OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW	
NDA/SDN/Supplement	209394/708/S13 (tablets, for oral use) 215110 (b) (4) (oral pellets)
Submission Type	Pediatric efficacy supplement for NDA209394 (tablets, for oral use) New drug application for NDA215110 (oral pellets)
Applicant Name	AbbVie Inc.
Submission Date	12/10/2020
Generic Name	Glecaprevir (GLE, ABT-493) and Pibrentasvir (PIB, ABT-530)
Brand Name	Mavyret
Dosage Form (Strength)	Tablets, for oral use (100 mg GLE and 40 mg PIB) Oral pellets (50 mg GLE and 20 mg PIB)
Indication	Treatment of adult and pediatric patients 3 years and older with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). Mavyret is also indicated for the treatment of adult and pediatric patients 3 years and older with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.
Review Team	Xiaoxia Yang, PhD, Jiajun Liu, PharmD, MSc, Justin Earp, PhD, and Mario Sampson, PharmD

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1. Background

Prior to submission of this supplement, Mavyret was approved for adult and pediatric patients 12 years and older or weighing at least 45 kg. The recommended oral dosage is three tablets taken at the same time once daily (total daily dose: GLE 300 mg and PIB 120 mg) with food for 8, 12, or 16 weeks depending on genotypes, cirrhotic status, and prior treatment history. This supplement contains two studies and one analysis report [the pivotal study M16-123 (R&D/20/0360) (part 2) in subjects 3 years to less than 12 years old weighing at least 12 kg administered oral pellets, a population pharmacokinetic (PopPK) analysis report (R&D/20/0613) based on data from study M16-123, and a relative bioavailability (relBA) study of GLE/PIB oral pellets and tablets in healthy adults (Study M17-142, R&D/18/0297)], along with revised labeling to extend the indication to include pediatric subjects 3 years to less than 12 years old.

2. Pellet dosing for pediatric patients <45 kg

The basis of approval of Mavyret in pediatric subjects 3 years to less than 12 years old is extrapolation of the efficacy from adult subjects. The focus of our review was whether comparability of systemic exposures of GLE and PIB in pediatrics vs adults was demonstrated. Based on our review of study M16-123 (part 2) and the favorable OSIS inspection of the analytical site (AbbVie, Inc.) conducted in February 2019, which falls within the surveillance interval (OSIS review, NDA 215110 dated 2/16/2021, and NDA 209394 dated 2/28/2019), we accept study M16-123 part 2 PK results for subjects 3 years to less than 12 years old weighing at least 12 kg. A total of three cohorts (cohorts 2-4) were included for part 2 of study M16-123: cohort 2, 9 to < 12 years old (30 to < 45 kg, N=29); cohort 3, 6 to < 9 years old (20 to < 30 kg, N=27); and cohort 4, 3 to < 6 years old (12 to < 20 kg, N=24).

According to the dosing card utilized in part 2 of study M16-123, caregivers were instructed that all oral pellets from each sachet (a total of 3 to 5 sachets) should be mixed into approximately 1 to 2 teaspoons (5 to 10 mL) of soft food, which has a low water content and does not require chewing, such as peanut butter (smooth, non-chunky), Nutella (chocolate hazelnut spread), cream cheese or thick jam. The child was to be instructed not to chew the mixture before swallowing. More soft food may be added if pellets are left uneaten (Response to IR submitted on 5/4/2021 under NDA215110). Instructions on preparation and administration of oral pellets with a soft food vehicle in the labeling are consistent with how caregivers were instructed to administer the oral pellets during the study. Thus, the labeling with regards to the preparation and administration of oral pellets is acceptable.

Geometric mean ratios (GMRs) in pediatrics vs. adults (calculated from non-compartment analysis (NCA) of intensive PK subjects who received the final proposed dosing regimen, N=13 for cohort 2, N=13 for cohort 3, and N=12 for cohort 4) of GLE and PIB C_{max} and AUC_{24} ranged from 1.15-2.68, whereas GMRs of GLE C_{trough} ranged from 0.506-0.951 and GMRs of PIB C_{trough} ranged from 0.948-1.93 (Response to IR submitted on 4/1/2021 under NDA 215110). All pediatric GLE and PIB PK parameter values fell within the range observed in non-cirrhotic HCV-infected adult subjects (Response to IR submitted on 8/17/2020 under IND 127416). Based on our conclusion that acceptable safety and efficacy was observed across the wide range of GLE and PIB exposures in adult trials (Refer to the subsection of *comparison of exposures in subjects 3 years to less than 12 years old vs. adults* for details), we do not consider the geometric mean exposure differences in pediatrics vs. adults to be clinically significant. In addition, the SVR_{12} rate in pediatrics who received the final proposed dosing regimen of GLE/PIB in cohorts 2-4 was 98% (61/62), with no cases of virologic failure.

We agree with the proposed dosing regimen based on body weight for subjects 3 years to less than 12 years old and recommend approval of this supplement. This submission fulfills the following PREA PMR 3246-1: *Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of glecaprevir and pibrentasvir in pediatric subjects 3 through less than 18 years of age with chronic hepatitis C virus infection.*

3. Pellet dosing for pediatric patients ≥ 45 kg

During the review cycle, we were asked by the Clinical review team to assess the appropriate GLE/PIB oral pellet dosing for pediatric patients weighing 45 kg and greater who could not swallow tablets. The relative bioavailability of GLE/PIB oral pellets vs. tablets (300/120 mg) was evaluated in healthy adults (Study M17-142). Because the Applicant [redacted] (b) (4)

(b) (4)

The analytical site (AbbVie, Inc.) used for trial M17-742 was inspected in February 2019 (OSIS review, NDA 209394 dated 2/28/2019) with the final classification of No Action Indicated (NAI), which falls within the surveillance interval. The OSIS concluded that an inspection of the analytical site is not warranted at this time (OSIS review, NDA 215110 dated 2/16/2021). The clinical site (AbbVie Clinical Pharmacology Research Unit, ACPRU) used for trial M17-742 was inspected in November 2017 (OSIS review, NDA210450, dated 1/16/2018) and the final classification was NAI. As noted in the OSIS review, "the data from other studies of similar design conducted at ACPRU before the end of the current Surveillance Interval should be accepted for review without an inspection", we determined that the favorable inspection results at ACPRU under NDA210450 can be applied to study M17-142. Based on our review of study M17-142 and favorable recent clinical and analytical site inspection findings, we accept PK results from study M17-142.

In the relBA study, pellets or tablets were taken with approximately 240 mL of water after at least a minimum 10-hour fast and approximately 4 hours before lunch for fasting conditions, and approximately 30 minutes after starting a moderate fat breakfast (consisting of 515 kcal, with approximately 40.6% content from fat, 28.6% content from carbohydrate, and 30.8% content from protein) for fed conditions. No soft food vehicles were administered with oral pellets for both fasting and fed conditions. Under fed conditions (GLE/PIB must be taken with food), while no statistically significant differences in geometric means for PIB C_{max}, $AUC_{t,}$ and C_{24} as well as GLE C_{24} were observed (Response to IR submitted on 2/23/2021 under NDA 215110), geometric means for GLE C_{max} and AUC_t were significantly less for oral pellets when compared with tablets, with GMRs of 0.66 and 0.79, respectively. However, based on the large variabilities (CV of 122%) of GLE AUC_t values observed in non-cirrhotic HCV-infected adult subjects administered tablets and the lack of clear evidence to show the relationship between GLE exposures and response rate of SVR_{12}, a mean GLE AUC_t reduction of ~20% following oral pellet use compared with tablets is not expected to impact efficacy. In addition, the applicant demonstrated that adding 6 sachets of oral pellets to 1-2 teaspoons of soft food is appropriate (Response to IR submitted on 5/4/2021 under NDA215110). Therefore, for pediatric patients weighing at least 45 kg who cannot swallow the intact tablets, the recommended dose (300 mg GLE/120 mg PIB) may be administered as oral pellets (6 sachets).

4. Labeling Updates (Clinical Pharmacology Relevant Sections Only)

- Section 2.4 Recommended Dosage in Pediatric Patients 3 Years of Age and Older

In the Applicant's [redacted] (b) (4)

(b) (4)

Based on the relBA study (Study M17-142) under fed conditions, while no statistically significant differences in geometric means for PIB C_{max}, $AUC_{t,}$ and C_{24} as well as GLE C_{24} were observed between oral pellets and tablets in healthy adults, geometric means for GLE C_{max} and AUC_t were significantly less for pellets when compared with tablets, with GMRs of 0.66 and 0.79, respectively. However, there was no

clear evidence to show the relationship between GLE exposure and response rate of SVR_{12} based on graphical assessment and multiple logistic regression analysis as established in adults. Therefore, considering the large variabilities (CV of 122%) of GLE AUC_t values observed in non-cirrhotic HCV-infected adult subjects administered with tablets, an average GLE AUC_t reduction of ~20% following pellet use compared with tablets is not expected to impact efficacy. In addition, the applicant demonstrated that adding 6 sachets of oral pellets to 1-2 teaspoons of soft food is appropriate. Thus, for pediatrics weighing at least 45 kg who cannot swallow the intact tablets, we recommended that the 300mg/120mg GLE/PIB dose may be administered as oral pellets.

- Section 12.3 Pharmacokinetics

In the Applicant's proposed labeling, (b) (4)

(b) (4)

(b) (4)

The review team appreciate the applicant's concerns. However, while the variability exists for the aforementioned reasons, the labeling may clearly indicate the pediatric PK parameters to be listed are from actual patients (and thus the large CV%). We recommend the addition of PK parameter GMRs where there were differences in peds/adults and describe clinical significance. This statement indicates that despite large variability, pediatric PK parameters fell within the adult range and the differences between pediatric and adult PK parameters are not clinically significant. Therefore, the variability observed in pediatrics as well as the difference in exposures across body weight groups of pediatrics vs. adults should not cause confusion in clinical practice.

5. Individual Study Review

5.1 Study M16-123

Title

An open-label, multicenter study to evaluate the pharmacokinetics, safety, and efficacy of Glecaprevir/Pibrentasvir in pediatric subjects with genotypes 1-6 chronic hepatitis C virus (HCV) infection (CSR R&D/20/0360).

Primary Objectives

- Assess the PK of GLE/PIB in pediatric subjects following multiple dosing by age group;
- Evaluate the safety and tolerability of GLE/PIB by age group, cirrhosis status, and across all subjects;
- Evaluate the percentage of subjects with sustained virologic response for 12 weeks posttreatment (SVR12) in HCV GT1-GT6 infected pediatric subjects

Study Design

Study M16-123 is a phase 2/3, open-label, multicenter study to evaluate the PK, efficacy, and safety of GLE/PIB for 8, 12, or 16 weeks in HCV GT1-GT6-infected pediatric subjects ≥ 3 to less than 18 years of age. The study was divided into 2 parts.

- Part 1 (Cohort 1): adolescent subjects 12 to < 18 years old who were willing to swallow the adult formulation of GLE/PIB (~N=44). Results from Part 1 of the study were previously reviewed to support approval for adolescents (NDA 209394, S-006).
- Part 2 (Cohorts 2-4): pediatric subjects (3 to < 12 years old) who received the pediatric oral pellet formulation; Part 2 (~N=81) was divided into three cohorts: Cohort 2 (9 to < 12 years old, 30 to < 45 kg), Cohort 3 (6 to < 9 years old, 20 to < 30 kg), and Cohort 4 (3 to < 6 years old, 12 to < 20 kg). Results from Part 2 of the study are submitted with this supplement and summarized below.

In Part 2, all oral pellets from each sachet (a total of 3 to 5 sachets) were mixed into approximately 1 to 2 teaspoons (5 to 10 mL) of soft food, which has a low water content and does not require chewing, such as peanut butter (smooth, non-chunky), Nutella (chocolate hazelnut spread), cream cheese or thick jam. The child was instructed not to chew mixture before swallowing. More soft food may be added if pellets are left uneaten (Dosing Information from the dosing card. Response to IR submitted on 5/4/2021 under NDA215110).

In each cohort of Part 2, subjects were enrolled first into the intensive PK (IPK) portion, followed by the non-IPK safety/efficacy portion. For the IPK portion, six subjects in each cohort received the initial GLE + PIB dose (40 mg/15 mg dose ratio) and the final doses were adjusted to a dose ratio of 50 mg/20 mg (GLE/PIB) for each cohort (Table 1) based on the analysis of the initial IPK data. Subjects who participated in the IPK analysis were instructed to not have a full meal before the visit, so that study drugs could be taken with soft food during the visit.

Table 1. GLE and PIB doses for the pediatric population.

Formulation	Age Group (yrs) & Weight Band (kg)	Initial Doses (mg)		Final Proposed Doses (mg)		
		GLE	PIB	GLE	PIB	Number of sachets[a]
Pediatric formulation	≥ 3 to < 6 yr 12 to < 20 kg	120	45	150	60	3
	≥ 6 to < 9 yr ≥ 20 to < 30 kg	160	60	200	80	4
	≥ 9 to < 12 yr ≥ 30 to < 45 kg	200	75	250	100	5
Adult formulation	≥ 12 to < 18 yr ≥ 45 kg	--	--	300	120	--

[a]Each sachet contains 50 mg/20 mg unit dose of GLE/PIB granules. Source: M16-123 Study report.

PK Assessment

In part 2 of Study M16-123, PK samples were collected on Day 1 (4 hours post dose), at Weeks 4, 8, 12, or 16 (regardless of the dosing time) for all subjects. In subjects who participated in the IPK sample collection, PK samples were also collected at Week 2 (pre-dose, 2, 4, 6, 12 hours post dose).

Demographics

In Part 2 of study M16-123, a total of 80 subjects received at least one dose of GLE/PIB. Subjects were mostly white (68.8%). The majority of subjects were HCV GT1 (N=58) or GT3-infected (N=18), the rest were HCV GT2 (N=2) or GT4 (N=2)-infected. There was no subject with cirrhosis.

Protocol Deviations

Ten protocol deviations were reported, including not satisfying entry criteria (N=3), missing dosing (N=1), and taking prohibited herb mediations for two days (N=1). Two of the five subjects (ID# (b) (6)

and ID# (b) (6) were in the IPK group, but neither of them was considered as outliers in the PK analysis. In addition, significant PK sampling time deviations occurred during the conduct of this study (N=5), but the actual sampling time was used in the calculation of the PK parameters. Overall, in our assessment, these protocol deviations are not expected to affect PK analysis.

Not satisfying entry criteria (N=3)
During screening, direct bilirubin was not measured for Subject (b) (6) and cirrhosis status was not determined for Subject (b) (6) One subject (ID# (b) (6) was on Kaletra (lopinavir/ritonavir, which was not an acceptable ART regimen due to potential inhibition of P-gp/CYP3A), in addition to abacavir and lamivudine for HIV-1 treatment, up to 18 days (last dose on (b) (6)) while on GLE/PIB treatment (starting from (b) (6) Two sparse PK samples were collected on days 1 and 14. The subject was not included for IPK data collection.

Missing dosing (N=1)
Subject (b) (6) missed study drug doses for 14 days, from day 32 to day 45, due to airway infection. Sparse PK samples were collected on days 1, 15, 29, and 52. Plasma concentrations of GLE/PIB are expected to reach steady-state by day 52 after re-initiation of the study drug, i.e. 7 days from day 46 which is greater than 5 half-lives of GLE ($t_{1/2}$= 6 hr) and PIB ($t_{1/2}$=13 hr).

Taking prohibited herb mediations for two days (N=1)
During Week 1 of the treatment period, Subject (b) (6) took the herbal medication Zarbees Cough for two days for treatment of influenza symptoms while on the study drug. Zarbees Cough is an herbal medication containing dark honey/grapefruit seed extract, which is not permitted per protocol while receiving GLE/PIB treatment. Given that IPK sample data were collected in Week 2, two days dosing of Zarbees during Week 1 of the treatment is unlikely to cause any significant effects on the IPK of GLE/PIB in Week 2 if there are any.

Sample Analysis
Plasma concentrations of GLE and PIB were measured using a validated LC-MS/MS method. The original validation report (R&D/14/0810, issued October 2014) and the stability and method update report 1 (R&D/16/0743, issued November 2016) have been reviewed previously by the Clinical Pharmacology review team (See clinical pharmacology review for the original NDA 209394 (dated 5/26/2017) and NDA 209394/S-6 (dated 3/29/2019)) and determined to be acceptable. The analytical site AbbVie Inc. was inspected in February 2019 and the final inspection classification is No Action Indicated (NAI) (OSIS review, NDA 209394, dated 2/28/2019). In the current submission, a stability and method update report 2 (R&D/19/0508, issued May 2019) was submitted (Table 2).

Of note, the original bioanalytical method (R&D/14/0810) was validated with two dynamic ranges (~0.2-102 ng/mL and 84 -10000 ng/mL for GLE; ~0.2-101 ng/mL and 84 -1040 ng/mL for PIB), while a single calibration range was used for sample analyses for Study M16-123 (~1-5000 ng/mL for GLE and ~1-751 ng/mL for PIB). In the stability and method update report 1 (R&D/16/0743, issued November 2016), a cross-validation was conducted for the reduced assay range (~1-5000 ng/mL for GLE and ~1-751 ng/mL for PIB), with acceptable accuracy and precision observed for calibration standards and QC samples (Table 2). Therefore, we concluded that the use of a single concentration calibration range is acceptable. In addition, we also reviewed the stability and method update report 2 (R&D/19/0508, issued May 2019) (Table 2) and study M16-123 sample analysis report (Table 3). These analytical methods were found to be acceptable.

Table 2. Assessment of LC-MS/MS method validation reports (ABT493= GLE; ABT530 = PIB).

Method	Calibration range	Accuracy and precision values of calibration and QC samples (including dilution samples) within 15% (20% at LLOQ)	Major deviations	Interference from other analytes	Duration of stability
R&D/14/0810	*Low assay range:* 0.198 to 102 ng/mL for ABT493 0.197 to 101 ng/mL for ABT530 *High assay range:* 84.6 to 10000 ng/mL for ABT493 84.1 to 1040 ng/mL for ABT530	Yes	No	No	At least 79 days stored at ~ -20°C and -70°C untreated for ABT493 and ABT530 At least 70 days stored at ~ -20°C and -70°C heat treated for ABT493 and ABT530
R&D/16/0743	*Low assay range:* 0.198 to 102 ng/mL for ABT493 0.197 to 101 ng/mL for ABT530 *High assay range:* 84.6 to 10000 ng/mL for ABT493 84.1 to 1040 ng/mL for ABT530 *Reduced assay range:* 1.00 to 5000 ng/mL for ABT493 1.00 to 751 ng/mL for ABT530	Yes	No	No	618 days stored at ~ -20°C untreated 609 days stored at ~ -20°C heat treated for ABT493 and ABT530 282 days stored at ~ -70°C untreated 273 days stored at ~ -70°C heat treated for ABT493 and ABT530
R&D/190/508	*Low assay range:* 0.198 to 102 ng/mL for ABT493 0.197 to 101 ng/mL for ABT530 *High assay range:* 84.6 to 10000 ng/mL for ABT493 84.1 to 1040 ng/mL for ABT530	Not submitted except a statement of "a separate set of QCs was used to accept the run".	No	No new chromatograms submitted in this amendment	1546 days stored at ~ -20°C untreated 609 days stored at ~ -20°C heat treated for ABT493 and ABT530

Source: Reviewer prepared from method validation reports R&D/14/0810, R&D/16/0743, and R&D/190/508.

Table 3. Assessment of LC-MS/MS method performance for study M16-123 (ABT493= GLE; ABT530 = PIB).

Calibration range	Calibration and QC samples (including dilution QC samples) (within 15%, 20% at LLOQ)	Major deviations	Samples measured within the duration of stability	Incurred sample reproducibility pass rate (67% should be ± 20% of the original)	Chromatograms
Reduced assay range: ABT493: ~ 1.00 to 5000 ng/mL ABT530: ~ 1.00 to 751 ng/mL	Yes	No	Yes	93% (80/86) for ABT493 94% (81/86) for ABT530	No anomalies observed in the submitted representative chromatograms

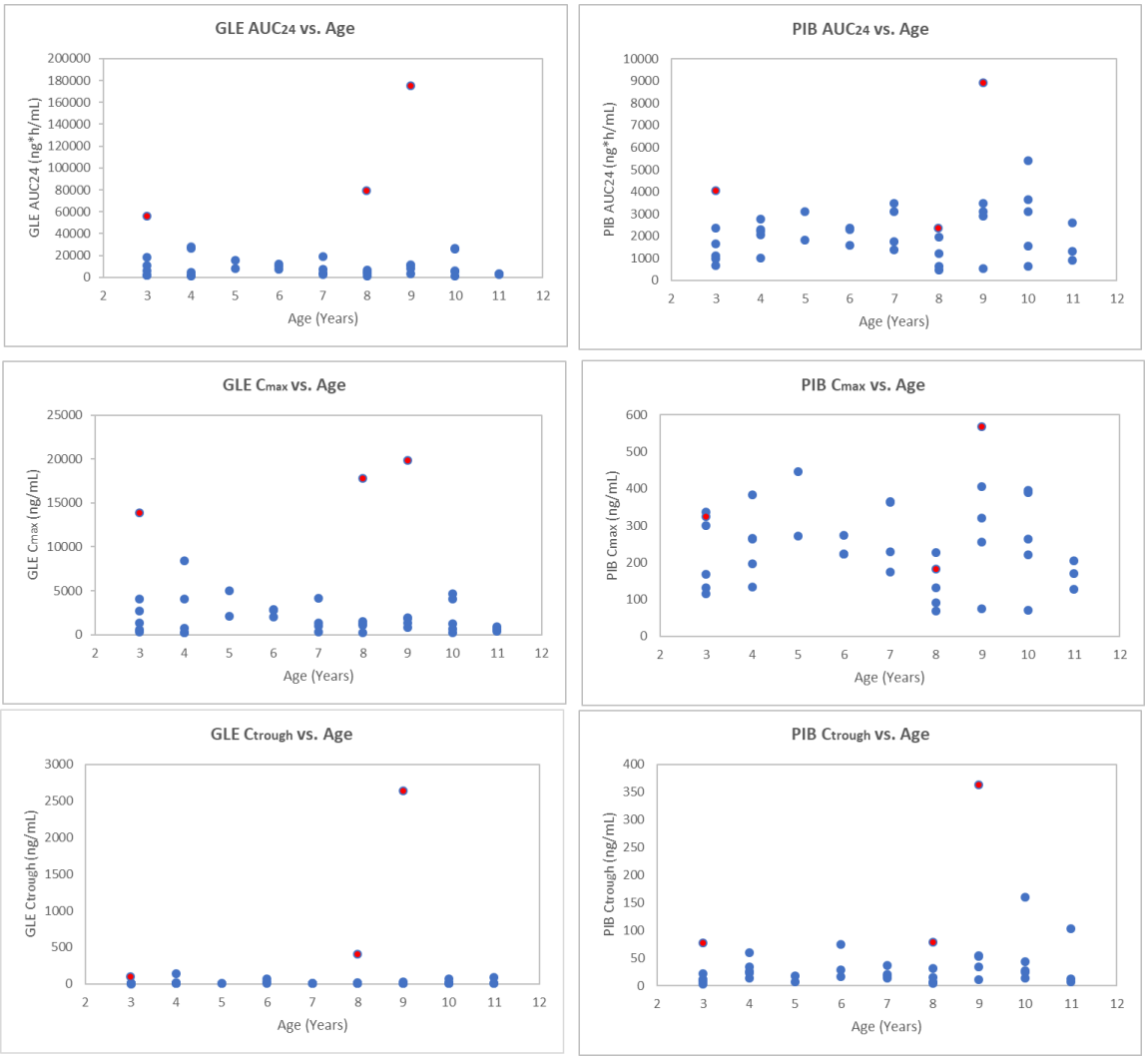
Source: Reviewer prepared from sample analysis reports for study M16-123.

PK Results

Of the 80 subjects who received at least one dose of the drug, 18 subjects received GLE/PIB at the initial dose (40mg/15mg dose ratio) for IPK analysis and 62 subjects received the final proposed dose (50mg/20mg dose ratio). Among those who received the final proposed dose, 39 subjects were enrolled into the IPK portion (Subject (b) (6) received double doses and the PK data were excluded for analysis), whereas a total of 23 subjects were enrolled into the non-IPK portion.

Subjects enrolled for the IPK portion who received the final proposed dose were in general evenly distributed within the evaluated age range (3 to less than 12 years old) and body weight range (12 to less than 45 kg). There was no correlation between exposures and age or body weight which supports the proposed weight-band based dosing for subjects 3 years to less than 12 years old (Figure 1 and Figure 2). Table 4 shows PK parameters for outlier subjects, which still fall within the adult range. Excluding the outlier subjects results in a decrease in geometric means of GLE/PIB exposures ranged from ~11 to 36%, but with same study outcomes achieved. Therefore, the outlier subjects were included in the analysis.

Figure 1. NCA PK parameters of GLE and PIB vs. age in IPK subjects 3 to less than 12 years old and 12 to less than 45 kg.



Source: Reviewer prepared from M16-123 Study report. Red circles represent outlier subjects (Subject ID (b) (6) 3 years old; ID (b) (6), 8 years old, and ID (b) (6), Age 9 years old).

Figure 2. NCA PK parameters of GLE and PIB vs. body weight in IPK subjects 3 to less than 12 years old and weighing 12 to less than 45 kg.

Source: Reviewer prepared from M16-123 Study report. Red circles represent outlier subjects (Subject ID (b) (6), BW 12.7 kg; ID (b) (6), BW 22.9 kg, and ID (b) (6), BW 31.5 kg).

Table 4. NCA PK parameters for each outlier subjects.

				GLE			PIB		
Cohort	**ID**	**Age**	**BW**	**Cmax (ng/ml)**	**AUC24 (ng*hr/mL)**	**Ctrough (ng/mL)**	**Cmax (ng/ml)**	**AUC24 (ng*hr/mL)**	**Ctrough (ng/mL)**
2	(b) (6)	9	31.5	19800	175000	2630	567	8900	363
3		8	22.9	17800	79000	404	181	2350	77.6
4		3	12.7	13800	55500	94.2	324	4050	76.7

Comparison of exposures in subjects 3 years to less than 12 years old vs. adults

PK data from non-cirrhotic HCV-infected adult subjects following administration of 300 mg/120 mg of phase 3 formulation of GLE/PIB tablets once daily were used as the adult reference exposure in the

previous approval for adolescents 12 years and older or children weighing at least 45 kg, and also for this supplement for ages 3 to <12 years.

For pediatric PK analysis, in addition to NCA, the applicant also performed population PK (PopPK) analyses (Study Report M16123-poppk-part2). Overall, the GLE and PIB PopPK models adequately described the PK data (Please refer to the popPK analysis section). Pediatric PK parameters determined using NCA and popPK from IPK subjects who received the final proposed dosing regimen were in agreement (Table 5). In the current review report, pediatric PK parameters obtained by NCA were used for the comparison of exposures in subjects 3 years to less than 12 years old vs. adults.

Table 5. Comparison of pediatric PK parameters from IPK subjects who received the final proposed dosing regimen obtained by NCA vs popPK model prediction.

	popPK predictions, geometric mean			**NCA, geometric mean**		
GLE	Cohort 2 (N=13)	Cohort 3 (N=13)	Cohort 4 (N=12)	Cohort 2 (N=13)	Cohort 3 (N=13)	Cohort 4 (N=12)
AUC_{24} (ng*hr/mL)	7570	6030	9760	7870	6860	7520
C_{max} (ng/mL)	1100	926	1590	1370	1600	1530
C_{trough} (ng/mL)	7.32	4.77	5.89	12.4	7.44	6.58
PIB						
AUC_{24} (ng*hr/mL)	2200	1760	1870	2200	1640	1790
C_{max} (ng/mL)	211	192	207	225	197	233
C_{trough} (ng/mL)	29.1	22.1	29.2	36.5	19.4	17.9

Source: Reviewer prepared from Responses to IR requests submitted on 3/23/2021 and 4/1/2021.

The GMRs (calculated from NCA of intensive PK subjects who received the final proposed dosing regimen, N=13 for cohort 2, N=13 for cohort 3, and N=12 for cohort 4) of GLE and PIB C_{max} and AUC_{24} in pediatrics vs. adults ranged from 1.15-2.68, whereas GMRs of GLE C_{trough} ranged from 0.506-0.951 and GMRs of PIB C_{trough} ranged from 0.948-1.93 (Response to IR submitted on 4/1/2021 under NDA 215110) (Table 6). In pediatrics, 10-41.7% of the subjects have C_{max} and AUC_{24} values of GLE and PIB exceeding the 95th percentile in adults; whereas 4.17-15% of the subjects have C_{trough} values of GLE and PIB below the 5th percentile in adults (Response to IR submitted on 1/19/2021 under NDA 215110). However, no pediatric subjects had GLE and PIB C_{max} and AUC_{24} values above the adult maximum GLE and PIB C_{max} and AUC_{24} values; and no pediatric subjects had GLE C_{trough} values below the adult minimum GLE C_{trough} value (Response to IR submitted on 8/17/2020 under IND 127416). All pediatric GLE and PIB PK parameter values fell within the range observed in non-cirrhotic HCV-infected adult subjects (Response to IR submitted on 8/17/2020 under IND 127416) (Figure 3).

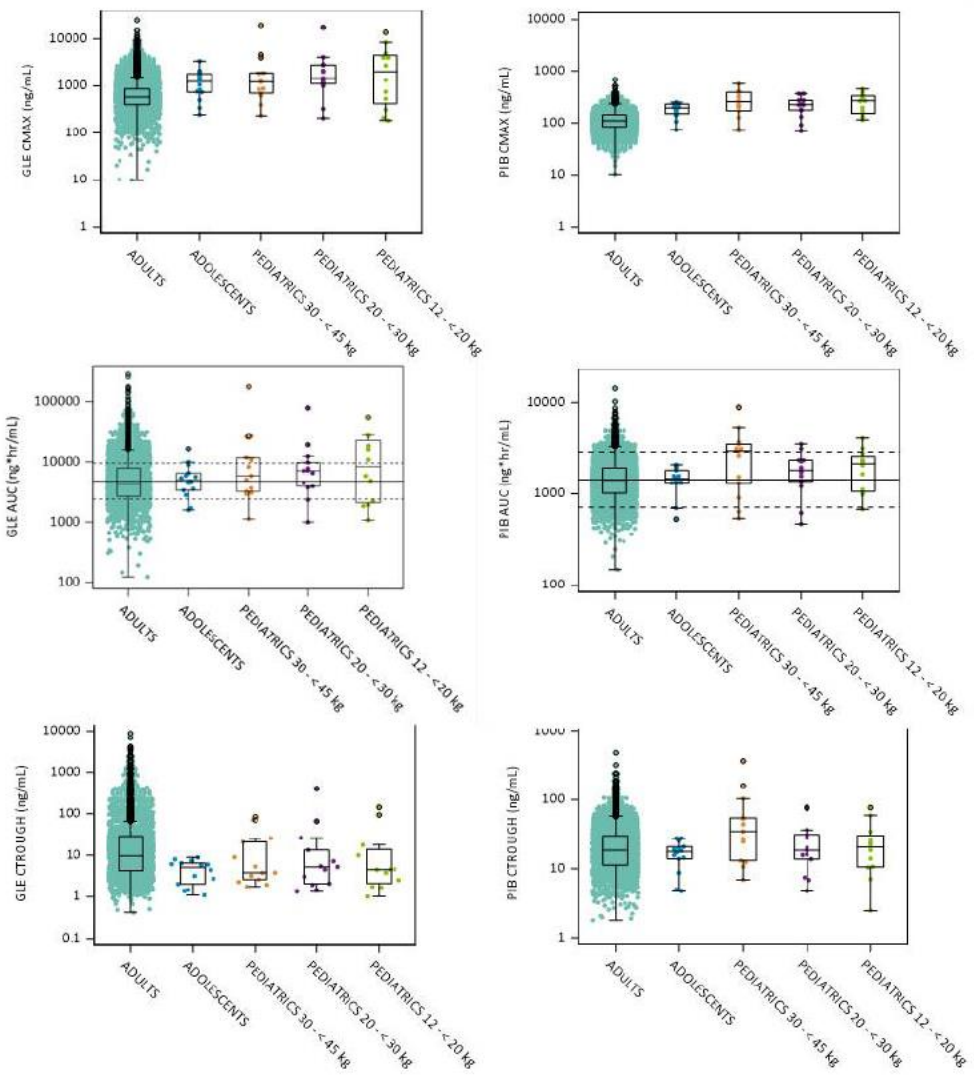
Table 6. Summary of pediatric/adult geometric mean ratios and 90% confidence intervals for subjects with intensive PK samples.

Parameter	Adults N=1804	Cohort 1 ≥ 45 kg N=14			Cohort 2 ≥ 30 to < 45 kg N=13			Cohort 3 ≥ 20 to < 30 kg N=13			Cohort 4 12 to < 20 kg N=12		
	Geometric Mean	Geometric Mean	Ratio	90% CI[a]	Geometric Mean	Ratio	90% CI[a]	Geometric Mean	Ratio	90% CI[a]	Geometric Mean	Ratio	90% CI[a]
Glecaprevir													
AUC_{24} (ng hr/mL)	4800	4790	0.998	0.733, 1.36	7870	1.64	0.921, 2.92	6860	1.43	0.803, 2.55	7520	1.57	0.860, 2.86
C_{max} (ng/mL)	597	1040	1.74	1.08, 2.81	1370	2.30	1.40, 3.78	1600	2.68	1.63, 4.41	1530	2.56	1.53, 4.30
C_{trough} (ng/mL)	13.0	3.79	0.292	0.207, 0.411	12.4	0.951	0.422, 2.15	7.44	0.572	0.254, 1.29	6.58	0.506	0.217, 1.18
Pibrentasvir													
AUC_{24} (ng hr/mL)	1430	1380	0.965	0.748, 1.25	2200	1.54	1.02, 2.32	1640	1.15	0.882, 1.50	1790	1.25	0.949, 1.64
C_{max} (ng/mL)	110	174	1.58	1.29, 1.94	225	2.05	1.49, 2.82	197	1.79	1.45, 2.21	233	2.12	1.70, 2.65
C_{trough} (ng/mL)	18.9	15.0	0.793	0.536, 1.17	36.5	1.93	1.29, 2.91	19.4	1.03	0.684, 1.54	17.9	0.948	0.620, 1.45

a. 90% CI = 90% confidence interval for the geometric mean of each cohort divided by the geometric mean of adults.

Source: Response to IR submitted on 4/1/2021 under NDA 215110.

Figure 3. Distribution of NCA PK Parameters (C_{max}, AUC_{24}, and C_{trough}) of GLE and PIB in pediatrics following the final proposed dosing regimens and in adolescents and adults following the GLE/PIB 300 mg/120 mg dose.



Source: Response to IR submitted on 8/17/2020 under IND 127416. For the AUC plots (middle panel), dashed lines show the target GLE AUC range of (2400-9600) ng•hr/mL and target PIB AUC range of (715-2860) ng•hr/mL, which are ± 2-fold of geometric mean exposures in adults.

To interpret the relatively higher GLE and PIB C_{max} and AUC_{24} and relatively lower GLE C_{trough} values in pediatrics vs. adults, we referred to the exposure-response analysis associated with safety and efficacy in adults. No outliers were identified in adult PK parameters used for exposure-response analysis (Exposure-Virologic Response submitted for NDA 209394, R&D/16/0236; Exposure-Safety Response submitted for NDA209394, R&D/16/0235).

The adverse effects (AEs) evaluated in the Applicant's exposure-safety analyses included post-nadir ALT elevation, post-baseline total bilirubin elevation, and diarrhea (Table 7). The dataset included 2660 subjects across nine clinical studies. Analyses included plots of AE frequency as a function of GLE or PIB AUC and C_{max} quartile as well as logistic regression with GLE and PIB C_{max} and AUC as predictors for probability of AE.

Table 7. Definitions of common terminology criteria for adverse events (CTCAE) grades for selected laboratory parameters.

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
ALT	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN	--
Total Bilirubin	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 10 × ULN	> 10 × ULN	--
Diarrhea	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

ULN = Upper limit of normal; ADL = Activity of daily living

Source: Exposure-Safety Response submitted for NDA209394, R&D/16/0235.

- Post-nadir ALT elevation: The incidence of ALT elevation was significantly lower following GLE+PIB treatment compared with placebo. The frequency of Grade ≥2 post-nadir ALT elevation ranged from ~0-1% across quartiles of GLE or PIB AUC and C_{max} and no association with exposure was identified in logistic regression. ALT elevation is not described in labeling under Adverse Reactions.
- Diarrhea: Across GLE or PIB AUC and C_{max} quartiles, the frequency of grade 1 and grade 2 diarrhea ranged from ~2-5% and ~0-1%. Frequency did not increase with exposure quartile and exposure was not associated with diarrhea incidence in logistic regression.
- Post-baseline total bilirubin elevation:
    - Across exposure quartiles, the frequency of grade 2 and grade 3 elevation ranged from ~1-5% and 0-1% and frequency increased with increased GLE and PIB AUC and C_{max} quartiles. In logistic regression, baseline total bilirubin and GLE exposure was associated with frequency of post-baseline total bilirubin elevation. The Adverse Reactions section of labeling states that elevation of total bilirubin ≥2 times the upper limit of normal was observed in 3.5% of adults treated with GLE/PIB. We do not consider the frequency of grade 2/3 bilirubin elevation in the highest vs lowest exposure quartile to be clinically significant.
    - According to the Clinical reviewer, clinically significant (grade 2 or higher) post-baseline total bilirubin increases were not observed through 4 weeks after treatment is complete in the pediatric trial.
- Overall, our conclusion from adult exposure-safety analysis is that acceptable safety was observed across the range of GLE and PIB exposures observed in adults.

The exposure-efficacy analysis was conducted using a dataset containing several studies; the population was divided into four subgroups:

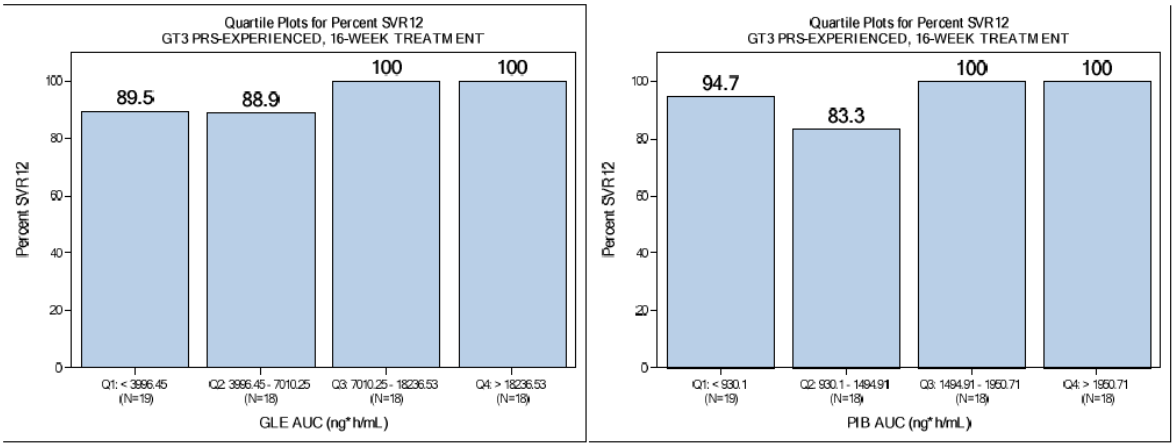
- Group 1: treatment-naïve and PRS-experienced GT1, GT2, GT4, GT5, and GT6 subjects (non-GT3 subjects) (TN, PRS experienced, non-GT3) (n=1755)
- Group 2: treatment-naïve GT3 subjects (GT3, TN) (n=608)
- Group 3: PRS-experienced GT3 subjects who received GLE/PIB for 16 weeks (GT3, PRS experienced) (n=73)
- Group 4: NS5A inhibitor-experienced subjects who received GLE/PIB for 16 weeks (NS5A experienced) (n=34)

The analyses included graphical analysis of SVR_{12} rate as a function of exposure quartile as well as multivariate logistic regression analyses that evaluated demographic covariates as well as GLE and PIB exposure as statistically significant ($p<0.05$) predictors of SVR_{12} rate.

In groups 1-2, the SVR_{12} rate ranged from ~95-100% across quartiles of GLE and PIB AUC and C_{trough} PIB AUC was the significant predictor of SVR_{12} for both groups whereas PIB C_{trough} was the significant predictor for group 2 in logistic regression.

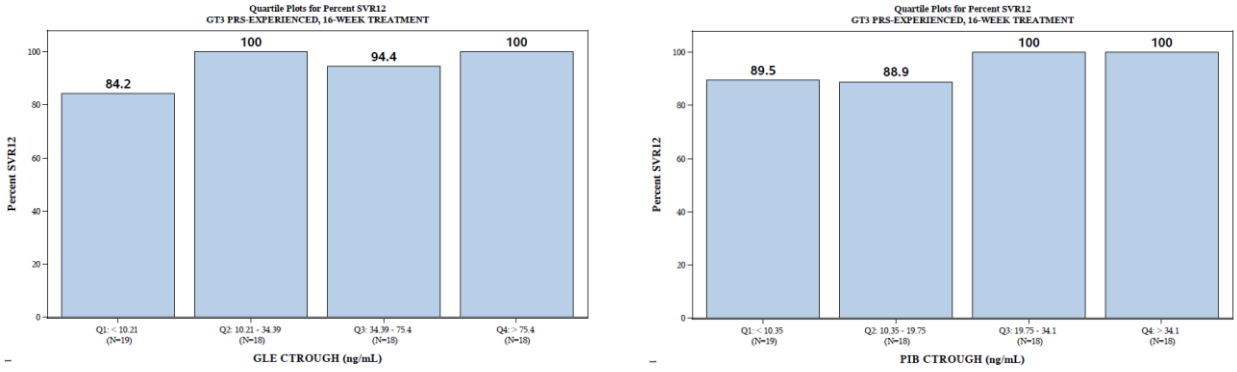
Groups 3-4 contained far fewer subjects and therefore it is difficult to draw conclusions regarding the effect of exposure on SVR12 rate (Figure 4, Figure 5, Figure 6 and Figure 7). In graphical analysis, group 3 SVR12 rate differed between the two lowest vs two highest GLE and PIB exposure quartiles. In group 4, association of exposure with SVR_{12} rate was unclear in that the highest exposure quartiles had the lowest SVR_{12} rates. In logistic regression analysis, there were no statistically significant predictors for group 3 and cirrhosis was a statistically significant predictor for group 4.

Figure 4. SVR12 rate versus GLE and PIB AUC quartiles for PRS-experienced GT3 subjects who received GLE/PIB for 16 weeks (GT3, PRS experienced) (n = 73).



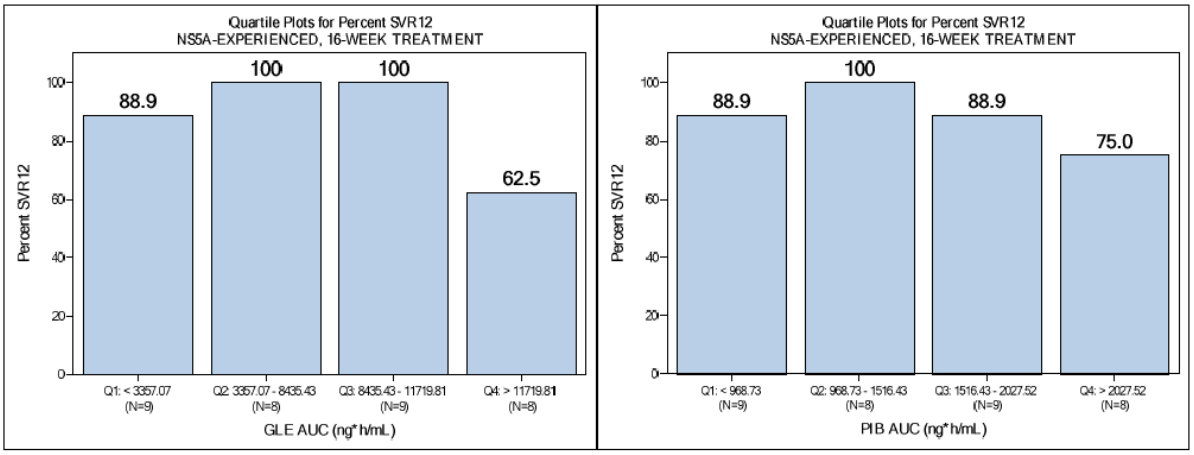
Source: Exposure-Virologic Response submitted for NDA 209394, R&D/16/0236.

Figure 5. SVR12 rate versus GLE and PIB C_{trough} quartiles for PRS-experienced GT3 subjects who received GLE/PIB for 16 weeks (GT3, PRS experienced) (n = 73).



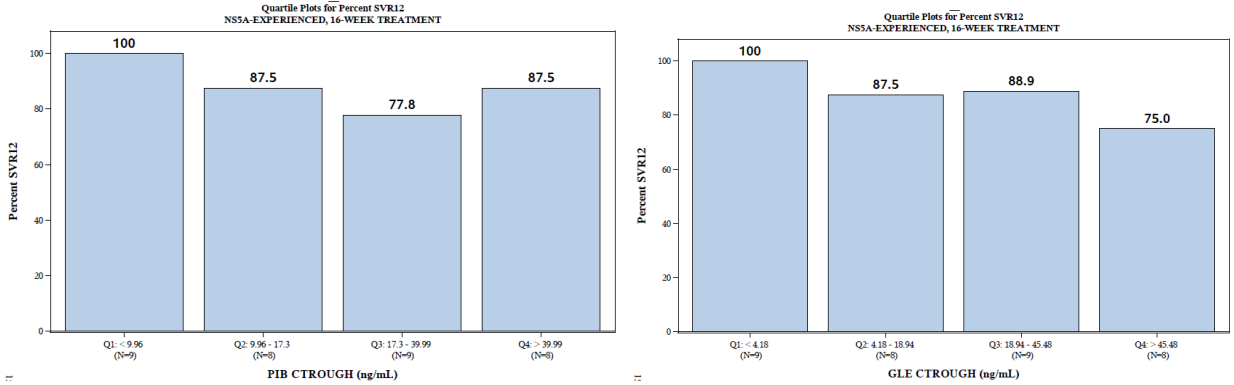
Source: Exposure-Virologic Response submitted for NDA 209394, R&D/16/0236.

Figure 6. SVR12 rate versus GLE and PIB AUC quartiles for NS5A inhibitor-experienced subjects who received GLE/PIB for 16 weeks (NS5A experienced, n = 34).



Source: Exposure-Virologic Response submitted for NDA 209394, R&D/16/0236.

Figure 7. SVR12 rate versus GLE and PIB C_{trough} quartiles for NS5A inhibitor-experienced subjects who received GLE/PIB for 16 weeks (NS5A experienced, n = 34).



Source: Exposure-Virologic Response submitted for NDA 209394, R&D/16/0236.

Overall, our conclusion from adult exposure-efficacy analysis is that acceptable efficacy was observed in subgroups 1-4 across the range of GLE and PIB exposures observed in adults.

In summary, the GMRs of GLE and PIB C_{max} and AUC_{24} in pediatrics vs. adults ranged from 1.15-2.68, whereas GMRs of GLE C_{trough} ranged from 0.506-0.951. All PK parameter values for individual subjects fell within the range of exposures in non-cirrhotic HCV-infected adults. We do not consider the exposure differences observed between pediatrics vs. adults to be clinically significant.

5.2 Study M17-142

Title
Bioavailability and food effect of experimental Glecaprevir + Pibrentasvir pediatric formulation in healthy adult subjects (CSR R&D/18/0297).

Primary Objectives

- Determine the bioavailability of the experimental GLE + PIB pediatric formulation relative to the reference Phase 3 adult formulation under fasting and non-fasting conditions (Part 1);
- Assess the effect of high-fat and low-fat meals on the experimental GLE + PIB pediatric formulation relative to fasting conditions (Part 2)

Study Design
This was a Phase 1, single-center, open-label, randomized study conducted in two parts. Part 1 was a four-sequence, four-period crossover design to evaluate the bioavailability of the experimental GLE + PIB pediatric formulation relative to the reference Phase 3 adult formulation under fasting and non-fasting conditions (Table 8). Part 2 was a three-sequence, three-period crossover design to evaluate the effect of high-fat and low-fat meals on the experiment GLE + PIB pediatric formulation relative to fasting conditions (Table 9).

Table 8. Sequence groups for part 1.

		Regimens			
Sequence Group	**N**	**Period 1**	**Period 2**	**Period 3**	**Period 4**
1	6	A	B	C	D
2	6	B	D	A	C
3	6	C	A	D	B
4	6	D	C	B	A

Regimen A = Single dose of GLE + PIB pediatric formulations administered under fasting conditions (300 mg + 120 mg in pellets) (Test 1).

Regimen B = Single dose of GLE + PIB pediatric formulations administered under non-fasting conditions (300 mg + 120 mg in pellets) (Test 2).

Regimen C = Single dose of GLE/PIB adult formulation administered under fasting conditions (300/120 mg, 3 × 100/40 mg tablets) (Reference 1).

Regimen D = Single dose of GLE/PIB adult formulation administered under non-fasting conditions (300/120 mg, 3 × 100/40 mg tablets) (Reference 2).

Source: M17-142 study report (Clinical Study Report R&D/18/0297).

Table 9. Sequence groups for part 2.

		Regimens		
Sequence Group	**N**	**Period 1**	**Period 2**	**Period 3**
1	5	E	F	G
2	5	F	G	E
3	5	G	E	F

Regimen E = Single dose of GLE + PIB pediatric formulations administered under high-fat conditions (300 mg + 120 mg in pellets) (Test 3).

Regimen F = Single dose of GLE + PIB pediatric formulations administered under low-fat conditions (300 mg + 120 mg in pellets) (Test 4).

Regimen G = Single dose of GLE + PIB pediatric formulations administered under fasting conditions (300 mg + 120 mg in pellets) (Reference 3 and Reference 4).

Source: M17-142 study report (Clinical Study Report R&D/18/0297).

On the dosing day (Day 1) in each period, subjects in fasting regimens (Regimens A, C, and G) were not served breakfast, subjects in non-fasting regimens (Regimens B, D, E and F) received a breakfast with different fat contents at approximately 30 minutes prior to dosing (B, D standard breakfast, 515 kcal; E, high-fat breakfast, 859.6 kcal; F, low-fat breakfast, 659 kcal). Subjects within each regimen received standardized meals during confinement. Each dose of study drug was taken orally with approximately 240 mL of water after at least a minimum 10-hour fast and approximately 4 hours before lunch for fasting regimens, and approximately 30 minutes after starting a breakfast for non-fasting regimens. An additional 240 mL of water was allowed to aid dosing. No soft food vehicles were administered with oral pellets for both fasting and fed conditions. Washout intervals of at least 4 days separated the doses of the four study periods in Part 1, and washout intervals of 5 days separated the doses of the three study periods in Part 2.

PK Analysis

Blood samples for GLE and PIB assay were collected prior to dosing (0-hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after dosing in each study period. Plasma concentrations of GLE and PIB were determined using a validated LC-MS/MS method.

Demographics

Adult male and female subjects (N = 39) were enrolled in the study, and 23 (fed)/24 (fasting) subjects completed all four periods of Part 1 and 15(fed)/15 (fasting) subjects completed all three periods of Part 2. One subject discontinued study drug in Part 1. Subjects were primarily white, with body weight of 77.5 ± 11.1 kg and 81.3 ± 13.8 kg for Part 1 and Part 2, respectively.

Protocol Deviations

No major protocol deviations were identified.

Sample Analysis

Plasma concentrations of GLE and PIB were measured using a validated LC-MS/MS method (Table 2). Consistent with the original validation method (R&D/14/0810, issued October 2014), two dynamic ranges (low assay range: 0.222 - 102 ng/mL and high assay range: 86.9 -10100 ng/mL for GLE; low assay range: 0.222-103 ng/mL and high assay range: 84.5 -1060 ng/mL for PIB) were used for sample analysis. No major issues were identified (Table 10).

Table 10. Assessment of method performance for GLE and PIB in study M17-142.

Major deviations	Accuracy and precision values of calibration and QC samples (including dilution QC samples) (within 15%, 20% at LLOQ)	Samples measured within the duration of stability	Incurred sample reanalysis pass rate (67% should be ± 20% of the original)	Chromatograms
No	Yes	Yes	Not evaluated	No anomalies observed in the submitted representative chromatograms

Source: Prepared by reviewer from bioanalytical report for Study M17-142.

PK Results

The PK parameters and statistical analyses are summarized in Table 11 and Table 12.

Similar with the tablet formulation, food increased bioavailability of the pediatric formulations, 2.3-2.7x fold for GLE and 1.6-2.1x fold for PIB, following a low- or high-fat breakfast relative to the exposures evaluated under fasting condition. As such, the oral pellets formulation is recommended to be administered with food as well without regard to fat or calorie content.

Under fed conditions, while no statistically significant differences in geometric means for PIB C_{max}, AUC_t, and C_{24} as well as GLE C_{24} were observed between pellets and tablets in healthy adults (Response to IR submitted on 2/23/2021 under NDA 215110), geometric means for GLE C_{max} and AUC_t were significantly less for pellets when compared with tablets, with GMRs of 0.66 and 0.79, respectively. In addition, GLE peak plasma concentrations occurred sooner for pellets than tablets (3.0 h vs. 4.0 h). Thus, pellet and tablet formulations did not demonstrate similarity in systemic exposures.

However, there was no clear evidence to show the relationship between GLE exposure and response rate of SVR_{12} based on graphical assessment and multiple logistic regression analysis as established in adults. Therefore, considering the large variabilities (CV of 122%) of GLE AUC_t values observed in non-cirrhotic HCV-infected adult subjects administered with tablets, an average GLE AUC_t reduction of ~20% following pellet use compared with tablets is not expected to impact efficacy. In addition, the applicant demonstrated that adding 6 sachets of oral pellets to 1-2 teaspoons of soft food is appropriate (Response to IR submitted on 5/4/2021 under NDA215110). Therefore, for pediatrics weighing at least 45 kg who cannot swallow the intact tablets, the recommended dose (300 mg GLE/120 mg PIB) may be administered as oral pellets (6 sachets).

Table 11. Geometric mean (Mean, % CV) PK parameters of GLE and PIB (part 1 and part 2)

PK parameters	Part 1				Part 2		
	Regimen A (N=24)	Regimen B (N=23)	Regimen C (N=24)	Regimen D (N=23)	Regimen E (N=15)	Regimen F(N=15)	Regimen G (N=15)
GLE							
C_{max} (ng/mL)	236 (356, 144)	621 (721, 51)	399 (583, 97)	946 (1300, 83)	284 (327, 64)	387 (437, 50)	134 (143, 40)
T_{max}[a] (h)	1.5 (1.0-6.0)	3.0 (1.5-6.0)	3.0 (2.0-6.0)	4.0 (2.0-6.0)	4.0 (1.5-6.0)	3.0 (1.0-6.0)	1.5 (1.0-2.0)
$t_{1/2}$[b] (h)	6.98 (2.58)	6.85 (1.45)	6.63 (1.58)	6.26 (1.55)	5.59 (1.80)	6.26 (1.21)	5.28 (1.94)
AUC_t (ng*h/mL)	1110 (1540-118)	2700 (3060, 50)	1830 (2330, 78)	3410 (4290, 76)	1350 (1500, 48)	1560 (1720, 46)	585 (643, 48)

AUC_{inf} (ng*h/mL)	1110 (1540-118)	2710 (3060, 50)	1830 (2340, 78)	3420 (4300, 76)	1360 (1500, 48)	1570 (1720, 46)	589 (647, 48)
PIB							
C_{max} (ng/mL)	102 (125, 61)	213 (247, 51)	124 (153, 63)	189 (224, 58)	189 (210, 54)	151 (173, 58)	82.2 (91.4, 46)
T_{max}[a] (h)	4.0 (3.0-5.0)	5.0 (3.0-6.0)	5.0 (2.0-6.0)	5.0 (2.0-8.0)	5.0 (2.0-6.0)	3.0 (2.0-5.0)	4.0 (2.0-5.0)
$t_{1/2}$[b] (h)	14.4 (1.89)	14.1 (1.38)	14.1 (1.63)	13.9 (1.57)	12.7 (1.22)	13.0 (1.53)	13.4 (1.30)
AUC_t (ng*h/mL)	869 (1070, 65)	1490 (1760-52)	1010 (1270, 67)	1240 (1490, 60)	1400 (1560, 52)	1020 (1190, 63)	653 (748, 49)
AUC_{inf} (ng*h/mL)	924 (1140, 64)	1580 (1870, 52)	1070 (1340, 68)	1310 (1580, 59)	1470 (1640, 52)	1070 (1250, 63)	686 (785, 49)

Regimen A = Single dose of GLE + PIB pediatric formulations administered under fasting conditions (300 mg + 120 mg in pellets) (Test 1).
Regimen B = Single dose of GLE + PIB pediatric formulations administered under non-fasting conditions (300 mg + 120 mg in pellets) (Test 2)
Regimen C = Single dose of GLE/PIB adult formulation administered under fasting conditions (300/120 mg, 3x100/40 mg tablets) (Reference 1)
Regimen D = Single dose of GLE/PIB adult formulation administered under non-fasting conditions (300/120 mg, 3x100/40 mg tablets) (Reference 2)
Regimen E = Single dose of GLE + PIB pediatric formulations administered under high-fat conditions (300 mg + 120 mg in pellets) (Test 3)
Regimen F = Single dose of GLE + PIB pediatric formulations administered under low-fat (300 mg + 120 mg in pellets) (Test 4)
Regimen G = Single dose of GLE + PIB pediatric formulations administered under fasting conditions (300 mg + 120 mg in pellets) (Reference 3 and Reference 4)
a. Median (minimum through maximum)
b. Harmonic mean (pseudo-standard deviation)
Source: Prepared by reviewer from M17-142 Study report and Response to IR on 2/23/2021.

Table 12. Relative bioavailability and 90% confidence intervals for GLE and PIB (part 1 and part 2).

Regimens Test vs. Reference	PK Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
PART 1					
GLE					
A vs. C (Pediatric vs. Adult formulation under fasting conditions)	**C_{max}**	236	399	0.591	(0.447, 0.782)
	AUC_t	1110	1830	0.606	(0.478, 0.768)
	AUC_{inf}	1110	1830	0.607	(0.479, 0.769)
	C_{24}	2.59	2.78	0.929	(0.785, 1.100)
B vs. D (Pediatric vs. Adult formulation under non-fasting conditions)	**C_{max}**	**631**	**949**	**0.664**	**(0.524, 0.842)**
	AUC_t	**2720**	**3420**	**0.794**	**(0.664, 0.949)**
	AUC_{inf}	**2730**	**3430**	**0.795**	**(0.665, 0.950)**
	C_{24}	**3.89**	**4.24**	**0.917**	**(0.772, 1.090)**
PIB					
A vs. C (Pediatric vs. Adult formulation under fasting conditions)	**C_{max}**	102	124	0.822	(0.659, 1.025)
	AUC_t	869	1010	0.859	(0.690, 1.070)
	AUC_{inf}	924	1070	0.862	(0.695, 1.070)
	C_{24}	7.24	8.40	0.862	(0.691, 1.074)
B vs. D (Pediatric vs. Adult formulation under non-fasting conditions)	**C_{max}**	**211**	**186**	**1.137**	**(0.908, 1.424)**
	AUC_t	**1480**	**1210**	**1.223**	**(0.977, 1.531)**
	AUC_{inf}	**1570**	**1290**	**1.219**	**(0.978, 1.520)**
	C_{24}	**12.3**	**10.5**	**1.174**	**(0.937, 1.471)**
PART 2					
GLE					
E vs. G (Pediatric formulation under high-fat vs. fasting conditions)	**C_{max}**	284	134	2.119	(1.732, 2.592)
	AUC_t	1350	585	2.310	(1.985, 2.688)
	AUC_{inf}	1360	589	2.305	(1.981, 2.681)
	C_{24}	2.92	1.73	1.688	(1.439, 1.980)
F vs. G (Pediatric formulation under low-fat vs. fasting conditions)	**C_{max}**	387	134	2.888	(2.361, 3.533)
	AUC_t	1560	585	2.676	(2.299, 3.114)
	AUC_{inf}	1570	589	2.666	(2.292, 3.101)
	C_{24}	2.49	1.73	1.439	(1.227, 1.688)

PIB					
E vs. G (Pediatric formulation under high-fat vs. fasting conditions)	**C_{max}**	189	82.2	2.300	(1.867, 2.834)
	AUC_t	1400	653	2.145	(1.750, 2.629)
	AUC_{inf}	1470	686	2.138	(1.750, 2.613)
	C_{24}	11.3	4.99	2.276	(1.852, 2.796)
F vs. G (Pediatric formulation under low-fat vs. fasting conditions)	**C_{max}**	151	82.2	1.834	(1.489, 2.260)
	AUC_t	1020	653	1.566	(1.277, 1.919)
	AUC_{inf}	1070	686	1.562	(1.278, 1.908)
	C_{24}	7.95	4.99	1.595	(1.298, 1.960)

Regimen A = Single dose of GLE + PIB pediatric formulations administered under fasting conditions (300 mg + 120 mg in pellets) (Test 1).
Regimen B = Single dose of GLE + PIB pediatric formulations administered under non-fasting conditions (300 mg + 120 mg in pellets) (Test 2)
Regimen C = Single dose of GLE/PIB adult formulation administered under fasting conditions (300/120 mg, 3x100/40 mg tablets) (Reference 1)
Regimen D = Single dose of GLE/PIB adult formulation administered under non-fasting conditions (300/120 mg, 3x100/40 mg tablets) (Reference 2)
Regimen E = Single dose of GLE + PIB pediatric formulations administered under high-fat conditions (300 mg + 120 mg in pellets) (Test 3)
Regimen F = Single dose of GLE + PIB pediatric formulations administered under low-fat (300 mg + 120 mg in pellets) (Test 4)
Regimen G = Single dose of GLE + PIB pediatric formulations administered under fasting conditions (300 mg + 120 mg in pellets) (Reference 3 and Reference 4)
Source: Prepared by reviewer from M17-142 Study report and Response to IR on 2/23/2021.

6. Pharmacometrics Review

6.1 Population PK analysis

6.1.1 Review summary

The Applicant conducted population pharmacokinetics (PopPK) analyses to assess the PK of glecaprevir (GLE) and pibrentasvir (PIB) in pediatric subjects with non-cirrhotic HCV (genotypes 1-6) between 3 to 11 years of age, inclusively. The objective of the PopPK analysis by the Applicant was to evaluate the PK profiles of GLE and PIB, coated (b) (4) formulation (oral pellets), in pediatric subjects weighing < 45 kg and whether the Applicant proposed weight-based dosing regimen provides acceptable drug exposure compared to HCV-infected adolescents (12-17 years of age) and adults.

In general, the Applicant's PopPK models provide acceptable fits to the GLE and PIB PK data and support for the purpose of pediatric dose selection.

6.1.2 Introduction

The primary objectives of applicant's analysis were to:

- Characterize the structural and final pharmacokinetic (PK) models of GLE and PIB
- Describe the effects of body weight on GLE and PIB exposure
- Compare PK parameters from NCA in subjects with intensive PK sampling to the PopPK parameters
- Generate exposure metrics from PopPK final model via simulation to support weight-based dosing approach in pediatric patients aged 3 to <12 years

6.1.3 Model development

Data

The combined PK data was obtained from Part 1 and Part 2 of Phase 2/3 Study M16-123 that includes both adolescent and pediatric data (age range, 3-17 years). For an overview of the studies, refer to Table 1 in Applicant's report 2/3 Study M16-123 on page 19.

For the PopPK data analysis, 126 subjects contributed 693 and 693 plasma concentrations for GLE and PIB, respectively. A total of 69 subjects contributed intensive PK sampling data. Of note, 47 adolescent subjects were categorized under Cohort 1 while 79 pediatric subjects were categorized into Cohorts 2-4 by age. Table 13 provides the summary for demographics and clinical covariates of studied subjects.

Table 13. Summary of demographics and clinical covariates for subjects included in the final PopPK model.

		SUBJECTS INCLUDED IN POPULATION ANALYSIS					
		ADOLESCENT	PEDIATRIC				
CHARACTERISTIC		COHORT 1	COHORT 2	COHORT 3	COHORT 4[a]	PEDIATRIC TOTAL	ADOLESCENT AND PEDIATRIC TOTAL
AGE (years)	N	47	29	27	23	79	126
	MEAN (SD)	14.26 (1.51)	10.00 (0.85)	7.11 (0.89)	3.83 (0.78)	7.22 (2.64)	9.84 (4.11)
	MEDIAN	14	10	7	4	7	10
	MIN, MAX	12, 17	9, 11	6, 9	3, 5	3, 11	3, 17
BODY SURFACE AREA (m^2)	N	47	29	27	23	79	126
	MEAN (SD)	1.62 (0.20)	1.21 (0.10)	0.92 (0.08)	0.66 (0.06)	0.95 (0.24)	1.20 (0.39)
	MEDIAN	1.62	1.22	0.90	0.65	0.94	1.18
	MIN, MAX	1.12, 2.26	1.04, 1.40	0.81, 1.07	0.56, 0.81	0.56, 1.40	0.56, 2.26

		SUBJECTS INCLUDED IN POPULATION ANALYSIS					
		ADOLESCENT	PEDIATRIC				
CHARACTERISTIC		COHORT 1	COHORT 2	COHORT 3	COHORT 4[a]	PEDIATRIC TOTAL	ADOLESCENT AND PEDIATRIC TOTAL
GENOTYPE	GENOTYPE 1	37 (78.72%)	19 (65.52%)	22 (81.48%)	17 (73.91%)	58 (73.42%)	95 (75.40%)
	GENOTYPE 2	3 (6.38%)	2 (6.90%)			2 (2.53%)	5 (3.97%)
	GENOTYPE 3	4 (8.51%)	8 (27.59%)	3 (11.11%)	6 (26.09%)	17 (21.52%)	21 (16.67%)
	GENOTYPE 4	3 (6.38%)		2 (7.41%)		2 (2.53%)	5 (3.97%)
JAPANESE RACE	NON-JAPANESE	43 (91.49%)	26 (89.66%)	24 (88.89%)	20 (86.96%)	70 (88.61%)	113 (89.68%)
	JAPANESE	4 (8.51%)	3 (10.34%)	3 (11.11%)	3 (13.04%)	9 (11.39%)	13 (10.32%)

		SUBJECTS INCLUDED IN POPULATION ANALYSIS					
		ADOLESCENT	PEDIATRIC				
CHARACTERISTIC		COHORT 1	COHORT 2	COHORT 3	COHORT 4[a]	PEDIATRIC TOTAL	ADOLESCENT AND PEDIATRIC TOTAL
RENAL FUNCTION	NORMAL	46 (97.87%)	29 (100%)	27 (100%)	23 (100%)	79 (100%)	125 (99.21%)
	MILD IMPAIRMENT	1 (2.13%)					1 (0.79%)
SEX	MALE	21 (44.68%)	14 (48.28%)	10 (37.04%)	11 (47.83%)	35 (44.30%)	56 (44.44%)
	FEMALE	26 (55.32%)	15 (51.72%)	17 (62.96%)	12 (52.17%)	44 (55.70%)	70 (55.56%)
TREATMENT EXPERIENCE	TREATMENT NAIVE	36 (76.60%)	27 (93.10%)	27 (100%)	23 (100%)	77 (97.47%)	113 (89.68%)
	TREATMENT EXPERIENCED	11 (23.40%)	2 (6.90%)			2 (2.53%)	13 (10.32%)
BODY WEIGHT (kg)	N	47	29	27	23	79	126
	MEAN (SD)	59.22 (14.08)	36.92 (4.44)	24.45 (3.50)	15.86 (2.01)	26.53 (9.35)	38.72 (19.48)
	MEDIAN	57.70	36.80	23.10	15.60	25.50	36.45
	MIN, MAX	32.00, 108.90	29.40, 44.30	19.60, 33.50	12.70, 21.20	12.70, 44.30	12.70, 108.90

SD = standard deviation; Min = minimum; Max = maximum; BSA = Body Surface Area; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus

a. Subject (b) (6) from Cohort 4 was partially dosed, discontinued from the study, and had no GLE or PIB plasma concentration measurements.

Cross reference: Table 14.2__1

Modeling Environment

Population pharmacokinetic models were built using nonlinear mixed effects modeling based on NONMEM 7.4.3 compiled with the GNU Fortran compiler (Version 4.8.3). The first-order conditional estimation method with η-ε interaction (FOCE-INT) was employed for all model runs within NONMEM.

Source: Applicant's report, Phase 2/3 Study M16-123, Part 2

Base model

GLE

A 1-compartment PK model with first-order absorption and elimination was fitted to the data with Ka parameterized into and CL/F parameterized from the central volume of distribution (V/F). Relative F was fixed at 0.8 for pediatric formulation (relative to 1.0 for adolescent) based on Study M17-142 *(see Clinical Pharmacology Review Section 4.2 above)*. Ka was constrained to be greater than elimination rate constant. Body weight was centered to 70 kg and allometrically scaled on CL and Vd. Allometric scaling was data-driven. Random effects were modeled for CL/F and V/F to describe inter-individual variability (IIV). Proportion error model was used for the residual error.

PIB

A 2-compartment PK model with first-order absorption with lag time and elimination was fitted to the PIB data. The structural PK model was parameterized with ALAG, CL/F, V/F (central), V/F (peripheral), Ka, and Q/F (between central and peripheral compartments). F was fixed to 1.2 relatively to adolescent subjects. Ka was constrained to be greater than elimination rate constant. Body weight was centered to 70 kg and allometrically scaled on CL and Vd. Allometric scaling was data-driven. Random effects were modeled for CL/F and V/F (central) to describe IIV. Proportion error model was used for the residual error.

Covariate analysis

The following covariates were examined for both GLE and PIB. Of note, body weight (centered to 70 kg) was included in the base structural model. Relative F (based on formulation) was fixed accordingly based on Study M17-142.

- CL/F: body weight, BSA, age, sex, race (categorical), Japanese race (categorical)
- V/F (central): body weight, BSA, age, Sex, race (categorical), Japanese race (categorical)

6.1.4 Final model

No covariates were retained in the final PopPK models for GLE and PIB. The final PK model parameter estimates are described in Table 14 and Table 15 for GLE and PIB, respectively.

Table 14. PK parameter estimates for final model for GLE.

	Population Value (θ)			Inter-Individual Variability (ω^2)		
Parameter	**Estimate (SEE)**	**%RSE**	**95% Confidence Interval**	**Variance (%CV)**	**% RSE**	**η-shrinkage (%)**
CL/F (L/day)[a]	1830 (388)	21.3	1220 - 2740	1.39 (174)	14.2	3.8
V2/F (L)[a]	358 (97.0)	27.1	216 - 593	1.52 (189)	15.1	5.1
Absorption Factor[b]	3.65 (0.438)	12.0	2.79 - 4.51	--	--	--
Formulation (Part 2) on F1	0.800 (FIX)	-	-	--	--	--
Body Weight on CL/F	1.04 (0.211)	20.3	0.626 - 1.45	--	--	--
Body Weight on V2/F	1.19 (0.246)	20.7	0.708 - 1.67	--	--	--
Derived Absorption Rate KA (1/day)[b]	18.6 (NA)	-	-	--	--	--
	Residual Variability (σ^2)					
Parameter	**Estimate (SEE)**	**%RSE**	**95% Confidence Interval**			
σ12 (Proportional)	0.568 (0.0320)	5.63	0.505 - 0.631	--	--	--

SEE = Standard Error of Estimate; %CV calculated as sqrt(exp[OMEGA] – 1) × 100 from the NONMEM output.

% Relative Standard Error (RSE) was estimated as the SEE divided by the population estimate multiplied by 100.

95% CI was approximated as the point estimate ± 1.96 × SEE.

a. Estimated in exponential transformation (base 10), transformed back for table. SEE calculated as sqrt((exp(STHETA**2)-1) × (exp(2 × THETA + STHETA**2))). STHETA denotes the standard error of the transformed THETA.

b. Absorption rate was estimated via a factor on elimination rate K = CL/V2 to avoid flip-flop behavior. Respective confidence intervals for KA are provided along with the bootstrap results (Table 4).

Source: Applicant's report, Phase 2/3 Study M16-123, Part 2, Table 3.

Table 15. PK parameter estimates for final model for PIB.

	Population Value (θ)			Inter-Individual Variability (ω^2)		
Parameter	**Estimate (SEE)**	**%RSE**	**95% Confidence Interval**	**Variance (%CV)**	**%RSE**	**η-shrinkage (%)**
CL/F (L/day)[a]	2170 (231)	10.7	1760 - 2660	0.359 (65.7)	18.2	4.9
V2/F (L)[a]	528 (86.2)	16.3	386 - 723	0.170 (43.0)	25.9	8.9
Q/F (L/day)[a]	765 (92.0)	12.0	606 - 966	--	--	--
V3/F (L)[a]	3750 (1421)	37.9	1900 - 7390	--	--	--
ALAG1 (days)	0.0556 (0.00242)	4.36	0.0510 - 0.0605	--	--	--
Absorption Factor[b]	2.47 (0.422)	17.1	1.64 - 3.30	--	--	--
Formulation (Part 2) on F1	1.20 (FIX)	-	-			
Body Weight on CL/F	0.440 (0.111)	25.2	0.222 - 0.658	--	--	--
Body Weight on V2/F	0.757 (0.116)	15.3	0.530 - 0.984	--	--	--
Derived Absorption Rate KA (1/day)[b]	10.1 (NA)	-	-	--	--	--
	Residual Variability (σ^2)					
Parameter	**Estimate (SEE)**	**%RSE**	**95% Confidence Interval**			
σ_1^2 (Proportional)	0.229 (0.0164)	7.16	0.197 - 0.261	--	--	--

SEE = Standard Error of Estimate; %CV calculated as sqrt(exp[OMEGA] – 1) × 100 from the NONMEM output.

% Relative Standard Error (RSE) was estimated as the SEE divided by the population estimate multiplied by 100.

95% confidence interval was approximated as the point estimate ± 1.96 × SEE.

a. Estimated in exponential transformation (base 10), transformed back for table. SEE calculated as sqrt((exp(STHETA**2)-1) × (exp(2 × THETA + STHETA**2))). STHETA denotes the standard error of the transformed THETA.

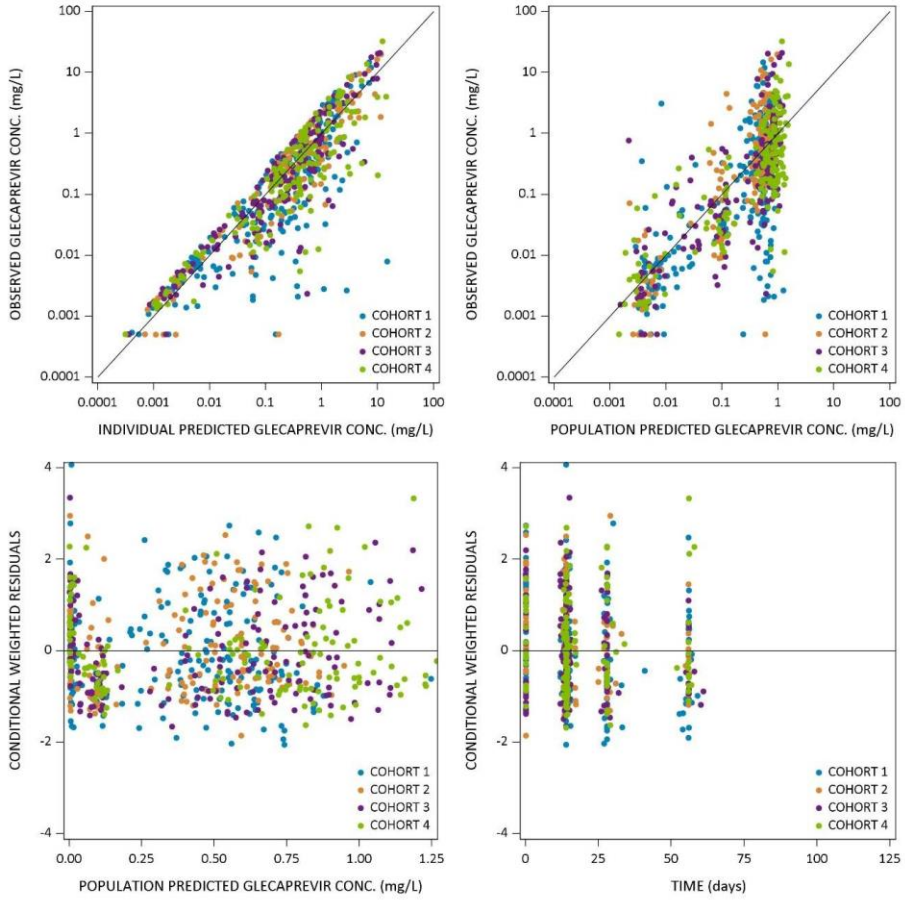
b. Absorption rate was estimated via a factor on elimination rate K = CL/V2 to avoid flip-flop behavior. Respective confidence intervals for KA are provided along with the bootstrap results (Table 6).

Source: Applicant's report, Phase 2/3 Study M16-123, Part 2, Table 5.

Reviewer's comments: the reviewer was able to reproduce the PopPK model parameter estimates. In general, the PK parameters have acceptable precision (<27.1% for GLE and < 37.9% for PIB) for simulation and generation exposure metrics. IIVs are high for CL and V (central) for GLE final PopPK model (173.6-189% for CL and V). In PIB final model, IIVs were moderate at 65.7% and 43% for CL and V (central), respectively. Limited sample size may be one contributor to the moderate to high IIVs of CL and V (central); however, the RSE% were generally low (< 25.9%) for IIVs of CL and V (central) across GLE and PIB final PopPK models. Both models are acceptable for generating exposure metrics (i.e., 24-h AUCs, Cmax).

The goodness-of-fit (GoF) and VPC plots for the final GLE PopPK model are shown in Figure 8 and Figure 9. GoF and VPC plots for PIB PopPK are shown in Figure 10 and Figure 11, respectively. Figure 12 and Figure 13 describes ETA plots for GLE and PIB, respectively.

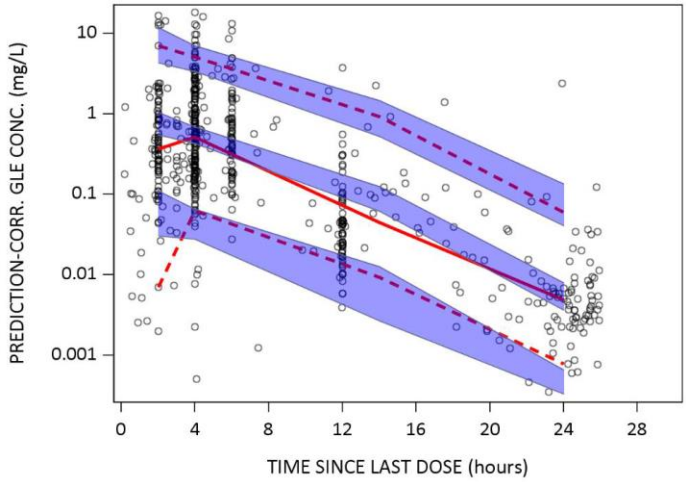
Figure 8. GoF plots for final GLE model.



Source: Applicant's report, Phase 2/3 Study M16-123, Part 2, Figure 1.

Reviewer's comments: the final model for GLE showed acceptable fits in describing the PK data for subjects between 3-17 years of age. No obvious model misspecification or bias are observed. CWRES vs population predicted and CWRES vs. time showed that residuals reasonably centered around x=0. No obvious trends are identified.

Figure 9. GLE pcVPC plots.



The shaded blue areas represent the 90% prediction interval of the 5th, 50th and 95th percentiles of simulated GLE concentrations, the solid red line represents median of observed GLE concentrations and dashed red lines represent the 5th and 95th percentile of the observed GLE concentrations. The open circles represent observed GLE concentrations.

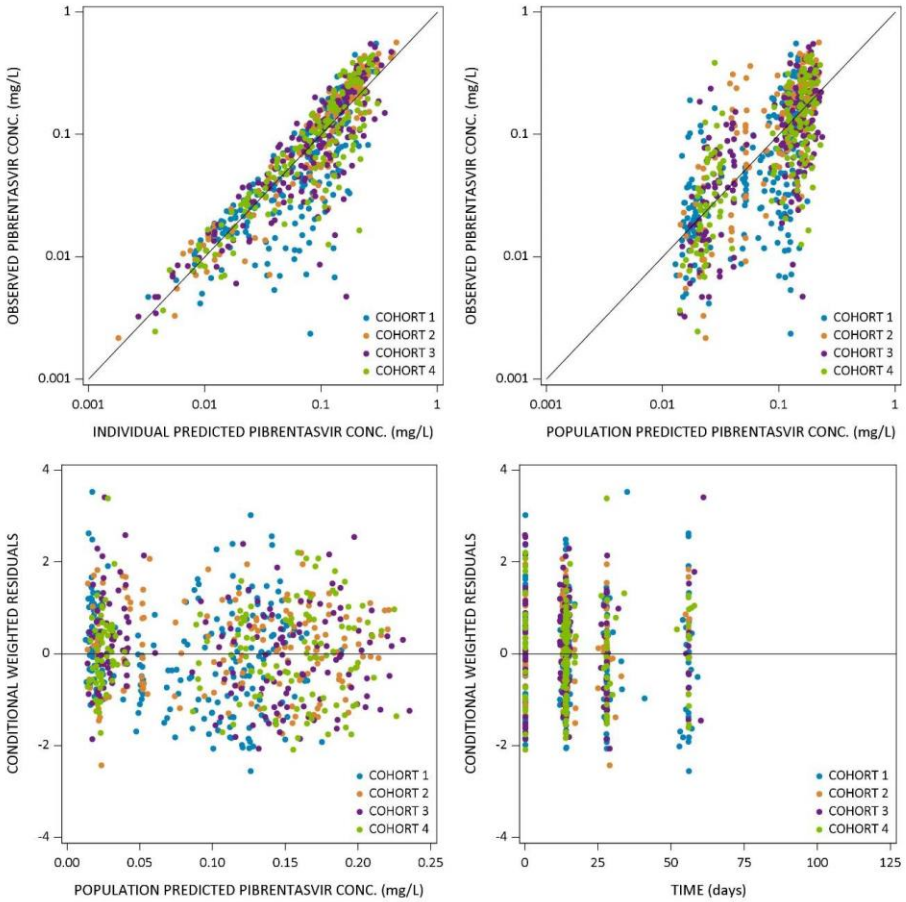
Note: VPCs are cut at 24 hours after last dose, as data are too sparse beyond.

Cross reference: Figure 14.7__1.1

Source: Applicant's report, Phase 2/3 Study M16-123, Part 2, Figure 2.

Reviewer's comments: the final GLE PopPK model overall captures central tendency in the prediction corrected VPC plot. Note that there are slight overpredictions around the 50th percentile over time for simulated GLE concentrations; however, the upper and lower bounds of PI (5th and 95% percentiles) and the associated CI reasonably described the observed data for exposure extrapolation and dose selection.

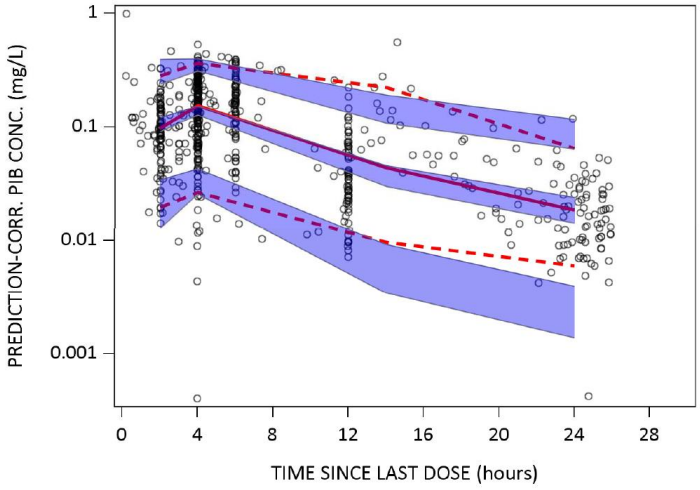
Figure 10. GoF plots for final PIB model.



Source: Applicant's report, Phase 2/3 Study M16-123, Part 2, Figure 6

Reviewer's comments: the final model for PIB showed acceptable fits in describing the PK data for subjects between 3-17 years of age. No obvious model misspecification or bias are observed. CWRES vs population predicted and CWRES vs. time showed that residuals reasonably centered around x=0 with no trends.

Figure 11. PIB pcVPC plots.



The shaded blue areas represent the 90% prediction interval of the 5th, 50th and 95th percentiles of simulated PIB concentrations, the solid red line represents median of observed PIB concentrations and dashed red lines represent the 5th and 95th percentile of the observed PIB concentrations. The open circles represent observed PIB concentrations.

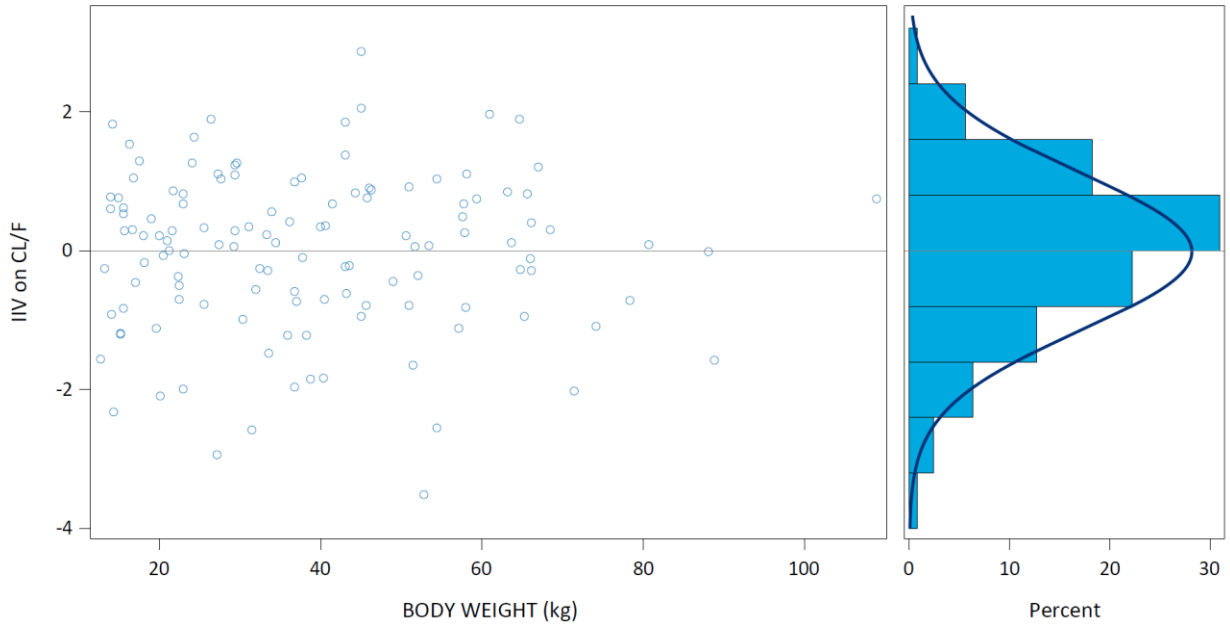
Note: VPCs are cut at 24 hours after last dose, as data are too sparse beyond.

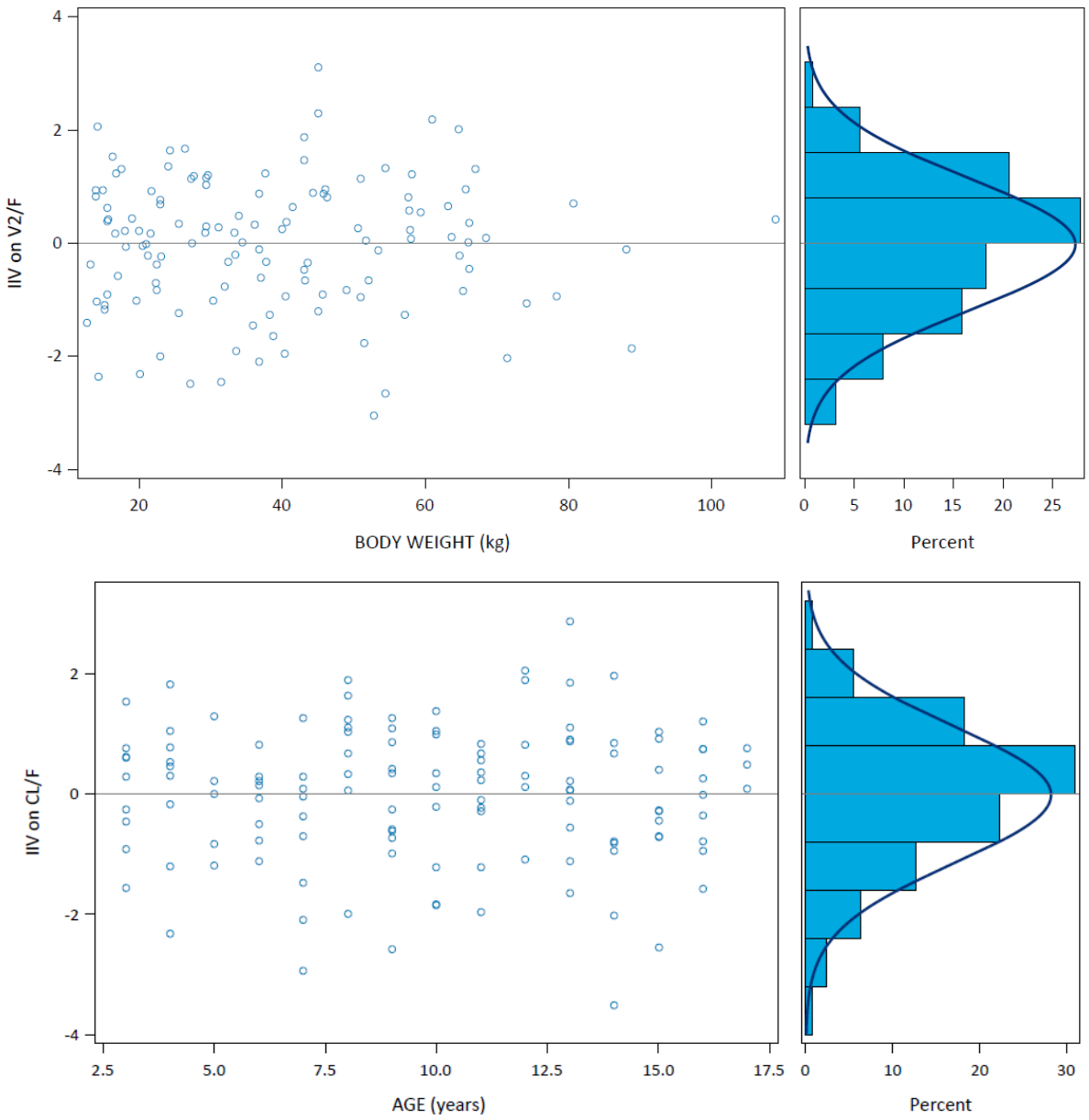
Cross reference: Figure 14.7__2.1

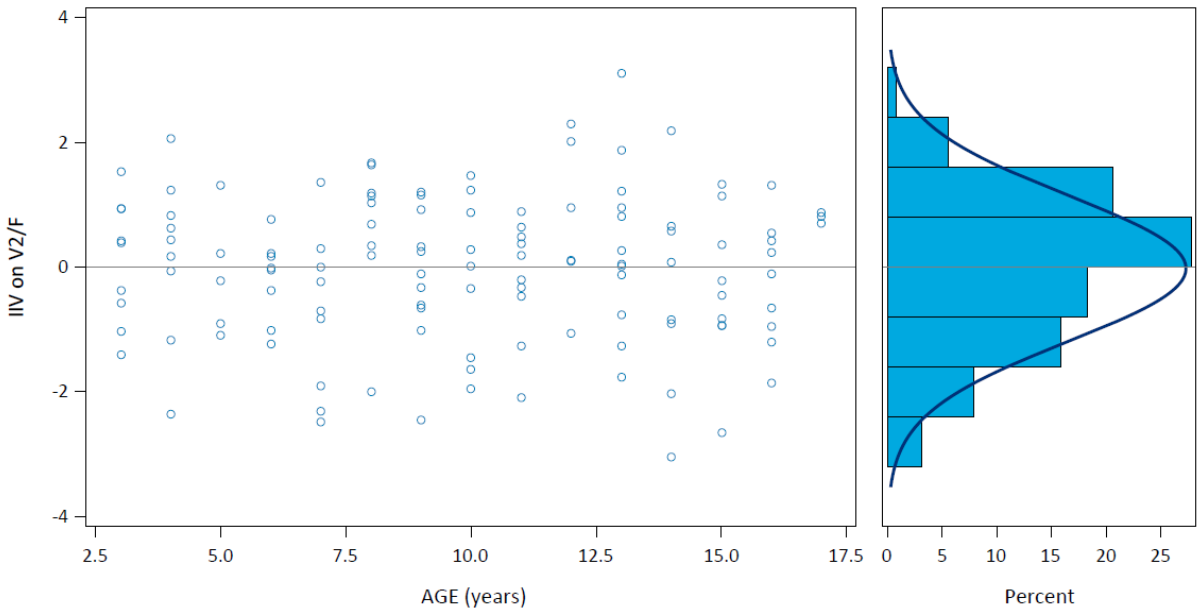
Source: Applicant's report, Phase 2/3 Study M16-123, Part 2, Figure 7

Reviewer's comments: the final GLE PopPK model shows acceptable central tendency in the prediction corrected VPC plot. Note that there are slight overpredictions around the 50th percentile over time for simulated GLE concentrations; however, the upper and lower bounds of PI (5th and 95% percentiles) and the associated CI reasonably described the observed data for exposure extrapolation and dose selection.

Figure 12. GLE final model ETA vs. PK parameter plots.



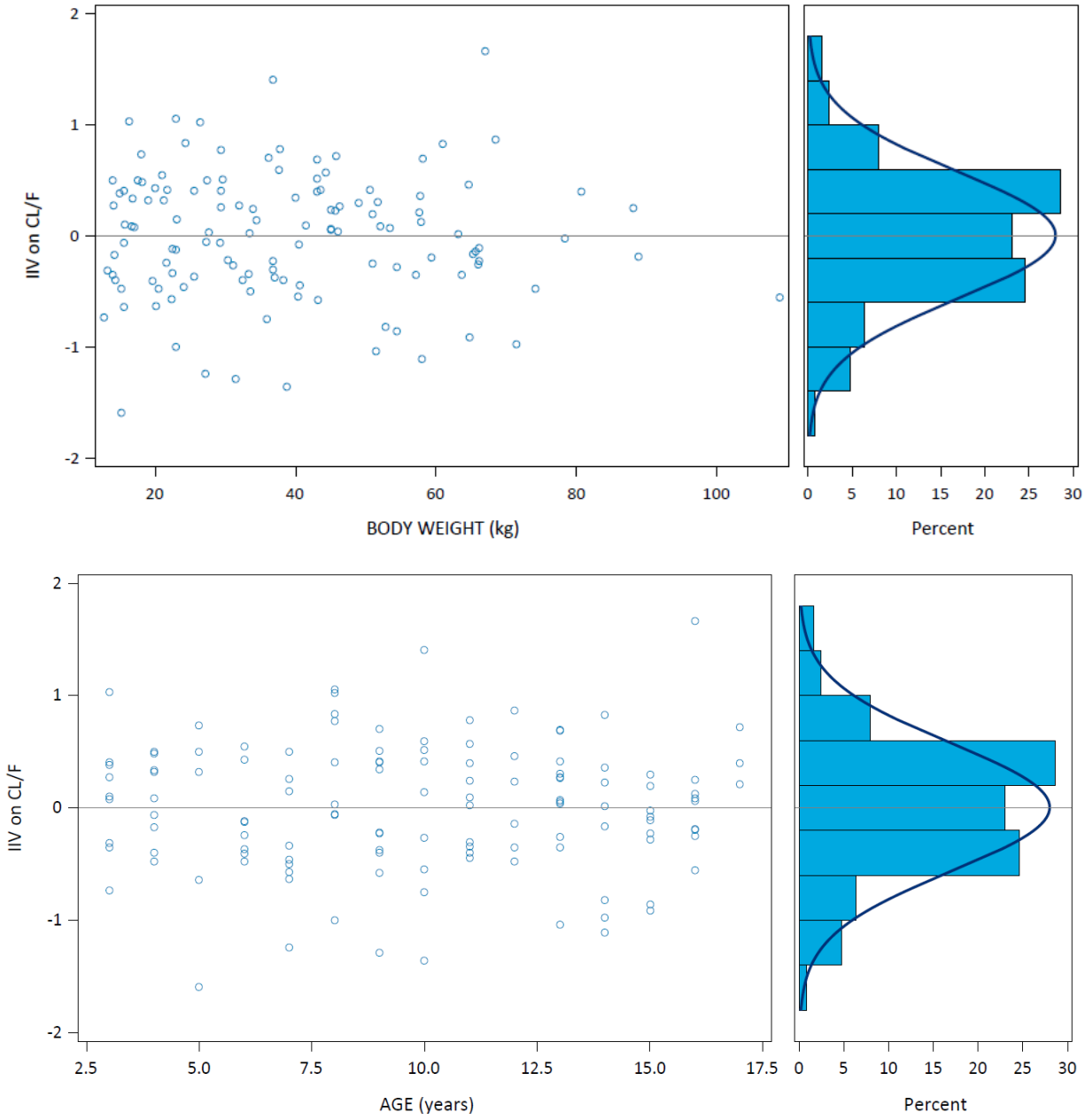


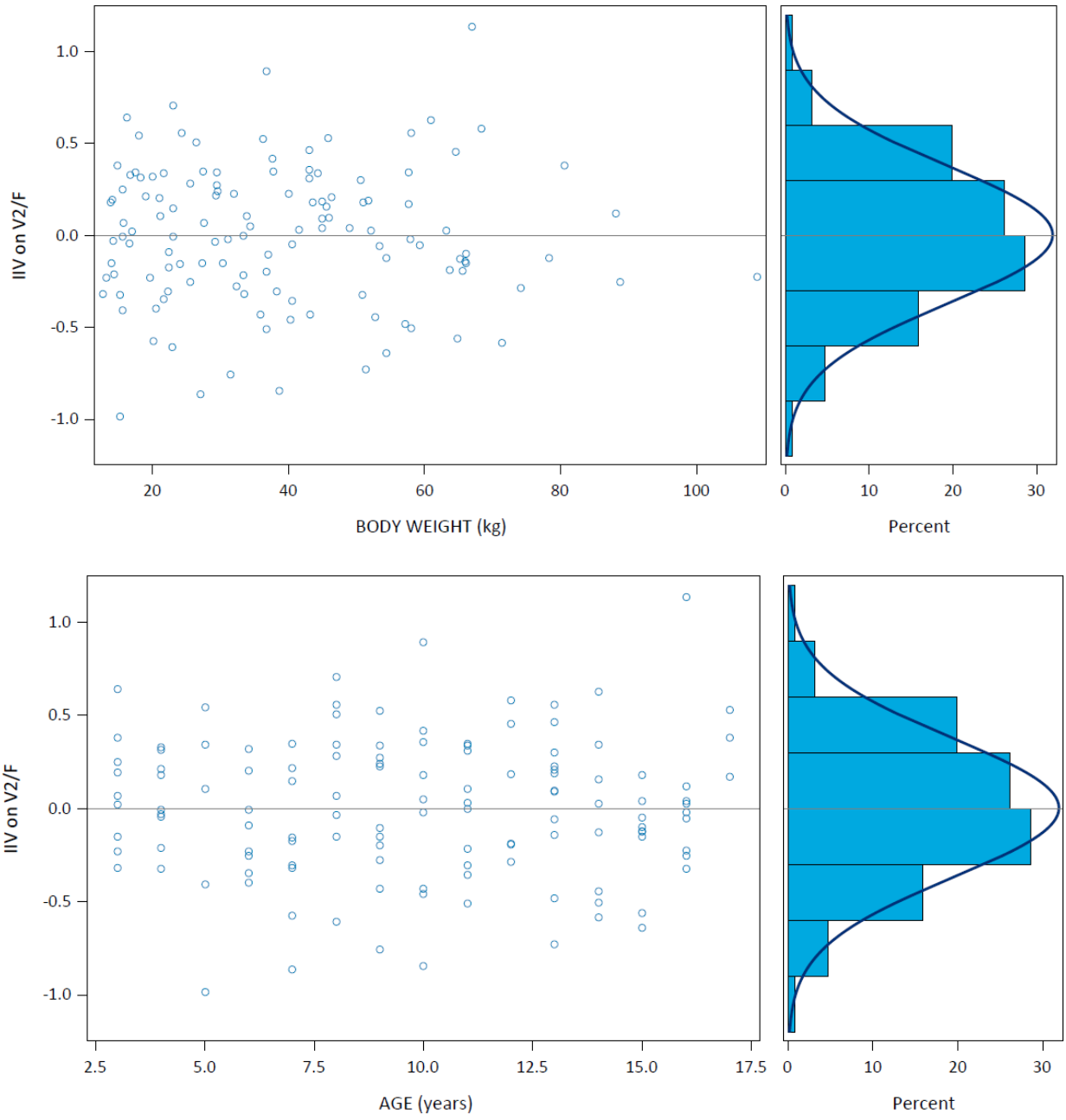


Source: Applicant's report, Phase 2/3 Study M16-123, Appendix 14.6

Reviewer's comments: the final GLE PopPK model shows acceptable distribution without trends around x=0 in the ETA vs. body weight and age plots. Refer to Applicant's report, Phase 2/3 Study M16-123 for additional ETA plots.

Figure 13. PIB final model ETA vs. PK parameter plots.





Source: Applicant's report, Phase 2/3 Study M16-123, Appendix 14.6.

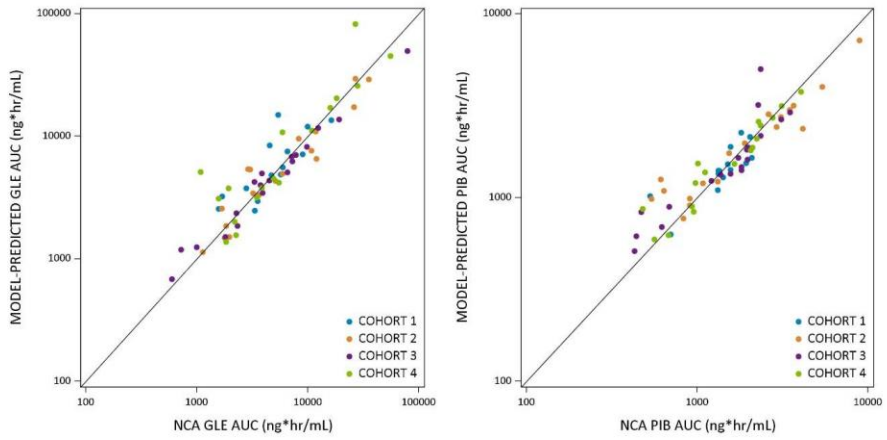
Reviewer's comments: the final PIB PopPK model shows acceptable distribution without trends around x=0 in the ETA vs. body weight and age plots. Refer to Applicant's report, Phase 2/3 Study M16-123 for ddditional ETA plots.

6.1.4.1 NCA vs. Final Model Performance

The applicant performed NCA on subjects with IPK samples and compared the NCA-derived 24-hour AUC to the *post hoc* drug exposure. Figure 14 demonstrates the model predicted GLE and PIB 24-hour AUC at

steady state vs. NCA-derived GLE and PIB 24-hour AUC in subjects with IPK. Table 16 describes the 24-hour AUC derived from NCA with studied dosing regimens. Table 17 provides the model-predicted 24-hour AUC for the proposed dosing regimen in pediatric patients (and adolescents).

Figure 14. Comparison between model-predicted and NCA GLE and PIB 24-hour AUCs.



Source: Applicant's report, Phase 2/3 Study M16-123, Figure 11.

Table 16. NCA of 24-hour AUC of GLE and PIB in pediatric and adolescent subjects.

	Dose(mg) GLE/PIB	N	GLE AUC_{24} (ng•hr/mL) Geometric Mean (%CV) [Range]	PIB AUC_{24} (ng•hr/mL) Geometric Mean (%CV) [Range]
HCV-infected adolescents Cohort 1 with IPK (12 – < 18 year, ≥ 45 kg)	300/120	14	4790 (67.1) [1580 - 16300]	1380 (30.6) [530 - 2090]
HCV-infected pediatric in Cohort 2 with IPK (9 – < 12 year, 30 - < 45 kg)	200/75	6	4080 (148) [1680 - 35500]	1250 (84.7) [611 - 4160]
	250/100	13	7870 (215) [1130 - 175000]	2200 (77.8) [539 - 8900]
HCV-infected pediatric in Cohort 3 with IPK (6 – < 9 year, 20 - < 30 kg)	160/60	6	1680 (63.6) [596 - 3870]	987 (63.7) [430 - 1990]
	200/80	13	6860 (162) [999 - 79000]	1640 (46.5) [470 - 3490]
HCV-infected pediatric in Cohort 4 with IPK (3 – < 6 year, 12 - < 20 kg)	120/45	5	3030 (46.0) [1580 - 5490]	871 (64.8) [479 - 2110]
	150/60	12	7520 (112) [1080 – 55500]	1790 (49.4) [679 - 4050]

IPK = Intensive PK

Cross reference: M16-123 CSR (R&D/20/0360)[7]

Note: the final dose ratio for GLE/PIB in cohorts 2, 3 and 4 are 250/100, 200/80, and 150/60, respectively.

Source: Applicant's report, Phase 2/3 Study M16-123, Table 7.

Table 17. Model-predicted GLE and PIB 24-hour AUC in pediatric and adolescent subjects.

	Geometric Mean (%CV) [Range]	
Population	**GLE AUC_{24} (ng•hr/mL)**	**PIB AUC_{24} (ng•hr/mL)**
HCV-infected adolescents Cohort 1 (12 – < 18 years, ≥ 45 kg, N = 44)	5020 (184) [366 - 183000]	1590 (56) [294 - 4540]
HCV-infected pediatric in Cohort 2 (9 – < 12 years, 30 - < 45 kg, N = 24)	7100 (140) [1130 – 82100]	2060 (71) [501 - 7160]
HCV-infected pediatric in Cohort 3 (6 – < 9 years, 20 < 30 kg, N = 20)	6960 (133) [1250 - 60200]	1900 (57) [693 - 5010]
HCV-infected pediatric in Cohort 4 (3 – < 6 years, 12 < 20 kg, N = 17)	8490 (175) [1380 - 82700]	1820 (66) [625 – 7960]
	Reference Exposures in Adult Subjects	
HCV-infected non-cirrhotic adults (N = 1804)	4800 (122) [123 – 297000]	1430 (57.2) [148 – 14200]

AUC_{24} = area under the plasma concentration-time curve from time 0 to 24 hours at steady-state; CV = coefficient of variation, calculated as $\%CV = 100 \cdot \sqrt{e^{[\sigma\,(\ln(P))]^2} - 1}$, where σ is the standard deviation and P is the pharmacokinetic parameter of interest; QD = once daily; Range = minimum to maximum value of the pharmacokinetic parameter of interest.

Source: Applicant's report, Phase 2/3 Study M16-123, Table 8

Reviewer's comments: in subjects with IPK, there is reasonable agreement between exposure metric (i.e., 24-hour AUC at steady state) derived from NCA vs. model predictions for both GLE and PIB components. In addition, all GLE and PIB 24-hour AUC ranges of the final GLE/PIB dose ratio, generated either from NCA in IPK subjects or model prediction from the final PopPK model, are generally contained in the HCV-infected non-cirrhotic adult reference exposure ranges (GLE, 123-297000; PIB, 148-14200). This overall supports the reasonable model fits to GLE and PIB data and utility of the final PopPK models of GLE and PIB for exposure matching and pediatric dose selection.

6.1.4.2 Simulations from the Final PopPK Models

The Applicant performed simulation with 10,000 virtual subjects to generate exposure metrics (i.e., 24-hour AUCs) for GLE and PIB with the proposed dose ratio, using the final PopPK models.

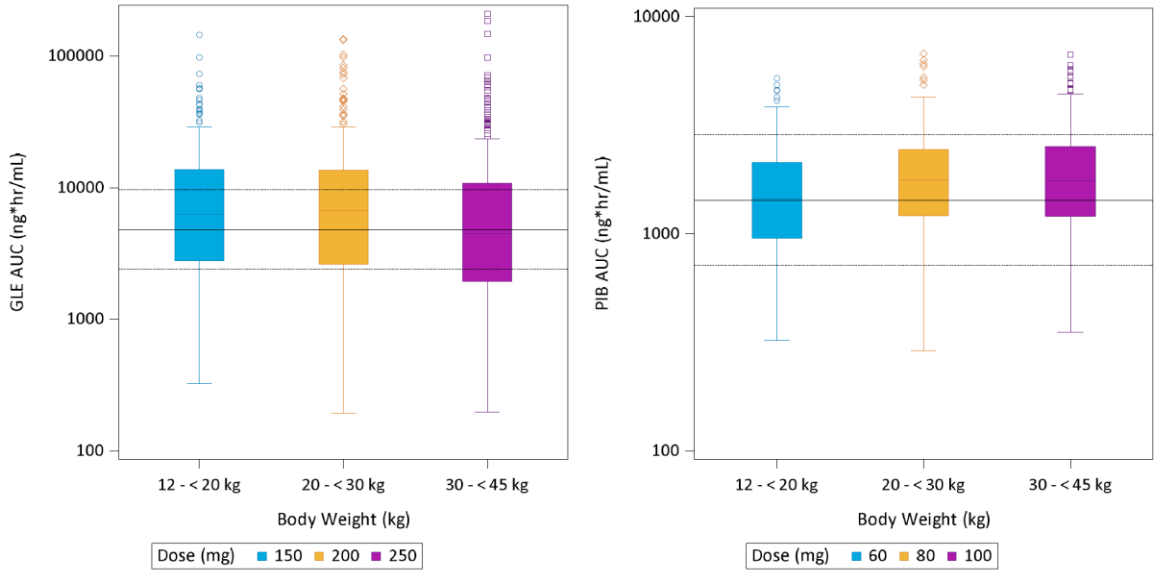
Table 18 describes the simulation results of 24-hour steady state AUCs for GLE and PIB. Figure 15 provides a graphical representation of the simulated 24-hour AUCs at steady state for GLE and PIB for pediatric subjects.

Table 18. Simulated GLE and PIB 24-hour AUC by weight groups.

Body Weight (kg)	Dose (mg)	Geometric Mean (P5, P95) GLE AUC_{24ss} (ng•hr/mL)	% Subjects GLE AUC_{24ss} < 2400 ng•hr/mL	% Subjects GLE AUC_{24ss} > 9600 ng•hr/mL
≥12 - < 20 kg	150	6340 (924, 43300)	21.6	34.2
≥20 - < 30 kg	200	6020 (831, 41300)	23.1	36.3
≥30 - < 45 kg	250	4600 (644, 34200)	29.1	27.2
		PIB AUC_{24ss} (ng•hr/mL)	**PIB AUC_{24ss} < 715 ng•hr/mL**	**PIB AUC_{24ss} > 2860 ng•hr/mL**
≥12 - < 20 kg	60	1410 (549, 3130)	13.0	9.7
≥20 - < 30 kg	80	1700 (700, 3640)	6.7	16.3
≥30 - < 45 kg	100	1720 (675, 3930)	5.6	17.9

Source: Applicant's report, Phase 2/3 Study M16-123, Table 9

Figure 15. Simulated GLE and PIB 24-hour AUCs at steady state by weight groups.



Dashed lines show the target GLE AUC range of (2400-9600) ng•hr/mL and target PIB AUC range of (715 - 2860) ng•hr/mL, which are ± 2-fold of geometric mean exposures in adults.

Source: Applicant's report, Phase 2/3 Study M16-123, Figure 14

Reviewer's comments: the 24-hour AUC ranges for GLE and PIB are contained within the range of adult reference exposure; however, some subjects may have risks of under-exposure or over-exposure (<0.5 AUC for adult and > 2*AUC for adult, respectively) as shown in Table 18. Despite such, the interquartile ranges of simulated exposure of GLE and PIB by weight groups (as shown in Figure 15) are*

generally within the exposure range of respective ±2-fold geometric mean adult 24-hour AUC. Furthermore, the median exposures across pediatric weight groups generally align with or exceeds the geometric mean adult 24-hour AUC. The large whiskers observed in Figure 15,representing the 1st and 3rd quantiles for GLE and PIB, could be driven by the limited sample size in the pediatric population, sparse PK sampling data, and the moderate to large IIVs observed in the final PopPK models for GLE and PIB. Overall, the simulated exposures from the final PopPK models for GLE and PIB support the Applicant's proposed dosage in pediatric patients ages of 3 to 17.

6.1.5 Listing of analyses codes and output files

File Name	Description	Location in \\cdsnas\pharmacometrics\
NONMEM run final GLE PopPK Model	Final GLE PopPK	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Mavyret_NDA_215110_NDA_209394S-13_JLIU\NONMEM\NDA215110_RD200613_3-17\runs\run3_493
NONMEM run final PIB PopPK Model	Final PIB PopPK	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Mavyret_NDA_215110_NDA_209394S-13_JLIU\NONMEM\NDA215110_RD200613_3-17\runs\run4_530
VPC	GLE, prediction corrected or no prediction correction	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Mavyret_NDA_215110_NDA_209394S-13_JLIU\NONMEM\NDA215110_RD200613_3-17\runs\run3_493\vpc_final493-ctl-part2-us_predcorr \\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Mavyret_NDA_215110_NDA_209394S-13_JLIU\NONMEM\NDA215110_RD200613_3-17\runs\vpc_493
VPC	PIB, prediction corrected or no prediction correction	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Mavyret_NDA_215110_NDA_209394S-13_JLIU\NONMEM\NDA215110_RD200613_3-17\runs\run4_530\vpc_run530_predcorr \\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Mavyret_NDA_215110_NDA_209394S-13_JLIU\NONMEM\NDA215110_RD200613_3-17\runs\vpc_530
Simulations	GLE and PIB	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Mavyret_NDA_215110_NDA_209394S-13_JLIU\NONMEM\NDA215110_RD200613_3-17\runs\run6_493_sim_above45kg

		\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Mavyret_NDA_215110_NDA_209394S-13_JLIU\NONMEM\NDA215110_RD200613_3-17\runs\run7_530_sim_above45kg

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