# Office of Clinical Pharmacology (OCP) Review

| NDA | 209394 S-6 (EDR) |
|---|---|
| **Brand Name (Generic Name)** | MAVYRET™ (Glecaprevir, Pibrentasvir]) |
| **Applicant** | Abbvie Inc. |
| **Submission Type** | Pediatric Efficacy Supplement |
| **Formulation/ Strength** | Oral tablet containing 100 mg glecaprevir and 40 mg pibrentasvir |
| **Proposed Indication** | Treatment of Chronic Hepatitis C infection in adolescent subjects |
| **Clinical Pharmacology Review Team** | Su-Young Choi, Pharm.D., Ph.D. <br> Simbarashe Zvada, Ph.D. <br> Chao Liu, Ph.D. <br> Vikram Arya, Ph.D., FCP. |

## 1. Executive Summary

MAVYRET™ is a fixed-dose combination of glecaprevir (GLE) and pibrentasvir (PIB) <sup>(b) (4)</sup>

MAVYRET™ is also indicated for subjects who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor (PI), but not both. The recommended oral dosage of MAVYRET™ is three tablets (each fixed dose combination tablet contains 100 mg GLE 100 mg and PIB 40 mg) taken at the same time once daily with food (total daily dose: GLE 300 mg and PIB120 mg; referred to as 300/120 mg in the remainder of the review) for 8, 12, or 16 weeks depending on genotypes, cirrhotic status, and prior treatment history.

The current efficacy supplement seeks to extend the indication to include pediatric subjects 12 years of age and older. To support the proposed indication, the sponsor conducted a clinical trial entitled "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 (DORA), Part 1" (M16-123). In the trial, 47 adolescent subjects with HCV infection received the approved adult dosing regimen (300/120 mg once daily) of MAVYRET™ and PK, antiviral activity, and safety data was collected. The basis of approval of MAVYRET™ in adolescent subjects is extrapolation of the efficacy from adult subjects by

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demonstrating comparability of systemic exposures of GLE and PIB between adults and adolescents with HCV infection.

The results indicated that the mean systemic exposures of GLE and PIB are comparable between adults and adolescent subjects when the adult dosing regimen of MAVYRET™ is administered to adolescent subjects (PK results). The safety and efficacy results observed in this study were consistent with those observed in clinical studies of MAVYRET™ in adults. The bioanalytical site (Abbvie) and one clinical site (Children's hospital of Pittsburgh) have been inspected by OSIS and the data are acceptable to be used to support the approval of the proposed dosing regimens in adolescents (see OSIS review dated 2/22/2019 and 2/28/2019 for additional details).

## 1.1 OCP Recommendations

The Office of Clinical Pharmacology has reviewed the application and determined that this sNDA is approvable from a clinical pharmacology perspective. This submission also partially 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.*

## 2. Summary of Labeling Recommendations (Clinical Pharmacology Relevant Sections Only)

The following clinical pharmacology related information will be added in MAVYRET™ USPI:

Section 2 Dosage and Administration
- Add a new population: pediatric subjects 12 years and older or weighing at least 45 kg.

Section 8 Specific Population
- Add the summary of findings in M16-123 under pediatrics sub-section.

Section 12.3 Pharmacokinetics
- Add the following statement and supporting PK data: Exposures of glecaprevir and pibrentasvir in pediatric subjects 12 years of age and older receiving a daily dose of MAVYRET (300 mg glecaprevir and 120 mg pibrentasvir) were comparable to those in adults from Phase 2/3 studies who received the same dose. The pharmacokinetics of glecaprevir and pibrentasvir have not been established in children less than 12 years of age.

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## 3. Individual Study Review

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 (DORA): M16-123

Primary Objectives
- 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 sustained virologic response for 12 weeks post-treatment ($SVR_{12}$) 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 $\geq 3$ 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 interferon (IFN) with or without ribavirin (RBV) or TE to sofosbuvir (SOF) plus RBV with or without IFN. The study is divided into 2 parts.
- Cohort 1: HCV GT1 – GT6 infected adolescent subjects 12 to < 18 years old who were willing to swallow the adult formulation of GLE/PIB (n=47 including 17 subjects who provided intensive PK samples).
- Cohort 2-4: HCV GT1 - GT6 infected pediatric subjects divided into the 9 to < 12 (Cohort 2), 6 to < 9 (Cohort 3), and 3 to < 6 (Cohort 4) years old age groups (approximately N=66 planned. Cohort 2-4 are ongoing, and results are not available in the current submission).

In Cohort 1, all subjects received GLE/PIB 300 mg/120 mg for 8, 12, or 16 weeks with food depending on their HCV genotype, cirrhosis status, prior treatment experience status, and geographical location. In each cohort, subjects were enrolled first into the intensive PK portion, followed by safety/efficacy/sparse PK portion. Safety and virologic response ($SVR_{12}$ and HCV RNA levels through Week144) were assessed throughout the study.

Pharmacokinetic Assessments
For all subjects, PK samples were collected on Day 1 (4 hours post dose), at Weeks 4, 8, 12, or 16 (regardless of the dosing time). In Japanese adolescent subjects, additional sparse samples were collected at Week 2 (pre-dose, 2 and 4 post dose) to further characterize GLE and PIB PK

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as GLE and PIB exposures tended to be higher in Japanese adult patients as compared to non-Japanese adult patients in the sponsor's previous popPK analysis. In subjects who participated in the intensive PK sample collection, PK samples were collected at Week 2 (pre-dose, 2, 4, 6, 12 hours post dose). To determine PK parameters, noncompartmental analyses were conducted using Week 2 intensive PK data collected in 17 subjects and a population pharmacokinetic analysis was conducted using all intensive and sparse PK data.

Bioanalysis

Plasma PK samples were analyzed using a validated LC/MS/MS method after liquid/liquid extraction. The method was adequately validated. The standard curve and QC data indicated that assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data.

*Reviewer comments*

*The bioanalytical method was validated having 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 concentration calibration range was used for sample analyses (1 - 5000 ng/mL for GLE and 1 - 751 ng/mL for PIB, respectively). In response to the information request regarding the use of two dynamic calibration ranges, the sponsor stated that the method was initially validated having two dynamic ranges based on the anticipated concentrations to be observed for this program in humans, and to minimize the number of dilutions. However, after Phase 1 studies, it was concluded that a single concentration range was sufficient for future clinical studies. This issue was also noted in the original clinical pharmacology NDA review. The review team agrees with the conclusions which were made in the original NDA review that while not ideal, the use of methods validated with two dynamic calibration ranges is acceptable.*

Results

1. Demographics and baseline characteristics

A total of 48 subjects were enrolled and 47 subjects received at least 1 dose of study drug. No subject prematurely discontinued study drug. Subjects were mostly White (74.5%) and the median age was 14 years old (range: 12-17 years old). Three subjects (6%) had body weight less than 45 kg at the time of enrollment, which was the protocol defined minimum weight for enrollment. Most subjects had HCV genotypes 1a (51%) or 1b (28%). There was no subject with cirrhosis.

2. Pharmacokinetic results

The mean pharmacokinetic parameters of GLE and PIB in adults and adolescents are summarized in Table 1. Results from the study demonstrated the mean steady-state exposures of GLE and PIB in HCV infected adolescent subjects were comparable to those observed in HCV-infected adult subjects.

**Table. 1: Comparison of the Mean Pharmacokinetic Parameters of GLE and PIB after administration of 300/120 mg once daily to Adolescents and Adult Subjects with Chronic Hepatitis C**

| Population | N | GLE | | | PIB | | |
|---|---|---|---|---|---|---|---|
| | | $C_{max}$ (ng/mL) | $AUC_{24}$ (ng·hr/mL) | $C_{min}$ (ng/mL) | $C_{max}$ (ng/mL) | $AUC_{24}$ (ng·hr/mL) | $C_{min}$ (ng/mL) |
| Adolescents, Intensive | 14* | 1040 (66%) [245, 3400] | 4790 (67%) [1580-16300] | 3.79 (61%) [0, 8.9] | 174 (28%) [72, 248] | 1380 (31%) [530, 2090] | 15.0 (43%) [4.7, 28] |
| Adolescents, Intensive | 17$ | 662 (83%) [57, 3400] | 3222 (84%) [473, 16300] | 3.0 (67%) [0, 8.9] | 133 (47%) [34, 248] | 1095 (46%) [329, 2090] | 13 (52%) [2.1,28] |
| Adolescents, PopPK | 47 | 525 (170%) [18, 7801] | 4504 (168%) [100, 80500] | 6.3 (480%) [0, 86] | 98 (43%) [18, 275] | 1375 (62%) [300, 3230] | 13.2 (55%) [0.101, 78.0] |
| Adults, PopPK | 1804# | 597 (114%) [127, 3322] | 4800 (122%) [123, 297000] | 4.86 (374%) [1.60, 288] | 110 (49%) [49, 238] | 1430 (57%) [148, 14200] | 7.06 (110%) [5.6, 74] |

Data are presented as geometric mean (%CV) [min-max]

Data from three subjects who had extremely low GLE/PIB concentrations (i.e., outliers) were excluded in the analyses. See "Key Review Issues"

$: Data from all subjects in the intensive PK group including the three outliers

PopPK results: Intensive PK data from three outlines were excluded, but sparse PK data from the same subjects were included as sparse samples were collected via venipuncture. Results are based on the review team's independent analysis.

#: Data were submitted in the original NDA

## 3. Efficacy and safety results

The safety profiles observed in this study were consistent with those observed in clinical studies of MAVYRET in adults. All subjects achieved $SVR_{12}$.

## *Key Review Issues*

### *1. Significantly lower exposures of glecaprevir and pibrentasvir in three subjects:*

*Significantly lower exposures of GLE and PIB were observed in three subjects in the intensive PK group (n=17) (Subject IDs:* <sup>(b) (6)</sup> *). Mean GLE and PIB exposures were approximately 90% and 70% lower, respectively, in these three subjects as compared to adults or other adolescent subjects. Despite significantly lower exposures of GLE and PIB, all three subjects achieved $SVR_{12}$. There was no remarkable difference with respect to intrinsic and extrinsic factors in these three subjects.*

*All three subjects were from the same study site (Children's hospital of Pittsburgh) and these three subjects were the only subjects enrolled in the intensive PK cohort. This suggested potential PK sampling errors at the clinical site. Site inspections for both clinical (Children's*

*hospital of Pittsburgh) and bioanalytical (Abbvie's bioanalytical site) were conducted by OSIS and no significant issues were identified upon the inspection. The sponsor also conducted their own investigation to identify the root cause of significantly lower concentrations of GLE and PIB in these three subjects. The only finding was the use of an intravenous line to collect blood samples which may have caused inadequate removal of solution in the IV line before collecting blood. The sponsor stated that the site has been excluded from enrolling subjects in Cohorts 2 through 4 (3 to less than 12 years old). Overall, the sponsor's rationale and steps taken to address this issue are reasonable. The review team agrees with excluding data from these three subjects as samples were potentially diluted with solution in the IV line.*

*2. Lower limit of body weight for adolescent subjects who can take the adult dose of MAVYRET:*

(b) (4)

*The review team confirmed that weight is not a significant covariate within the data observed (Fig 3, 3-2 population pharmacokinetic analysis). However, limited PK and safety data are available in adolescent subjects weighing less than 45 kg (n=3).*

(b) (4)

Conclusion

Results from the study demonstrated that the mean steady-state exposures of GLE and PIB in HCV infected adolescent subjects were comparable to those observed in HCV-infected adult subjects when GLE/PIB 300 mg/120 mg were administered once daily under fed conditions.

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## 3-2 Population Pharmacokinetics

The Applicant performed a population PK analysis to evaluate if the proposed dosing regimens of GLE and PIB in pediatric subjects 12 to 18 years of age, with Genotypes 1 - 6 Chronic Hepatitis C Virus (HCV) infection, would result in comparable exposure to those observed in adults. The data used for characterizing the population PK of GLE and PIB combination (GLE/PIB) was obtained from Study M16-123 Part 1 (Table 2). A total of 47 adolescents were included in the PPK analysis.

- **Methods**

The Applicant developed Population PK models using nonlinear mixed effects modeling based on NONMEM 7.4.2. Population PK models were developed separately for GLE and PIB. Model selection was based on diagnostic plots and visual predictive check (VPC). The Applicant used a stepwise inclusion of covariates which involved testing the effect of each covariate on all appropriate model parameters, each in separate model runs. A significance level of $\alpha = 0.01$ was used for all statistical tests except for tests in the backward elimination step of the covariate selection procedure, which were assessed with n $\alpha = 0.001$ significance level.

- **Results**

The applicant concluded that a one-compartment model with a lag time followed by first-order absorption and elimination could adequately describe the GLE concentration-time data, where a two compartment was not supported by the data. The model was parameterized in terms of CL/F, V2/F, absorption rate constant (KA) and absorption lag time (ALAG1). Relative bioavailability (F1) was fixed to 1. In order to avoid flip-flop behavior, the applicant parametrized the absorption rate constant so as to constrain it to be greater than the elimination rate constant (K = CL/V2). A structurally similar model was used for PIB. The VPCs for the final population PK models for GLE and PIB are shown in Figure 1.

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**Figure. 1: GLE and PIB Concentration Visual Predictive Check Versus Time Since Last Dose**
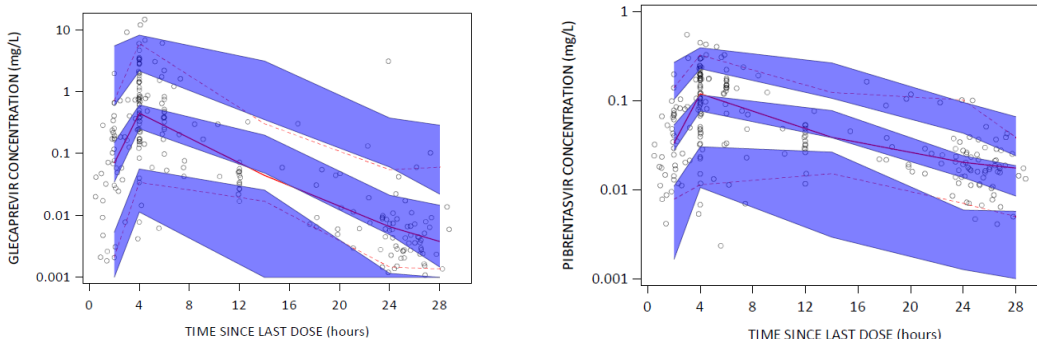


The shaded blue areas represent the 90% prediction interval of the 5th, 50th and 95th percentiles of simulated GLE/PIB concentrations, the solid red line represents median of observed GLE/PIB concentrations and dashed red lines represent the 5th and 95th percentile of the observed GLE concentrations. The open circles represent observed GLE/PIB concentrations. (Source: Applicant's population PK report, Page 34, Figure 2).

- Associations between exposures of GLE / PIB and subjects' intrinsic factors

The applicant evaluated the relationships between model-predicted steady-state GLE and PIB exposures ($AUC_{24}$) from population pharmacokinetic analyses and subjects' age and weight. No clinically meaningful relationships between weight and model-predicted steady-state $AUC_{24}$ or between age and $AUC_{24}$ were observed.

- Comparison of GLE and PIB exposures between adolescents and adults

The model-predicted steady-state exposures of GLE and PIB in HCV-infected adolescent subjects (12 to < 18 years of age) were similar to the exposures in HCV-infected adult subjects following administration of GLE/PIB 300 mg/120 mg ($\leq$ 9% difference in $AUC_{24}$) as shown in Table 2.

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**Table. 2: Model-Predicted GLE and PIB Steady-State AUC24 in HCV-Infected Adolescent and Adult Subjects**

| Population | GLE/PIB 300 mg/120 mg QD Adult Formulation Geometric Mean (%CV) [Range] | |
| --- | --- | --- |
| | GLE AUC$_{24}$ (ng•hr/mL) | PIB AUC$_{24}$ (ng•hr/mL) |
| HCV-infected adolescents (12 to < 18 years of age, N = 47) | 4380 (157) [268 – 70300] | 1440 (47) [428 – 3380] |
| HCV-infected non-cirrhotic adults (N = 1804) | 4800 (122) [123 – 297000] | 1430 (57) [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 $\sigma$ 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 population PK report, Page 50, Table 7).

- Comparison of GLE and PIB exposures between Japanese and non-Japanese adolescent subjects

The population PK model-predicted mean GLE and PIB steady-state exposures (AUC$_{24}$) in Japanese adolescents and non-Japanese adolescents were 87 % and 36 % higher, respectively, than the exposures in non-Japanese adolescents. Of note, the predicted exposures in Japanese adolescent subjects were within the exposure ranges from adults in global studies and Japanese HCV-infected adults.

**Applicant's Conclusion**
The population PK results support the use of the approved adult regimen of GLE/PIB 300 mg/120 mg QD in HCV-infected adolescent subjects (12 to < 18 years of age). Using the proposed dosing regimen, the model-predicted GLE and PIB steady-state exposures were similar between HCV-infected adolescent subjects enrolled in Study M16-123 and the HCV adult population. All tested covariates, including body weight and age, did not significantly affect the pharmacokinetics of GLE or PIB in HCV-infected adolescent subjects.

*Review team's assessment of the applicant's analysis*

*The results of the applicant's population PK analysis is reproducible. To test the adequacy of the population PK model developed by the applicant, the review team performed independent analysis to further explore whether the Pop PK model can be further refined to describe the PK of GLE and PIB. Model refinement was explored because the percentiles of the observed GLE and PIB concentrations did not completely fit within the corresponding 90% model prediction intervals.*

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## 3.3 Review Team's Independent Analysis

- **Objective**

The objective of the review team's analysis was to verify the Applicant's population PK model and explore if improvements in the applicant's final population PK model can be made by incorporating a peripheral compartment for both GLE and PIB.

- **Methodology**

The data sets used in the analyses ([EDR link](#)) were analyzed using NONMEM 7 and R.

- **Results**

The review team repeated the population PK analysis with the applicant's models and successfully reproduced the applicant's population PK analysis. By incorporating a peripheral compartment in the applicant's original model, there was improvement in model fitting as evidenced by 18 and 22 units drop in objective function value (OFV) for GLE and PIB, respectively. The parameter estimates for the revised 2-compartment models are shown in Table 3.

**Table. 3: Parameter Estimates for the Final GLE and PIB Pharmacokinetic Models.**

| Parameter | Median GLE estimate (95% Confidence interval) | Median PIB estimate (95% Confidence interval) |
|---|---|---|
| CL/F (L/day) | 1769 (1338, 2391) | 2240 (1702, 2870) |
| Vc/F (L) | 213 (137, 341) | 372 (269, 537) |
| Vp/F (L) | 28.6 (14.2, 68.2) | 3710 (1083, 6397) |
| Q/F (L/day) | 90.9 (50.6, 191) | 1040 (789, 1351) |
| Absorption factor | 1.63 (1.09, 2.91) | 1.07 (0.53, 2.61) |
| ALAG (days) | 0.072 (0.06, 0.08) | 0.070 (0.06, 0.08) |
| Variance on CL/F | 0.96 (0.47, 1.73) | 0.21 (0.14, 0.33) |
| Variance on Vc/F | 1.1 (0.65, 1.94) | 0.22 (0.13, 0.36) |
| Proportional error (%) | 50.5 (28.1, 69.0) | 24.9 (11.0, 41.1) |

Source: Data generated based on review team's independent analysis.

The VPCs for GLE and PIB are shown in Figure 2. Both VPCs show that the model adequately described the concentration-time profiles of both drugs.

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**Figure. 2: GLE and PIB Visual Predictive Check**
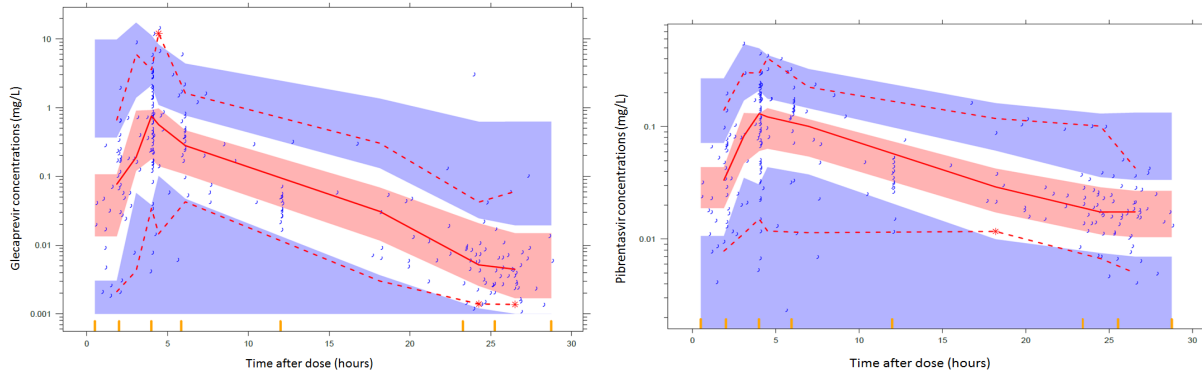


The shaded areas represent the 90% prediction interval of the 5th, 50th and 95th percentiles of simulated GLE/PIB concentrations, the solid red line represents median of observed GLE/PIB concentrations and dashed red lines represent the 5th and 95th percentile of the observed GLE/PIB concentrations.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

- Comparison in exposure between adolescents and pediatrics

Model-predicted (using the revised model as described above) steady-state exposures of GLE and PIB in HCV-infected adolescent subjects (12 to < 18 years of age) were similar to the exposures in HCV-infected adult subjects as shown in Table 4.

**Table. 4: Model-Predicted GLE and PIB Steady-State AUC24 in HCV-Infected Adolescent and Adult Subjects**

| Population | N | GLE | | | PIB | | |
|---|---|---|---|---|---|---|---|
| | | $C_{max}$ (ng/mL) | $AUC_{24}$ (ng·hr/mL) | $C_{min}$ (ng/mL) | $C_{max}$ (ng/mL) | $AUC_{24}$ (ng·hr/mL) | $C_{min}$ (ng/mL) |
| Adolescents, PopPK | 47 | 525 (170%) [18, 7801] | 4504 (168%) [100, 80500] | 6.3 (480%) [0, 86] | 98 (43%) [18, 275] | 1375 (62%) [300, 3230] | 13.2 (55%) [0.101, 78.0] |
| Adults, PopPK | 1804 | 597 (114%) [127, 3322] | 4800 (122%) [123, 297000] | 4.86 (374%) [1.60, 288] | 110 (49%) [49, 238] | 1430 (57%) [148, 14200] | 7.06 (110%) [5.6, 74] |

There were no trends observed clearance of either GLE or PIB was plotted against various covariates factors as shown in Figure 3. Notably, the difference in GLE and PIB exposure was not significant between Japanese and non-Japanese patients, based on reviewer's PPK model.

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**Figure. 3: The plot of GLE and PIB clearance versus covariates.**
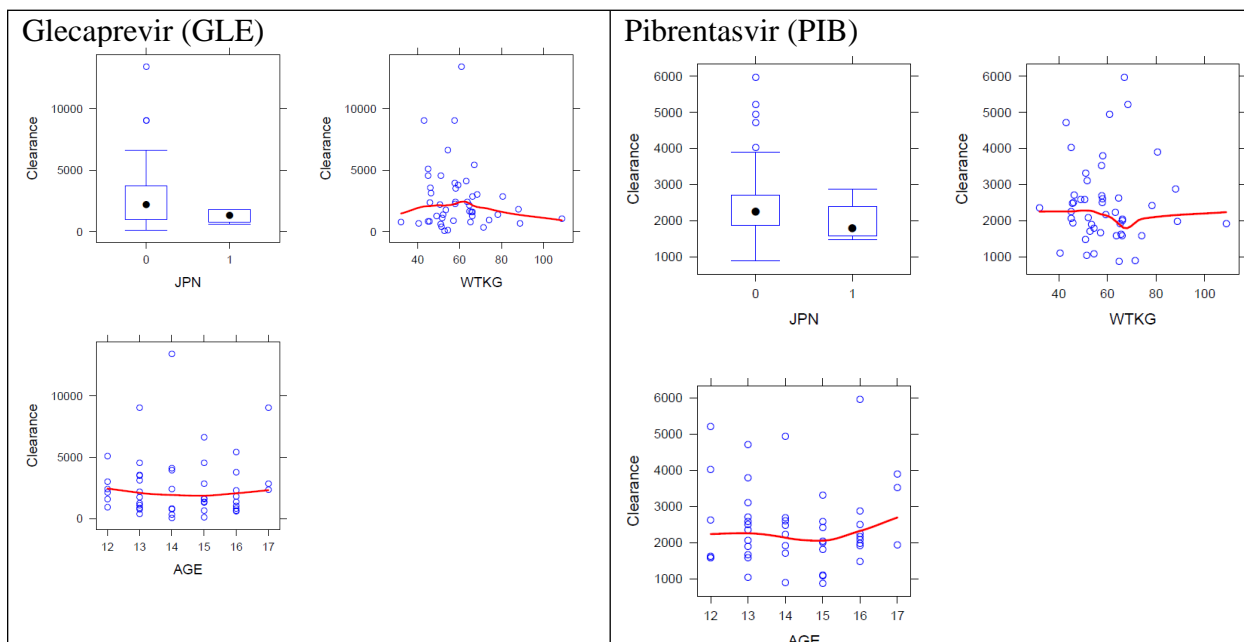


JPN 0: non-Japanese. JPN 1: Japanese. WTKG: total body weight in kilograms. AGE is in years. Each individual's clearance is indicated by a blue circle. The red lines are LOWESS (Locally Weighted Scatterplot Smoothing), a smooth line through a scatter plot to see relationship between clearance and weight or age.

*Review Team's Conclusion:*

1. *Compared with the applicant's one compartment model, the revised two compartment model (which incorporates the peripheral compartment) better described the observed PK data of GLE and PIB (as evidenced by reduction in OFV).*
2. *After administration of 300/120 mg once daily to adolescents, predicted GLE and PIB exposures using the revised model are similar to the GLE and PIB exposures in adults following GLE/PIB 300 mg/120 mg QD regimen.*
3. *Covariate analysis using the revised POP PK model did not suggest any trends between the systemic exposure of GLE or PIB and evaluated covariates.*

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/s/

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