CLINICAL PHARMACOLOGY REVIEW

NDA (supplement)	208261 (S-7)
Submission date	02/19/2021
Submission type	Pediatric efficacy supplement
Drug	ZEPATIER® (Elbasvir/Grazoprevir) Tablets, 50 mg/100 mg
Applicant	Merck Sharp & Dohme Corp.
Indication	Approved indication: Treatment of chronic HCV genotype 1 or 4 infection in adults; Proposed indication: Extension of the indication to pediatric patients 12 years of age and older who weigh at least 30 kg
OCP Division	DIDP
OND Division	DAV
Review Team	Yang Zhao, Ph.D., Eliford Kitabi, Ph.D., Jenny Zheng, Ph.D.

Executive Summary:

ZEPATIER® (Elbasvir/Grazoprevir) Tablets, 50 mg/100 mg was approved by the FDA on 01/28/2016, for the treatment of chronic HCV genotype 1 or 4 infection in adults. The Applicant submitted this efficacy supplement to extend to pediatric patients 12 years of age and older weighing at least 30 kg.

The Applicant provided the following reports to support the proposed dosing recommendations:

- Final report for the study P079 (link), a Phase IIb Clinical Study to Assess the Pharmacokinetics, Safety, and Efficacy of the Combination Regimen of Elbasvir (EBR)/Grazoprevir (GZR) in Participants Aged 3 to less than 18 Years with Chronic Hepatitis C Infection. Study P079 contains PK data of EBR and GZR in pediatric patients 12 years of age and older who weigh at least 30 kg.
- A population PK modeling and simulation (M&S) report (link) (PMAR-2007).

Phase 2b, open-label clinical trial P079 contains PK data from 22 pediatric subjects (n=21 for genotype 1; n=1 for genotype 4) 12 years of age and older (adolescents), without cirrhosis, who were treated with one ZEPATIER tablet once daily for 12 weeks. The studied dosing regimen in adolescents is the same as the approved ZEPATIER regimen for adults.

Upon reviewing these reports, the Clinical Pharmacology Review Team has determined that the proposed ZEPATIER dosage of one tablet taken orally once daily for pediatric patients 12 years of age and older or weighing at least 30 kg resulted in comparable steady-state AUC values of EBR and GZR as those in adults.

The Office of Clinical Pharmacology review team finds the application acceptable and recommends approval of ZEPATIER for pediatric patients 12 years of age and older or weighing at least 30 kg.

1. Summary of clinical pharmacology assessment:

1.1 Elbasvir (EBR)/Grazoprevir (GZR) dosing regimen for pediatric patients ≥12 years:

The study P079 PK data and Applicant's population PK analysis and simulations suggest that the proposed dosing regimen of EBR 50 mg/GZR 100 mg once daily (same as the adult dosing regimen) in pediatric patients ≥12 years with body weight ≥ 30 kg is appropriate. The proposed regimen provides comparable EBR and GZR exposures in adolescents to the exposures in adults.

1.2 Labeling Changes (Clinical Pharmacology relevant portion):

In Sections 1 and 2, the labeling changes include the indication and recommended dosage for pediatric patients 12 years of age and older or who weighing at least 30 kg.

The review team determined the labeling language of "12 years of age and older or who weighing at least 30 kg", based on several considerations: (a) U.S. adolescents are likely to weigh over 30 kg, based on CDC Clinical Growth Charts (link); (b) the safety data for the study P079 Age cohort 2 (7 years to less than 12 years) receiving EBR/GZR oral granules 30 mg/60 mg QD for 12 weeks demonstrated no significant safety concerns; (c) the efficacy results demonstrated that 100% of subjects in the cohort 2 achieved Sustained Virologic Response 12 weeks (SVR12 defined as HCV RNA <lower limit of quantification 12 weeks after the end of the therapy, is the primary efficacy endpoint in the current study).

In Section 12.3, the labeling also includes the following statement and the steady-state PK data for pediatric subjects ages 12 to <18 years from Study P079 (Table 8 in the package insert):

> The pharmacokinetics of elbasvir and grazoprevir were evaluated in 22 pediatric subjects 12 years of age and older, with HCV genotype 1 or 4, who received a daily dose of ZEPATIER (50 mg elbasvir/100 mg grazoprevir). The pharmacokinetic properties of elbasvir and grazoprevir in pediatric subjects 12 years of age and older are provided in Table 8. Exposures in pediatric subjects were comparable to those observed in adults.
>
> **Table 8: Geometric Mean (90% Confidence Interval) for Elbasvir and Grazoprevir Steady State Pharmacokinetic Parameter Values in Non-Cirrhotic HCV-Infected Pediatric Subjects Ages 12 to <18 Years**

PK Parameters*	Geometric Mean (90% Confidence Interval)		
	AUC_{0-24} (ng•hr/mL)	C_{max} (ng/mL)	C_{24} (ng/mL)
EBR	2120 (1800, 2510)	167 (140, 199)	50.3 (41.7, 60.6)
GZR	1110 (871, 1410)	188 (140, 253)	11.7 (9.43, 14.5)

*AUC_{0-24} and C_{max} N=22; C_{trough} N=21

2. Assessment of individual study:

The following is the summary of individual study reports that support the Clinical Pharmacology review. The Applicant's conclusions are found to be acceptable unless noted otherwise in a Reviewer's Assessment section.

2.1 Summary of Bioanalytical Method Validation and Performance

Table 1: Summary of Bioanalytical Method Validation and Performance compiled by the Reviewer for the study P079

Analyte	EBR	GZR
Method	UPLC-MS/MS	UPLC-MS/MS
Matrix	Human plasma (EDTA K2)	Human plasma (EDTA K2)
Validation report	Provided and acceptable	Provided and acceptable
Performance report	Provided	Provided
Samples analyzed within established stability period	☒Yes ☐No	☒Yes ☐No
Quality control (QC) samples range acceptable	☒Yes ☐No	☒Yes ☐No
Chromatograms provided	☒Yes ☐No	☒Yes ☐No
Accuracy and precision of the calibration curve acceptable	☒Yes ☐No	☒Yes ☐No
Accuracy and precision of the quality control samples acceptable	☒Yes ☐No	☒Yes ☐No
Incurred sample reanalysis (ISR)	Acceptable	Acceptable
Overall performance reasonable	**Acceptable**	**Acceptable**
Inspection for bioanalytical site	N/A	N/A
Linearity, ng/mL	0.25–250	1–1000
lower limit of quantification (LLOQ)	0.25 (0.283 nM)	1 (1.30 nM)

2.2 Study P079: Multicenter study of pharmacokinetics, safety, and efficacy of the combination regimen of elbasvir/grazoprevir (EBR/GZR) in pediatric participants with chronic HCV

Study Design:

P079 is a Phase IIb clinical study to assess the pharmacokinetics, safety, and efficacy of the combination regimen of Elbasvir (EBR)/Grazoprevir (GZR) in non-Asian subjects aged 3 to less than 18 years with chronic hepatitis C GT1 or GT4 infection. All subjects received EBR/GZR, either as the fixed-dose combination (FDC) tablet or granule formulation for 12 weeks, with an additional 24 weeks of posttreatment follow-up. The study enrolled subjects into 3 age cohorts:

- Age cohort 1: 22 subjects aged 12 years to less than 18 years (11 female and 11 male, body weight range: 28.1–96.5 kg) receiving 1 approved EBR/GZR FDC tablet QD for 12 weeks;
- Age cohort 2: 17 subjects aged 7 years to less than 12 years receiving EBR/GZR oral granules 30 mg/60 mg QD for 12 weeks;
- Age cohort 3: 18 subjects aged 3 years to less than 7 years receiving EBR/GZR oral granules 15 mg/30 mg, or 15 mg/50 mg, or 25 mg/50 mg QD for 12 weeks.

Each age cohort consisted of a Mini cohort (initial enrolled subjects) before enrolling additional subjects into the Expanded cohort (additional enrolled subjects). The Age Cohort 1 consisted of 7 subjects in Mini cohort and 15 subjects in Expanded cohort.

In this review, only the results from the Cohort 1 are discussed to support the indication in adolescents. The Applicant reported that two subjects in the cohort 1 had protocol deviations, one subject in Age Cohort 1 entered the study without documented child assent; and the other subject in Age Cohort 1 entered the study with a history of gastroduodenal surgery, a condition specified as exclusionary in the protocol. No subject in the cohort 1 was excluded from PK data analyses.

Pharmacokinetic Sampling:
At Day 1, intensive PK sampling (predose, 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours postdose) was available for 7 subjects in Mini cohort 1 and 1 subject in Expanded cohort 1, while sparse sampling was collected for other subjects. At Week 4, intensive PK sampling (predose, 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours postdose) was available for all subjects. At Week 8, sparse sampling was available for all subjects.

Baseline Demographics:
Table 2: Baseline demographic data for the study P079 cohort 1 22 subjects

HCV genotype	Race	Gender	Age, years	Body weight, kg
16 (1a) 5 (1b) 1 (4b)	21 white +1 multiple	11 female +11 male	14.1±1.9 (mean±SD), 13.5 (median)	53±16 (mean±SD), 47.5 (median)

Clinical Pharmacology Results:
The primary PK endpoints for EBR and GZR are steady-state plasma AUC_{0-24}, C_{max}, C_{trough}, and CL/F, measured at week 4. Following summarizes the PK results:

(1) Mean EBR AUC_{0-24h} in the cohort 1 adolescent patients were comparable to the mean adult steady-state AUC_{0-24h} value (2120 ng•hr/mL in adolescents vs. 1920 ng•hr/mL in adults, refer to NDA-208261 labeling for adult AUC values), while mean GZR AUC_{0-24h} were slightly lower than the mean adult value (1110 ng•hr/mL vs. 1420 ng•hr/mL) (Table 3).

Table 3: Geometric Mean (90% confidence interval) for elbasvir (EBR) and grazoprevir (GZR) steady state pharmacokinetic parameter values in non-cirrhotic HCV-infected pediatric subjects ages 12 to <18 years (seen in page 28 in submitted clinical pharmacology summary in S-7)

PK Parameters*	Geometric Mean (90% Confidence Interval)		
	AUC_{0-24h} (ng•hr/mL)	C_{max} (ng/mL)	C_{24h} (ng/mL)
EBR	2120 (1800, 2510)	167 (140, 199)	50.3 (41.7, 60.6)
GZR	1110 (871, 1410)	188 (140, 253)	11.7 (9.43, 14.5)

*AUC_{0-24} and C_{max} N=22; C_{24h} N=21

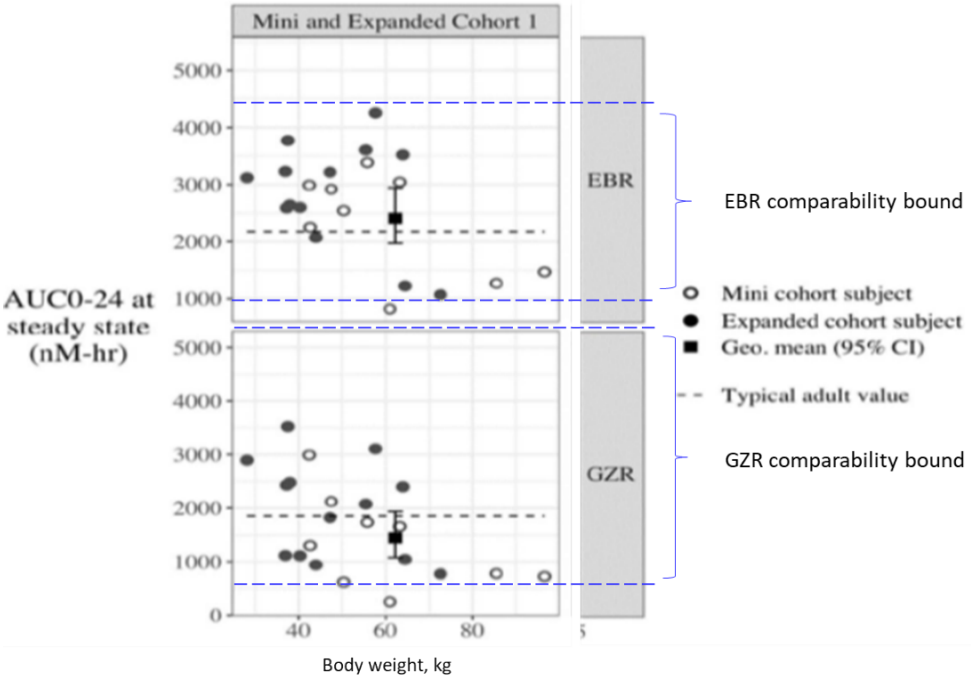
(2) Mean steady-state AUC_{0-24h} values for EBR and GZR after QD dosing of 1 EBR/GZR FDC tablet are within comparability bounds established for adults. The original NDA-208261

Clinical Pharmacology Review (link) stated that comparability bounds refer to the steady-state AUC range that would be expected to have comparable safety and efficacy and the established comparability bounds are 960–3840 ng•hr/mL (ie., 0.5-fold to 2-fold of mean steady-state $AUC_{0\text{-}24h}$ of 1920 ng•hr/mL) for EBR and 568–4260 ng•hr/mL (ie., 0.4-fold to 3-fold of mean steady-state $AUC_{0\text{-}24h}$ of 1420 ng•hr/mL) for GZR (refer to NDA-208261 labeling for adult AUC values, link).

(3) Individual steady-state $AUC_{0\text{-}24h}$ at week 4 for both EBR and GZR after QD dosing of 1 EBR/GZR FDC tablet in 21 individuals out of 22 pediatric subjects age cohort 1, fell within comparability bounds established for adults (Figure 1).

Steady-state $AUC_{0\text{-}24h}$ at week 4 for both EBR and GZR components from one subject who weighed 61 kg fell slightly below the established comparability lower bound (Figure 1). Efficacy results demonstrated that 100% of subjects in the cohort 1 achieved Sustained Virologic Response 12 weeks (SVR12) and Sustained Virologic Response 24 weeks (SVR24), and no subject experienced virologic failure. Therefore, this lower plasma $AUC_{0\text{-}24h}$ at steady state did not raise efficaciousness concerns of QD oral dosing of 1 EBR/GZR 50 mg/100 mg, FDC tablet in adolescent HCV patients.

Figure 1: Plasma $AUC_{0\text{-}24h}$ (based on NCA analysis) of EBR and GZR at steady state (week 4) in 22 pediatric HCV patients age cohort 1 compared to mean adult steady state $AUC_{0\text{-}24h}$ values following QD oral administration of 1 EBR/GZR FDC tablet



(4) Steady-state plasma exposures for both EBR and GZR were achieved by week 4. The week 4 C_{24h} concentration is similar to the week 8 predose concentration (Table 4), demonstrating that

steady state was achieved for both components of EBR and GZR by week 4 in adolescent patients.

Table 4: Plasma trough concentrations (C_{24h} or Predose) of EBR and GZR at week 4 and week 8 following oral administration of EBR/GZR FDC tablet QD to pediatric HCV patients age cohort 1

Cohort	Week 4 C_{24} (nM)			Week 8 Predose (nM)			Week 8 / Week 4	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
EBR (MK-8742)								
Mini + Exp. Coh. 1	21	56.99	(45.48, 71.40)	21	55.39	(44.52, 68.91)	0.97	(0.75, 1.25)
GZR (MK-5172)								
Mini + Exp. Coh. 1	21	15.23	(11.75, 19.72)	21	13.12	(9.10, 18.92)	0.86	(0.60, 1.24)

(5) Accumulation ratio of EBR and GZR are 1.8 at the steady state compared to the Day 1. In addition, tmax of 2–3 hours and initiation of the terminal elimination phase on Day 1 of drug treatment are similar to Week 4 (Table 5).

Table 5: Plasma pharmacokinetics of EBR and GZR at Week 4 versus Day 1 following oral QD administration of 1 EBR 50 mg / GZR 100 mg FDC to pediatric HCV patients cohort 1

Pharmacokinetic Parameter	Day 1			Week 4			Week 4 / Day 1	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
EBR (MK-8742)								
$AUC_{0\text{-}4}$ (µM•hr)	20	0.28	(0.17, 0.46)	22	0.53	(0.42, 0.66)	1.92	(1.25, 2.95)
$AUC_{0\text{-}24}$ (µM•hr)	8	1.34	(0.76, 2.35)	22	2.41	(1.97, 2.94)	1.80	(1.25, 2.58)
C_{max} (µM)	8	0.11	(0.07, 0.17)	22	0.19	(0.15, 0.23)	1.69	(1.20, 2.37)
C_{24} (nM)	8	35.26	(16.81, 73.97)	21	56.99	(45.48, 71.40)	1.62	(1.04, 2.51)
T_{max} (hr)	8	3.02	(2.04, 4.47)	22	2.51	(2.04, 3.09)	0.83	(0.60, 1.16)
CL/F (L/hr)*	**	**	**	22	23.53	(19.25, 28.75)	**	**
GZR (MK-5172)								
$AUC_{0\text{-}4}$ (µM•hr)	20	0.27	(0.15, 0.48)	22	0.49	(0.33, 0.74)	1.85	(1.04, 3.30)
$AUC_{0\text{-}24}$ (µM•hr)	8	0.81	(0.31, 2.08)	22	1.45	(1.08, 1.94)	1.79	(1.02, 3.15)
C_{max} (µM)	8	0.11	(0.04, 0.30)	22	0.25	(0.17, 0.35)	2.31	(1.20, 4.45)
C_{24} (nM)	8	20.96	(7.50, 58.59)	21	15.23	(11.75, 19.72)	0.73	(0.41, 1.27)
T_{max} (hr)	8	2.41	(1.73, 3.34)	22	2.48	(1.97, 3.13)	1.03	(0.73, 1.46)

* Apparent clearance not reported for GZR due to nonlinear PK
** Not Available

Applicant's conclusions:

- QD dosing of 1 EBR 50 mg/GZR 100 mg FDC tablet in adolescent HCV patients resulted in steady-state AUC values within comparability bounds established for adults.
- All subjects achieved SVR12 (primary efficacy endpoint) and SVR24 after the end of all study intervention.
- Steady-state plasma exposures were achieved by week 4 for both components of EBR and GZR.

Reviewer's assessment: Agree with the Applicant's assessment.

2.3 Pharmacometrics Review:
For population pharmacokinetic analysis, dataset included 352 EBR plasma concentration records and 345 GZR plasma concentration records from 22 adolescents in the cohort 1, following QD oral administration of the FDC tablet, with two goals: (1) assessing whether QD administration of the FDC tablet results in comparable exposures between adult and adolescent populations; (2) determining the minimum body weight in adolescents for which exposures of both EBR and GZR remain within clinical comparability bounds.

The PopPK models to characterize adolescent PK of EBR and GZR were based on model previously used to characterize adult PK. The structural model for both components is two-compartment models with first-order absorption and first-order elimination and fixed standard weight-based allometric scaling for clearance, volume, and rate constants. Interindividual variability (IIV) of the PK parameters (e.g., clearance (CL)) was incorporated using a lognormal random effects model in exponential form. The random effects were assumed to follow a normal distribution with zero mean and variance ω2. This Reviewer considers that the PopPK models for adolescent population are reasonable.

PopPK Results:
The Applicant reported PopPK parameter estimates for the age cohort 1 (12 to <18 years) for EBR and GZR (shown in Appendix 1).

(1) PopPK simulation demonstrate that drug steady-state exposures decrease with body weight, and EBR and GZR mean steady state $AUC_{0\text{-}24h}$ exposures for adolescent patients weighing between 30 kg−105 kg are within the established comparability bounds of AUC (Figures 2 and 3, see Appendix). This Reviewer's simulation generated similar results as the Applicant's reported values.

It is noted that not entire 90% confidence interval (CI) of steady state $AUC_{0\text{-}24h}$ fell within the established comparability bounds, in particular in subjects with body weight over 90 kg. This Reviewer considers that some portion of 90% CI of steady state $AUC_{0\text{-}24h}$ falling below the established comparability lower bound will not have clinical relevance, due to several reasons: (a) the proposed dosing regimen is efficacious for overweight adult patients (up to 159 kg); and (b) 100% of adolescent subjects in the cohort 1 achieved SVR12 (primary efficacy endpoint) and SVR24.

Therefore, comparable plasma exposures of EBR and GZR between adolescents and adults support the safety and efficacy of Elbasvir/Grazoprevir FDC Tablets for adolescent patients with CHC.

Figure 2: EBR steady-state AUC (blue vertical bar is 90% CI, point is the mean) following oral administration of 1 EBR/GZR FDC QD to adolescents (12 to <18 years), by weight band, compared to the established comparability bounds (horizontal dashed lines) (page 24 in Clinical Pharmacology summary)

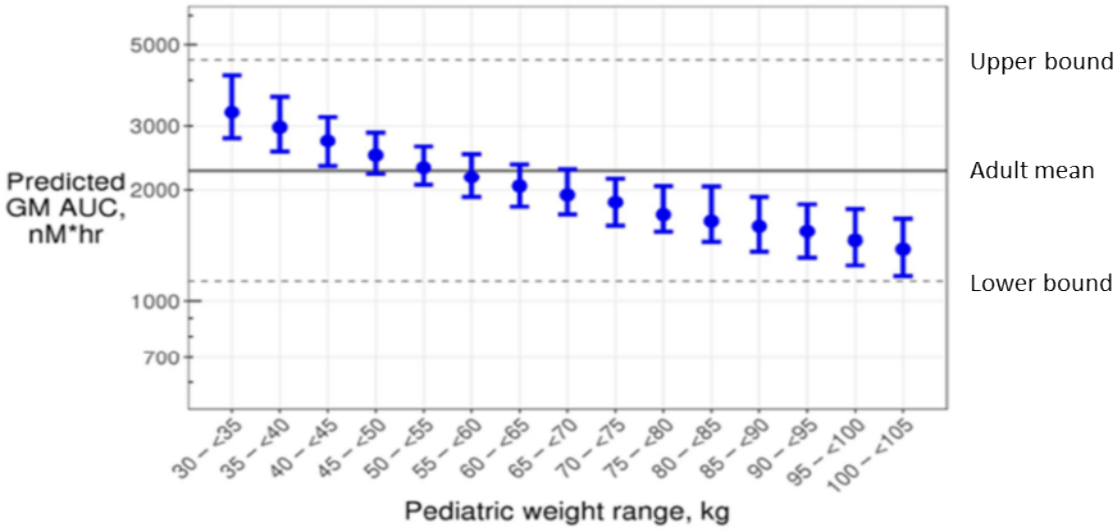
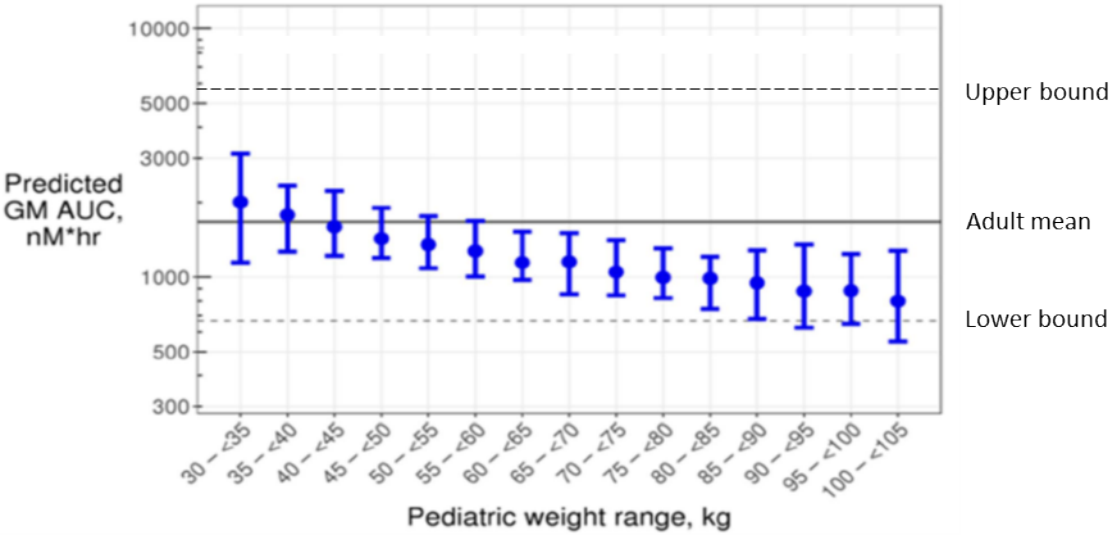


Figure 3: GZR steady-state AUC (blue vertical bar is 90% CI, point is the mean) following oral administration of EBR/GZR FDC QD to adolescents (12 to <18 years), by weight band, compared to the established comparability bounds (horizontal dashed lines) (page 26 in Clinical Pharmacology summary)



(2) PopPK demonstrated that QD dosing of FDC generated comparable steady state PK profiles between adolescents and adults (Figures 4 and 5). This Reviewer's simulation generated similar results as the Applicant's reported values.

It is noted that PopPK simulation demonstrated that the predicted drug exposures for both EBR and GZR are slightly lower in the virtual population than their respective observed exposure in P079 study (Figures 4 and 5). The Applicant reported that this difference could be partly explained by the fact that the median body weight in the adolescent subjects in P079 study is 24% lower than that in the virtual adolescent population (49 kg vs. 61 kg). The Applicant constructed the virtual

adolescent population dataset (containing 2644 non-Asian adolescents 12 to <18 years of age with the disease conditions of non-cirrhotic and non-chronic kidney disease, median body weight=61 kg, body weight range: 27.7−163.6 kg) based on the National Health and Nutrition Examination Survey (NHANES) three recent database combined (2011–2012, 2013–2014, 2015–2016). This Reviewer considered the constructed virtual adolescent population dataset acceptable for the purpose of simulation and therefore the difference in the median body weight in the virtual adolescent population from that in the adolescent subjects in P079 study is reasonable.

Figure 4: Observed (left) and predicted (right) EBR steady-state PK profiles in the age cohort 1 (with median BW=49 kg) and in virtual pediatric population (with median BW=61 kg) overlaid with PK profiles in adult population (page 53 in PopPK report)

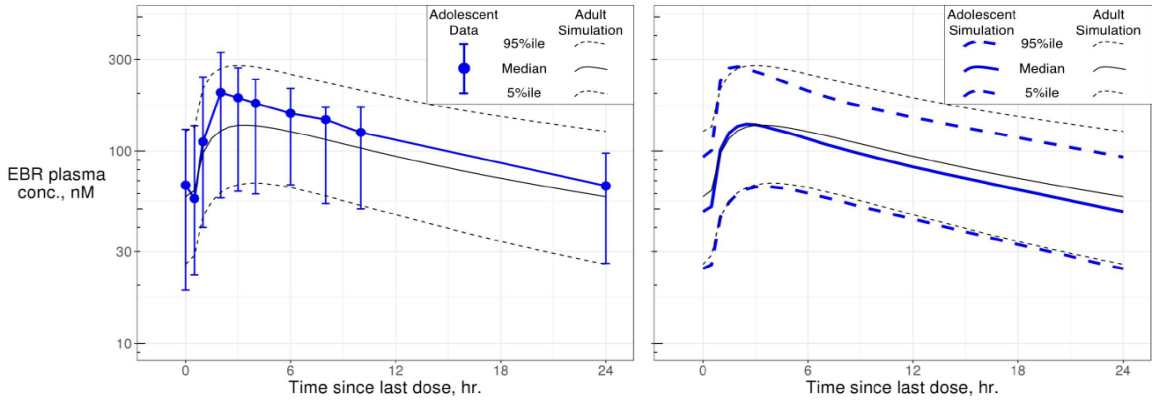
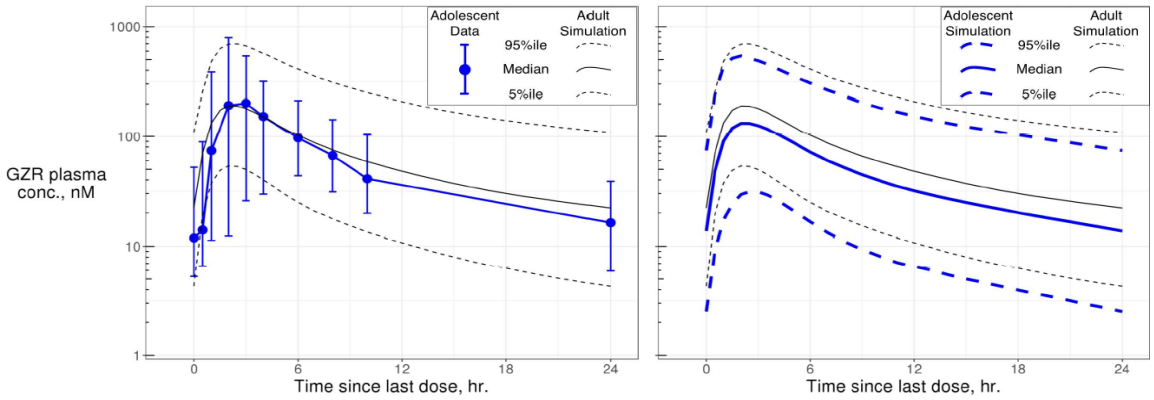


Figure 5: Observed (left) and predicted (right) GZR steady-state PK profiles in the age cohort 1 (with median BW=49 kg) and in virtual pediatric population (with median BW=61 kg) overlaid with PK profiles in adult population (page 54 in PopPK report)



Applicant's conclusions:

- PopPK simulation demonstrate that drug steady-state exposures decrease with body weight, and EBR and GZR mean steady state $AUC_{0\text{-}24h}$ exposures for adolescent patients weighing between 30 kg−105 kg are within the established comparability bounds of AUC.
- PopPK demonstrated QD doing of EBR/GZR (50 mg/100 mg) FDC generated comparable drug exposures between adolescents and adults.

Reviewer's assessment: Agree with the Applicant's assessment.

Appendix 1 Additional PopPK results

Table: EBR PopPK parameter estimates for the study age cohort 1 (12 to <18 years) (page 38 in PopPK report). Parameter estimates by this Reviewer's run agree with the Applicant's reported values.

Parameter	Estimate	RSE	90% CI
KA (hr^{-1})	0.826	17.4%	(0.589, 1.06)
CL/F (L/hr)	22.9	7.3%	(20.1, 25.6)
V2/F (L)	284	12.3%	(227, 342)
Q/F (L/hr)	40.9	12.9%	(32.2, 49.6)
V3/F (L)	166	1.3%	(162, 170)
Absorption lag (hr)	0.477	2.9%	(0.454, 0.500)
WT on CL[a]	0.75 (fixed)	N/A	N/A
WT on V2[a]	1 (fixed)	N/A	N/A
WT on Q[a]	0.75 (fixed)	N/A	N/A
WT on V3[a]	1 (fixed)	N/A	N/A
Proportional RV	0.222	12.1%	(0.178, 0.266)
Additive RV (nM)	11.4	24.0%	(6.88, 15.9)
IIV KA (ω^2)	0.496[b]	42.1%	(0.153, 0.840)
IIV CL/F (ω^2)[c]	0.109[b]	24.5%	(0.0654, 0.154)
IIV V2/F (ω^2)	0.238[b]	17.6%	(0.169, 0.307)
Covariance (IIV CL/F, IIV V2/F)[c]	0.135[d]	20.5%	(0.0892, 0.180)

Abbreviations: RSE, relative standard error; RV, residual variability; IIV, interindividual variability; CI, confidence interval; WT, body weight; N/A, not appliable.
[a] Parameter represents the θx term in equation $\theta_{TV} = \theta_{REF}*(WT/Median\ WT)^{\theta x}$
[b] Coefficient of variation (CV) for KA, CL/F and V2/F are 80%, 34% and 52%, respectively, calculated as $\sqrt{e^{(\omega^2)} - 1}$.
[c] Estimates of covariance (IIV CL/F, IIV V2/F) and IIV CL/F are highly correlated (0.916).
[d] Correlation of IIV CL/F and IIV V2/F is 0.833.

Table: GZR PopPK parameter estimates for the study age cohort 1 (12 to <18 years) (page 41 in PopPK report). Parameter estimates by this Reviewer's run agree with the Applicant's reported values.

Parameter	Estimate	RSE	90% CI
CL/F (L/hr)	96.8	12.1%	(77.6, 116)
V/F (L)	262	34.4%	(114, 410)
K23 (hr^{-1})	0.357	28.4%	(0.190, 0.524)
K32 (hr^{-1})	0.145	17.7%	(0.103, 0.187)
KA fasted (hr^{-1})	0.879	24.8%	(0.521, 1.24)
KA fed (hr^{-1})	0.970	19.2%	(0.664, 1.28)
WT on CL[a]	0.75 (fixed)	N/A	N/A
WT on V[a]	1 (fixed)	N/A	N/A
WT on K23[a]	-0.25 (fixed)	N/A	N/A
WT on K32[a]	-0.25 (fixed)	N/A	N/A
Proportional RV	0.570	7.1%	(0.503, 0.636)
Additive RV (ng/mL)	0 (fixed)	N/A	N/A
IIV K (ω^2)	0.129[b]	51.6%	(0.0194, 0.238)
IIV V/F (ω^2)	0.575[b]	50.8%	(0.0935, 1.06)
IIV KA (ω^2)	0.320[b]	40.3%	(0.108, 0.533)

Abbreviations: RSE, relative standard error; RV, residual variability; IIV, interindividual variability; CI, confidence interval; WT, body weight; N/A, not appliable.
[a] Parameter represents the θx term in equation $\theta_{TV} = \theta_{REF}*(WT/Median\ WT)^{\theta x}$
[b] Coefficient of variation (CV) for K, V/F and KA are 37%, 88% and 61%, respectively, calculated as $\sqrt{e^{(\omega^2)} - 1}$.

Table: PopPK simulated steady state AUC for EBR and GZR by weight bin in adolescent population (IR response dated 09/17/2021 to IR dated 09/10/2021)

Weight Bin (kg)	N[a]	EBR AUC (nM*hr)				GZR AUC (nM*hr)			
		Geometric Mean (90% CI)[b]	Median[c]	CV[d]	90% PI[e]	Geometric Mean (90% CI)[b]	Median[c]	CV[d]	90% PI
30 – 35	10	3270 (2780 – 4120)	3370	31%	2220 – 5000	2010 (1140 – 3130)	1880	92%	751 – 5860
35 – 40	36	2980 (2550 – 3600)	2970	33%	1800 – 4840	1780 (1270 – 2330)	1760	97%	516 – 6230
40 – 45	63	2730 (2340 – 3170)	2740	33%	1620 – 4460	1600 (1220 – 2220)	1560	96%	451 – 5950
45 – 50	109	2500 (2220 – 2880)	2500	32%	1500 – 4080	1430 (1190 – 1900)	1410	96%	385 – 5540
50 – 55	136	2310 (2060 – 2640)	2320	32%	1380 – 3830	1350 (1080 – 1760)	1320	99%	360 – 5290
55 – 60	120	2170 (1910 – 2510)	2180	32%	1310 – 3580	1270 (1000 – 1680)	1230	96%	345 – 4970
60 – 65	118	2050 (1800 – 2360)	2070	32%	1220 – 3340	1140 (973 – 1530)	1160	97%	303 – 4560
65 – 70	99	1940 (1710 – 2290)	1930	33%	1150 – 3220	1150 (854 – 1500)	1120	96%	305 – 4480
70 – 75	67	1850 (1600 – 2140)	1880	32%	1110 – 3060	1050 (844 – 1410)	1030	98%	290 – 3970
75 – 80	58	1710 (1540 – 2050)	1720	32%	1050 – 2780	996 (823 – 1300)	976	97%	273 – 3720
80 – 85	41	1640 (1450 – 2040)	1680	33%	1000 – 2700	988 (743 – 1210)	927	94%	274 – 3490
85 – 90	34	1590 (1360 – 1910)	1590	33%	949 – 2580	948 (679 – 1280)	958	95%	282 – 3300
90 – 95	23	1540 (1320 – 1830)	1520	33%	942 – 2420	878 (625 – 1350)	879	98%	272 – 2990
95 – 100	17	1460 (1250 – 1770)	1430	31%	937 – 2340	882 (649 – 1240)	889	96%	275 – 2910
100 – 105	13	1390 (1170 – 1670)	1410	32%	918 – 2160	800 (550 – 1280)	760	92%	314 – 2550

[a] Median number of virtual patients in the weight bin, summarized across simulations
[b] Median and 5th – 95th percentiles of the geometric mean, summarized across simulations
[c] Median of the median, summarized across simulations
[d] Median of the geometric CV ($\sqrt{\exp(s^2) - 1}$, where s is the (unbiased) standard deviation of natural log-transformed values), summarized across simulations
[e] Median of the 5th and 95th percentiles of patients, summarized across simulations.

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/

YANG ZHAO
11/10/2021 08:25:47 AM

ELIFORD N KITABI
11/10/2021 09:21:18 AM

HUIMIN ZHENG
11/12/2021 08:14:05 AM