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APPLICATION NUMBER:

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MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Clinical Review, Cross-Discipline Team Leader Review and Division Director Summary Review

Review Completion Date	May 28, 2021
From	Gillian Taormina, DO, Clinical Reviewer Prabha Viswanathan, MD, Cross-Discipline Team Leader Poonam Mishra, MD, MPH, Deputy Division Director (Safety)
Subject	Combined Clinical, Cross-Discipline Team Leader Review and Division Director Summary Review
NDA #	215110 (Original), 209394/S-13
Applicant	AbbVie Inc.
Date of Submission	December 10, 2020
Priority or Standard	Priority
PDUFA Goal Date	June 10, 2021
Proprietary Name	Mavyret®
Non-Proprietary Name	Glecaprevir (GLE)/Pibrentasvir (PIB)
Dosage form(s) / Strength(s)	GLE 50 mg/PIB 20 mg oral pellets in packets
Applicant Proposed Indication(s)/Population(s)	Treatment of pediatric patients 3 years and older (b) (4) with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of pediatric patients 3 years and older with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A)

1. Introduction

This combined Clinical Review, Cross Discipline Team Leader (CDTL) Review and Division Director Summary Review provides an overview of the submitted clinical data, summarizes the findings of the FDA multi-disciplinary team of reviewers, describes the conclusions and recommendations presented by all disciplines, and provides an overall risk-benefit assessment of once daily glecaprevir/pibrentasvir (GLE/PIB) use in pediatric patients ages ≥ 3 to <12 years of age with chronic hepatitis C virus (HCV) genotype (GT) 1, 2, 3, 4, 5, and 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A).

According to the 2017 WHO Global Hepatitis Report, there are over 71 million individuals living with chronic HCV infection worldwide[1]. Although the prevalence of chronic HCV infection is lower in children than in adults, an estimated 3.5 to 5 million children worldwide have HCV infection[2,3]. The National Health and Nutrition Examination Survey (NHANES) conducted between 2003 and 2010 indicated that 0.2% of 6- to 11-year-olds (31,000 children)

and 0.4% of 12- to 19-year-olds (101,000 adolescents) in the US are chronically infected with HCV[3]. There are 8 identified HCV genotypes (GT), with GT 1 being the most prevalent in the US and worldwide. HCV GT2 and GT3 infections are more common in Latin America (5%-30%), Europe (20%-40%), and Asia (30%-45%). HCV GT4 is found in parts of Africa and the Middle East and GT6 is primarily found in southeast Asia. GT7 and GT8 have recently been described and have yet to be characterized.

As stated in the HCV treatment guidelines developed by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA), "the goal of treatment for HCV-infected patients is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response (SVR)"[5]. Historically, the first effective treatment for chronic HCV infection included a combination of recombinant interferon and ribavirin (a synthetic antiviral nucleoside analogue) but these regimens were complicated by relatively low SVR rates and a multitude of side effects. An improved understanding of the HCV genome has enabled efforts to improve the efficacy and tolerability of HCV treatment in recent years. This has led to the development of multiple direct-acting antivirals (DAAs), which are medications targeted at specific steps within the HCV life cycle. The current classes of DAAs include:

- **NS3/4A protease inhibitors** that inhibit the NS3/4A serine protease, an enzyme involved in post-translational processing and replication of HCV (**glecaprevir**, grazoprevir, paritaprevir, simeprevir, voxilaprevir).
- **NS5A inhibitors** that inhibit the NS5A protein, which is thought to play a role in both viral replication and assembly of HCV, although the precise molecular mechanisms of this function are uncertain (daclatasvir, elbasvir, ledipasvir, ombitasvir, **pibrentasvir**, velpatasvir).
- **NS5B RNA-dependent RNA polymerase inhibitors** inhibit the HCV RNA polymerase NS5B and come in two classes:
    - Nucleoside polymerase inhibitors (NPIs) which compete with nucleotides and cause chain termination during RNA replication (sofosbuvir).
    - Non-nucleoside polymerase inhibitors (NNPIs) which act directly on NS5B to inhibit RNA replication (dasabuvir).

Current standard-of-care utilizes multiple DAAs in combination (often fixed-dose combination regimens) to maximize SVR while limiting viral resistance and side effects. The choice of a specific regimen is based on the individual patient and depends on a combination of factors including HCV genotype, prior treatment experience, presence of HCV resistance substitutions, and cirrhosis. The increased availability of multi-genotypic or pan-genotypic DAA regimens has greatly simplified selecting treatment regimens.

The combinations of ledipasvir/sofosbuvir (SOF) and SOF + ribavirin (RBV) are approved for use in children 3 years of age and older, though neither combination covers all major genotypes.

There is only one pan-genotypic RBV-free treatment option available for children less than 12 years of age (SOF/velpatasvir) and none are available for children less than 6 years of age.

These NDA applications request approval of GLE/PIB for treatment of chronic HCV GT 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis in pediatric patients ≥3 to <12 years of age using a new oral pellet formulation. The data discussed are derived from Part 2 of Study M16-123: 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.

2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The safety and efficacy data submitted in this efficacy supplement support approval of glecaprevir/pibrentasvir (Mavyret®, GLE/PIB) for the treatment of chronic hepatitis C virus infection in children greater than 3 to less than 12 years of age. Throughout the review of this supplemental New Drug Application (sNDA) and NDA for a new pediatric formulation, no deficiencies that would preclude approval were identified. Mavyret was studied in a multicenter, open-label trial (Study M16-123/DORA) in two parts. Data from Study M16-123 Part 1 formed the basis of approval for pediatric patients 12 to less than 18 years of age of weighing at least 45 kg. Study M16-123 Part 2 studied 80 pediatric subjects aged ≥ 3 to < 12 years with chronic HCV infection. A new oral pellet formulation was used in this study and the recommended dose for each weight band was determined based on data from an initial intensive pharmacokinetic (IPK) phase of the study and exposure matching to adult subjects. The oral pellets contain a fixed ratio of 50 mg GLE and 20 mg PIB.

The primary efficacy outcome of sustained virologic response 12 weeks after treatment (SVR12) was met by 61/62 (98.3%) of subjects who received the recommended dose. The only subject who did not achieve SVR12 in this group discontinued the study drug due to a Grade 3 adverse reaction of erythematous rash on Day 1. An additional 18 subjects received lower doses and were therefore not included in the primary efficacy analysis. There were two subjects who did not achieve SVR12 in this group: one who discontinued on Day 1 due to refusal to swallow the dose, and one patient with GT3b HCV who relapsed after completion of treatment.

Mavyret was safe and well-tolerated with no deaths, no drug-related serious adverse events (SAEs), and only 1 ≥ Grade 3 treatment-emergent adverse reaction (Grade 3 erythematous rash), which also led to the only AE-related discontinuation. There were no concerning laboratory trends. The safety profile was overall comparable to adolescents and adults with the exception of vomiting, rash and abdominal pain, which were observed more frequently in pediatric patients <12 years of age.

In conclusion, the benefit of Mavyret for the treatment of chronic hepatitis C virus infection outweighs the risks demonstrated in this study and the review team recommends approval of Mavyret for the treatment of chronic hepatitis C virus infection in children ≥3 years of age. I, the signatory authority for this application, concur with the recommendations made by the multi-disciplinary review team.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Chronic HCV (CHC) infection remains a significant global cause of chronic liver disease, cirrhosis, hepatocellular carcinoma and death. • Hepatitis C virus (HCV) is easily transmissible through percutaneous and parenteral exposure, but the majority of pediatric HCV infections in the US are the result of vertical transmission. • Children with CHC tend to have a mild clinical course, but in some cases, can develop serious liver inflammation and even liver failure. The long-term complications of liver fibrosis and cirrhosis can occur over many years, and when HCV infection starts in early childhood, the likelihood of developing these complications by early adulthood is high. • There is no vaccine and no post-exposure immunoprophylaxis available for HCV.	CHC remains a major cause of morbidity and mortality worldwide. While it has a mild prognosis in most children, it can become serious in some cases. Furthermore, when acquired early in childhood, it can lead to the development of serious or fatal complications by early adulthood. This can result in a debilitating disease with significant limitations in a person's professional and personal activities, disability, reduced healthy life expectancy, and potential years of life lost.
Current Treatment Options	• Currently, there are no pan-genotypic ribavirin (RBV)-free regimens approved for pediatric patients <6 years old with chronic HCV infection • SOF/VEL (Epclusa) is approved for children ≥6 years of age with HCV genotype (GT) 1-6 infection • LDV/SOF (Harvoni) is approved for children ≥3 years of age with HCV GT 1, 4, 5, or 6 infection • SOF with RBV is approved for children ≥3 years of age with HCV GT 2 or 3 infection. RBV is associated with numerous side effects and a prolonged treatment course of 24 weeks is needed for GT3 infection. • Pegylated interferon alfa with ribavirin (PEG-IFN/RBV) is approved for children ≥ 3 years but has a poor tolerability and safety profile and is curative in only about 50% of children.	There is an unmet medical need for RBV-free treatment options for children living with chronic HCV infection. Highly efficacious, well tolerated, RBV-free pangenotypic DAA regimens are most desirable for this population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• To support an efficacy claim for the use of GLE/PIB (Mavyret) for the treatment of children with CHC infection in children 3 to < 12 years old, the applicant submitted the 12 Week efficacy and safety results from a single study, Study M16-123 • 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, with or without compensated cirrhosis, with or without human immunodeficiency virus (HIV) coinfection, who were either treatment-naïve (TN), treatment-experienced (TE) to IFN with or without RBV or TE to sofosbuvir (SOF) plus RBV with or without IFN. • In this study, 80 subjects aged 3 years to less than 12 years of age with chronic HCV infection were treated with GLE/PIB once daily based on body weight.; 62/80 received the recommended dose. Subjects received 8-16 weeks of treatment with GLE/PIB; duration of treatment followed the recommendation for adults with corresponding HCV GT, treatment history, and cirrhosis status. • The primary efficacy endpoint was SVR12. • The study demonstrated a high rate of efficacy among those who received the final recommended dose; 61/62 (98.3%) of patients who received the recommended dose achieved a SVR12 which is an indication of complete viral clearance and cure. The one subject who did not achieve SVR prematurely discontinued treatment due to an adverse reaction early in the treatment course. There were no on-	GLE/PIB was highly efficacious in children 3 to < 12 years old, as evidenced by a high rate of subjects achieving SVR12. Long-term studies in adults show that clearance of HCV (spontaneously or by treatment) prevents or reduces liver inflammation and long-term complications such as fibrosis, cirrhosis, liver failure and hepatocellular cancer (HCC) complications. It is reasonable to assume that long-term viral suppression in children 3 to < 12 years old would also prevent or lead to fewer complications later in their life. The one true virologic failure in Part 2 occurred in a child with GT3b infection, which is naturally less susceptible to NS5A inhibitors. Data from adults have established a slightly lower SVR12 rate among subjects with GT3b compared to other GTs and subtypes. The potential for failure in this participant may have been potentiated due to suboptimal drug exposure given that this subject did not receive the final recommended dose.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment failures. • One subject with HCV GT3b infection who received a dose lower than the final recommended dose experienced a post-treatment relapse. This subject had a treatment-emergent NS5A Y93H substitution at relapse.	
Risk and Risk Management	GLE/PIB was associated with several mild adverse reactions, the most common of which were rash, abdominal pain, fatigue, headache, and vomiting. All were categorized as mild (Grade 1 or 2) except one Grade 3 rash. There were no drug-related Serious Adverse Events and no deaths. Only two children discontinued the drug, one due to adverse event (Grade 3 rash) and one due to refusal to take the drug. There were no notable negative effects of treatment on laboratory parameters, EKGs, vital signs, or growth parameters.	The adverse events observed in this study were mild and similar to those noted in adolescents and adults, with the addition of vomiting, rash and abdominal pain. No new safety signals were detected that require risk management beyond routine pharmacovigilance.

3. Regulatory Background

Glecaprevir, an HCV nonstructural viral protein 3/4A (NS3/4A) protease inhibitor, and pibrentasvir, an HCV nonstructural viral protein 5A (NS5A) inhibitor, are denoted “next generation” compounds because each demonstrated potent antiviral activity against GT1 through GT6 in vitro and have a high genetic barrier to resistance with no or little loss of potency against common resistance-associated substitutions. Additive or synergistic in vitro anti-HCV activity were demonstrated with the combination of GLE and PIB.

On August 3, 2017, MAVYRET, a fixed-dose combination of GLE/PIB, was approved for two indications: 1) adult patients with chronic hepatitis C virus genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis; 2) adult patients with HCV GT1 infection who previously have been treated with a regimen containing either an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.

To assess the safety and effectiveness of GLE/PIB regimens in pediatric patients, PREA PMR 3246-1 was issued with the original NDA approval:

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 infection.

The requirement for studies in pediatric patients from birth to <3 years of age was previously waived on the basis that necessary clinical studies in this age group are impossible or highly impracticable. This is because the number of patients requiring treatment is very small due to a high rate of spontaneous HCV clearance and lack of significant disease progression in children younger than 3 years of age.

Study M16-123 was developed in accordance with the agreed initial Pediatric Study Plan (iPSP) and Pediatric Investigational Plan (PIP) for GLE/PIB for the treatment of chronic HCV infection (US IND Number 127416, Reference ID: 3959249, (b) (4) on July 15, 2016, FDA confirmed its agreement with the iPSP for GLE/PIB. (b) (4) . FDA also issued a Written Request (NDA 209394, Sequence 0064, January 23, 2018) for pediatric studies in children 3 to < 18 years of age.

The results from Study M16-123 Part 1, which evaluated the adult GLE/PIB formulation in children ≥12 to < 18 years of age, were previously submitted as a partial response to the PREA PMR. GLE/PIB was approved for children ≥12 to <18 years of age or weighing at least 45 kg on April 30, 2019 at a dose of GLE 300 mg and PIB 120 mg using the adult tablet formulation. Data from Part 2, which evaluated a pediatric formulation comprised of film-coated pellets of GLE and PIB in packets for a convenient QD oral administration for children ≥3 to < 12 years of age, is submitted to fulfill the PREA PMR and Written Request requirements. The sponsor also requests pediatric exclusivity with this application.

4. Chemistry

The product quality assessment of the oral pellet formulation did not reveal any major concerns. The reviewers from the biopharmaceutics (Drs. Gerlie Gieser and Elsbeth Chikhale), Drug Substance (Drs. Karina Zuck and Ali Al Hakim), and Drug Product (Dr. George Lunn) teams all recommended approval; please see their reviews for further detail.

Inspections were conducted virtually by the Office of Pharmaceutical Manufacturing Assessment (OPMA) due to the COVID-19 pandemic. The manufacturing and testing facilities were deemed acceptable.

5. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology data for GLE and PIB were extensively reviewed in the original GLE/PIB NDA review. No new nonclinical pharmacology/toxicology studies were conducted to support this application. Juvenile animal studies were not done because the original nonclinical studies did not suggest that there might be different effects on pediatric patients as compared with adult patients.

6. Clinical Pharmacology

This section summarizes the key points of the Clinical Pharmacology review by Dr. Xiaoxia Yang and colleagues; please see their review for complete details of the clinical pharmacology and pharmacometrics evaluation.

Along with supportive efficacy (SVR12) data from Study M16-123, the basis of approval of GLE/PIB in pediatric subjects is extrapolation of efficacy from adult subjects by matching systemic exposures of GLE and PIB in children to the exposure found to be efficacious in adults with chronic HCV infection. The main parameters reported in this study were C_{min}, C_{trough} and AUC_{24}. In short, data from Study M16-123 Part 2 demonstrate that the mean systemic exposures of GLE and PIB are comparable between pediatric and adult subjects when pediatric subjects were given the final recommended dose. The pediatric PK parameters are summarized in **Table 1**.

Table 1: Pediatric PK Parameters for GLE/PIB

Age and Weight (kg)	N	Total Daily Dose of GLE/PIB (mg)	PK Parameter	Geometric Mean (%CV)	
				GLE	PIB
12 to < 18 years, ≥ 45 kg	14	300/120	AUC_{24} (ng•h/mL)	4790 (72)	1380 (40)
			C_{max} (ng/mL)	1040 (86)	174 (36)
			C_{trough} (ng/mL)	3.79 (82)	15.0 (61)
9 to < 12 years, 30 to < 45 kg	13	250/100	AUC_{24} (ng•h/mL)	7870 (209)	2200 (99)
			C_{max} (ng/mL)	1370 (169)	225 (72)
			C_{trough} (ng/mL)	12.4 (856)	36.5 (164)
6 to < 9 years, 20 to < 30 kg	13	200/80	AUC_{24} (ng•h/mL)	6860 (142)	1640 (63)
			C_{max} (ng/mL)	1600 (155)	197 (52)
			C_{trough} (ng/mL)	7.44 (383)	19.4 (103)
3 to < 6 years, 12 to < 20 kg	12	150/60	AUC_{24} (ng•h/mL)	7520 (205)	1790 (58)
			C_{max} (ng/mL)	1530 (280)	233 (48)
			C_{trough} (ng/mL)	6.58 (318)	17.9 (119)

Source: Adapted from Clinical Pharmacology Review

Of note, GLE and PIB C_{max} and AUC_{24} were relatively higher in pediatric subjects compared to adults. For reference, the geometric mean (%CV) C_{max} in noncirrhotic adults was 597 (114) ng/mL and 110 (49) ng/mL for GLE and PIB, respectively. AUC in noncirrhotic adults was 4800 (122) ng•h/mL and 1430 (57) ng•h/mL for GLE and PIB, respectively. There was also relatively lower GLE C_{trough} in pediatric subjects compared with noncirrhotic adults, for whom the geometric mean (%CV) was 13.0 (334). However, despite the relative differences in the pediatric PK parameters, all values were within the range observed among adults in Phase 3 trials (see Figure 1).

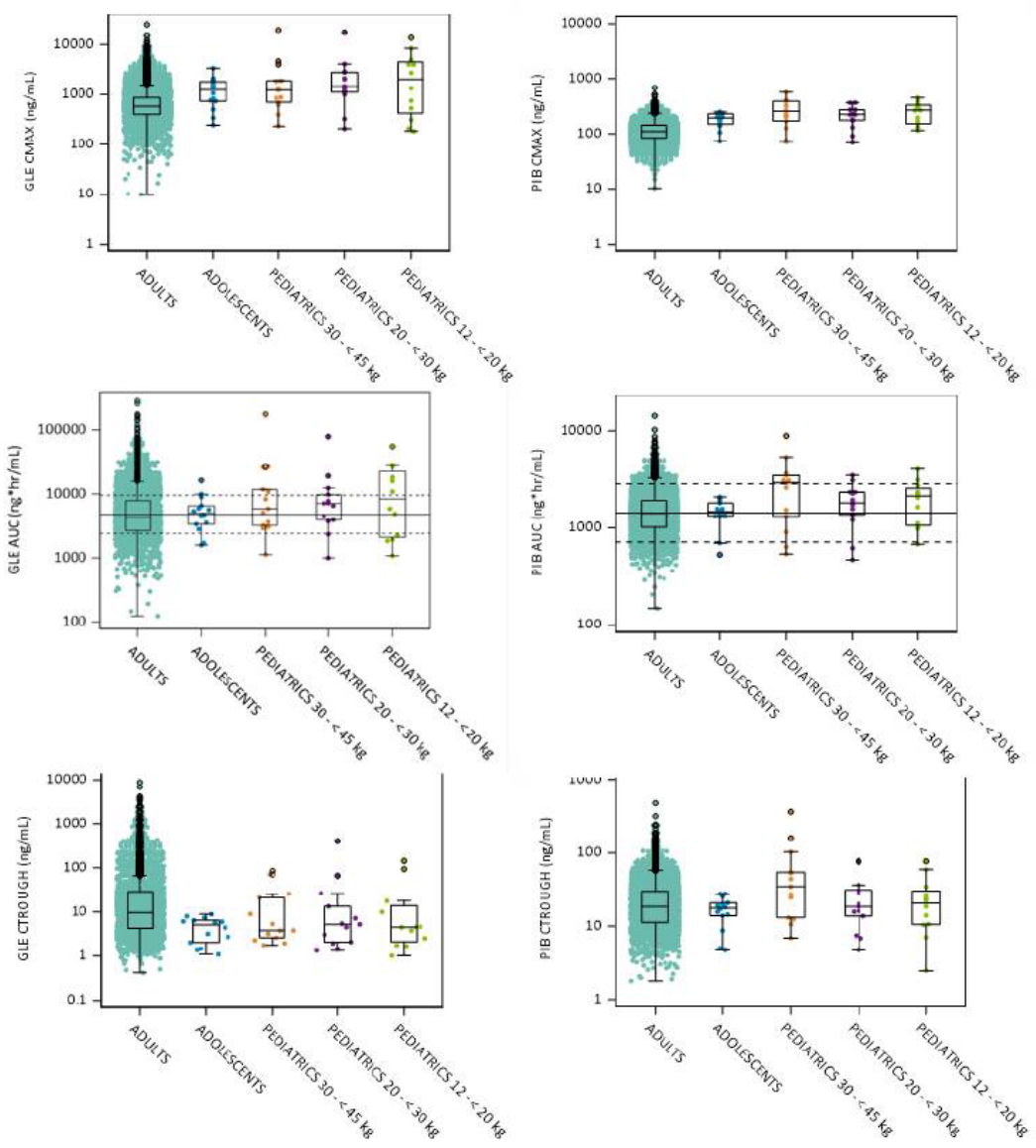


Figure 1: Comparison of Exposures of GLE/PIB between Pediatric and Adult Subjects
Source: Clinical Pharmacology Review

In order to understand the potential clinical consequences of lower GLE C_{trough} on the efficacy of GLE/PIB for pediatric patients, the exposure-response (SVR12) relationships in adults were reviewed. The exposure-response (E-R) analyses were conducted using data from several studies evaluating adults with chronic HCV infection, broken down into subpopulations based on HCV GT and prior treatment status. Groups 1 and 2 represent the majority of pediatric subjects.

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

Overall, SVR12 rate did not vary significantly with quartiles of GLE or PIB AUC_{24} or C_{trough}, likely because the SVR12 rate was almost 100%. Although the E-R assessment is somewhat limited by the lack of multiple GLE and PIB doses evaluated in Phase 3, the flat E-R curve provides reassurance that nearly all subjects were receiving therapeutic doses. The one subject who experienced virologic failure in Study M16-123 Part 2 was a 9-year-old treatment naïve male with GT 3b HCV who received a GLE/PIB dose that is lower than the final recommended dose (please see Section 7 for details). His GLE and PIB AUC and C_{trough} values were lower than the median value observed in adults but not notably lower than other children who achieved SVR12. Therefore, this subject's virologic relapse is unlikely due to lower GLE/PIB dosing alone, but rather more attributable to intrinsic characteristic of HCV GT3b or a combination of both dose and viral factors.

Exposure-safety analyses in adults were also reviewed to assess the potential implications of higher GLE and PIB AUC and C_{trough}. Overall, the GLE/PIB exposures in Phase 3 studies were not associated with major safety concerns The adverse events of interest in the exposure-safety analyses were elevations in ALT, elevations in bilirubin, and diarrhea, which were selected because they have been associated with HCV protease inhibitors. A minor relationship was noted between GLE exposures and bilirubin elevations, but these events did not lead to discontinuation; no association was noted with ALT or diarrhea. Exposure-response analyses for safety in Study M16-123 Part 2 did not reveal any clinically significant associations with adverse events.

Reviewer Comment: The GLE/PIB doses administered to pediatric subjects in Study M16-123 Part 2 yielded drug exposures comparable to the exposures proven to be efficacious in adults and therefore support approval of these doses for children 3 to < 12 years of age with chronic HCV infection and compensated liver disease. Although GLE and PIB AUC and C_{max} are higher among pediatric subjects, they are within the overall range observed in adult trials and there is no signal for an exposure-safety concern (among patients with compensated liver disease) based on the clinical events observed in the adult and pediatric clinical development program. Similarly, the lower GLE Ct_{rough} does not appear to compromise the efficacy of the doses evaluated in Study M16-123 Part 2, as evidenced by the high rates of SVR12 in Study M16-123

Part 2, and supported by exposure-response analyses in adults that do not show an association between low GLE levels and lower SVR12 rates.

Dosing Strategies for Children Weighing ≥ 45 kg Who Cannot Swallow Tablets

The clinical review team was concerned that some pediatric patients <12 years of age may weigh >45 kg but may not be able to swallow tablets. This group of patients was not evaluated in Study M16-123 because all subjects less than 12 years of age in Study M16-123 Part 2 weighed less than 45 kg and all subjects in Study M16-123 Part 1 were at least 12 years of age. This prompted the review team to explore whether there were sufficient data to support the use of oral pellets for this population.

The sponsor initially stated in the proposed label that (b) (4) the Clinical Pharmacology review team analyzed exposures for the pellet vs. tablet in the fed state in healthy adults. They determined that the differences in exposures were not statistically significant and are not expected to affect efficacy based on exposure-response analyses from Phase 3 trials. The decision was made to provide the recommendation that pediatric patients who weigh >45 kg but who cannot swallow tablets can take 6 packets of oral pellets instead of tablets at the same total dose of GLE/PIB 300/120 mg. This provision was not meant to be extended to adult subjects who are unable to swallow tablets, therefore the label only reflects this for pediatric sections of the product labeling.

Another option (b) (4)

Inspections

A bioequivalence establishment inspection was not performed by the Office of Study Integrity and Surveillance (OSIS) because a satisfactory inspection of the analytical site had been performed in February 2019 under NDAs 211675 and 209394/S-006.

7. Clinical Virology

Please refer to Clinical Virology review by Patrick Harrington, Ph.D for a more detailed assessment. Briefly, the efficacy supplement is considered approvable from a Clinical Virology perspective based on the high efficacy of GLE/PIB observed in pediatric subjects in Part

2/Cohort 2-4 of M16-123 with SVR12 achieved in 77/80 subjects (97.5%). SVR12 was achieved in 61/62 (98.3%) subjects who received the final dose ratio.

Two subjects (Subjects (b) (6)) did not achieve SVR12 due to failure to complete treatment.

The only subject to experience true virologic failure in Study M16-123 (Subject (b) (6)) was a 9-year-old treatment-naïve male with HCV GT3b infection with a very high baseline HCV viral load (13.8 million copies/mL) who was treated with GLE 200 mg + PIB 75 mg QD, which was not the final proposed dose ratio, for 8 weeks. No HCV RNA was detected at Day 56, but HCV RNA was detected at post-treatment day 29. There were no reports of noncompliance, and palatability questionnaire results showed successful administration. This subject had baseline substitutions often seen in GT3b infections (K30 and M31) which are known to be associated with decreased susceptibility to PIB and NS5A inhibitors in general. He was found to have a treatment emergent NS5A Y93H substitution at relapse.

No changes were proposed by the Sponsor for Section 12.4 (Microbiology) of the prescribing information, which the clinical virology team found acceptable given the limited resistance data included for this supplement and existing information in the current labeling that adequately characterizes activity of GLE/PIB in patients with GT3b HCV infection.

Sample sizes were not adequate to assess efficacy across all key HCV subgroups (e.g., GT3, treatment-experienced), and certain subgroups included in the approved indication were not represented (e.g., patients with cirrhosis, prior DAA experience, or HCV GT5 or GT6). Nevertheless, the efficacy and resistance characteristics of GLE/PIB are anticipated to be similar across these groups, provided that drug exposures are comparable.

8. Efficacy

Efficacy Summary

The totality of the PK and antiviral activity (SVR12) data establish the efficacy of GLE/PIB for treatment of HCV GT1-6 infection in children 3 years of age and older with chronic HCV infection.

- As discussed in Section 6, pharmacokinetic data provide the pivotal data to support approval of GLE/PIB for pediatric patients. Section 8 summarizes the SVR12 data for Study M16-123, which provide supportive evidence of efficacy.

- The antiviral activity data demonstrate that administration of GLE/PIB oral pellets in packets with a fixed dose ratio of 50mg GLE to 20mg PIB in pediatric participants ages ≥3 to <12 years with chronic HCV GT 1, 2, 3, or 4 infection was efficacious. In Study M16-123 Part 2, 97.5% percent of participants achieved SVR12. No participants

experienced virologic breakthrough; one participant who received a lower GLE/PIB dose experienced viral relapse as discussed below. HCV GT does not affect GLE/PIB pharmacokinetics and previous trials in adults have demonstrated that equivalent GLE/PIB exposure is efficacious in adults with chronic HCV GT 5 and 6 infection and adults with compensated cirrhosis. Although there were no children with cirrhosis or GT 5 or 6 in this study, efficacy in these groups can be extrapolated from adult data.

Background

Extrapolation of efficacy for HCV DAAs such as GLE/PIB can be made based on the presumption that the course of chronic HCV disease and the effects of the drugs are sufficiently similar in adults and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c). DAV agrees that HCV disease in pediatric subjects is similar but not identical to adult HCV disease, noting that the routes of transmission may be different. Vertical transmission from mother to child is the predominant route of infection for young children, in contrast to adolescent and adult subjects in whom injection drug use are the primary modes of transmission. Once infected, the pathophysiology of HCV disease is similar in adult and pediatric subjects, although disease progression (e.g., cirrhosis, hepatocellular carcinoma, liver failure) is observed less frequently during childhood, largely because duration of infection appears to be an important factor affecting disease progression. Comorbid conditions such as underlying liver disease and alcohol or recreational drug use are also less common among children with HCV, which also contributes to slower disease progression during childhood.

For both children and adults, response to treatment of chronic HCV infection is measured by SVR12 (virologic cure). Several studies have shown achievement of SVR is associated with improvement of hepatic and extrahepatic manifestations, thereby improving overall health status. Consequently, treatment recommendations are very similar across all age groups for whom DAAs are available.

8.1 Review Strategy

The clinical reviewer used the Applicant's ADaM datasets to analyze demographic and efficacy data. Unless otherwise specified, all analyses included in this review were performed by the clinical reviewer using JMP Clinical (Version 6) software.

8.2 Indication

AbbVie requests approval of GLE/PIB for treatment of pediatric patients aged 3 to less than 12 years (b) (4) with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). The new oral pellet formulation was developed to support dosing for this younger population.

8.3 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, with or without compensated cirrhosis, with or without human immunodeficiency virus (HIV) coinfection, who were either treatment-naïve (TN), treatment-experienced (TE) to IFN with or without RBV or TE to sofosbuvir (SOF) plus RBV with or without IFN. The study is divided into two parts:

- Part 1 Population: Adolescent subjects 12 to < 18 years old with HCV GT1 – GT6 infection (Cohort 1) who were willing to swallow the adult formulation of GLE/PIB (n=47 including 17 subjects who provided intensive PK samples).
- Part 2 Population: Pediatric subjects 3 to < 12 years old with HCV GT1 - GT6 infection divided into 3 groups based on age: 9 to < 12 years (Cohort 2), 6 to < 9 years (Cohort 3), and 3 to < 6 years (Cohort 4). Eighty subjects were enrolled across the 3 cohorts.

The primary objectives of the study are to:
- Assess the steady state area under the concentration-time curve (AUC), and to assess the pharmacokinetics (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 SVR12 in pediatric subjects with chronic HCV GT1 – GT6 infection

Key Inclusion Criteria
- Male or female
- Positive anti-HCV Ab and plasma HCV RNA viral load ≥ 1000 International Unit (IU)/mL at Screening Visit.
- Chronic HCV infection (positive for anti-HCV Ab or HCV RNA at least 6 months before Screening)
- Subjects with HIV-1 coinfection must have been on stable anti-retroviral therapy (ART) for at least 8 weeks prior to screening (qualifying regimens are listed in the study protocol)
- Subjects must have a weight consistent with recommended weight band for age at time of screening. Subjects that fall out of the weight band for their age at the time of Screening could be screened into the safety and efficacy parts of the study upon therapeutic area medical director approval.

Key Exclusion Criteria
- Female subjects who are pregnant, breastfeeding, or considering becoming pregnant
- Recent history of drug or alcohol abuse
- Any cause of liver disease other than chronic HCV infection
- Current hepatitis B virus infection at screening

- Current or past evidence of Child-Pugh B or C classification or history of liver decompensation such as ascites, variceal bleeding, or hepatic encephalopathy
- Confirmed presence of hepatocellular carcinoma (HCC)
- History of severe, life-threatening, or other significant sensitivity to any excipients of the study drug.

Dose selection for pediatric participants targeted systemic exposures similar to those observed in adults at the marketed dose. Approximately 12 patients per cohort were planned to participate in the intensive pharmacokinetic (IPK) portion of the study. Subjects in the IPK portion had to be HCV treatment-naive and HIV-negative, and the HCV genotype must have been identified. Subjects in the IPK portion were specified to take either 8 or 12 weeks of treatment.

The non-IPK safety/efficacy portion of both Part 1 and Part 2 included pediatric subjects with or without compensated cirrhosis who were TN or TE (prior IFN, RBV or SOF exposure), with or without HIV-1 coinfection, and could include subjects with mixed or indeterminate HCV genotype. Subjects in the non-IPK safety/efficacy portion of the study were specified to take 8, 12, or 16 weeks of treatment depending on their HCV genotype, prior treatment experience, cirrhosis status, and geographical location. All subjects were to be followed for 144 weeks after the end of treatment.

The following table shows the initial and final proposed doses:

Table 2: Initial and Final Proposed GLE/PIB Doses for Study M16-123

		Initial Doses (mg)		**Final Proposed Doses (mg)**		
Formulation	**Age Group & Weight Band**	**GLE**	**PIB**	**GLE**	**PIB**	**Number of Packets**
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	--

Source: Modified from sponsor's CSR Table 3, Module 5.3.5.2

Both Part 1 and Part 2 of the study consisted of a screening period, treatment period and post-treatment period. Safety and efficacy were assessed throughout the study. See Section 9 for more details of the safety assessments.

Screening consisted of informed consent, history and physical exam, ECG, baseline laboratory evaluation (hematology, chemistry, coagulation panel, urinalysis, FSH, HbsAg, Anti-HCV Ab, Anti-HIV Ab, HIV RNA, HCV RNA, HCV genotype and subtype), assessment of cirrhosis (by history of biopsy, FibroScan assessment, FibroTest), Child-Pugh score, HCC assessment (liver ultrasound and AFP), and concomitant medication assessment.

Visits during the treatment period took place on Day 1, Week 2, Week 4, Week 8, Week 12 and EOT and consisted of assessments including history and physical, laboratory studies, PK sampling, and adverse event assessment.

Visits during the post-treatment (PT) period took place on PT Week 4, PT Week 12, PT Week 24, PT Week 36, PT Week 48, PT Week 96, and PT Week 144. Visits included vital signs, Fibrotest, laboratory studies, HCC assessment, adverse event assessment, and HCV RNA and resistance samples.

8.4 Demographics and Clinical Characteristics

Eighty subjects ranging in age from 3 to 11 years with a mean age of 7 years were enrolled across Cohorts 2-4. Select demographics are summarized in Table 3 by age cohort.

Table 3: Baseline Demographic Characteristics in Study M16-123 Part 2

	Cohort 4 ≥3 to <6 years n=24 (%)	**Cohort 3 ≥6 to <9 years n=26 (%)**	**Cohort 2 ≥9 to <12 years n=30 (%)**	**Cohort 2-4 Total n=80 (%)**
Sex				
Female	12 (50)	17 (65)	15 (50)	44 (55)
Male	12 (50)	9 (35)	15 (50)	36 (45)
Weight (kg)				
≥12 to <20	23 (96)	1 (4)	0	24 (30)
≥20 to <30	1 (4)	24 (92)	3 (10)	28 (35)
≥30 to <45	0	1 (4)	27 (90)	28 (35)
Race				
American Indian or Alaska Native	1 (4)	0	1 (3)	2 (3)
Asian	4 (17)	5 (19)	5 (17)	14 (17)
Black or African American	1 (4)	1 (4)	1 (3)	3 (4)
Multiple	1 (4)	3 (12)	1 (3)	5 (6)
Native Hawaiian or Other Pacific Islander	1 (4)	0	0	1 (1)
White	16 (67)	17 (65)	22 (73)	55 (69)
Ethnicity				

	Cohort 4 ≥3 to <6 years n=24 (%)	**Cohort 3 ≥6 to <9 years n=26 (%)**	**Cohort 2 ≥9 to <12 years n=30 (%)**	**Cohort 2-4 Total n=80 (%)**
Hispanic or Latino	4 (17)	4 (15)	5 (17)	13 (16)
Not Hispanic or Latino	20 (83)	22 (85)	25 (83)	67 (84)
Region				
Europe	5 (21)	6 (23)	10 (33)	21 (26)
Japan	3 (12)	3 (12)	3 (10)	9 (11)
North America	16 (67)	17 (65)	17 (57)	50 (63)
Country				
Belgium	1 (4)	1 (4)	1 (3)	3 (4)
Canada	0	3 (11)	2 (7)	5 (6)
Germany	1 (4)	1 (4)	2 (7)	4 (5)
Spain	1 (4)	1 (4)	2 (7)	4 (5)
United Kingdom	2 (8)	2 (8)	2 (7)	6 (8)
Japan	3 (13)	3 (11)	3 (10)	9 (11)
Puerto Rico	0	2 (8)	1 (3)	3 (4)
Russia	0	1 (4)	3 (10)	4 (5)
United States	16 (67)	12 (46)	14 (46)	42 (52)

Source: Analysis by Clinical Reviewer using ADSL dataset

There was a comparable number of male and female subjects. Weight bands generally corresponded with age cohorts: 96% of Cohort 4 was in the ≥12 to <20kg weight band, 92% of Cohort 3 was in the ≥20 to <30kg weight band, and 90% of Cohort 2 was in the ≥30 to <45kg weight band. The most predominant race was white (69%) followed by Asian (17%). Sixty-three percent of patients were from North America.

Reviewer comment: Although the majority of subjects were white, the sponsor has made an adequate effort to represent minority populations at risk for HCV infections by enrolling globally including 4 study sites in Japan.

The number of subjects in Cohort 2 and 3 differ by one subject compared to the sponsor's analyses because they included a 9-year-old patient (Subject (b) (6) *in Cohort 3 in their analyses.*

Select baseline disease characteristics of the study population are summarized in Table 4.

Table 4: Baseline Disease Characteristics in Study M16-123 Part 2

	Cohort 4 ≥3 to <6 years n=24 (%)	**Cohort 3 ≥6 to <9 years n=26 (%)**	**Cohort 2 ≥9 to <12 years n=30 (%)**	**Cohort 2-4 Total n=80 (%)**
Cirrhotic				
No	24 (100)	26 (100)	30 (100)	80 (100)
Yes	0	0	0	0
HIV Co-infection				
No	24 (100)	26 (100)	29 (97)	79 (99)
Yes	0	0	1 (3)	1 (1)
HCV Genotype/Subtype				
1A	14 (58)	12 (46)	11 (37)	37 (46)
1B	3 (13)	9 (35)	9 (30)	21 (26)
2B	0	0	2 (7)	2 (3)
3	1 (4)	0	0	1 (1)
3A	5 (21)	3 (11)	7 (23)	15 (19)
3B	1 (4)	0	1 (3)	2 (3)
4	0	1 (4)	0	1 (1)
4A/4C/4D	0	1 (4)	0	1 (1)
HCV Treatment History				
Experienced	0	0	2 (7)	2 (3)
Naïve	24 (100)	26 (100)	28 (93)	78 (97)
Baseline HCV RNA (IU/ml)				
<1,000,000	14 (58)	14 (54)	11 (37)	39 (49)
≥1,000,000- <2,000,000	1 (4)	4 (15)	8 (26)	13 (16)
≥2,000,000	9 (38)	8 (31)	11 (37)	28 (35)
Fibrosis Stage				
F0-F1	24 (100)	25 (96)	29 (97)	78 (97)
F2	0	1 (4)	1 (3)	2 (3)

Source: Analysis by Clinical Reviewer using ADSL dataset

Reviewer comment: The study population included no cirrhotic subjects or subjects with HCV GT 5 or 6 infections, which is not surprising because these genotypes are much less common than GT 1-4 worldwide. There was one subject with HIV co-infection. There were two (3%) treatment-experienced subjects with history of treatment using IFN-based regimens, one with GT3a and one with GT1b infection. It is expected that there would be fewer treatment-experienced patients in this young age group as compared with the adolescent portion of the study.

8.5 Participant Disposition

The mean and median exposure to study drug were both 57 days with a range of 1-112 days.

Participant disposition is summarized in Table 5.

Table 5: Study M16-123 Part 2 Subject Disposition

	Cohort 4 ≥3 to <6 years n=24 (%)	**Cohort 3 ≥6 to <9 years n=26 (%)**	**Cohort 2 ≥9 to <12 years n=30 (%)**	**Cohort 2-4 Total n=80 (%)**
ITT Population	24 (100)	26 (100)	30 (100)	80 (100)
Safety Population	24 (100)	26 (100)	30 (100)	80 (100)
Intensive PK Population Flag				
No	8 (33)	10 (38)	14 (47)	32 (40)
Yes	16 (67)	16 (61)	16 (53)	48 (60)
Treatment Interruption				
No	24 (100)	26 (100)	29 (97)	79 (99)
Yes	0	0	1^ (3)	1 (1)
Completed Treatment				
No	1 (4)	0	1 (3)	2 (3)
Yes	23 (96)	26 (100)	29 (97)	78 (97)
Reasons for Discontinuation from Treatment				
Adverse Event	0	0	1 (3)	1 (1)
Other	1 (4)	0	0	1 (1)
Actual Treatment Arm				
GLE + PIB 120 mg + 45 mg once daily (QD) for 8 weeks	6 (25)	0	0	6 (7)
GLE + PIB 150 mg + 60 mg QD for 8 weeks *	10 (42)	0	0	10 (13)
GLE + PIB 160 mg + 60 mg QD for 8 weeks	0	6	0	6 (7)
GLE + PIB 200 mg +75 mg QD for 8 weeks	0	0	6 (20)	6 (7)
GLE + PIB 200 mg + 80 mg QD for 8 weeks *	0	10 (38)	0	10 (13)
GLE + PIB 250 mg +100 mg QD for 8 weeks *	0	0	10 (33)	10 (13)
GLE + PIB 50 mg +20 mg film coated granules 30 sachet/carton for 12 weeks*	0	0	1 (3)	1 (1)

	Cohort 4 ≥3 to <6 years n=24 (%)	Cohort 3 ≥6 to <9 years n=26 (%)	Cohort 2 ≥9 to <12 years n=30 (%)	Cohort 2-4 Total n=80 (%)
GLE + PIB 50 mg +20 mg film coated granules 30 sachet/carton for 16 weeks*	0	0	1 (3)	1 (1)
GLE + PIB 50 mg +20 mg film coated granules 30 sachet/carton for 8 weeks*	8 (33)	10 (38)	12 (40)	30 (38)
Dose				
GLE 120 mg + PIB 45 mg	6 (25)	0	0	6 (7)
GLE 150 mg + PIB 60 mg*	17 (71)	0	0	17 (21)
GLE 160 mg + PIB 60 mg	0	6 (23)	0	6 (7)
GLE 200 mg + PIB 75 mg	0	0	6 (20)	6 (7)
GLE 200 mg + PIB 80 mg*	1 (4)	19 (73)	1 (3)	21 (26)
GLE 250 mg + PIB 100 mg*	0	1 (4)	23 (77)	24 (30)

Source: Analysis by Clinical Reviewer using ADSL dataset
^Subject (b) (6) had an interruption in treatment for 4 days due to a respiratory infection
*Final dose ratio (n=62)

The various dosing regimens and durations are displayed in Table 5; 62 subjects were treated with the final proposed dose ratio of GLE/PIB (50mg/20mg). All subjects except the two treatment-experienced subjects were treated with a duration of 8 weeks.

There were 2 subjects who did not complete treatment. Subject (b) (6) was an 11-year-old female who discontinued study drug on Day 4 due to a Grade 3 adverse event of rash which occurred on Day 1; she was the only subject assigned to the final dose ratio who did not achieve SVR12. Subject (b) (6) was a 3-year-old male who did not complete treatment due to refusal to take the drug. He refused to swallow the entire dose on Day 1 and then discontinued from the study.

8.6 Analysis of Primary Endpoint

The primary efficacy endpoint of Study M16-123 was SVR12. SVR12 was achieved by 77/80 (96%) subjects overall and 61/62 (98%) of those who were treated with the final dose ratio.

Among the 3 subjects who did not achieve SVR12, only one subject had true virologic failure. As discussed in Section 7, a 9-year-old TN male with GT3b infection had undetectable HCV RNA by the end of the treatment period but experienced virologic relapse at the PT Week 4. He was noted to have the Y93H substitution at the time of relapse, which is a common substitution observed among subjects with GT3 infection who fail after treatment with NS5A inhibitors. The other 2 subjects (Subjects (b) (6)) who did not achieve SVR12 did not complete treatment. Subject (b) (6) was the only subject assigned to the final dose ratio who did not achieve SVR12, but this was due to discontinuation on Day 4 due to an adverse event of rash.

Subject (b) (6) did not continue after Day 1 due to refusal to swallow the medication. These adverse events that occurred in these subjects are described further in Section 9.

8.7 Analysis of Secondary Endpoints

The secondary efficacy endpoints for M16-123 included on-treatment virologic failure, viral relapse, and viral reinfection. There was one subject who experienced relapse (Subject (b) (6)), who is described in Sections 7 and 8.6. No subjects experienced on-treatment virologic failure or viral reinfection.

Seventy-five of 77 (97.4%) subjects achieved HCV RNA <LLOQ by Week 4. Concordance between SVR4 and SVR12 was 100%.

Partial SVR24 data was submitted with the 4-month safety update. SVR24 was 73/80 (91.3%), which decreased from 77/80 due to 4 patients with incomplete SVR24 data; there were no further virologic failures, relapses, or re-infections.

8.8 Subgroup Analyses

Because there was only one participant who experienced viral relapse or viral breakthrough, formal subpopulation analyses were not conducted to assess for differences in efficacy based on demographics or baseline disease characteristics.

9. Safety

Safety Summary

Results from Study M16-123 Part 2 demonstrate that GLE/PIB was safe and well-tolerated in pediatric patients aged 3 to less than 12 years. Overall, the adverse events observed were similar to those observed in adult clinical trials, with the exception of vomiting, rash and abdominal pain in pediatric patients less than 12 years of age.

9.1. Methods

All 80 enrolled participants in Study M16-123 Part 2 were included in the safety analysis of GLE/PIB in pediatric participants ages ≥ 3 to < 12 years.

Adverse events (AEs) are defined as any unfavorable and/or unintended sign, symptom, or disease temporally associated with GLE/PIB regardless of causality. Treatment-emergent AEs are defined as any AE with an onset date that is after the first dose of study drug and no more

than 30 days after the last dose of study drug. Adverse drug reactions (ADRs) are defined as AEs deemed to be at least possibly related to GLE/PIB by the investigator's causality assessment.

AEs of special interest (AESI) for this study included the following:

- Hepatic decompensation/hepatic failure events, identified using the AbbVie Product MedDRA Query (PMQ) for "Hepatic Decompensation and Hepatic Failure"
- Hepatocellular carcinoma events, identified using the preferred terms of hepatocellular carcinoma, hepatic neoplasm, hepatic cancer, hepatic cancer metastatic, and hepatic cancer recurrent

AEs are coded using MedDRA version 23. AbbVie's coding of AE verbatim terms to preferred terms is generally appropriate. The National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 was used to grade severity of adverse events.

Unless otherwise specified, all the analyses used to support this review were conducted with JMP Clinical (Version 6) software. Analyses are based on the data submitted with the NDA.

9.2 Adequacy of Safety Assessments

The safety monitoring plan implemented in Study M16-123 was adequate.

Study visits in the Treatment Phase occurred on Day 1 and at the end of weeks 1, 2, 4, 8, 12, and 16. Visits at the end of weeks 12 and 16 only applied to treatment-experienced participants on longer durations of treatment. Each follow-up visit included: a focused physical examination with vital signs; an assessment of AEs, medication adherence, and concomitant medications; and safety and virology laboratory studies. Post-treatment follow-up is planned to continue through 144 weeks after last dose of study medication (post-treatment week 4, 12, 24, 48, 96 and 144 follow-up visits) and includes vital signs, weight/height/BMI checks, longitudinal Fibrotest and AST-platelets ratio index (APRI), HCC assessment (both liver ultrasound and alpha fetoprotein), concomitant medication assessment, AE assessment, and HCV RNA samples.

9.3 Major Safety Results

Deaths: There were no deaths reported.

Serious Adverse Events (SAEs): There was one SAE of osteomyelitis that was not treatment-emergent and not thought to be related to study drug. Subject (b) (6) was a 5-year-old female who was diagnosed with methicillin-sensitive *S. aureus* (MSSA) bacteremia and osteomyelitis of the hip/pelvic bone on post-treatment day 171.

Reviewer comment: This SAE of osteomyelitis is not considered treatment-emergent and is not likely to be related to the study drug or the subject's underlying HCV diagnosis. Osteomyelitis is

a common pediatric infection, and MSSA is one of the most common pathogens causing osteomyelitis.

Adverse Events of Special Interest: None of the prespecified AESI (treatment-emergent hepatic decompensation/hepatic failure events or post-baseline events of HCC) occurred.

There were no new safety signals identified as of the 4-month safety update.

9.4 Dropouts and Discontinuations

There was one dropout due to an AE (Subject (b) (6)), a 3-year-old male who refused to take the study drug on Day 1 and subsequently dropped out.

There was one discontinuation due to an AE. Subject (b) (6) was an 11-year-old female who discontinued study drug on Day 4 due to an adverse event of Grade 3 "rash erythematous" which occurred on Day 1. There were no other concomitant medications reported and her medical history included HCV infection, duplex kidney and vesicoureteral reflux. The event resolved after discontinuation of study drug and treatment with cetirizine. There were no other reported symptoms to suggest a more systemic reaction such as anaphylaxis.

Reviewer comment: Subject (b) (6) 's refusal to take the study drug could have been due to several factors that commonly arise in childhood such as behavioral or cooperation issues, or potential palatability issues with the pellet formulation.

The rash in Subject (b) (6) could have plausibly been related to study drug based on the timing of the AE and resolution after stopping study drug, although treatment with cetirizine could have also led to improvement whether the rash was related to study drug or not.

9.5 Adverse Events and Adverse Drug Reactions

This section summarizes the TEAEs and ADRs that occurred in Study M16-123 Part 2.

Treatment-Emergent Adverse Events

There were 168 TEAEs that occurred in 57 of 80 subjects. TEAEs that occurred at a rate of at least 5% are shown in Table 6 below. Some similar preferred terms were combined by the reviewer as shown in the footnotes.

Table 6: TEAEs occurring at a rate of ≥5%

Preferred Term	**N=80** **n (%)**
Nausea	5 (6)
Pyrexia	6 (8)

Preferred Term	**N=80 n (%)**
Cough	7 (9)
Fatigue	7 (9)
Abdominal pain[1]	8 (10)
Diarrhea	8 (10)
Headache	11 (14)
Vomiting[2]	12 (15)
Upper respiratory tract infection[3]	20 (25)

Source: Analysis by Clinical Reviewer using ADAE dataset

1. combines terms “abdominal pain” and “abdominal pain upper”
2. combines terms “vomiting” and “post-tussive vomiting”
3. combines terms “nasopharyngitis,” "respiratory tract infection," "respiratory tract infection viral," "upper respiratory tract infection," "viral upper respiratory tract infection," and "viral infection"

Most of the TEAEs were Grade 1-2. There were only two Grade 3 AEs: osteomyelitis (which was not treatment-emergent) and rash erythematous. There were no Grade 4-5 TEAEs. The system organ class (SOC) that included the most TEAEs was gastrointestinal disorders, as shown in Table 7.

Table 76: TEAEs by SOC in Study M16-123 Part 2

SOC	**Number of TEAEs**
Blood and lymphatic system disorders	1
Renal and urinary disorders	1
Cardiac disorders	2
Investigations	2
Musculoskeletal and connective tissue disorders	2
Ear and labyrinth disorders	3
Metabolism and nutrition disorders	4
Eye disorders	6
Injury, poisoning and procedural complications	6
Psychiatric disorders	8
Skin and subcutaneous tissue disorders	8
Nervous system disorders	16
General disorders and administration site conditions	17
Respiratory, thoracic and mediastinal disorders	23
Infections and infestations	32
Gastrointestinal disorders	37
Total	168

Source: Analysis by Clinical Reviewer using ADAE dataset

Due to their high frequency, gastrointestinal events were further analyzed by age cohort as shown in Table 8. Other SOCs with large numbers of events such as Infections and Infestations and Respiratory, Thoracic and Mediastinal disorders were not analyzed further because most of

these events were common pediatric illnesses such as upper respiratory infections that are unlikely to be related to subject characteristics or study drug.

Table 8: Gastrointestinal TEAEs by Age Cohort

Preferred Term	Cohort 4 ≥3 to <6 years n=24 (%)	Cohort 3 ≥6 to <9 years n=26 (%)	Cohort 2 ≥9 to <12 years n=30 (%)	Total n=80 (%)
Oral pain	0	0	1	1 (1)
Toothache	0	0	1	1 (1)
Aphthous ulcer	0	0	1	1 (1)
Cheilitis	1	0	0	1 (1)
Nausea	1	2	2	5 (6)
Abdominal pain[1]	2	2	4	8 (10)
Diarrhea	2	4	2	8 (10)
Vomiting[2]	5	6	1	12 (15)

Source: Analysis by Clinical Reviewer using ADAE dataset

1. Combines terms "abdominal pain" and "abdominal pain upper"
2. Combines terms "vomiting" and "post-tussive vomiting"

Abdominal pain was more common in the oldest age group (Cohort 2) than in the younger age groups (Cohorts 3 and 4), whereas vomiting was more common in the younger age groups.

Reviewer comment: These differences in gastrointestinal events by age group are likely influenced by the developmental stages of the subjects. Older children are able to communicate that they have abdominal pain. Younger children may have more issues with palatability and with expressing abdominal discomfort and may be more likely to vomit.

Adverse Drug Reactions

There were 44 ADRs occurring in 23 subjects. As shown in Table 9, the most common ADRs were rash (5%), abdominal pain (5%), fatigue (8%), headache (8%), and vomiting (8%).

Table 9: Adverse Drug Reactions in Study M16-123 Part 2

Preferred Term	N=80 n (%)
Decreased appetite	1 (1)
Dizziness	1 (1)
Increased appetite	1 (1)
Irritability	1 (1)
Mood altered	1 (1)
Palpitations	1 (1)
Restlessness	1 (1)
Urine odor abnormal	1 (1)

Preferred Term	**N=80 n (%)**
Malaise	2 (3)
Pruritus	2 (3)
Diarrhea	3 (4)
Nausea	3 (4)
Rash[1]	4 (5)
Abdominal pain[2]	4 (5)
Fatigue	6 (8)
Headache	6 (8)
Vomiting	6 (8)

Source: Analysis by Clinical Reviewer using ADAE dataset

1. Combines terms "rash" and "rash erythematous"
2. Combines terms "abdominal pain" and "abdominal pain upper"

With the exception of vomiting, rash and abdominal pain which occurred more frequently in pediatric patients <12 years of age, the ADRs in this study are similar to what has been seen in adolescents and adults.

Reviewer comment: Rash and abdominal pain were not included in the sponsor's proposed prescribing information because prior to reviewer combination of similar terms as shown in the footnotes of Table 9, neither occurred at a rate of ≥5%. The review team proposed adding these after pooling terms, but the Applicant noted that reporting of frequency of adverse drug reactions in previous sections of the prescribing information had not been based on pooled terms, which would make it difficult to compare pediatric results to results from previous studies. Instead, the review team proposed including rash (without pooling with the term rash erythematous) and abdominal pain upper (each occurring at 4%) because they were observed more frequently in pediatric subjects less than 12 years of age compared to adults, which was thought to be important to communicate with providers. The Applicant agreed with this approach.

Subgroup Analyses

Subpopulation analyses were performed by the clinical reviewer to assess differences in safety between key groups. There were no patterns observed when ADRs were examined by race, ethnicity or sex. These subgroup analyses were limited by small sample size overall and within the subgroups.

9.6 Laboratory Findings

Maximum post-baseline laboratory values (with increased grade from baseline) are shown in Table 10. The majority were Grade 1. Grade 2 and Grade 3 increases were further reviewed for clinical significance.

Table 10: Maximum Post-Baseline Laboratory Values by Grade

Laboratory Test	Toxicity Grade		
	Grade 1	Grade 2	Grade 3
Activated Partial Thromboplastin Time (sec)	2	0	0
Alkaline Phosphatase (U/L)	12	0	0
Aspartate Aminotransferase (U/L)	2	0	0
Bilirubin (µmol/L)	3	0	0
Creatinine (µmol/L)	1	1	0
Creatinine Clearance (ml/min)	1	0	0
Glucose (mmol/L)-High	19	1	0
Glucose (mmol/L)-Low	8	1	0
Hemoglobin (g/L)	5	2	0
Leukocytes (10^9/L)	6	0	0
Magnesium (mmol/L)-High	14	0	0
Neutrophils (10^9/L)	0	2	1
Platelets (10^9/L)	3	0	0
Potassium (mmol/L)-High	1	0	0
Potassium (mmol/L)-Low	1	0	0
Prothrombin Intl. Normalized Ratio (ratio)	4	1	0

Source: Analysis by Clinical Reviewer using ADLBGRD dataset

The sponsor proposed to report specific laboratory values in the statistical analysis plan (SAP) and provided reference ranges for each grade.

There was only one Grade 3 change from baseline. Subject (b) (6) had a Grade 3 decrease in neutrophils on Day 14 (ANC went from 2280 at baseline to 580 on Day 14), but his neutrophil count returned to normal by Day 32. He had a recorded AE of viral illness on Day 9.

Reviewer comment: Subject (b) (6) 's neutropenia was likely due to myelosuppression related to the acute viral illness, as it occurred around the time of a viral illness and resolved without discontinuation of study drug.

There was one Grade 2 increase in creatinine in Subject (b) (6). His creatinine increased from 44 mmol/L at baseline to 159 mmol/L (0.49 to 1.79 mg/dL) on Day 28. He had a normal pH and specific gravity on urinalysis. A repeat creatinine on Day 33 was 44 mmol/L. This subject did not have any clinical AEs related to the increased creatinine. No narrative was provided.

Reviewer comment: This increase in creatinine was likely a laboratory error based on the fact that the subject had a normal value on repeat 5 days later with no reported change to study drug or clinical adverse events.

All other Grade 1 and Grade 2 changes from baseline were not clinically significant.

There were also no clinically significant mean changes from baseline for hematologic parameters, creatinine, electrolytes, or urinalysis values.

9.6.1 Liver Toxicity

Study M16-123 included several AEs of special interest, however, none were found amongst the study population during the trial period. These AEs of special interest included:

- All AEs of HCC identified using the preferred terms of hepatocellular carcinoma, hepatic neoplasm, hepatic cancer, hepatic cancer metastatic, and hepatic cancer recurrent
- Treatment-emergent hepatic decompensation/hepatic failure AEs, defined as ascites, hepatic encephalopathy, esophageal variceal bleeding, or spontaneous bacterial peritonitis.
- On treatment-hepatic laboratory parameters of interest
    - confirmed post-nadir ALT > 5 x ULN.
    - post-nadir ALT > 3 x ULN and concurrent total bilirubin > 2 x ULN with direct/total bilirubin > 0.4.

Additionally, no subjects had any laboratory values within the following parameters:

- Total bilirubin ≥ 2 × ULN and > baseline
- Post-nadir ALT > 3 × ULN and total bilirubin > 2 × ULN
- Post-nadir ALT > 3 × ULN and total bilirubin ≤ 2 × ULN

There were no clinically significant mean changes from baseline for bilirubin or alkaline phosphatase. There was a mean reduction from baseline to the final treatment visit for ALT (51 to 16 U/L), AST (47 to 27 U/L) and GGT (19 to 10 U/L).

Reviewer comment: The overall mean decreases in ALT, AST and GGT were likely related to the successful treatment of chronic HCV in the study population.

In summary, no safety concerns related to liver toxicity in the pediatric population were identified.

9.7 Vital Signs

There were no clinically significant trends in vital signs observed over time.

9.8 ECG Parameters

Two subjects had abnormal ECG findings. Subject (b) (6) had an ECG consistent with left ventricular hypertrophy at screening and at Day 15. Subject (b) (6) had an ECG consistent with possible atrial septal defect on Day 15. Neither of these subjects experienced cardiac AEs.

Reviewer comment: These ECG findings represent structural cardiac abnormalities which were likely present prior to the study, and therefore unlikely to be related to study drug.

9.9 Product-Specific Primary Safety Concerns

The Warnings and Precautions Section of the GLE/PIB label includes risk of Hepatitis B Virus reactivation in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals and were not receiving HBV antiviral therapy. There is also a risk of hepatic decompensation or failure in patients with evidence of advanced liver disease. No additional product-specific primary safety concerns were identified in this pediatric supplement.

9.10 Growth and Development

Height, weight, and BMI were assessed at baseline and at all study visits with plans to continue through post-treatment week 144. In the data submitted through post-treatment week 48, there was no observed clinically significant impact of treatment on growth rate. Overall, mean BMI increased by a z-score of 0.27 (SD 1.182) for all subjects in Cohorts 2-4 by the final treatment visit. As there is significant variation in growth by sex and age, and there was a relatively short duration of exposure to study drug, it is difficult to make meaningful conclusions about any impact of study drug on growth, especially over a short study period.

10. Subpopulations

The adult GLE/PIB development program included dedicated clinical trials to assess the efficacy and safety of GLE/PIB in several subpopulations of patients including those with cirrhosis, HIV-1/HCV coinfection, advanced kidney disease, or receipt of a liver or kidney transplant. The FDA recommended studying these populations because it was not yet clear whether these clinical factors would affect the safety or efficacy of GLE/PIB. As discussed in Dr. Larissa Stabinski's Primary Clinical Review and completed supplements, clinical trial results demonstrate a favorable risk/benefit assessment of GLE/PIB in these populations and provided the rationale for expanding the indications for use in adults.

This section focuses on subpopulations that were unrepresented or represented in small numbers in Study M16-123 and outlines the clinical review team's rationale for recommending inclusion of pediatric patients with HCV GT 5 and 6, compensated cirrhosis, or HIV-1/HCV coinfection in this pediatric approval.

Compensated Cirrhosis (Child-Pugh A)

Cirrhosis is uncommon among children with chronic HCV infection. However, children with cirrhosis are at risk of disease progression without treatment. Clinical trials in adults demonstrated the safety profile of GLE/PIB in adults is similar over 12-16 weeks and the presence of compensated cirrhosis (Child-Pugh A) did not have a significant impact on safety. The presence of compensated cirrhosis is not expected to alter PK exposures in children relative to adults where GLE/PIB has been previously found to be effective when given the appropriate durations.

Study M16-123 was open to both treatment-naïve and treatment experienced pediatric participants with compensated cirrhosis, however, the trial did not enroll any participants with cirrhosis. There are no differences in the target exposures for patients with compensated cirrhosis vs non-cirrhotic patients. Given the sufficient similarity in the natural history of chronic HCV disease between children and adults, extrapolation of efficacy between populations is possible. Therefore, the clinical team recommends extending approval to pediatric patients from age 3 to less than 12 years of age with compensated cirrhosis (Child-Pugh A).

HIV-1/HCV Co-infection

Among pediatric patients in the United States, HIV-1/HCV co-infection is rare and Study M16-123 included only 3 participants in this subgroup (two in Part 1 and one in Part 2). All participants completed treatment and achieved SVR12. No subjects experienced any Grade 2-4 AEs, AEs leading to study drug discontinuation, serious AEs, or Grade 3-4 laboratory abnormalities. Adult trials of GLE/PIB in adult participants with HIV-1/HCV co-infection have demonstrated high SVR12 rates comparable to subjects with HCV mono-infection with a similar safety profile. Data from HIV/HCV coinfected adults show that HIV-1 co-infection does not impact GLE/PIB response rates or safety profile. The adolescent approval was extended to this population for these reasons. Using similar rationale, the clinical team recommends use of GLE/PIB in pediatric patients from 3 to less than 12 years of age with HIV-1/HCV co-infection.

HCV GT 5 and 6

Infection with GT 5 or 6 is rare in the United States and worldwide. Although the trial was open to pediatric participants with these GTs, none were enrolled during Part 1 or Part 2 of the trial. HCV GT does not affect GLE/PIB exposure and previous trials in adults have demonstrated that equivalent GLE/PIB exposure is efficacious in adults with chronic HCV GT 5 and 6. Therefore, the submitted PK data are adequate to support the efficacy of GLE/PIB for treatment of HCV GT 5 or 6 in pediatric patients 3 to less than 12 years of age.

11. Human Factors

The oral pellets are supplied in child-resistant packets each containing 50 mg GLE and 20 mg PIB. A human factors study was conducted to assess use of these packets for administration of the proper dosing regimen using the Instructions for Use (IFU) document provided by the Sponsor. A total of 31 untrained participants (16 pediatric participants and 15 caregivers) were tested. An additional 15 trained pediatric participants were added after 13/16 original untrained pediatric participants reported that once their caregiver helped them with the first administration, they would complete the process on their own in subsequent administrations. Of note, the pediatric participants had "proxy conditions" other than HCV due to the rarity of HCV in the United States.

Of the untrained caregivers, 13/15 completed all tasks correctly. The two who did not complete all tasks correctly had errors that were related to incorrect food vehicle or incorrect number of packets given. The untrained pediatric participants performed poorly (only 3/16 without errors) but the trained pediatric participants did well with 13/15 completing the tasks without errors. The sponsor concluded that the IFU was appropriate for caregivers of pediatric patients aged 3-12 and for pediatric patients aged 10-12 who have been shown how to use the medication.

Division of Medication Error Prevention and Analysis (DMEPA) reviewed this study along with the PI and IFU and made several recommendations to make the IFU more clear in terms of the order of steps in the administration of the dose, selection of the correct number of packets per dose, and the avoidance of chewing or dissolving the pellets. Please see the DMEPA review for further detail.

12. Palatability

Palatability questionnaires were provided to subjects at Week 2, Week 8, and the Final Treatment Visit. Results from the Final Treatment Visit (n=78) will be summarized here. Dose preparation was reported to be convenient in 32.1% of subjects and very convenient in 39.7% of subjects. The medication was reported to be very easy to swallow by 37.7% of subjects or easy to swallow by 50.6% of subjects. There was a reported dislike for taste in 82.4% of subjects and dislike for texture in 52.9% of subjects. However, 75.3% reported successful administration of whole dose with soft food and 84.6% took the whole dose within 5 minutes or less. Although there was one subject who dropped out on Day 1 after refusing to take the medication, and vomiting was seen as an adverse reaction, neither palatability nor administration issues had a significant effect on efficacy.

13. Advisory Committee Meeting

An Advisory Committee meeting was not needed for these applications.

14. Pediatrics

One PREA Postmarketing Requirement (PMR) for pediatric patients was issued in the initial approval letter for the GLE/PIB NDA 209394 dated August 3, 2017.

4326-1 *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.*

Results of Study M16-123 Part 1, which included data for pediatric participants ages 12 to less than 18, partially addressed PMR 4326-1. The review team agreed that the above PMR will be fulfilled with the current submission of data for pediatric participants ages 3 to less than 12 enrolled in Part 2 of Study M16-123. FDA previously waived the pediatric study requirements from birth to less than 3 years because necessary studies are highly impractical due to the high rate of spontaneous HCV clearance in that age group. This submission was discussed at the Pediatric Review Committee (PeRC) meeting held on May 18, 2021 and the committee agreed with the Division that the submitted data supported approval for this pediatric population.

Pediatric exclusivity was requested by AbbVie and was granted by the Pediatric Exclusivity Board on May 12, 2021.

15. Recommendations

Recommended Regulatory Action

Based on the totality of the data presented and input from each of the review disciplines, the clinical review team recommends approval of GLE/PIB oral pellets for the treatment of pediatric patients from 3 to less than 12 years of age with chronic HCV GT 1, 2, 3, 4, 5 and 6 infection without cirrhosis or with compensated cirrhosis. The sponsor initially (b) (4) Pediatric patients weighing more than 45 kg can take 6 packets of oral pellets daily if they are unable to swallow the adult tablets. The recommended dosing regimen by weight band is shown in Table 11 below.

Table 11: Recommended GLE/PIB Dosing for Pediatric Patients

Body Weight (kg)/ Age (yrs)	Daily Dose of GLE/PIB	Dosing of MAVYRET
Less than 20 kg	150 mg/60 mg per day	Three 50 mg/20 mg packets of oral pellets once daily
20 to less than 30 kg	200 mg/80 mg per day	Four 50 mg/20 mg packets of oral pellets once daily
30 to less than 45 kg	250 mg/100 mg per day	Five 50 mg/20 mg packets of oral pellets once daily
45 kg and greater OR 12 years of age and older	300 mg/120 mg per day	Three 100 mg/40 mg tablets once daily[1]

Source: modified from draft label

1. Pediatric patients weighing 45 kg and greater who are unable to swallow tablets may take six 50 mg/20 mg packets of oral pellets once daily. Dosing with oral pellets has not been studied for pediatric patients weighing greater than 45 kg.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

This review identified no new safety information necessitating REMS.

Recommendation for other Postmarketing Requirements and Commitments

The FDA will not issue any new PMR or PMC as a result of this review.

16. Labeling

A summary of major changes made to the prescribing information (PI) is listed below:

- Indications and Usage
  - Extended the age of indication down to 3 years
- Dosage and Administration
  - Separated dosage instructions for adults (Section 2.3) and pediatric patients 3 years and older (Section 2.4)
  - Removed sponsor's statement that the two dosage forms are not interchangeable
  - Updated pediatric dosing table (Table 3 in PI)
    - Remove (b) (4)
    - Provide the number of packets of oral pellets or number of tablets recommended for daily dosing of each weight band, or age group in the case of adolescents 12 years and older
    - Include the allowance for pediatric patients 45 kg and greater who cannot swallow tablets to take six packets daily instead of tablets
- Dosage Forms and Strengths: added oral pellets
- Contraindications: no major changes

- Warnings and Precautions no major changes
- Adverse Reactions
    - Section 6.1 updated to include adverse reactions in pediatric subjects 3 years and older; the sponsor agreed to the following language: "The adverse reactions observed in subjects 3 years to less than 12 years of age were consistent with those observed in clinical trials of MAVYRET in adults with the exception of vomiting (occurring at 8%), rash, and abdominal pain upper (each occurring at 4%) which were observed more frequently in pediatric subjects less than 12 years of age compared to adults. Other adverse reactions observed in greater than or equal to 5% of subjects receiving MAVYRET in DORA-Part 2 include fatigue and headache, each occurring at 8%. One subject discontinued treatment due to an adverse reaction of erythematous rash (Grade 3). All other adverse reactions were Grade 1 or 2 and no subjects interrupted treatment due to an adverse reaction *[see Use in Specific Populations (8.4), Clinical Studies (14.10)]*."
- Drug Interactions: no major changes
- Use in Specific Populations
    - Section 8.4 Pediatric Use
        - Added safety information as above in Section 6.1
        - Efficacy results are consistent with adult trials
        - Safety and efficacy for pediatric patients with cirrhosis, history of a kidney and/or liver transplant, or HCV GT5 or 6 infection are supported by comparable GLE and PIB exposures between pediatric subjects and adults
- Clinical Pharmacology
    - Section 12.3 Pharmacokinetics
        - Included C_{trough} in tables of PK parameters (Tables 8 and 9)
        - Added the following information about the PK in pediatric patients compared to adults: "GMRs of glecaprevir and pibrentasvir C_{max} and AUC_{24} in HCV-infected pediatrics vs. adults ranged from 1.58-2.68 and 0.965-1.64, respectively. GMRs of glecaprevir C_{trough} ranged from 0.292-0.954 and GMRs of pibrentasvir C_{trough} ranged from 0.794-1.93. All pediatric glecaprevir and pibrentasvir PK parameter values fell within the range observed in adult subjects. These differences were not considered clinically significant. The pharmacokinetics of glecaprevir and pibrentasvir have not been established in children less than 3 years of age."
        - Included statement about clinically insignificant differences in exposures between pellets and tablets in adult subjects under non-fasting conditions to provide support for use of pellets in pediatric patients weighing 45 kg or greater who cannot swallow tablets
    - Section 12.4 Microbiology: no changes
- Nonclinical Toxicology: no changes
- Clinical Studies
    - Section 14 updated to include Study M16-123 (DORA) Part 2 including demographics and SVR12 information

- Section 14.10: Separated Part 1 and Part 2 and included more comprehensive demographics for both
- Changed language from [redacted] (b) (4) to "weight-based recommended dose" to avoid prescriber confusion about the meaning of the word [redacted] (b) (4)

17. References

1. WHO 2017 Global Hepatitis Report. Accessed March 31, 2021. https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/
2. Indolfi G, Easterbrook P, Dusheiko G, et al. Hepatitis C virus infection in children and adolescents. Lancet Gastroenterology and Hepatology. 2019;4(6): 477-487.
3. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. Journal of Hepatology. 2014;61(1 Suppl):S45 0 57.
4. Denniston MM, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Ann Intern Med. 2014;160(5):293-300.
5. AASLD-IDSA. When and in Whom to Initiate HCV Therapy. https://www.hcvguidelines.org/evaluate/when-whom. Accessed April 28, 2021.
6. AASLD-IDSA. HCV in Children. https://www.hcvguidelines.org/unique-populations/children. Accessed April 28, 2021.

18. Other Relevant Regulatory Issues

Clinical Investigator Financial Disclosure Review Template.
Application Number: 215110/209394 S-13

Submission Date(s): December 10, 2020

Applicant: AbbVie Inc.

Product: Mavyret (Glecaprevir/Pibrentasvir)

Reviewer: Gillian Taormina, DO

Date of Review: May 17, 2021

Covered Clinical Trial (Name and/or Number): M16-123

Was a list of clinical investigators provided:	**Yes** ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 157		

<table>
<tr><td colspan="3">Number of investigators who are sponsor employees (including both full-time and part-time employees): 0</td></tr>
<tr><td colspan="3">Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0</td></tr>
<tr><td colspan="3">If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0

Significant payments of other sorts: 0

Proprietary interest in the product tested held by investigator: 0

Significant equity interest held by investigator in sponsor of covered study: 0</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>N/A ☒</td><td>No ☐ (Request details from applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☒ (section 1.3.4.1)</td><td>No ☐ (Request information from applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0</td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>N/A ☒</td><td>No ☐ (Request explanation from applicant)</td></tr>
</table>

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the Guidance for Industry: *Financial Disclosure by Clinical Investigators*. None of the 157 investigators had reportable financial disclosures or certifications of due diligence.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GILLIAN A TAORMINA
05/28/2021 11:09:21 AM

PRABHA VISWANATHAN
05/28/2021 12:42:24 PM

POONAM MISHRA
05/28/2021 12:49:24 PM

OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW	
NDA/SDN/Supplement	209394/708/S13 (tablets, for oral use) 215110/001 (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

Table of Contents

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 (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 (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

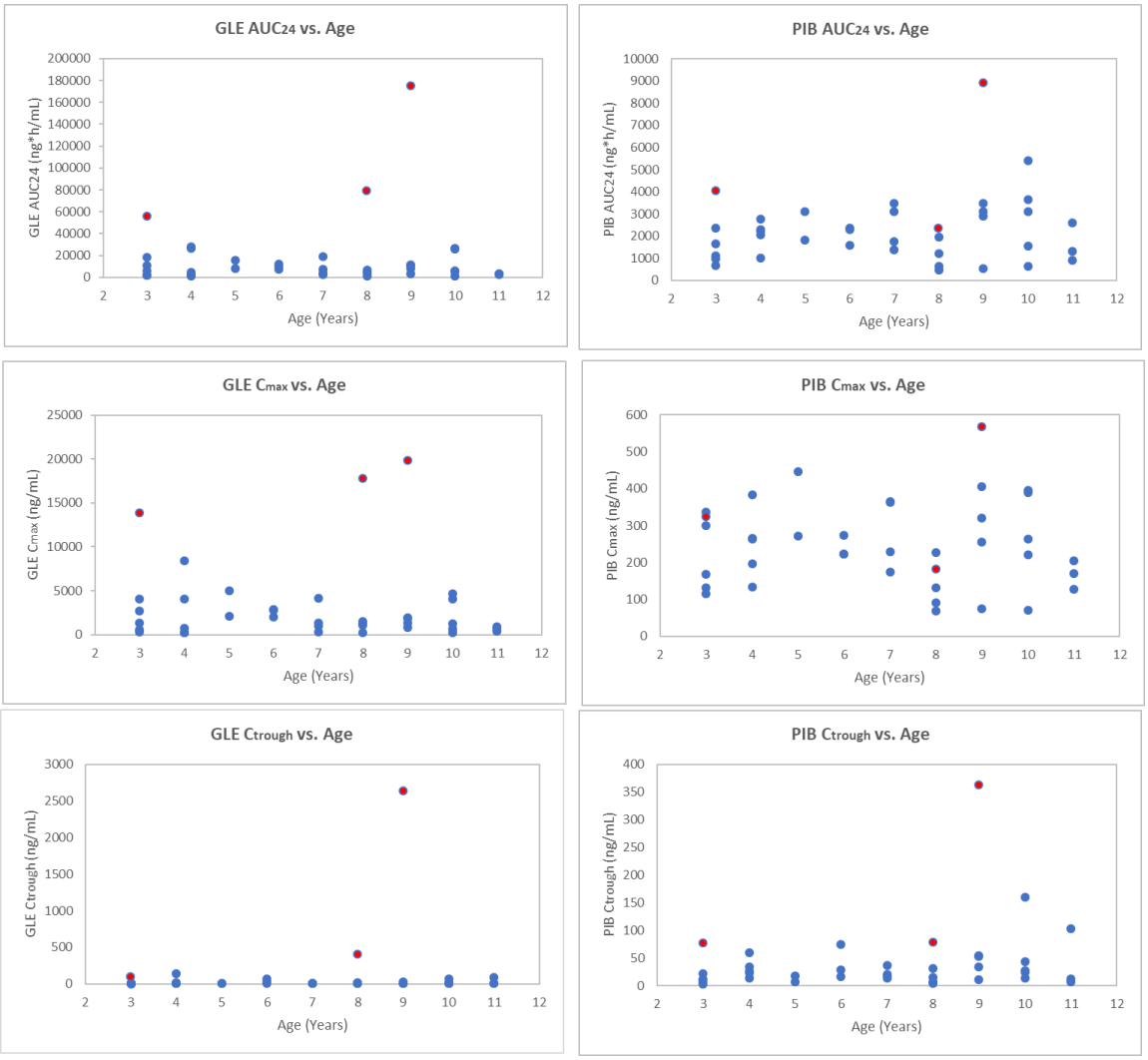
Source: Reviewer prepared from sample analysis reports for study M16-123.

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).

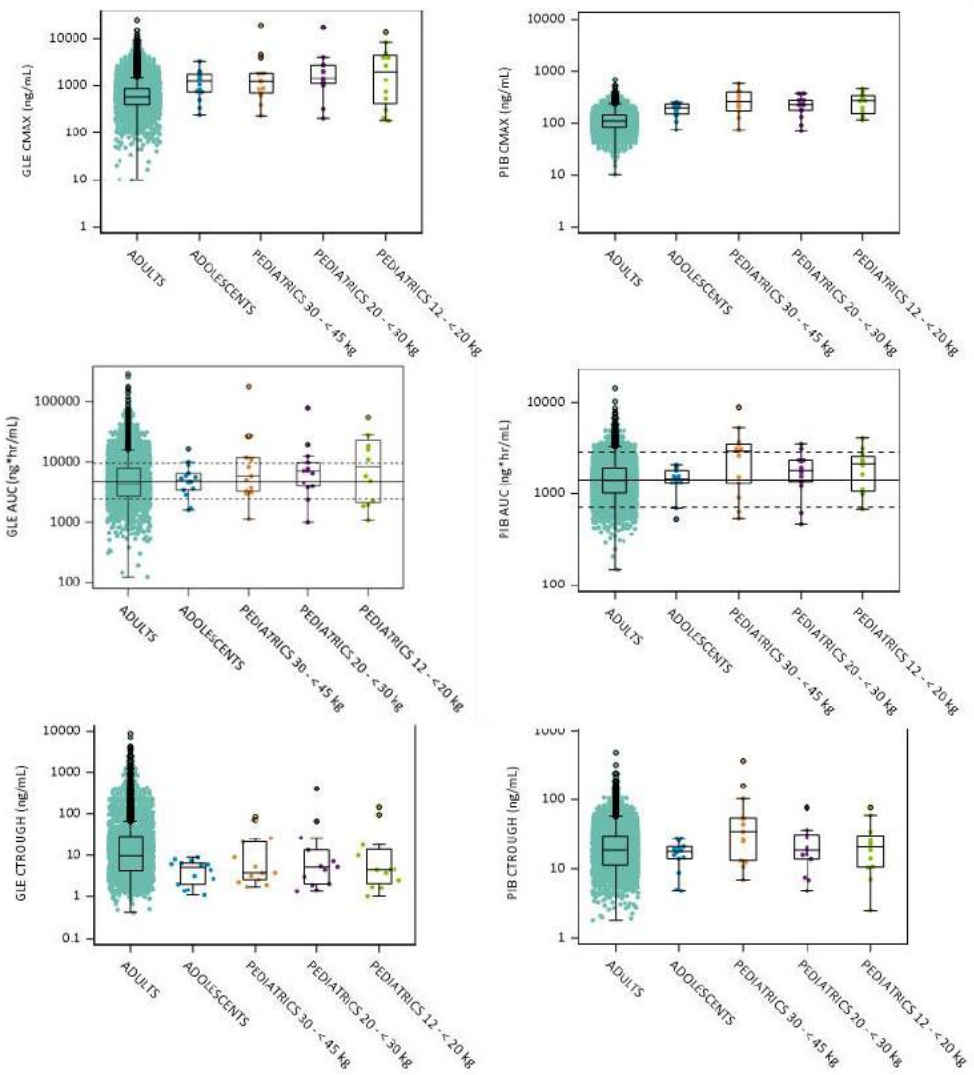
Table 6. Summary of pediatric/adult geometric mean ratios and 90% confidence intervals for subjects with intensive PK samples.

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:

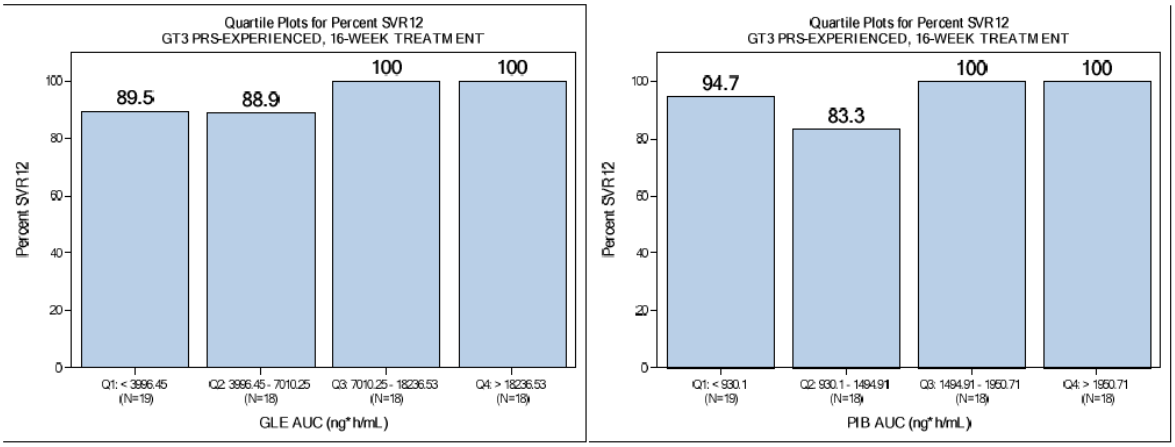
- Group 1: treatment-naïve and PRS-experienced GT1, GT2, GT4, GT5, and GT6 subjects (non-GT3 subjects) (TN, PRS experienced, non-GT3) (n=1755)
- Group 2: treatment-naïve GT3 subjects (GT3, TN) (n=608)
- Group 3: PRS-experienced GT3 subjects who received GLE/PIB for 16 weeks (GT3, PRS experienced) (n=73)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

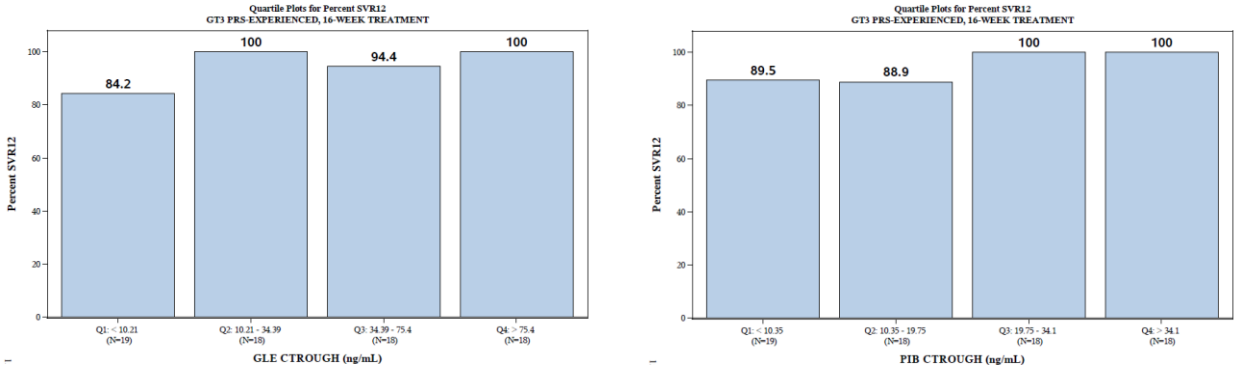
Groups 3-4 contained far fewer subjects and therefore it is difficult to draw conclusions regarding the effect of exposure on SVR12 rate (Figure 4, Figure 5, Figure 6 and Figure 7). In graphical analysis, group 3 SVR12 rate differed between the two lowest vs two highest GLE and PIB exposure quartiles. 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).



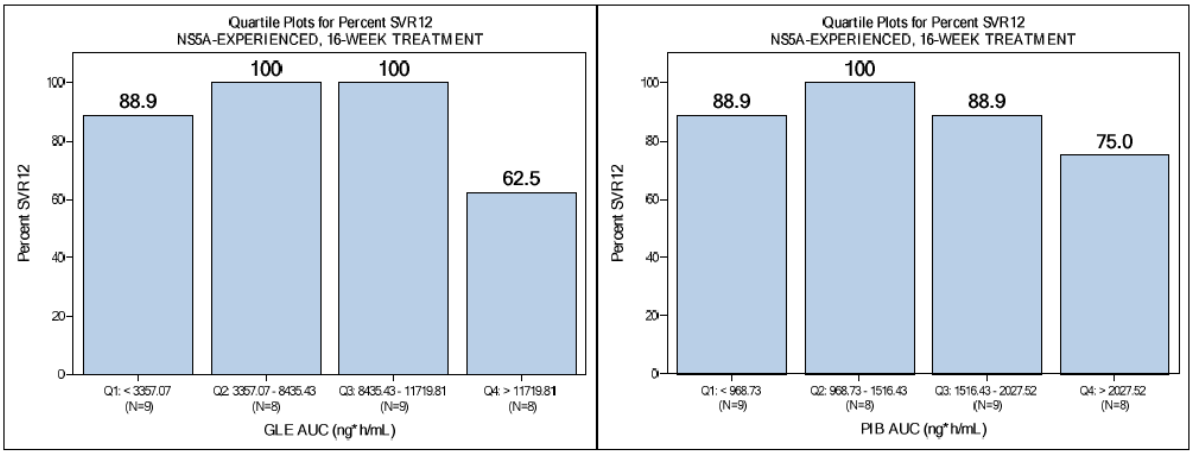
Source: Exposure-Virologic Response submitted for NDA 209394, R&D/16/0236.

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).



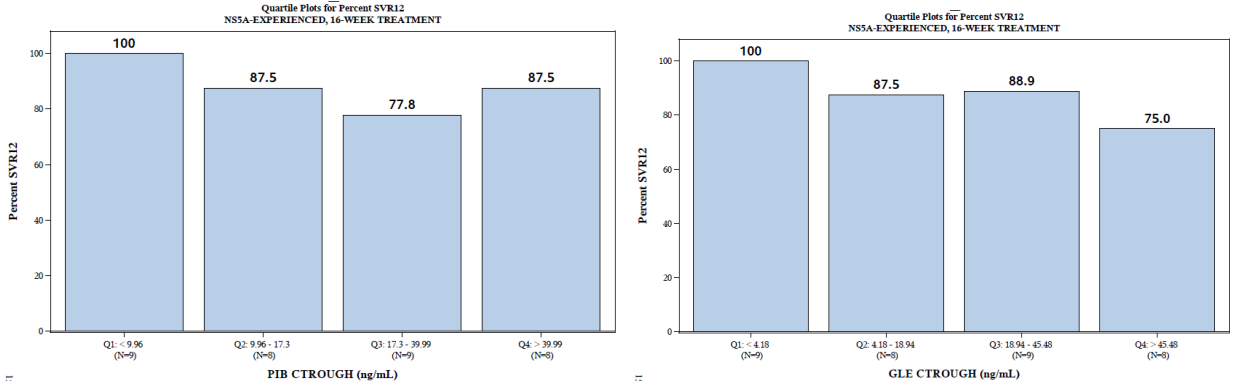
Source: Exposure-Virologic Response submitted for NDA 209394, R&D/16/0236.

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
CIRRHOSIS	WITHOUT CIRRHOSIS	47 (100%)	29 (100%)	27 (100%)	23 (100%)	79 (100%)	126 (100%)
HCV-HIV COINFECTION FLAG	NO	45 (95.74%)	29 (100.00%)	26 (96.30%)	23 (100.00%)	78 (98.73%)	123 (97.62%)
	YES	2 (4.26%)		1 (3.70%)		1 (1.27%)	3 (2.38%)
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.

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

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.

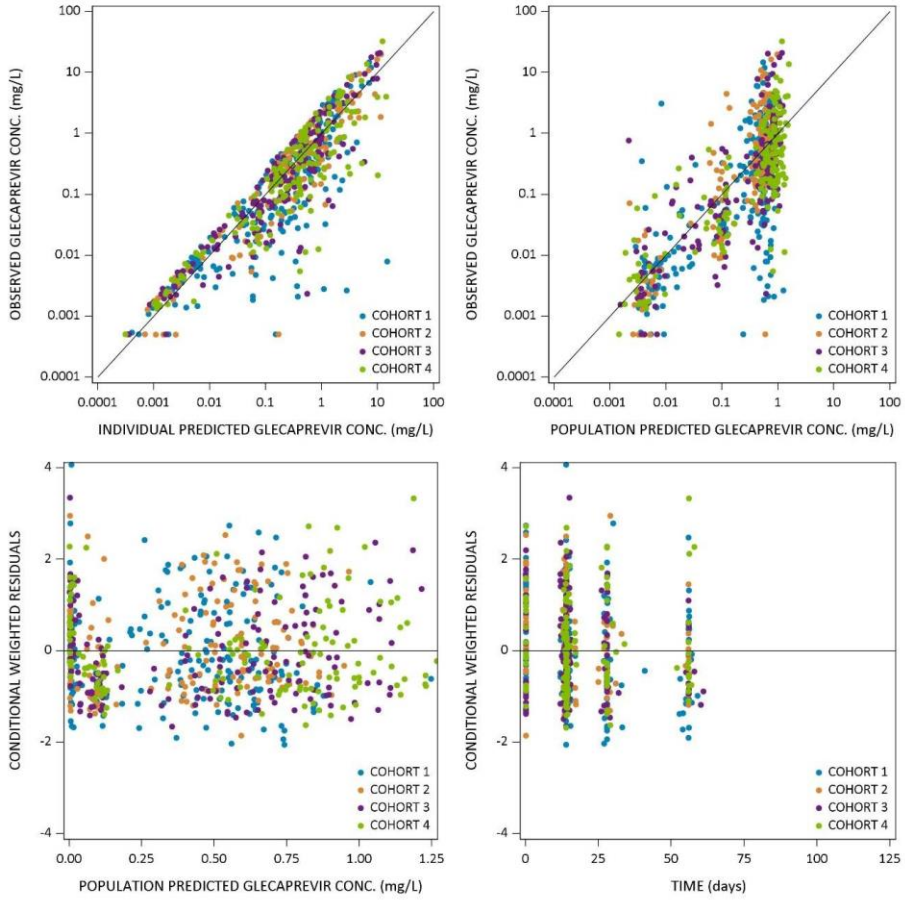
b. Absorption rate was estimated via a factor on elimination rate K = CL/V2 to avoid flip-flop behavior. Respective confidence intervals for KA are provided along with the bootstrap results (Table 6).

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.

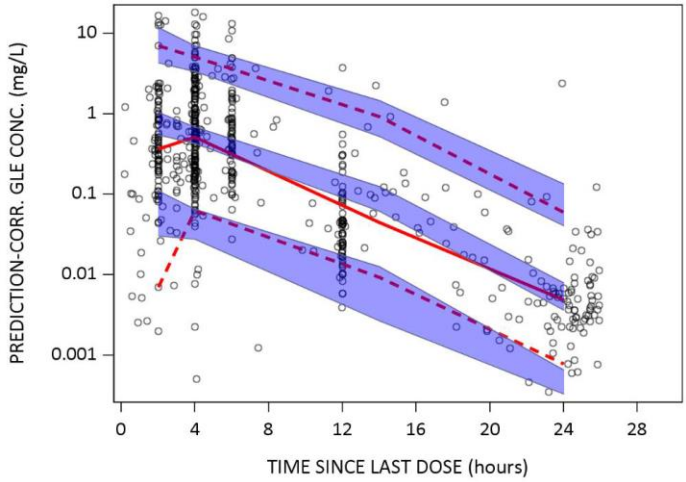
Figure 8. GoF plots for final GLE model.



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.

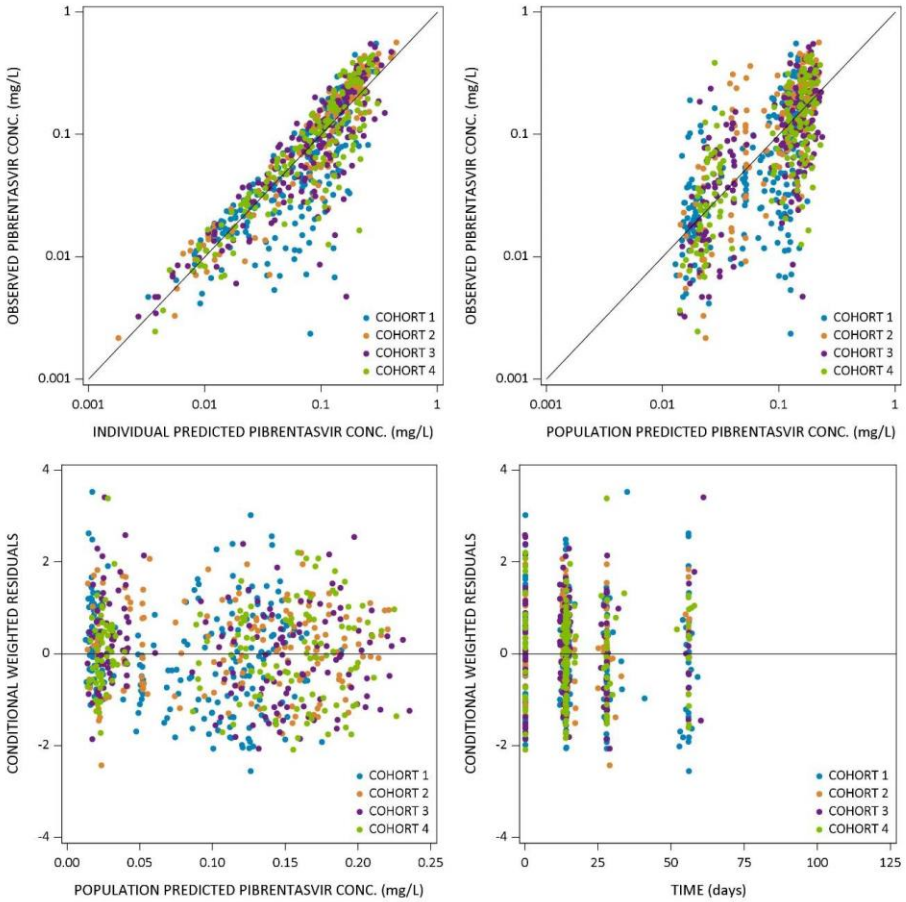
Note: VPCs are cut at 24 hours after last dose, as data are too sparse beyond.

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.

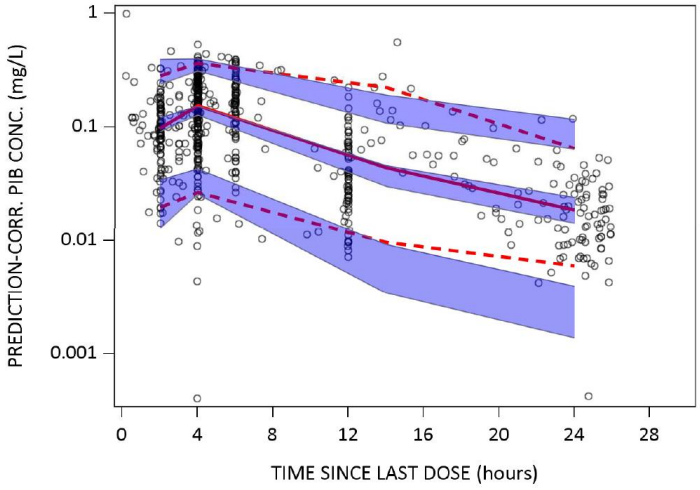
Figure 10. GoF plots for final PIB model.



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.

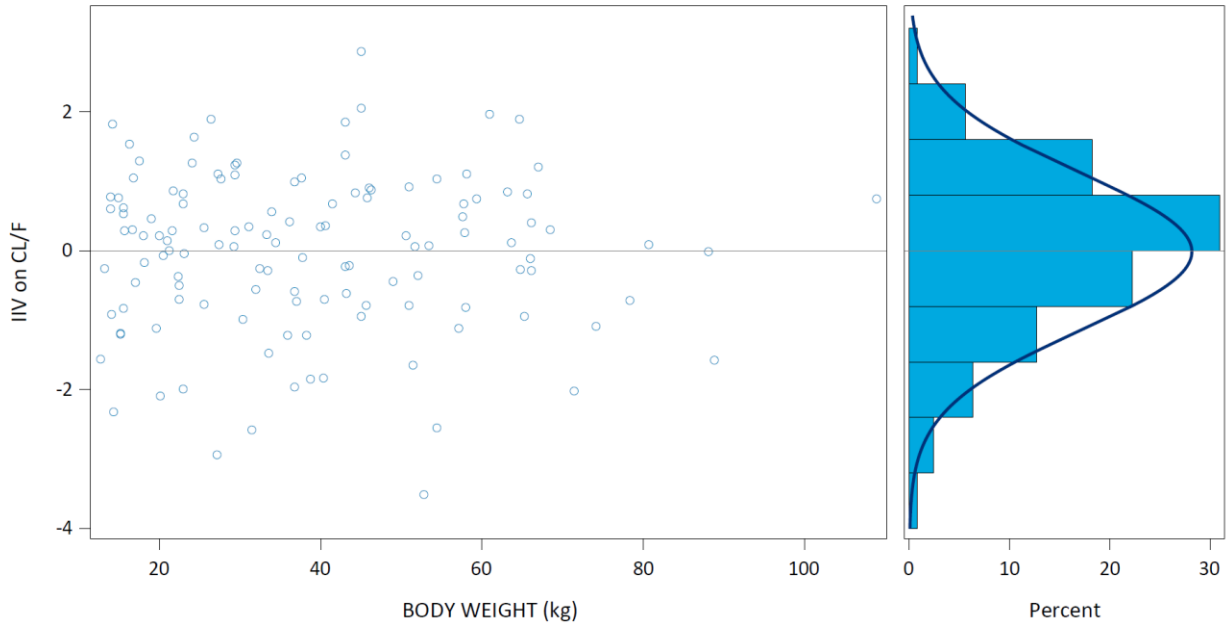
Note: VPCs are cut at 24 hours after last dose, as data are too sparse beyond.

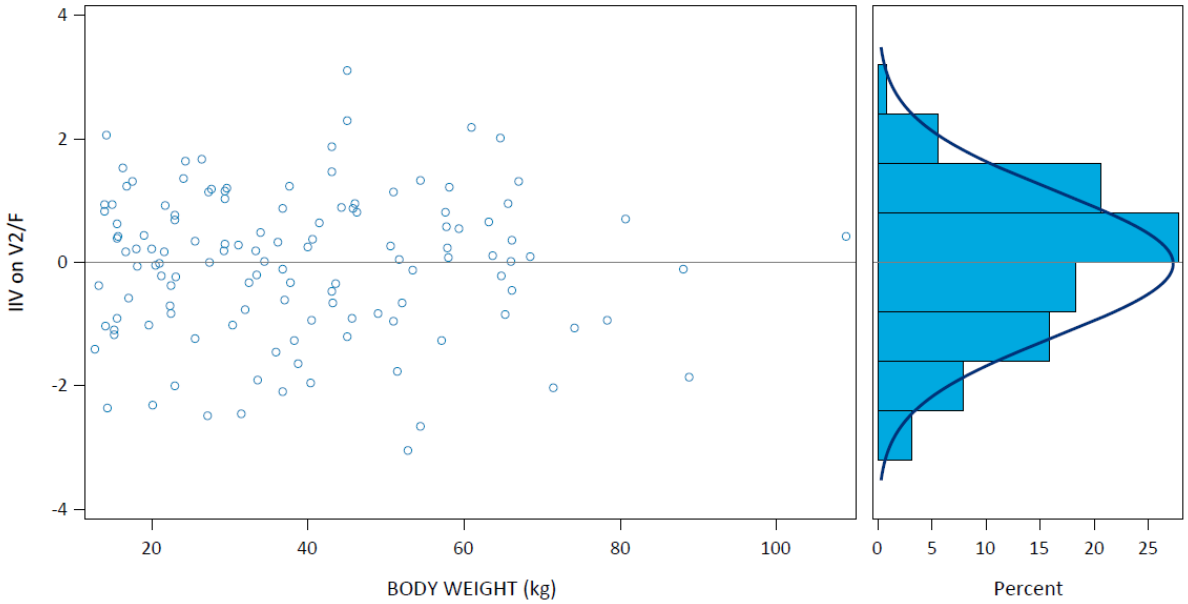
Cross reference: Figure 14.7__2.1

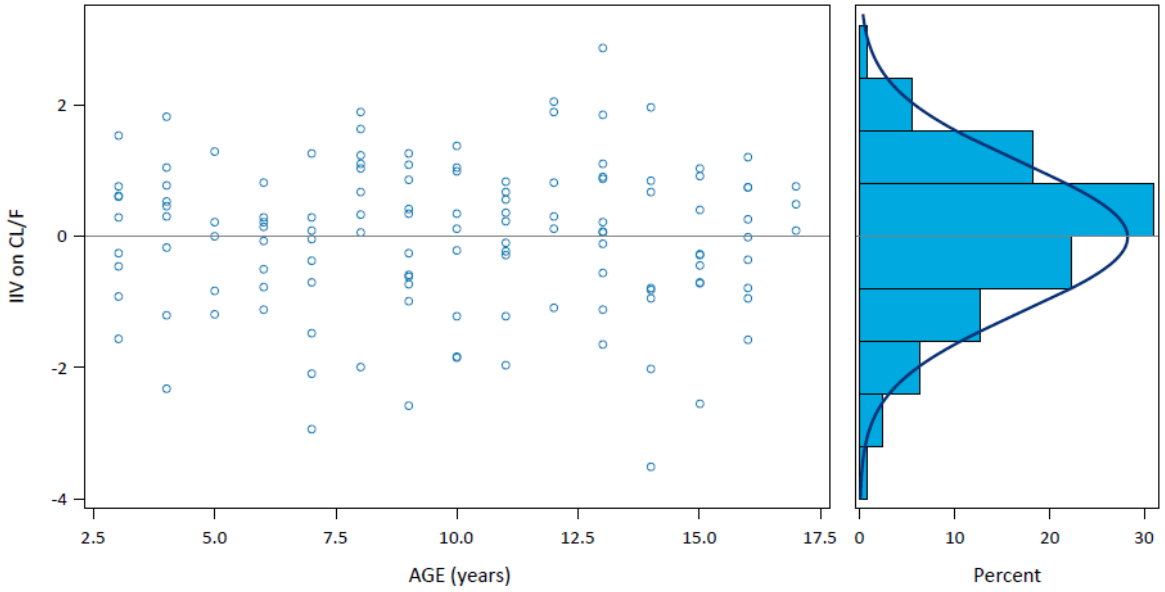
Source: Applicant's report, Phase 2/3 Study M16-123, Part 2, Figure 7

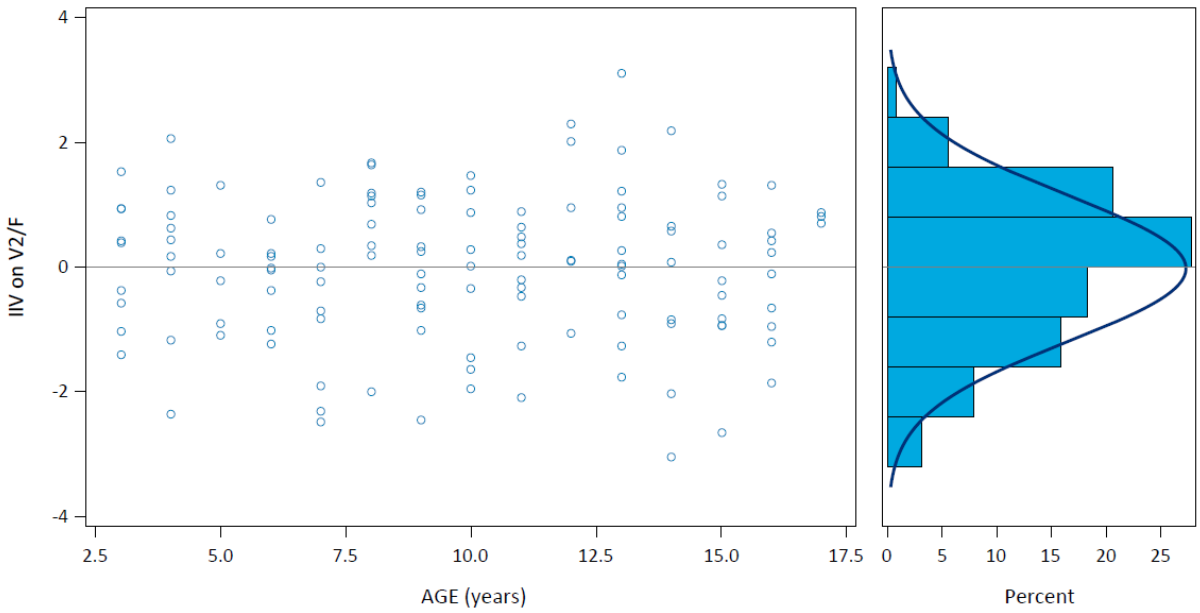
Reviewer's comments: the final GLE PopPK model shows acceptable central tendency in the prediction corrected VPC plot. Note that there are slight overpredictions around the 50th percentile over time for simulated GLE concentrations; however, the upper and lower bounds of PI (5th and 95% percentiles)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





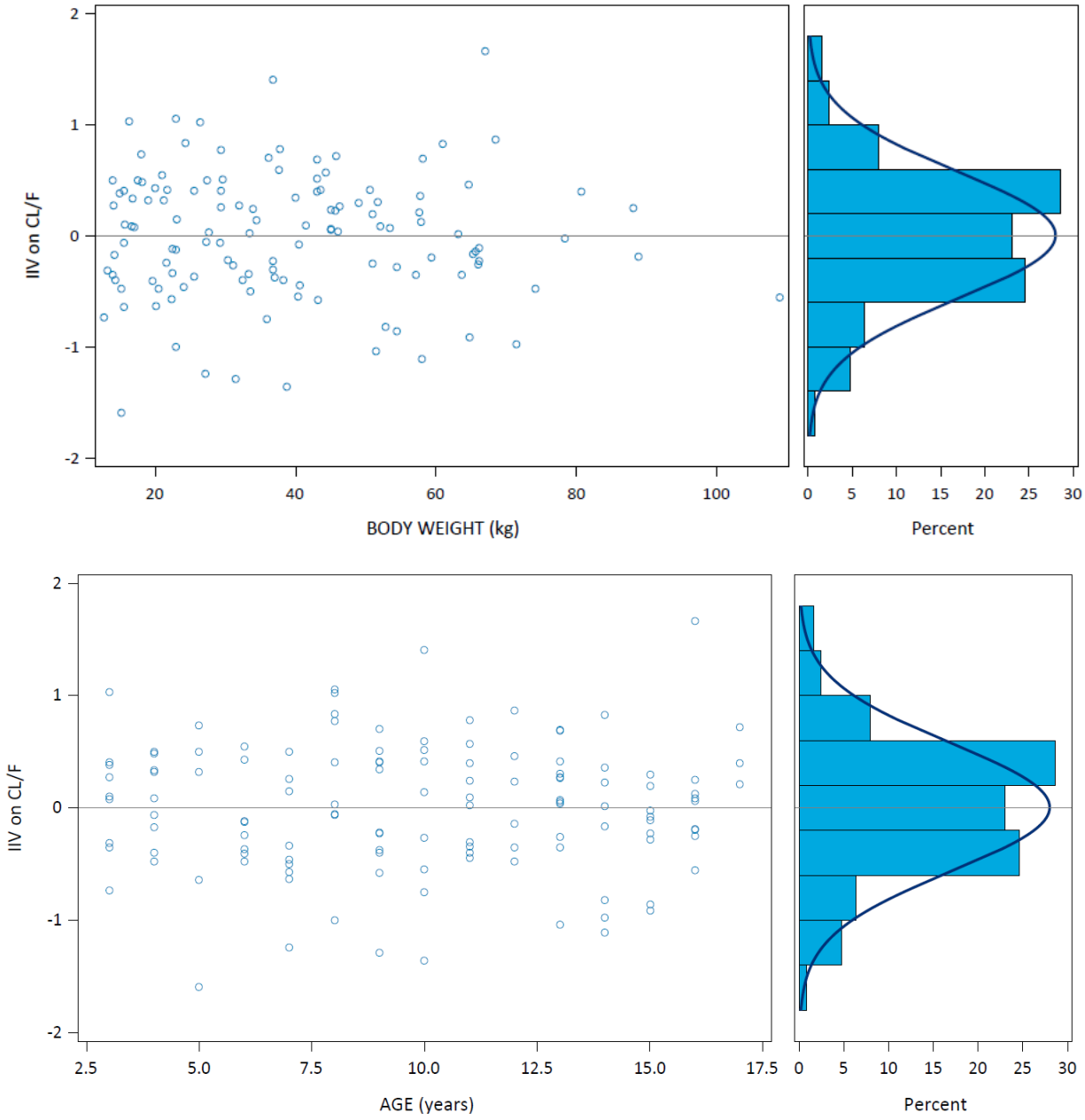


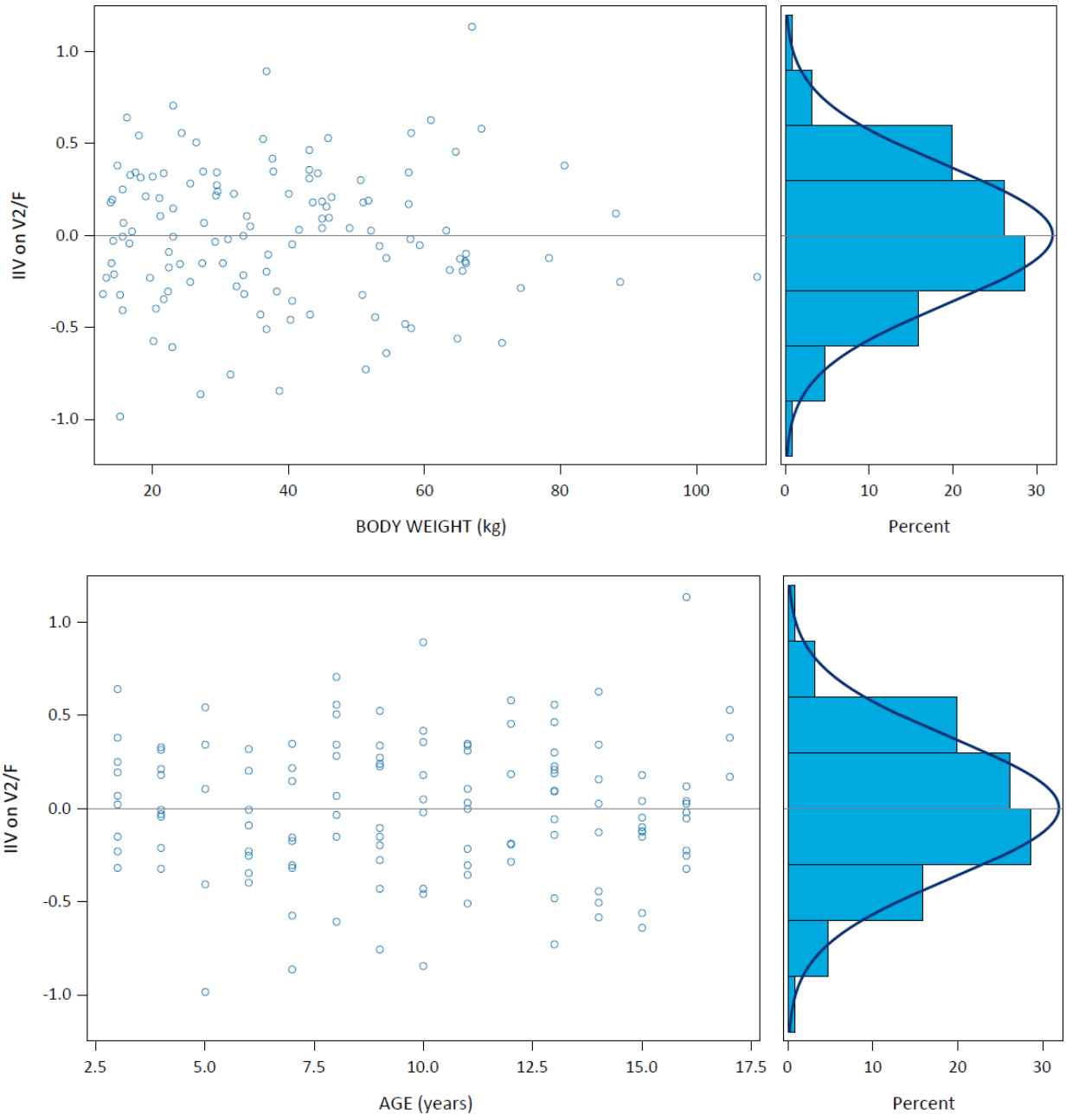


Source: Applicant's report, Phase 2/3 Study M16-123, Appendix 14.6

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.

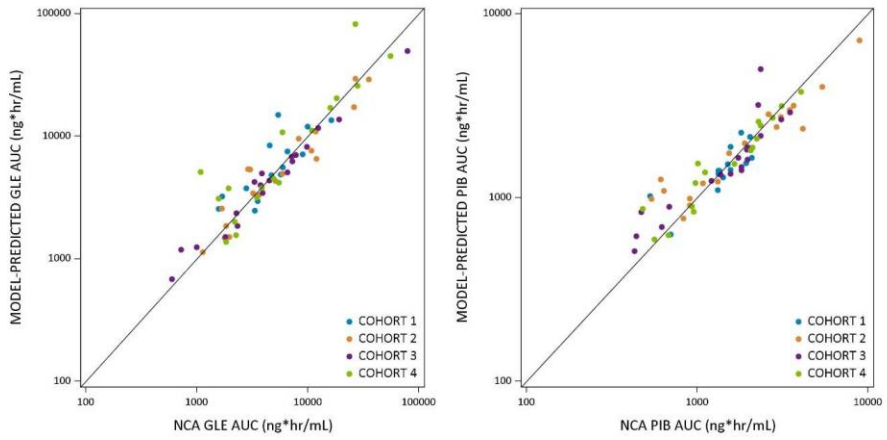
Reviewer's comments: the final PIB PopPK model shows acceptable distribution without trends around x=0 in the ETA vs. body weight and age plots. Refer to Applicant's report, Phase 2/3 Study M16-123 for ddditional ETA plots.

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.

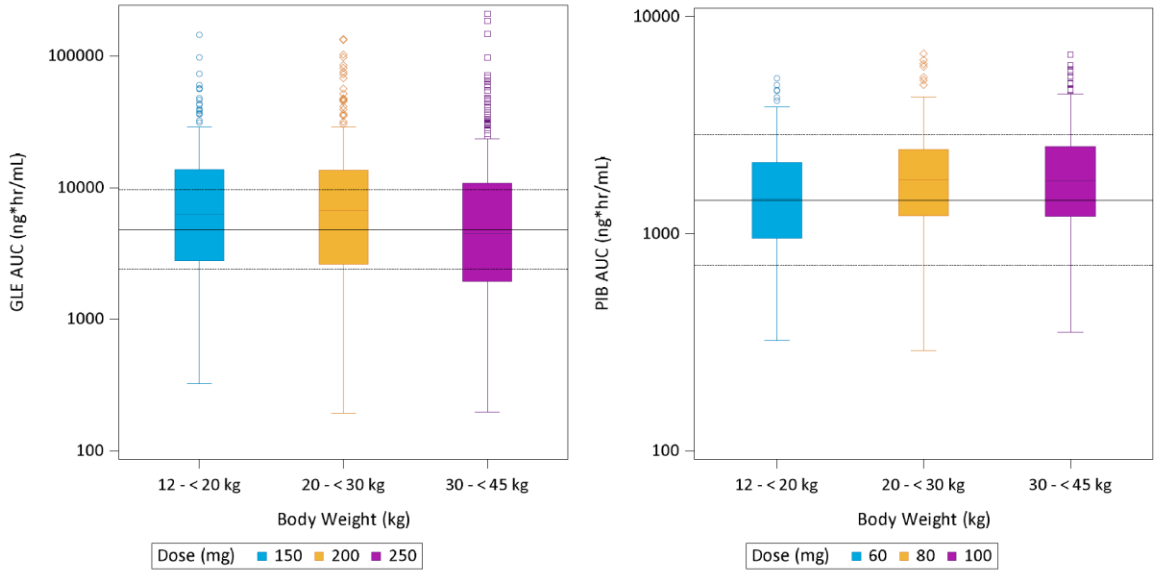
Table 18 describes the simulation results of 24-hour steady state AUCs for GLE and PIB. Figure 15 provides a graphical representation of the simulated 24-hour AUCs at steady state for GLE and PIB for pediatric subjects.

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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