3, 4, 5, or 6 infection, HCV RNA  $\geq$  1000 IU/mL, and were HCV treatment naive or experienced. Weight limits were defined for subjects enrolled in the PK lead-in phase only: subjects in Cohort 2 (6 to < 12 years old) were required to weigh  $\geq$  17 kg and < 45 kg, and Cohort 3 was to include at least 4 subjects weighing  $\geq$  17 kg and at least 4 subjects weighing < 17 kg. Weight limits did not apply to additional subjects of each age group enrolled in the treatment phase.

### Test Product, Dose and Mode of Administration:

#### Test product:

- LDV/SOF FDC (90/400-mg tablet) (adult-strength tablet)
- LDV/SOF FDC (22.5/100-mg tablet) (low-dose tablet)
- LDV/SOF FDC (11.25/50-mg packets containing granules)
- Placebo-to-match LDV/SOF FDC (90/400-mg tablet)
- Placebo-to-match LDV/SOF FDC (22.5/100-mg tablet)
- RBV 40-mg/mL oral solution

#### Dosages and formulations by age group:

- 6 to < 12 years weighing  $\geq$  45 Kg: once oral daily dose of LDV/SOF 90/400 mg (adult dose).
- 6 to < 12 years weighing  $\geq$  35 to < 45 Kg: once oral daily dose of LDV/SOF 45/200 mg (of note, LDV/SOF 45/200 is the per protocol dose. However, the currently approved dose of subjects weighing  $\geq$  35 Kg is LDV/SOF 90/400).

- 6 to < 12 years weighing  $\geq 17$  to < 35 Kg: once oral daily dose of LDV/SOF 2  $\times$  22.5/100-mg tablets or LDV/SOF 4  $\times$  11.25/50-mg packets containing granules.
- 3 to < 6 years weighing  $\geq 17$  kg: once oral daily dose of LDV/SOF 4  $\times$  11.25/50-mg packets containing granules.
- 3 to < 6 years weighing < 17 kg: once oral daily dose of LDV/SOF 3  $\times$  11.25/50-mg packets containing granules.
- RBV: the following RBV doses were used as indicated based on the genotype.

Body Weight (kg)	Oral Ribavirin Daily Dosage <sup>a, b</sup>
less than 47	15 mg per kg per day (divided dose AM and PM)
47–49	600 mg per day (1 x 200 mg AM, 2 x 200 mg PM)
50–65	800 mg per day (2 x 200 mg AM, 2 x 200 mg PM)
66–80	1000 mg per day (2 x 200 mg AM, 3 x 200 mg PM)
greater than 80	1200 mg per day (3 x 200 mg AM, 3 x 200 mg PM)

a. The daily dosage of ribavirin is weight-based and is administered orally in two divided doses with food.

b. Ribavirin dosage regimens used in this study were slightly different than those listed in REBETOL® USPI.

#### 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 calibration curve and QC runs. All samples were analyzed within the long-term storage stability duration.

#### Results:

##### *Main Subject Demographics and Baseline Disease Characteristics*

##### 6 to < 12 Years Old

Ninety two subjects were enrolled, of which, 89 subjects were enrolled to receive LDV/SOF for 12 weeks, 1 subject was enrolled to receive LDV/SOF for 24 weeks, and 2 subjects with genotype 3 HCV infection were enrolled to receive LDV/SOF+RBV for 24 weeks. Most subjects had genotype 1 HCV infection (95.7%, 88 subjects). Two subjects (2.2%) had genotype 3 HCV infection, and 2 subjects (2.2%) had genotype 4 HCV infection. Two subjects (2.2%) had cirrhosis. The mean (SD) baseline eGFR using the Schwartz formula was 156.4 (24.38) mL/min/1.73 m<sup>2</sup>.

Most subjects were males (58.7%), white (79.3%), and non-Hispanic/Latino (84.8%), with a mean age of 9 years. The mean (SD) body weight for subjects was 32.8 (10.84) kg. Most subjects were treatment naive (78.3%).

### 3 to < 6 Years Old

Thirty four subjects were enrolled and received LDV/SOF for 12 weeks. All subjects completed study treatment except for one subject who prematurely discontinued study treatment due to an AE of product taste. Most subjects were female (70.6%), white (79.4%), and non-Hispanic/Latino (82.4%), with a mean age of 4 years. The mean (SD) body weight for subjects was 19.2 (5.03) kg. Most subjects had genotype 1 HCV infection (97.1%, 33 subjects). One subject (2.9%) had genotype 4 HCV infection. No subjects had cirrhosis. The mean (SD) baseline eGFR using the Schwartz formula was 169.1 (28.04) mL/min/1.73 m<sup>2</sup>. All subjects were treatment naive (100.0%).

### Pharmacokinetics

Exposures of LDV, SOF, and GS-331007 in the PK Lead-In phase were compared with population PK (POPPK)-derived exposure data from adult Phase 2/3 studies (Table 1). In addition, a POPPK modeling approach was used to estimate LDV, SOF, and GS-331007 PK parameters in pediatrics. Table 2. represents a comparison of exposures of LDV, SOF and GS-331007 based on POPPK analyses and POPPK-derived exposure data from adult Phase 2/3 studies (Please refer to section 7, Pharmacometrics review for more details about the POPPK analyses). Overall, there were no clinically significant differences between pediatrics and adults with respect to exposures of LDV, SOF, and GS-331007. The popPk analyses demonstrated similar results (Refer to Section 7, Pharmacometrics review for further details).

Table 1. Statistical Analysis of Intensive LDV, SOF and GS-331007 Exposures in Pediatric Subjects from the PK Lead-In phase Compared with Population PK-Based Exposures in the Adult Phase 2/3 Population

Analyte	PK Parameter	Pediatric Subjects vs Adult Phase 2/3 Population %GMR (90% CI)		
		12 to < 18 years old (≥ 45kg) LDV/SOF 90/400 mg N = 10	6 to < 12 years old (≥ 17 kg and < 45 kg) LDV/SOF 45/200 mg N = 10 <sup>a</sup>	3 to < 6 years old LDV/SOF 45/200 mg or LDV/SOF 33.75/150 mg <sup>b</sup> N = 13 <sup>c</sup>
LDV	AUC <sub>tau</sub>	127.18 (94.89, 170.45)	82.25 (61.34, 110.30)	120.46 (93.18, 155.73)
	C <sub>max</sub>	161.64 (125.30, 208.54)	112.59 (87.23, 145.34)	157.69 (126.13, 197.15)
SOF	AUC <sub>tau</sub>	159.88 (137.89, 185.37)	129.48 (110.79, 151.32)	187.76 (143.41, 245.82)
	C <sub>max</sub>	155.58 (127.18, 190.32)	143.11 (117.16, 174.82)	192.41 (161.16, 229.71)
GS-331007	AUC <sub>tau</sub>	105.20 (90.61, 122.13)	65.76 (56.62, 76.37)	94.08 (82.51, 107.27)
	C <sub>max</sub>	138.92 (119.84, 161.04)	109.66 (94.60, 127.12)	138.26 (121.46, 157.39)

GMR = geometric mean ratio

a For SOF AUC<sub>tau</sub>, n = 9.

b Subjects 3 to < 6 years old weighing ≥ 17 kg received LDV/SOF 45/200 mg while those < 17 kg received LDV/SOF 33.75/150 mg

c For SOF AUC<sub>tau</sub>, n = 3.

Source: Clinical Study Report, P. 147

Table 2. Statistical Comparison of SOF, GS-331007 and LDV Exposures (based on population PK analyses) Between Pediatric Subjects 3 to < 12 Years Old and the Adult Phase 2/3 Population

Analyte	PK Parameter	6 to < 12 Years Old LDV/SOF 45/200 mg (N = 62 for SOF and N = 92 for GS-331007 or LDV)		3 to < 6 Years Old LDV/SOF 45/200 mg or 33.75/150 mg <sup>a</sup> (N = 33 for SOF, GS-331007, and LDV)	
		Mean (CV%)	% GMR (90% CI) Pediatric Subjects / Phase 2/3 Adult Population	Mean (CV%)	% GMR (90% CI) Pediatric Subjects / Phase 2/3 Adult Population
SOF	AUC <sub>tau</sub> (h•ng/mL)	1291.5 (28.8)	93.95 (88.43, 99.82)	1759.0 (31.9)	126.86 (116.83, 137.75)
	C <sub>max</sub> (ng/mL)	617.6 (22.2)	97.47 (89.91, 105.67)	806.4 (22.6)	127.18 (113.90, 142.02)
GS-331007	AUC <sub>tau</sub> (h•ng/mL)	10,114.1 (36.2)	80.11 (76.16, 84.26)	11,911.7 (16.1)	98.32 (90.55, 106.76)
	C <sub>max</sub> (ng/mL)	893.4 (30.9)	120.89 (115.01, 127.06)	1052.4 (15.1)	146.98 (135.49, 159.44)
LDV	AUC <sub>tau</sub> (h•ng/mL)	8887.6 (48.5)	109.59 (99.37, 120.86)	9120.7 (42.9)	116.62 (99.23, 137.06)
	C <sub>max</sub> (ng/mL)	429.9 (46.3)	120.01 (110.18, 130.73)	470.2 (37.4)	137.60 (119.56, 158.35)
	C <sub>tau</sub> (ng/mL)	299.1 (52.0)	125.94 (114.05, 139.06)	282.8 (50.8)	121.50 (103.17, 143.09)

CV = coefficient of variation; GMR = geometric mean ratio

<sup>a</sup> Subjects weighing ≥ 17 kg received LDV/SOF 45/200 mg, while subjects weighing < 17 kg received LDV/SOF 33.75/150 mg.

Source: Ad Hoc Tables 9867.8 and 9867.9

Source: Summary of Clinical Pharmacology, P. 20

### Reviewer's analyses

The applicant submitted the summary results by age groups. However, as the dosing recommendation will be based on body weight, exposures (determined by intensive PK) of proposed body weight bands were compared. In addition, exposures were compared between the tablet and granule formulations to confirm that there is no formulation-dependent differences in exposures in pediatric patients.

#### 1. Exposures of SOF, GS331007, and LDV by weight bands

There were lower exposures of SOF, GS-331007 and LDV in subjects weighing ≥ 35 to < 45 kg (Figure 1). This is mainly attributed to the subjects receiving the lower dose (LDV/SOF; 45/200 mg QD) per protocol than the approved dose (LDV/SOF; 90/400 mg QD).

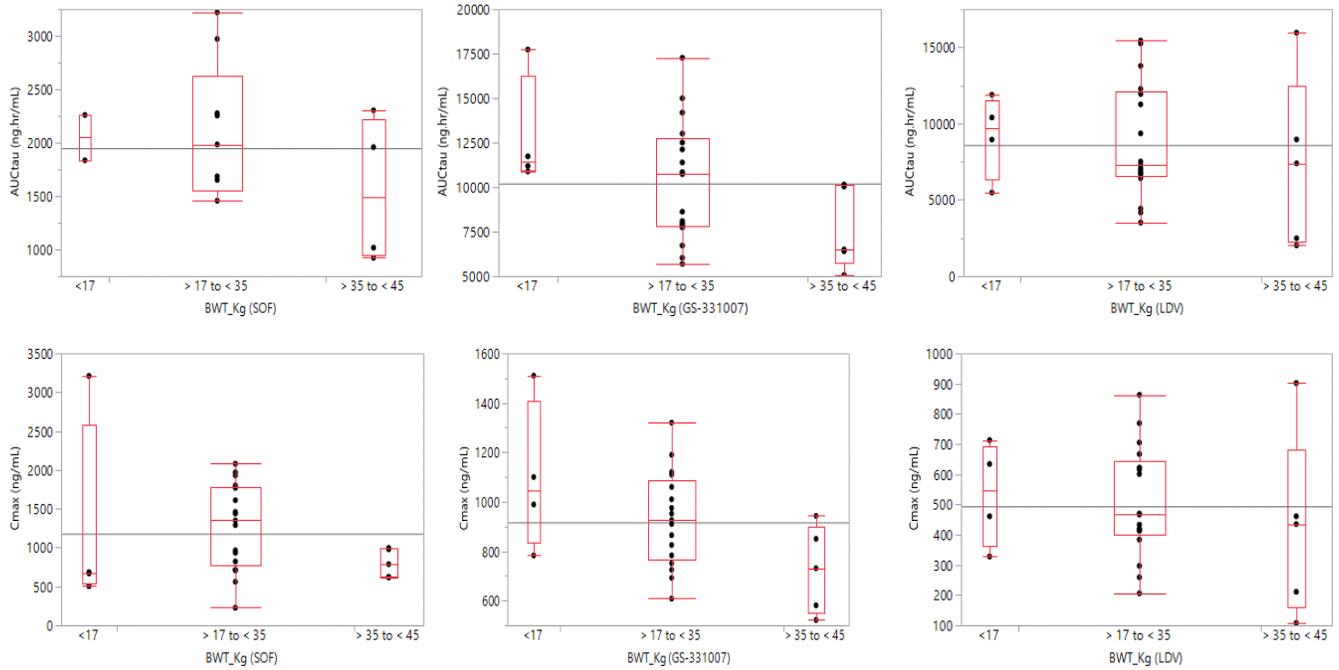
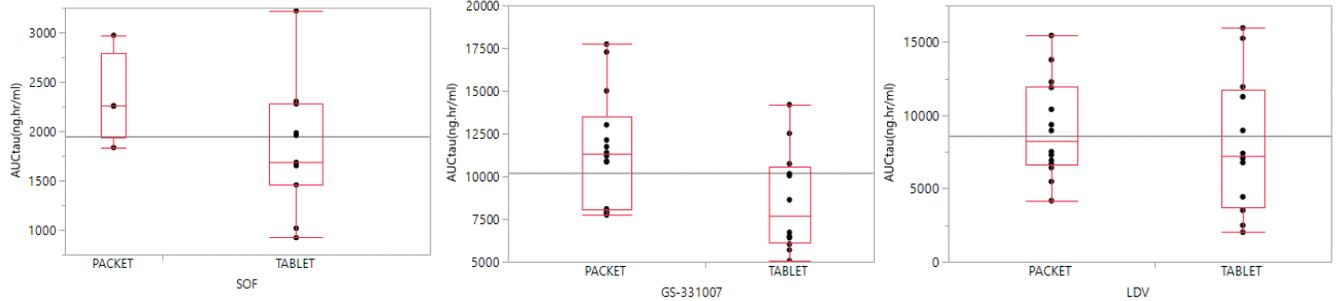


Figure 1. Exposures of SOF, GS-331007 and LDV by body weight bands. Based on intensive PK data. No subjects weighed > 45 Kg. Solid horizontal lines represent mean pediatric exposure values across all body weight bands.

2. Exposures of SOF, GS331007, and LDV by formulation

There were trends towards lower exposures of SOF ( $AUC_{\tau}$ ) and GS-331007 ( $AUC_{\tau}$  and  $C_{max}$ ) in subjects who were administered tablets versus those who were administered packets (granules) (Figure 2). This is likely due to the fact that subjects with higher body weight within a weight band tended to receive tablets rather than granules.



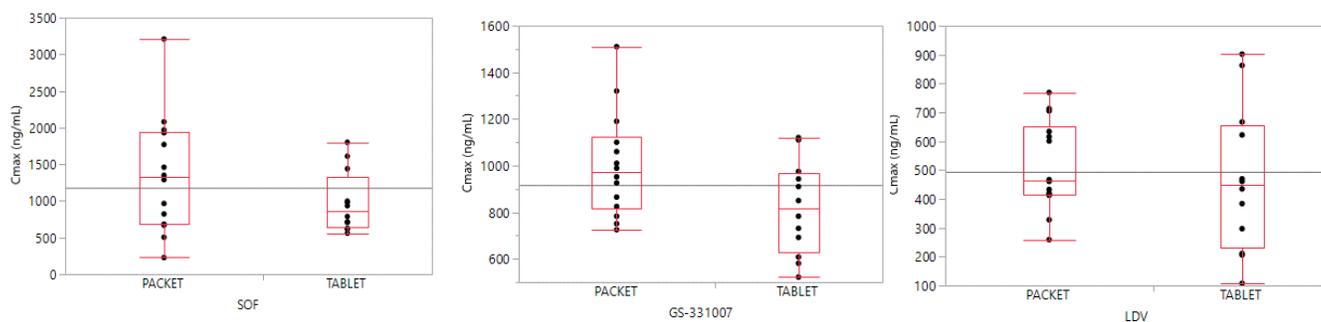


Figure 2. Exposures of SOF, GS-331007 and LDV by formulation. Based on intensive PK data. Packet (granules) and Tablets were of LDV/SOF 11.25/50 and 22.5/100 mg strength, respectively. Solid horizontal lines represent mean pediatric exposure values across formulations.

### 3. Exposures of SOF, GS331007, and LVD in one subject who experienced relapse.

Subject (b) (6) experienced a treatment relapse. Subject (b) (6) is an 8 years old, white, female, HCV genotype 1 infected subject weighing 26.5 kg who received LDV/SOF 45/200 mg as granules. LDV exposure in this subject was noticeably lower than the typical population LDV exposure (Table 3). However, it is unclear if the relapse was mainly due to the lower exposures of LDV or SOF as these exposures are still expected to be efficacious based on the exposure-response relationship observed in pediatrics and adults.

Table 3: PK Exposure parameters of SOF, GS-331007 and LDV in Subject (b) (6)

	AUC <sub>tau</sub> (hr·ng/mL)	C <sub>max</sub> (ng/mL)	C <sub>tau</sub> (ng/mL)
SOF	967 (1454)	525.2 (683.2)	--
GS-331007	8252 (10590)	914.9 (935.1)	--
LDV	3986 (8949)	206.5 (440.5)	121.7 (294.8)

Mean values for subjects (3 to <12 yr) are in parenthesis.

Source: POPPK Study Report. P.121

### Conclusions

- Following the administration of proposed doses of HARVONI, there are no clinically significant differences between pediatrics (3 to <12 years old) and adults with respect to exposures of SOF, GS-331007 and LDV.

Study # 2/ GS-US-337-2091 ([EDR Link](#))

Title:

A Phase 1 Relative Bioavailability and Food Effect Study of a Pediatric Oral Granule Formulation of Ledipasvir/Sofosbuvir in Healthy Adult Subjects.

Study Period: 24 May 2016 – 27 July 2016

Objectives:

Primary objectives:

- To evaluate the relative bioavailability of a pediatric oral granule formulation of LDV/SOF relative to tablet formulation
- To evaluate the effect of concomitant food intake on the PK of a pediatric oral granule formulation of LDV/SOF

Trial Design:

This was a Phase 1, randomized, open-label, single-center, single-dose, 3-period, crossover study that evaluated the BA of a pediatric oral granule formulation of LDV/SOF relative to the adult tablet formulation in healthy adult subjects. The safety and tolerability of the pediatric oral granule formulation of LDV/SOF and the effect of food on its PK were also evaluated. A total of 42 eligible subjects were randomized to 1 of 6 treatment sequences, with a 9-day washout interval between each treatment, as follows:

- Treatment A: Single dose of LDV/SOF tablet (90/400 mg; 1 × 90/400 mg tablet) administered orally under fasted condition.
- Treatment B: Single dose of LDV/SOF oral granules (90/400 mg; 8 × 11.25/50 mg units) administered orally under fasted condition.
- Treatment C: Single dose of LDV/SOF oral granules (90/400 mg; 8 × 11.25/50 mg units) administered orally under fed condition.

Product, Dose and Mode of Administration:

Test product:

- Treatment B: LDV/SOF oral granules (90/400 mg; 8 × 11.25/50 mg units) were administered orally as a single dose under fasted condition.
- Treatment C: LDV/SOF oral granules (90/400 mg; 8 × 11.25/50 mg units) were administered orally as a single dose under fed condition (high fat meal).

Reference product:

- Treatment A: LDV/SOF tablet (1 × 90/400 mg tablet) was administered orally under fasted condition.

Bioanalytical method:

All PK samples were analyzed using validated LC/MS/MS methods. The precision and accuracy were acceptable for calibration curve and QC runs. All samples were analyzed within the long-term storage stability duration.

Results:

*Main Subject Demographics and Baseline Characteristics*

Most subjects were male (71.4%, 30 subjects), white (54.8% white, 23 subjects), and of Hispanic or Latino ethnicity (66.7% Hispanic or Latino, 28 subjects). Subjects had a mean (SD) age of 29 (6.0) years, mean (SD) BMI of 25.0 (2.81) kg/m<sup>2</sup>, and mean (SD) CLcr of 117.17 (21.142) mL/min at baseline.

Pharmacokinetics

Table 4: Relative bioavailability data between LDV/SOF oral granules and LDV/SOF FDC Tablet

PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI)
	Treatment A	Treatment B	
	LDV/SOF Tablet Formulation (1 × 90/400 mg) fasted (Reference)	LDV/SOF Oral Granule Formulation (8 × 11.25/50 mg units) fasted (Test)	LDV/SOF Oral Granules vs LDV/SOF FDC Tablet
<b>LDV (N = 42 reference/N = 39 test)<sup>a</sup></b>			
AUC <sub>last</sub> (ng*h/mL)	7362.3 (48.3)	6242.5 (40.7)	87.76 (77.94, 98.82)
AUC <sub>inf</sub> (ng*h/mL)	8467.5 (54.4)	7088.4 (46.3)	88.36 (78.43, 99.54)
C <sub>max</sub> (ng/mL)	261.3 (43.5)	214.8 (38.2)	84.59 (74.69, 95.81)
<b>GS-331007 (N = 42 reference/N = 42 test)</b>			
AUC <sub>last</sub> (ng*h/mL)	11146.3 (26.9)	11525.8 (26.3)	103.14 (96.71, 110.00)
AUC <sub>inf</sub> (ng*h/mL)	11720.0 (26.1)	12095.0 (24.4)	103.64 (98.48, 109.07)
C <sub>max</sub> (ng/mL)	833.9 (23.6)	951.9 (27.0)	112.81 (104.12, 122.22)
<b>SOF (N = 42 reference/N = 42 test)</b>			
AUC <sub>last</sub> (ng*h/mL)	1559.8 (40.5)	1676.9 (43.7)	102.13 (87.16, 119.67)
AUC <sub>inf</sub> (ng*h/mL)	1580.8 (40.2)	1684.1 (43.5)	101.60 (86.67, 119.10)
C <sub>max</sub> (ng/mL)	1221.0 (38.5)	1266.7 (46.6)	95.98 (78.00, 118.11)
<b>GS-566500 (N = 42 reference/N = 42 test)</b>			
AUC <sub>last</sub> (ng*h/mL)	1846.6 (31.4)	1952.9 (33.5)	100.59 (88.89, 113.83)
AUC <sub>inf</sub> (ng*h/mL)	1894.9 (30.8)	2009.7 (33.0)	101.37 (90.17, 113.96)
C <sub>max</sub> (ng/mL)	475.1 (33.9)	511.3 (34.9)	103.04 (91.06, 116.60)

a Subjects (b) (6) and (b) (6) in Treatment B were excluded since their LDV predose plasma concentration was > 5% of C<sub>max</sub>.

Source: Clinical Study report, P. 6

- There were slight decreases in LDV and SOF exposures; however, they are not clinically significant based on exposure-response relationship.

Table 5. Food effect on exposures of LDV/SOF after oral granules administration with high fat meal.

PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI)  LDV/SOF Oral Granules High-Fat Meal vs Fasted
	Treatment B	Treatment C	
	LDV/SOF Oral Granule Formulation (8 × 11.25/50 mg units) fasted (Reference)	LDV/SOF Oral Granule Formulation (8 × 11.25/50 mg units) fed (Test)	
<b>LDV (N = 39 reference/N = 40 test)<sup>a,b</sup></b>			
AUC <sub>last</sub> (ng*h/mL)	6242.5 (40.7)	5149.6 (26.2)	87.62 (79.65, 96.39)
AUC <sub>inf</sub> (ng*h/mL)	7088.4 (46.3)	5748.3 (29.0)	87.06 (78.95, 96.00)
C <sub>max</sub> (ng/mL)	214.8 (38.2)	159.8 (28.9)	78.15 (71.26, 85.71)
<b>GS-331007 (N = 42 reference/N = 42 test)</b>			
AUC <sub>last</sub> (ng*h/mL)	11525.8 (26.3)	11653.6 (18.9)	103.12 (97.61, 108.94)
AUC <sub>inf</sub> (ng*h/mL)	12095.0 (24.4)	12220.6 (18.3)	102.26 (98.18, 106.52)
C <sub>max</sub> (ng/mL)	951.9 (27.0)	583.1 (24.2)	62.01 (56.90, 67.59)
<b>SOF (N = 42 reference/N = 42 test)</b>			
AUC <sub>last</sub> (ng*h/mL)	1676.9 (43.7)	2577.2 (33.1)	166.11 (145.00, 190.30)
AUC <sub>inf</sub> (ng*h/mL)	1684.1 (43.5)	2597.7 (32.9)	166.18 (145.56, 189.71)
C <sub>max</sub> (ng/mL)	1266.7 (46.6)	1236.3 (49.0)	100.32 (84.83, 118.65)
<b>GS-566500 (N = 42 reference/N = 42 test)</b>			
AUC <sub>last</sub> (ng*h/mL)	1952.9 (33.5)	2931.7 (19.1)	163.23 (144.62, 184.23)
AUC <sub>inf</sub> (ng*h/mL)	2009.7 (33.0)	2988.8 (18.7)	160.65 (143.40, 179.99)
C <sub>max</sub> (ng/mL)	511.3 (34.9)	593.9 (31.0)	122.12 (108.28, 137.73)
a	Subjects (b) (6) and (b) (6) in Treatment B were excluded since their LDV predose plasma concentration was > 5% of C <sub>max</sub> .		
b	Subjects (b) (6) and (b) (6) in Treatment C were excluded since their LDV predose plasma concentration was > 5% of C <sub>max</sub> .		

Source: Clinical Study report, P. 7

- The 90 % CI of the GLSM ratios of test versus reference formulations are outside of the predefined no-effect boundary (80 – 125%) for LDV C<sub>max</sub> (90% CI; 71.26 – 85.71), for GC-331007 C<sub>max</sub> (90% CI; 59.90 – 67.59) and SOF AUC (90% CI; 145.00 – 190.30). These are not considered clinically significant based on exposure-response relationship and food effect results from historical data listed in Harvoni USPI.

### Conclusions

- There are no clinically significant differences in exposures of LDV/SOF after administration of oral granules relative to LDV/SOF tablet.
- The LDV/SOF oral granule formulation can be administered without regard to food.

## 6. Data Integrity-Related Consults (OSIS Inspections)

Clinical site inspection for Study GS-US-337-2091 and Analytical site inspection for Studies GS-US-337-2091 and GS-US-337-1116 were not conducted by the Office of Study Integrity and Surveillance (OSIS) because clinical and analytical inspections were conducted in December 2017 and January 2019, respectively, which fall within the surveillance interval. The inspections were conducted under the following submissions: [REDACTED] (b) (4) [REDACTED]. The final classification for the inspections was No Action Indicated (NAI). (Refer to Dr. James J Lumalcuri's memorandum for details).

## 7. Pharmacometrics Review

Population pharmacokinetics (PPK) models were developed by the Applicant for both Harvoni and Sovaldi to describe the PK of sofosbuvir (SOF) and its primary metabolite, GS-331007, in hepatitis C virus (HCV)-infected pediatric subjects administered SOF+ ribavirin (RBV) or ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) +/- RBV. The impact of statistically significant covariates on SOF, GS-331007 and LDV exposures in pediatrics were explored by sensitivity analysis. The exposures of SOF, GS-331007 and LDV in pediatric patients were estimated and compared with the exposures in adult patients. In this review, the FDA Pharmacometrics Reviewer evaluated the Applicant's PPK model for SOF, GS-331007 and LDV, and the Applicant's exposure-response analysis for safety.

Two clinical studies were included in the PPK model development as summarized in Table 1.

Table 1 Summary of participants included in the PPK analysis

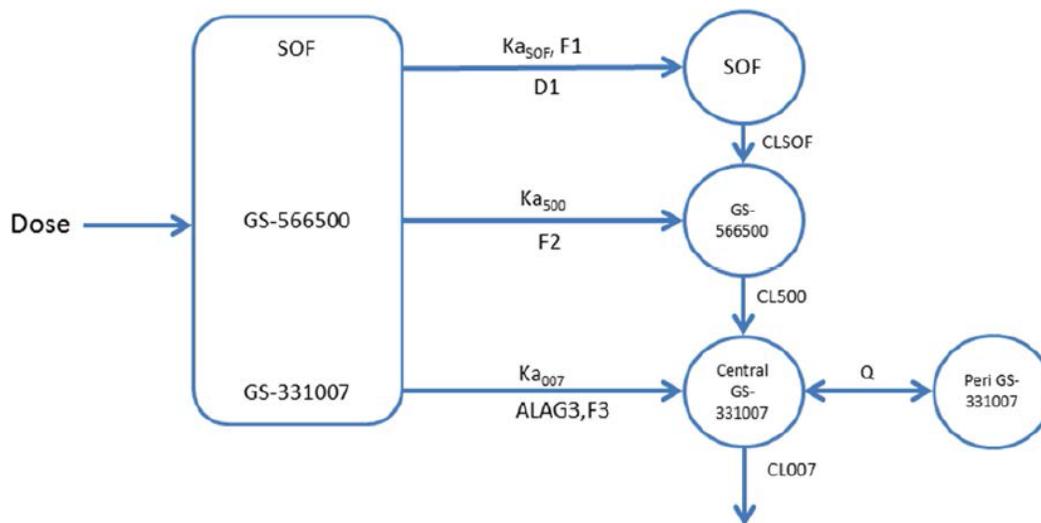
Study	Population	Phase	Treatment	Sampling (Intensive/Sparse)
GS-US-334-1112	Pediatrics aged 3 to < 18 years with chronic genotype 2, 3 HCV infection.	2	a. 200 mg SOF for subjects 6 to <12 years old; b. 200 mg SOF for subjects 3 to <6 years old weighing > 17 kg; c. 150 mg for subjects 3 to <6 years old weighing <17 kg.	Intensive PK in PK lead-in phase; Sparse PK in treatment phase.
GS-US-337-1116	Pediatrics aged 3 to < 18 years with chronic genotype 1, 3, 4, 5, or 6 HCV infection.	2	a. 45/200 mg LDV/SOF for subjects 6 to <12 years old; b. 45/200 mg LDV/SOF for subjects 3 to <6 years old weighing > 17 kg; c. 33.75/150 mg LDV/SOF for subjects 3 to <6 years old weighing <17 kg.	Intensive PK in PK lead-in phase; Sparse PK in treatment phase.

Source: adapted from Applicant's population PK report.

### 7.1. SOF Joint Model

Applicant developed a semi-mechanistic joint parent-metabolite PPK model to describe the exposures of SOF and GS-331007 (primary metabolite) in a pooled population of pediatric (3 to <18 years) HCV-infected subjects administered SOF + ribavirin (RBV) or LDV/SOF fixed dose combination (FDC) +/- RBV. Overall, the model development dataset had a total of 1579 SOF data points from 245 subjects, 1642 GS-566500 data points from 330 subjects, and 2392 GS-331007 data points from 330 subjects. The structural model, depicting metabolism of SOF to the intermediate metabolite GS-566500, which is subsequently metabolized to and cleared from the body as GS-331007, is illustrated in Figure 1.

Figure 1 PPK model diagram for SOF and SOF metabolites



Source: Applicant's PPK study report page 30 Figure 2

Parameter estimates for the final PPK model are provided in Table 2.

Table 2 Summary of final model PK parameters

Parameter	Parameter Description		Population Estimate	Change from Typical (%)	Inter-Individual Variability
$\exp(\theta_1)$	Absorption rate constant for SOF, KaSOF (hr <sup>-1</sup> )		3.06	--	--
$\exp(\theta_2)$	Absorption rate constant for GS-566500, Ka500 (hr <sup>-1</sup> )		0.100	--	†
$\exp(\theta_3)$	Absorption rate constant for GS-331007, Ka007 (hr <sup>-1</sup> )		0.0534	--	--
$\exp(\theta_4)$	Apparent clearance for SOF, CLSOF (L/hr)		34.5	-	37.9
$\exp(\theta_4 + \theta_{19} * \log(\frac{WT}{42}))$	Influence of WT on CLSOF	5 <sup>th</sup> %ile of WT	23.5	-32.9	
		95 <sup>th</sup> %ile of WT	45.6	32.2	
$\exp(\theta_5)$	Apparent volume for SOF, VSOF (L)		26.3	--	--
$\exp(\theta_5 + \theta_{20} * \log(\frac{WT}{42}))$	Influence of WT on VSOF	5 <sup>th</sup> %ile of WT	16.0	-39.2	
		95 <sup>th</sup> %ile of WT	37.9	44.1	
$\exp(\theta_6)$	Apparent clearance for GS-566500, CL500 (L/hr)	without RBV	36.6	--	--
$\exp(\theta_{25})$		with RBV	68.7	87.7	
$\exp(\theta_6 + \theta_{21} * \log(\frac{WT}{42}))$	Influence of WT on CL500	5 <sup>th</sup> %ile of WT	23.0	-37.2	
		95 <sup>th</sup> %ile of WT	51.6	41.0	
$\exp(\theta_7)$	Apparent volume for GS-566500, V500 (L)		62.8	--	56.3
$\exp(\theta_7 + \theta_{22} * \log(\frac{WT}{42}))$	Influence of WT on V500	5 <sup>th</sup> %ile of WT	24.7	-60.7	
		95 <sup>th</sup> %ile of WT	125	99.0	
$\exp(\theta_8)$	Apparent clearance for GS-331007, CL007 (L/hr)	without RBV	13.1	--	35.6
$\exp(\theta_{26})$		with RBV	13.7	4.58	
$\exp(\theta_8 + \theta_{23} * \log(\frac{WT}{42}))$	Influence of WT on CL007	5 <sup>th</sup> %ile of WT	6.95	-46.9	
		95 <sup>th</sup> %ile of WT	20.8	58.8	
$\exp(\theta_8 + \theta_{27} * \log(\frac{CLCRSW}{153}))$	Influence of CLCRSW on CL007	5 <sup>th</sup> %ile of CLCRSW	10.6	-19.1	
		95 <sup>th</sup> %ile of CLCRSW	16.3	24.4	
$\exp(\theta_9)$	Apparent central volume for GS-331007, Vc007 (L)		4.95	--	--
$\exp(\theta_9 + \theta_{24} * \log(\frac{WT}{42}))$	Influence of WT on Vc007	5 <sup>th</sup> %ile of WT	1.52	-69.3	
		95 <sup>th</sup> %ile of WT	11.8	138	
$\exp(\theta_{10})$	Apparent inter-compartment clearance for GS-331007, Q007 (L/hr)		4.62	--	--
$\exp(\theta_{11})$	Apparent peripheral volume for GS-331007, Vp007 (L)		196	--	--
$\exp(\theta_{12})$	Duration of zero order input for SOF, D1 (hr)		1.65	--	--

Parameter	Parameter Description		Population Estimate	Change from Typical (%)	Inter-Individual Variability
$\theta_{13}$	Relative molar% of dose absorbed for SOF	without LDV	13.7	--	--
$\theta_{13}*(1+\theta_{14})$		with LDV	21.4	56.2	--
$\theta_{15}$	Fraction of relative molar% of dose absorbed for GS-566500		16.1	--	--
$\theta_{18}$	Absorption lag time for GS-331007		1.88	--	--
$\sqrt{\theta_{28}}$	Residual error for SOF (%)		127		
$\sqrt{\theta_{16}}$	Residual error for GS-566500 (%)		76.5		
$\sqrt{\theta_{17}}$	Residual error for GS-331007 (%)		59.2		

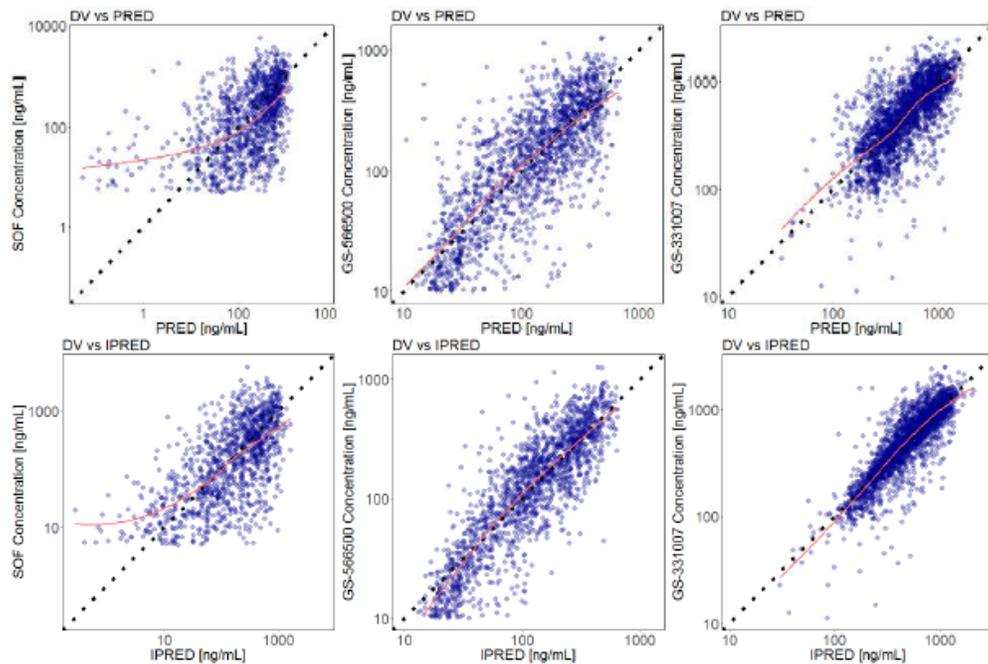
5<sup>th</sup> and 95<sup>th</sup> %ile of WT are 16.7 kg and 82.7 kg respectively; 5<sup>th</sup> and 95<sup>th</sup> %ile of CLCRSW are 113 ml/min/1.73m<sup>2</sup> and 209 ml/min/1.73m<sup>2</sup> respectively

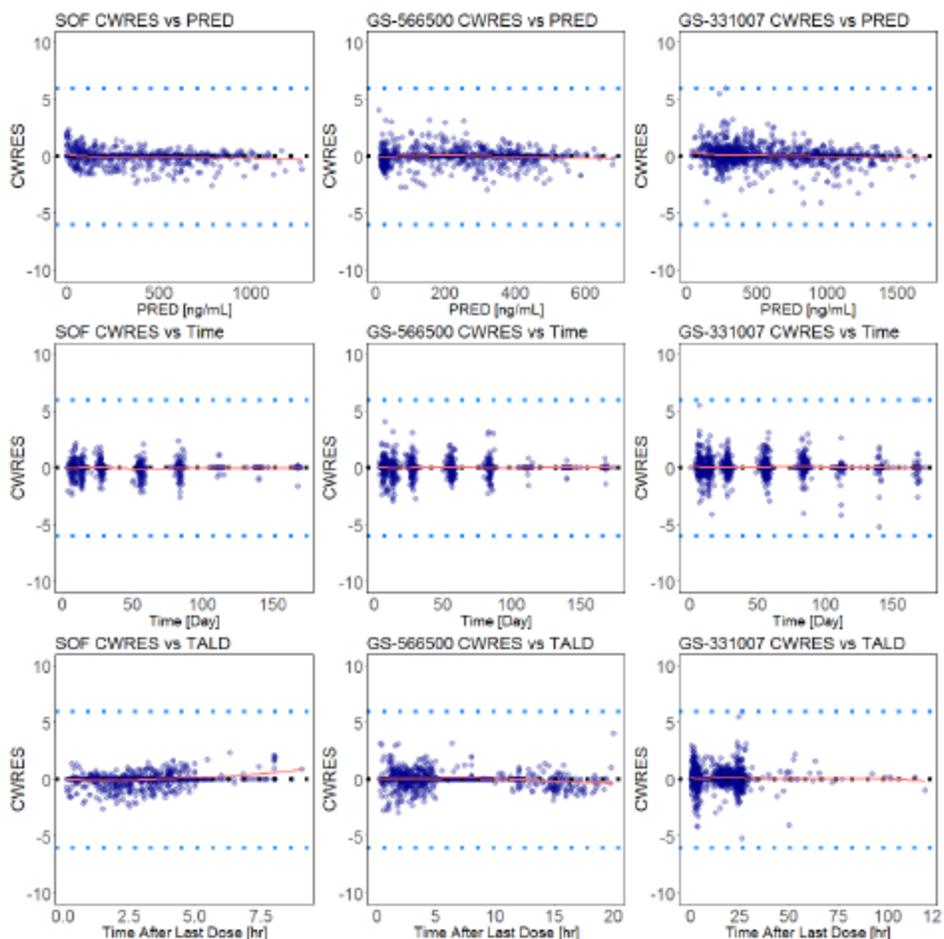
Source:

Applicant's PPK study report page 34 Table 3

The goodness-of-fit plots of the joint PPK model for pediatric subjects are shown in Figure 2.

Figure 2 Goodness-of-fit plots for the final joint PPK model





Source: Applicant's PPK study report page 37 Figure 3 & 4

Shrinkage of the final model parameters is presented in Table 3.

Table 3 Shrinkage estimates of inter-individual in the final model

Parameter	Parameter Description	Shrinkage (%)
$\omega_{CLSOF}$	IIV of CLSOF	31.2
$\omega_{V500}$	IIV of V500	17.1
$\omega_{CL007}$	IIV of CL007	17.2
$\sigma$	Residual error (%)	1.51

Source: Applicant's PPK study report page 45 Table 6

The Applicant conducted sensitivity analysis to evaluate the impact of statistically significant covariates on steady-state SOF and GS-331007 exposures. The effect of total body weight (WT) was the most influential covariate with  $\leq$  ~50% change in SOF exposures for subjects with extreme covariate values (i.e., 5th and 95th WT percentile) relative to the median exposures. The covariate effect of LDV usage

on F1 results in an approximately 50% increase in SOF exposures in pediatric subjects receiving LDV/SOF compared to subjects without LDV. The hypothetical combination of WT and LDV accounted for the majority of the observed PK variability, with an approximately -50% to +90% change in exposures for subjects with extreme covariate values relative to the median exposures. Other covariates, including age, sex, race, ethnicity, baseline creatinine clearance derived by the Schwartz equation (CLCRSW), HCV genotype (HCVGT), food, BSA, IL28B, or BMI did not show a statistically significant impact on the PK of SOF.

Within pediatric subjects, WT was the most influential covariate with  $\leq$  an approximately 50% change in GS-331007 exposures for subjects with extreme covariate values (i.e., 5th and 95th WT percentile) relative to the median exposures. The covariate effect of CLCRSW on CL007 resulted in  $\leq$  40% change in GS-331007 exposures for the observed range of CLCRSW. The covariate effect of LDV resulted in an approximately 15% increase in GS-331007 exposures in subjects receiving LDV/SOF compared to subjects receiving SOF. Other covariates, including age, sex, race, ethnicity, HCVGT, food, BSA, IL28B, or BMI did not show a statistically significant impact on the PK of GS-331007.

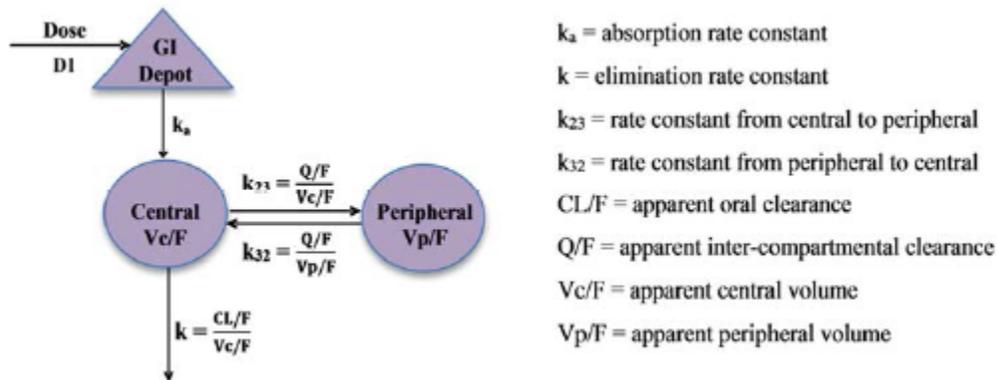
*Reviewer's comment: The Applicant's final joint PPK model is acceptable. The goodness-of-fit plots show a good agreement between the predicted concentrations and the observed concentrations for the metabolites GS-566500 and GS-331007. For the parental drug SOF, the model was slightly underestimated at lower concentrations. Overall, no apparent bias was observed in the residual plots versus time, time after last dose, and population predicted concentrations. Therefore, the final joint PPK model was reliable for prediction of  $CL_{SOF}$ ,  $V_{500}$  and  $CL_{007}$ , and comparison to simulated values in adults (discussed in section 7.4). WT was identified as a significant covariate that could affect  $\leq$  ~50% change in SOF and GS-331007 exposures for subjects with extreme body weights (95<sup>th</sup> percentile WT: 86.2 kg; 5<sup>th</sup> percentile WT: 17.5 kg). Thus, it is reasonable to propose dosing regimens based on weight bands for pediatric subjects (discussed in the section 7.4). GS-331007 is renally eliminated. In adult patients, renal function was observed as a statistically significant covariate, while it was not in pediatric patients. One possible reason is that all pediatric subjects had relatively normal renal function in the pediatric clinical study.*

## 7.2. LDV Model

The model development dataset had a total of 1445 data points from 225 subjects.

A 2-compartment model was used to describe the pediatric data, with a zero-order input followed by first order absorption and first order elimination from the central compartment (Figure 3).

Figure 3 PPK model diagram for LDV



Source: Applicant's PPK study report page 59 Figure 16

Parameter estimates for the final PPK model are provided in Table 4.

Table 4 Summary of final model PK parameters for LDV

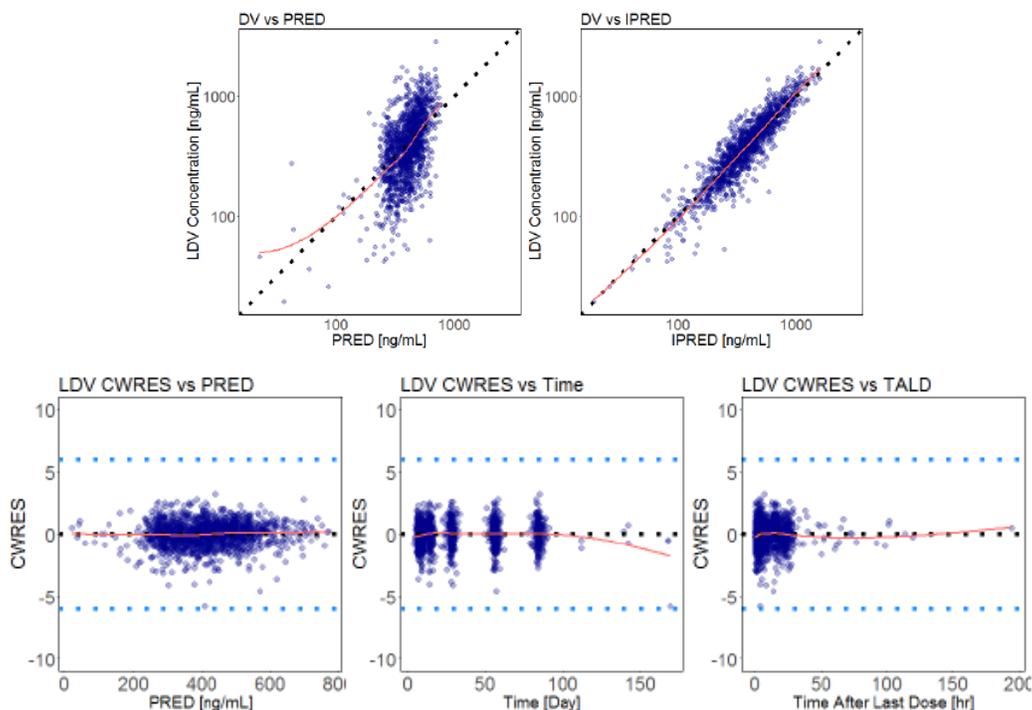
Parameter	Parameter Description	Population Estimate	Change from Typical (%)	Inter-Individual Variability
$\exp(\theta_1)$	Apparent clearance for LDV, CL/F (L/hr)	6.36	--	43.6
$\exp(\theta_1 + \theta_8 * \log(\frac{WT}{42}))$	Influence of WT on CL/F	5th%ile of WT	-32.5	
		95th%ile of WT	39.0	
$\exp(\theta_2)$	Apparent volume for LDV, Vc/F (L)	308	--	78.6
$\exp(\theta_2 + \theta_9 * \log(\frac{WT}{42}))$	Influence of WT on Vc/F	5th%ile of WT	-77.4	
		95th%ile of WT	244	
$\exp(\theta_3)$	Apparent intercompartment clearance for LDV, Q/F (L/hr)	94.6	--	--
$\exp(\theta_4)$	Apparent peripheral volume for LDV, Vp/F (L)	83.1	--	--
$\exp(\theta_5)$	Absorption rate constant for LDV, Ka (hr <sup>-1</sup> )	0.891	--	--
$\exp(\theta_6)$	Duration of zero order input for LDV, D1 (hr)	3.10	--	--
$\sqrt{\theta_7}$	Residual error for LDV (%)		53.2	

5<sup>th</sup> and 95<sup>th</sup> %ile of WT are 17.5 kg and 86.2 kg respectively

Source: Applicant's PPK study report page 61 Table 27

The goodness-of-fit plots of the LDV PPK model in pediatric subjects are shown in Figure 4.

Figure 4 Goodness-of-fit plots for LDV final PPK model



Source: Applicant's PPK study report page 63 Figure 17 & 18

Shrinkage of the final model parameters is presented in Table 5.

Table 5 Shrinkage estimates of inter-individual in the final model of LDV

Parameter	Parameter Description	Shrinkage (%)
$\omega_{CL/F}$	IIV of CL/F	4.16
$\omega_{Vc/F}$	IIV of Vc/F	30.41
$\sigma$	Residual error (%)	10.6

Source: Applicant's PPK study report page 67 Table 30

The Applicant conducted sensitivity analysis to evaluate the impact of statistically significant covariates on steady-state LDV exposures. The sensitivity analysis showed that within pediatric subjects, the effect of WT was the most influential covariate with  $\leq \sim 70\%$  change in LDV exposures for subjects with extreme covariate values (i.e., 5th and 95th WT percentile) relative to the median exposures. Other covariates, including age, sex, race, ethnicity, CLCRSW, HCVGT, food, BSA, IL28B, BMI, or RBV usage did not show a statistically significant impact on the PK of LDV.

*Reviewer's comment: The Applicant's final LDV PPK model is generally acceptable. The goodness-of-fit plots show a good agreement between the observations and individual predictions. No significant bias*

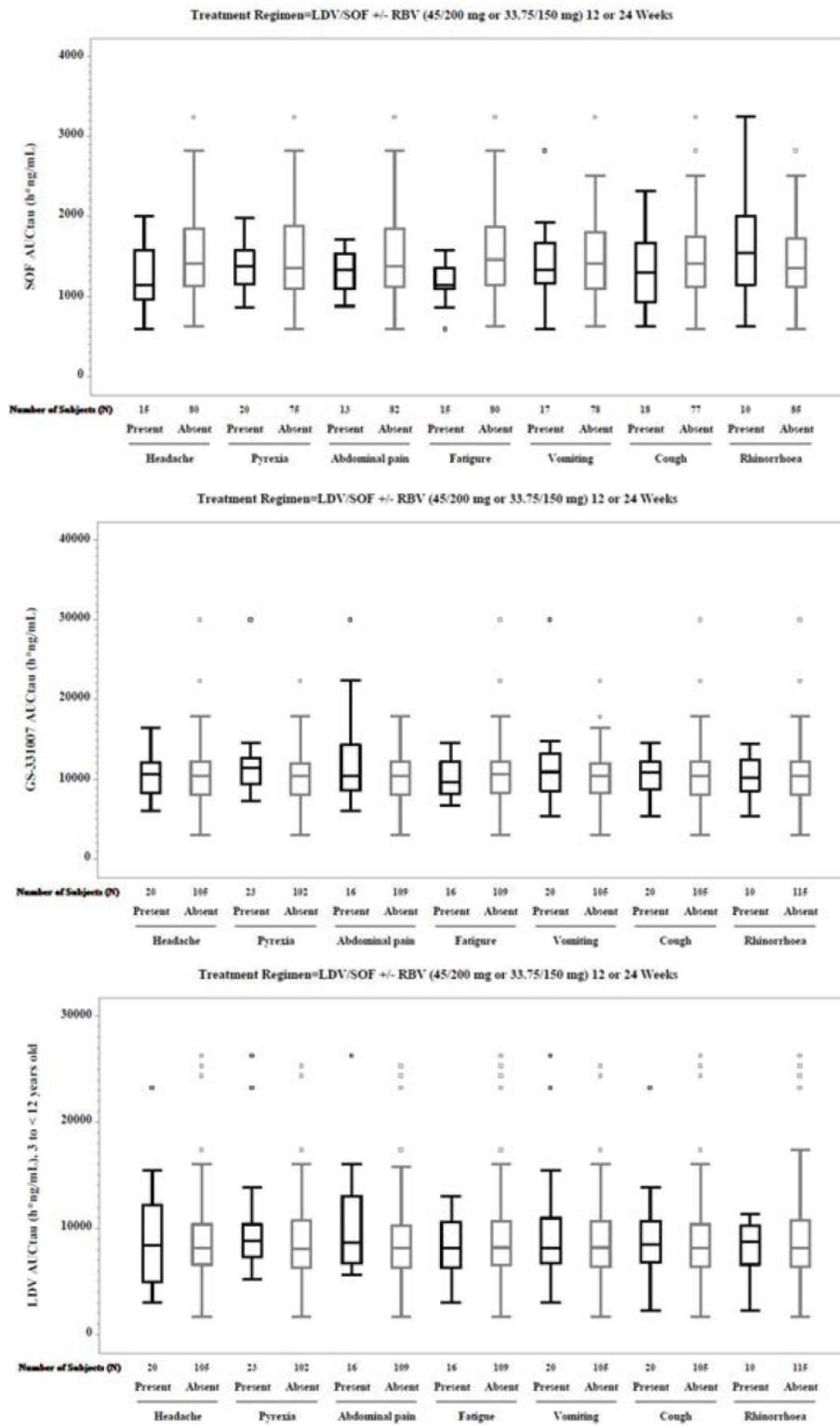
*was observed in the residual plots versus time, time after last dose, and population predicted concentrations. Thus, the final PPK model for LDV was acceptable for describing LDV PK in pediatric subjects, and for simulations of the pediatric exposures at steady-state (discussed in section 7.4). Weight was identified as a significant covariate with substantial impact on LDV exposures ( $\leq$  ~70% change in LDV exposures for subjects with extreme covariate values). Thus, it is reasonable to propose dosing regimens based on weight bands in pediatric subjects (discussed in section 7.4).*

### 7.3. Exposure-response analyses

The Applicant conducted exposure-response analyses based the estimated individual exposures of SOF, GS-331007 and LDV in the pediatric population. Due to the high sustained virologic response (SVR) rate in subjects 6 to < 12 years old (98.9%, 91 of 92 subjects) and subjects 3 to <6 years old (97.1%, 33 of 34 subjects) and low number of virologic failures (one subject in 6 to < 12 years old age group), exposure-response (E-R) relationships for efficacy were not evaluated.

The Applicant performed E-R analyses for the 4 most commonly reported AEs in subjects 6 to < 12 years old and subjects 3 to < 6 years old in Study GS-US-337-1116. For subjects 6 to < 12 years old, the 4 most commonly reported AEs were headache (18.5%), pyrexia (17.4%), abdominal pain (15.2%), and fatigue (15.2%). For subjects 3 to < 6 years old, the 4 most commonly reported AEs were vomiting (23.5%), pyrexia (20.6%), cough (20.6%), and rhinorrhea (17.6%). The E-R analysis dataset included all pediatric subjects 3 to < 12 years old with chronic HCV infection who received LDV/SOF and had evaluable PPK data and  $AUC_{\tau}$  estimates for SOF (N = 95), GS-331007 (N = 125) and LDV (N = 125). As shown in Figure 5, overall, SOF, GS-331007, and LDV exposures in pediatric subjects were similar regardless of the presence or absence of the evaluated AEs (headache, pyrexia, abdominal pain, fatigue, vomiting, cough, or rhinorrhea).

Figure 5 Exposure-response of SOF, GS-331007 and LDV to safety in all pediatric subjects 3 to < 12 years old across treatment groups



Note: For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and the outliers (beyond 1.5 × interquartile range) are displayed as small squares. SOF AUC<sub>tau</sub> is shown in the upper panel, GS-331007 AUC<sub>tau</sub> is shown in the middle panel, and LDV AUC<sub>tau</sub> is shown in the lower panel. AUC<sub>tau</sub> is the population PK-predicted exposure in pediatric subjects receiving LDV/SOF in Study GS-US-337-1116.

Source: Applicant’s Summary of Clinical Pharmacology page 34 Appendix Figure 2.

Reviewer’s comment: In Applicant’s exposure-response analyses for safety based on the data from Study GS-US-337-1116, the pediatric subjects aged 3 to < 12 years old and weighing ≥ 17 kg were administered with LDV/SOF FDC 45/200 mg. Based on the Applicant proposed dose in the label as shown in Table 6, the recommended dosage for pediatric patients 3 years to < 12 years of age weighing ≥ 35 kg is 90/400 mg. While there are no available safety data to evaluate the exposure-response relationship for the 90/400 mg dose in pediatric patients 3 years to < 12 years of age weighing ≥ 35 kg, PK and safety data from the previous submission in adolescents support the use of the adult dose in any pediatric patients weighing 35 to < 45 kg. See 7.4 for additional discussions regarding the dosing regimen for pediatric patients weighing 35 to < 45 kg.

Table 6 Proposed dosing for pediatric patients 3 years (b) (4) using HARVONI tablets or oral granules

Body Weight (kg)	Dosing of HARVONI Tablets or Oral Granules	Ledipasvir/Sofosbuvir Daily Dose
at least 35	one 90/400 mg tablet once daily or two 45/200 mg tablets once daily or two 45/200 mg packets of granules once daily	90/400 mg/day
17 to less than 35	one 45/200 mg tablet once daily or one 45/200 mg packet of granules once daily	45/200 mg/day
less than 17	one 33.75/150 mg packet of granules once daily	33.75/150 mg/day

Source: Applicant proposed labeling Table 2.

#### 7.4. Simulations

The Applicant conducted simulations to evaluate SOF, GS-331007 and LDV steady state exposures (AUC<sub>tau</sub>) for the following pediatric populations and dosing scenarios as shown in Table 6. Figure 6 shows the comparison between the simulated steady-state AUC<sub>tau</sub> of SOF, GS-331007 and LDV in pediatrics 3 to < 12 years old and the AUC<sub>tau</sub> in adult patients. The predicted pediatric exposures were within the range of adult exposures.

To determine whether an alternative dosing regimen could provide more comparable exposures to adults, we sent an information request (IR) to the Applicant for simulations based on different body weight bands during the review. In addition, we requested the Applicant to compare the exposures between the studied dose (SOF/LDV 45/200 mg) and the approved dose (90/400 mg) in patients weighing 35 to < 45 kg to ensure that use of the adult dose in pediatric patients weighing 35 to < 45 kg could still be supported by the currently submitted data and popPK approach. The details of the IR and results are shown below:

*Comment 1:*

*We request additional simulated exposures for SOF and LDV/SOF to determine the appropriate weight bands in pediatric patients. Specifically, significant variability in SOF and LDV exposures is predicted due to the wide range of body weights for the 17 to < 35 kg weight band. Please submit the simulated exposures for SOF + RBV or LDV/SOF FDC dosing regimens for different weight band scenarios as follows. Submit the results in graph and table formats.*

- *No less than 33 kg, 400 mg SOF or 90/400 mg LDV/SOF;*
- *20 to less than 33 kg, 200 mg SOF or 45/200 mg LDV/SOF;*
- *Less than 20 kg, 150 mg SOF or 33.75/150 mg LDV/SOF.*

*Comment 2*

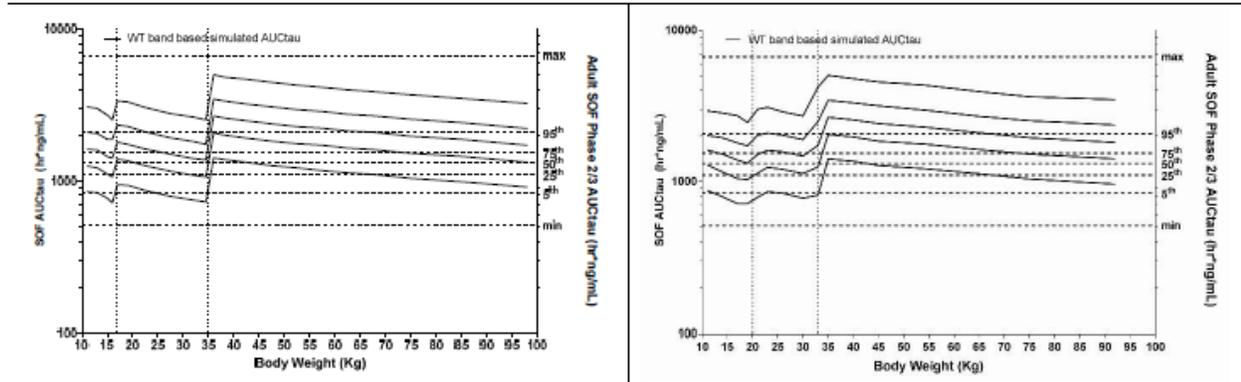
*Compare the simulated exposures between the lower doses of SOVALDI (200 mg) and HARVONI (45/200 mg) and the adult doses of those drugs for the 35 kg to < 45 kg weight band.*

The Applicant provided simulation results as shown in Figure 6, Table 7 and Table 8. The Applicant concluded that the new simulations and comparisons support the applicability of the originally proposed weight band based dosing in pediatric subjects 3 to <12 years old.

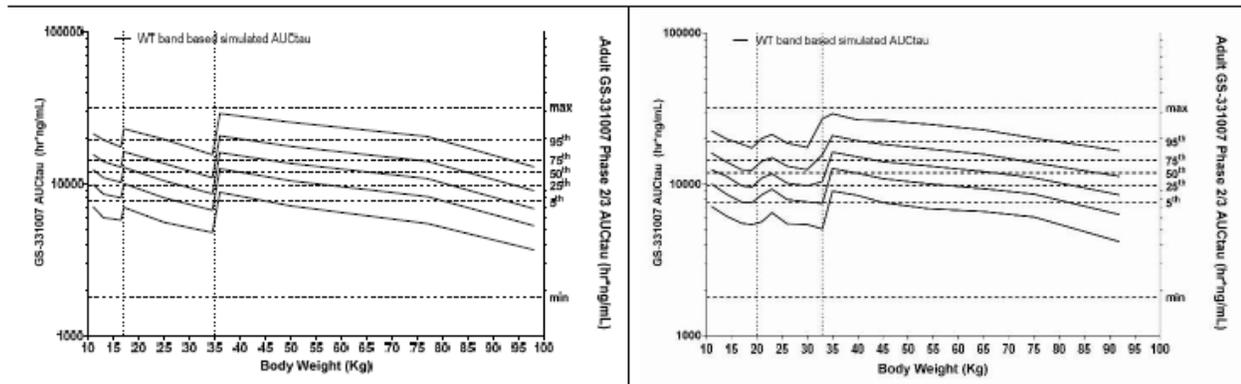
Figure 6 Graphical representation of original and requested weight-band simulations for HARVONI

Original Weight-Band Simulation	Requested Weight-Band Simulation
<ul style="list-style-type: none"> <li>Children <math>\geq 35</math> kg received LDV/SOF 90 mg/400 mg</li> <li>Children 17 to <math>&lt; 35</math> kg received LDV/SOF 45 mg/200 mg</li> <li>Children <math>&lt; 17</math> kg received LDV/SOF 33.75 mg/150 mg</li> </ul>	<ul style="list-style-type: none"> <li>Children <math>\geq 33</math> kg received LDV/SOF 90 mg/400 mg</li> <li>Children 20 to <math>&lt; 33</math> kg received LDV/SOF 45 mg/200 mg</li> <li>Children <math>&lt; 20</math> kg received LDV/SOF 33.75 mg/150 mg</li> </ul>

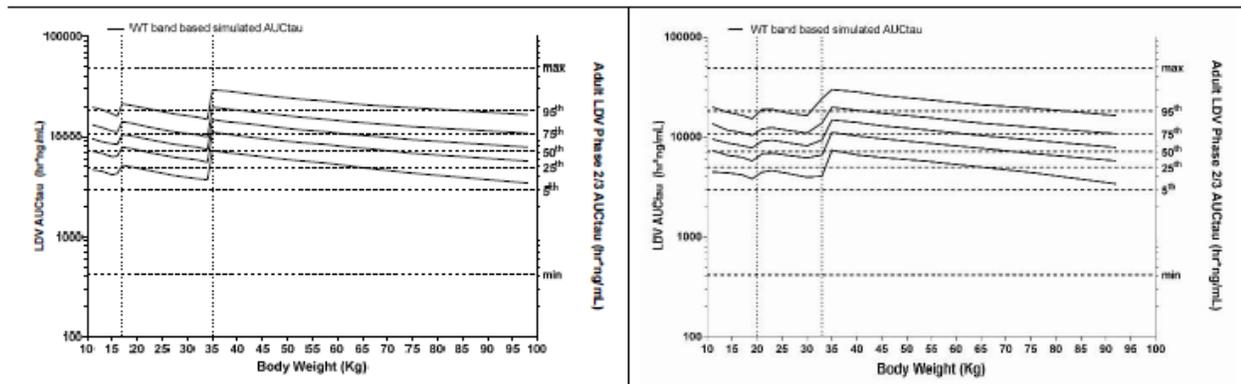
**Harvoni SOF**



**Harvoni GS-331007**



**LDV**



Note: 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 17kg and 35kg cutoffs. Adult exposures are the

PopPK-predicted exposures from LDV/SOF (Harvoni®) Phase 2/3 studies; Min, 5th, 25th, 50th, 75th, 95th percentiles, and Max are shown.

Source: Applicant's response to FDA Clinical Pharmacology comments.

Table 7 Summary of predicted percent of subjects above adult maximum exposures in the original and requested weight-band simulations for HARVONI

	LDV/SOF Dose				
	33.75/150 mg	45/200 mg	90/400 mg		
Lowest weight in weight band	Percent of Subjects (%) above Adult Maximum				
	Not altered by requested simulations	17 kg Original	20 kg Requested	35 kg Original	33 kg Requested
SOF		<1%	<1%	1%	1%
GS-331007		<1%	<1%	3%	4%
LDV		<1%	None	<1%	2%

Source: Applicant's response to FDA Clinical Pharmacology comments.

In addition, less than 1% of subjects were predicted to achieve exposures below the minimum exposures observed in adults in the proposed dosing regimen and the alternative dosing regimen.

Table 8 Simulated exposures ( $AUC_{\tau}$ ) of SOF, GS-331007 and LDV in children 35 kg to < 45 kg administered LDV/SOF 90/400 mg or 45/200 mg compared to observed adult exposures

	SOF $AUC_{\tau}$ (hr*ng/mL)			GS-331007 $AUC_{\tau}$ (hr*ng/mL)			LDV $AUC_{\tau}$ (hr*ng/mL)		
	Children 35 to <45 kg		Adult Exposure	Children 35 to <45 kg		Adult Exposure	Children 35 to <45 kg		Adult Exposure
	200 mg	400 mg		200 mg	400 mg		200 mg	400 mg	
Min	272	544	511	1584	3169	1789	1303	2606	416
5 <sup>th</sup> %tile	680	1359	838	4200	8399	7605	3382	6764	2979
25 <sup>th</sup> %tile	986	1972	1103	5979	11958	9812	5157	10314	4979
50 <sup>th</sup> %tile	1282	2564	1313	7701	15402	11893	6933	13867	7163
75 <sup>th</sup> %tile	1660	3321	1539	9888	19775	14474	9268	18536	10807
95 <sup>th</sup> %tile	2404	4807	2074	13965	27930	19233	14004	28008	18211
Max	6116	12232	6686	30159	60318	32000	35838	71677	49143

Source: Applicant's response to FDA Clinical Pharmacology comments.

The comparisons in Table 8 show that administration of the lower dose of HARVONI (45/200 mg) to children weighing 35 to <45 kg will likely result in SOF exposures that are less than the minimum exposures observed in adults.

Reviewer's comment: Based on the Applicant's simulations and comparisons, by lowering the minimum body weight for the adult strength tablet to 33 kg from 35 kg, a slightly greater proportion of subjects is expected to exceed the maximum exposure observed in adults (Table 7). Using 20 kg as the body weight cutoff (Table 9, FDA requested weight band simulations for HARVONI) would be likely to produce lower GS-331007 AUC<sub>tau</sub> than the observed adult exposures (Table 8). Thus, to avoid under-exposure of GS-331007, the current proposed weight cut off of 17 kg would be reasonable.

Table 9 GS-331007 AUC<sub>tau</sub> for the requested weight band simulations for HARVONI (WT <20 kg part)

Weight Bin (kg)	GS-331007 AUC <sub>tau</sub> (hr*ng/mL)				
	5 <sup>th</sup> %tile	25 <sup>th</sup> %tile	50 <sup>th</sup> %tile	75 <sup>th</sup> %tile	95 <sup>th</sup> %tile
<12	7136	10053	12495	16095	22581
12 to <16	6155	8601	11280	14059	19943
16 to <18	5531	7620	9766	12470	18449
18 to <20	5413	7544	9574	12406	17389

Source: Applicant's response to FDA Clinical Pharmacology comments.

The FDA reviewer also conducted independent simulations to evaluate C<sub>max</sub> following dosing regimens based on different weight bands. The results are shown in Table 10 and Table 11. Similar trends with AUC<sub>tau</sub> were observed in C<sub>max</sub> analysis.

Table 10 Summary of simulated steady-state C<sub>max</sub> for SOF and GS-331007 in 3 to < 12 yr pediatric subjects compared to adults

Dosing regimen #1				
<ul style="list-style-type: none"> <li>• ≥ 17 kg, 45/200 mg LDV/SOF</li> <li>• &lt; 17 kg, 33.75/150 mg LDV/SOF</li> </ul>				
Analytes	PK Parameter	Pediatric Subjects		Adults
		<17 kg (N=5000)	≥17 kg (N=58000)	
SOF	C <sub>max</sub> (ng/mL)	727.8 (26.0)	698.9 (28.5)	659 (34.0) (N=1542)
GS-331007	C <sub>max</sub> (ng/mL)	1075.1 (30.1)	936.7 (38.2)	736 (28.2) (N=2113)
Dosing regimen #2				
<ul style="list-style-type: none"> <li>• ≥ 35 kg, 90/400 mg LDV/SOF</li> <li>• ≥ 17 kg and &lt; 35 kg, 45/200 mg LDV/SOF</li> <li>• &lt; 17 kg, 33.75/150 mg LDV/SOF</li> </ul>				

Analytes	PK Parameter	Pediatric Subjects			Adults
		<17 kg (N=5000)	≥17 kg and <35 kg (N=43000)	≥35 kg (N=15000)	
SOF	$C_{max}$ (ng/mL)	727.8 (26.0)	744.4 (26.2)	1137.4 (25.4)	659 (34.0) (N=1542)
GS-331007	$C_{max}$ (ng/mL)	1075.1 (30.1)	1025.408 (34.1)	1364.5 (35.2)	736 (28.2) (N=2113)
<b>Dosing regimen #3</b> <ul style="list-style-type: none"> <li>• ≥ 33 kg, 90/400 mg LDV/SOF</li> <li>• ≥ 20 kg and &lt; 33 kg, 45/200 mg LDV/SOF</li> <li>• &lt; 20 kg, 33.75/150 mg LDV/SOF</li> </ul>					
Analytes	PK Parameter	Pediatric Subjects			Adults
		<20 kg (N=13000)	≥20 kg and <33 kg (N=32500)	≥33 kg (N=17500)	
SOF	$C_{max}$ (ng/mL)	687.9 (26.6)	745.7 (28.6)	1160.2 (25.7)	659 (34.0) (N=1542)
GS-331007	$C_{max}$ (ng/mL)	1001.0 (31.8)	1018.2 (35.0)	1404.0 (35.5)	736 (28.2) (N=2113)

Note: Values are presented as mean (CV%).

Source: Reviewer's independent analysis.

Table 11 Summary of simulated steady-state  $C_{max}$  for LDV in 3 to < 12 yr pediatric subjects compared to adults

<b>Dosing regimen #1</b> <ul style="list-style-type: none"> <li>• ≥ 17 kg, 45/200 mg LDV/SOF</li> <li>• &lt; 17 kg, 33.75/150 mg LDV/SOF</li> </ul>					
Analytes	PK Parameter	Pediatric Subjects			Adults
		<17 kg (N=5000)	≥17 kg (N=52000)		
LDV	$C_{max}$ (ng/mL)	501.7 (39.6)	457.3 (45.4)		364 (51.4) (N=2113)
<b>Dosing regimen #2</b> <ul style="list-style-type: none"> <li>• ≥ 35 kg, 90/400 mg LDV/SOF</li> <li>• ≥ 17 kg and &lt; 35 kg, 45/200 mg LDV/SOF</li> <li>• &lt; 17 kg, 33.75/150 mg LDV/SOF</li> </ul>					
Analytes	PK Parameter	Pediatric Subjects			Adults
		<17 kg (N=5000)	≥17 kg and <35 kg (N=43000)	≥35 kg (N=15000)	
LDV	$C_{max}$ (ng/mL)	501.7 (39.6)	495.2 (42.4)	697.6 (44.7)	364 (51.4) (N=2113)

<i>Dosing regimen #3</i>					
<ul style="list-style-type: none"> <li>• <math>\geq 33</math> kg, 90/400 mg LDV/SOF</li> <li>• <math>\geq 20</math> kg and <math>&lt; 33</math> kg, 45/200 mg LDV/SOF</li> <li>• <math>&lt; 20</math> kg, 33.75/150 mg LDV/SOF</li> </ul>					
Analytes	PK Parameter	Pediatric Subjects			Adults
		$<20$ kg (N=12000)	$\geq 20$ kg and $<33$ kg (N=32500)	$\geq 33$ kg (N=18500)	
SOF	$C_{max}$ (ng/mL)	462.5 (40.3)	485.9 (42.0)	721.9 (44.6)	364 (51.4) (N=2113)

Note: Values are presented as mean (CV%).

Source: Reviewer's independent analysis.

### 7.5 Conclusion

The popPK modeling and simulation results support the approval of SOVALDI in pediatric patients 3 years of age and older. The Applicant's proposed dosing regimens are acceptable.

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/s/  
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