CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209394Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	209394
Link to EDR	NDA 209394 EDR Link
Submission Date	12/14/2016
Submission Type	New Molecular Entity; Priority
Brand Name	Mavyret®
Generic Name	Gelcaprevir (GLE), Pibrentasvir (PIB)
Dosage Form and Strength	Oral tablets: 100 mg GLE; 40 mg PIB
Route of Administration	Oral
Proposed Indication	Treatment of chronic hepatitis C infection
Applicant	AbbVie Inc.
Associated IND	INDs 127416 (GLE/PIB), 116170 (PIB), and 116169 (GLE)
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1. EXECUTIVE SUMMARY

Glecaprevir (GLE, ABT-493)/pibrentasvir (PIB, ABT-530) is a fixed dose combination (FDC) direct acting antiviral (DAA) tablet (100 mg GLE/40 mg PIB) with pangenotypic antiviral activity indicated for the treatment of chronic hepatitis C virus (HCV) infection in adult patients with compensated liver disease (with or without cirrhosis). Clinical trials conducted by the applicant include subjects with Stage 4 or 5 chronic kidney disease (CKD). GLE and PIB are both New Molecular Entities. The proposed treatment regimen consists of GLE/PIB 300 mg/120 mg administered once daily (QD) with food, with different treatment durations based on HCV genotype and patient factors such as cirrhosis and prior treatment experience.

The efficacy and safety for GLE/PIB FDC tablets administered once daily with food was evaluated in six Phase 3 studies and parts of two Phase 2 studies across HCV genotypes 1 to 6. SVR rates >90% were observed across all genotypes, patients with cirrhosis, and patients previously treated with interferon or DAA-regimens (see Section 2.2 for additional details). No significant safety signals associated with GLE/PIB treatment were identified from the Phase 3 trials.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 209394. The clinical pharmacology information submitted in the application supports the approval of GLE/PIB for the treatment of chronic HCV in adults. The key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The primary evidence of effectiveness for GLE/PIB is provided by six Phase 3 studies and parts of two Phase 2 studies across HCV genotypes 1 to 6. Supportive evidence of effectiveness is provided by parts of three Phase 2 studies and a dose-ranging monotherapy study.
General dosing instructions	The proposed dosage regimen is 300 mg GLE/120 mg PIB once daily taken with food. Recommended treatment durations vary according to HCV genotype, cirrhosis status (Child-Pugh A), and prior treatment experience. See Section 2.2.1 (General Dosing) for proposed treatment durations. Final treatment durations are expected to be different from those initially proposed by the applicant.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Intrinsic factors (Refer to Section 3.3.3.): - GLE/PIB is not recommended in subjects with moderate hepatic impairment (Child-Pugh Class B) - GLE/PIB is contraindicated in subjects with severe hepatic impairment (Child-Pugh Class C) Extrinsic factors (Refer to Section 3.3.4.) - The co-administration of GLE/PIB is contraindicated with the following

	drugs: ▪ P-gp inducers (including rifampin, carbamazepine, efavirenz, and St. John's Wort) ▪ Atazanavir/ritonavir -The co-administration of GLE/PIB with dabigatran should be avoided in subjects with creatinine clearance < 30 mL/min. -The co-administration of GLE/PIB with the following drugs is not recommended: ▪ Darunavir/ritonavir ▪ Lopinavir/ritonavir ▪ Atorvastatin ▪ Lovastatin ▪ Simvastatin ▪ Ethinyl estradiol containing products - The dose of the following drugs should be adjusted when co-administered with GLE/PIB: ▪ Digoxin ▪ Dabigatran in subjects with creatinine clearance (calculated using the Cockcroft-Gault equation) between 30 and 50 mL/min. ▪ Pravastatin ▪ Rosuvastatin ▪ Fluvastatin ▪ Pitavastatin - The clinical recommendation regarding the coadministration of GLE/PIB with omeprazole is not finalized.
Labeling	Generally acceptable. The review team has specific content recommendations (Refer to Section 2.4.)
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation (b) (4) film-coated bilayer tablet) was used in all Phase 3 trials.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Note that majority of the clinical pharmacokinetics data reported in this review are those observed following the administration of GLE/PIB under fed conditions.

Mechanism of Action:

GLE is a nonstructural (NS) protein 3/NS protein 4A (NS3/NS4A) protease inhibitor of hepatitis C virus (HCV). PIB is an NS protein 5a (NS5A) inhibitor.

Absorption

When GLE and PIB are co-administered, the T_{max} of GLE occurs 3 to 5 hours after dosing and the T_{max} of PIB occurs approximately 5 hours after dosing. Mean GLE and PIB exposures increased by 163% and 40%, respectively, with moderate fat meals, and by 83% and 53%, respectively, with high fat meals.

Distribution

GLE is approximately 97.5% bound to human plasma proteins independent of concentration from 0.1 to 30 μM (800 to 25,200 ng/mL). Mean human blood-to-plasma ratio of GLE is 0.57. The steady state apparent volume of distribution is 170 L.

PIB is greater than 99.9% bound to human plasma proteins, independent of concentration from 0.1 to 30 μM (110 to 33400 ng/mL). Mean human blood-to-plasma concentration ratio of PIB is 0.62. The steady state apparent volume of distribution is 3630 L.

Metabolism

GLE exhibited limited metabolism in vitro, predominantly by CYP3A4/5 and to a much less extent by CYP2D6, CYP2C9, and CYP2C8. Metabolism plays no role in the elimination of PIB.

Excretion

Both GLE and PIB are predominantly excreted through the biliary-fecal route with 92.1% and 96.6% of the administered dose recovered in the feces, respectively. The terminal elimination half-life of GLE and PIB is 6 hours and 13 hours, respectively.

Drug-Drug Interaction Potential

GLE is a substrate and inhibitor of the efflux transporters P-gp and BCRP as well as hepatic uptake transporters OATP1B1 and OATP1B3. PIB is a substrate of P-gp and/or BCRP and an inhibitor of P-gp, BCRP, and OATP1B1. GLE/PIB weakly inhibited cytochrome P450 (CYP)-3A, CYP1A2 and UGT1A1, but did not inhibit CYP2C9, CYP2C19, CYP2D6 or UGT1A4.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The applicant proposes an oral dosing regimen of GLE (300 mg) and PIB (120 mg) once daily administered with food across genotypes 1 to 6. The duration of treatment varies (Table 2.2.1-1) depending on prior treatment history and the presence of cirrhosis. Overall, GLE/PIB treatment achieved high SVR_{12} rates of > 90% in genotype 1 to 6 HCV infected subjects who were either treatment-naïve or treatment experienced.

Table 2.2.1-1. Proposed GLE/PIB Treatment Duration. Table is adapted from the labeling proposed by the applicant at the time of submission. For final recommendations regarding treatment duration refer to the final approved labeling.

2.2.2 Therapeutic individualization

Hepatic Impairment: GLE AUC and PIB AUC are 11-fold and 2-fold, respectively, higher in subjects with Child-Pugh C cirrhosis relative to healthy subjects. Therefore GLE/PIB is contraindicated in subjects with Child-Pugh C cirrhosis. GLE AUC was numerically higher (AUC ratio= 2.0) and PIB AUC did not change in subjects with Child-Pugh B cirrhosis relative to healthy subjects. GLE/PIB administration in HCV subjects with Child-Pugh B cirrhosis is not recommended because GLE/PIB efficacy and safety have not been established in this population. Moreover, post-marketing cases of hepatic decompensation and failure have been reported for regimens containing other HCV protease inhibitors in patients with Child-Pugh Class B

cirrhosis. GLE/PIB can be administered without dosage adjustment in subjects with Child Pugh A cirrhosis.

P-gp inducers: The co-administration of GLE/PIB with P-gp inducers results in a significant decrease in GLE and PIB exposures. GLE/PIB AUC decreased by 88%/87% and 67%/51% when co-administered with rifampin and carbamazepine, respectively. Moreover, following co-administration with efavirenz, GLE and PIB exposures in subjects infected with HIV were more than 50% lower when compared to GLE/PIB exposures observed in healthy subjects. The co-administration of GLE/PIB and P-gp inducers, including St. John's Wort, is contraindicated. Note that GLE and PIB are not metabolized and are P-gp substrates.

HIV Protease Inhibitors: The co-administration of GLE/PIB with HIV protease inhibitors results in a significant increase in GLE and PIB exposures. Atazanavir (ATV)/ritonavir (RTV), lopinavir (LPV)/RTV, and darunavir (DRV)/RTV increased GLE AUC by 6.35-, 4.97-, and 4.38- fold respectively. ALT elevations were observed upon co-administration of GLE/PIB and ATV/RTV in healthy subjects. Therefore, the co-administration of GLE/PIB and ATV/RTV is contraindicated. The co-administration of GLE/PIB with LPV/RTV or DRV/RTV is not recommended due to GLE exposure increase.

Cyclosporine: The administration of a single 100 mg and single 400 mg cyclosporine dose increases GLE AUC by 37% and 5-fold, respectively. GLE exposure may increase more when co-administered with multiple doses of cyclosporine. The co-administration of GLE/PIB with cyclosporine is not recommended due to GLE exposure increase.

Ethinyl Estradiol containing medications: The co-administration of GLE/PIB with two oral contraceptive medications containing ethinyl estradiol resulted in ALT elevations in healthy subjects. There were no changes in the exposure of GLE, PIB, or the components of oral contraceptive. The co-administration of GLE/PIB with medications containing ethinyl estradiol is not recommended.

Digoxin: The co-administration of GLE/PIB with digoxin increases digoxin AUC by 50%. Digoxin dose should be reduced by 50% when co-administered with GLE/PIB.

Dabigatran: The co-administration of GLE/PIB with dabigatran increases dabigatran AUC by 2.38-fold. Dabigatran dose should be reduced to 75 mg BID when co-administered with GLE/PIB in subjects with creatinine clearance between 30 and 50 mL/min. The co-administration of GLE/PIB with dabigatran should be avoided in subjects with creatinine clearance < 30 mL/min.

HMG-CoA Reductase Inhibitors: The co-administration of GLE/PIB with statins increases atorvastatin, simvastatin, simvastatin hydroxyl acid, lovastatin, lovastatin hydroxy acid AUC, by 8.27-, 2.32-, 4.48-, 1.70-, and 4.10-fold, respectively. The co-administration of GLE/PIB with simvastatin, lovastatin, and atorvastatin is not recommended. The co-administration of GLE/PIB increases pravastatin and rosuvastatin AUC by 2.30- and 2.15-fold, respectively. When co-administered with GLE/PIB, pravastatin dose should be reduced by 50% and rosuvastatin dose should not exceed 10 mg. GLE/PIB may increase the exposures of fluvastatin and pitavastatin. Therefore, the lowest approved fluvastatin and pitavastatin should be used when co-administered

with GLE/PIB. If higher doses of fluvastatin or pitavastatin are needed, the lowest necessary dose should be used based on a risk/benefit assessment.

Omeprazole: The co-administration of GLE/PIB with omeprazole (40 mg) reduces GLE AUC by 50% and does not affect PIB AUC. Dosing recommendation regarding the co-administration of GLE/PIB and omeprazole were not finalized at the time of this review and will be addressed in a review addendum.

2.3 Outstanding Issues

The clinical recommendation regarding coadministration of GLE/PIB and omeprazole is still under discussion.

2.4 Summary of Labeling Recommendations

The following information is not in the Applicant's proposed labeling and should be added:

1. The co-administration of P-gp inducers with GLE/PIB is contraindicated.
2. The co-administration of cyclosporine with GLE/PIB is not recommended.
3. Dabigatran dose should be reduced to 75 mg BID when co-administered with GLE/PIB in subjects with creatinine clearance between 30 and 50 mL/min. The co-administration of GLE/PIB with dabigatran should be avoided in subjects with creatinine clearance < 30 mL/min.
4. The lowest approved dose of fluvastatin and pitavastatin should be used when GLE/PIB is co-administered with either fluvastatin or pitavastatin.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The applicant developed the GLE/PIB combination treatment regimen for use in treatment-naïve (TN) and treatment-experienced (TE) hepatitis C virus (HCV) genotype (GT) 1- to GT6-infected subjects with compensated liver disease (with or without cirrhosis (Child-Pugh A)), including subjects with Stage 4 or 5 chronic kidney disease (CKD).

The proposed formulation is a fixed dose combination (FDC) tablet of GLE/PIB containing 100 mg GLE and 40 mg PIB. The proposed dosing regimen is GLE/PIB 300 mg /120 mg (3 X 100/40 mg tablets) once daily with food.

3.2 General Pharmacology and Pharmacokinetic Characteristics

At the clinically recommended dose of GLE/PIB (300/120 mg), GLE increased PIB mean C_{max} and AUC_{24hrs} by 2.86-fold and 3.1-fold, respectively. PIB does not affect GLE exposure.

	GLE		PIB	
Pharmacology				
Mechanism of Action	NS3/4A Protease Inhibitor		NS5A Inhibitor	
QT Prolongation	Does not prolong QT interval (supra-therapeutic dose = 600 mg)		Does not prolong QT interval (supra-therapeutic dose = 240 mg)	
General Information				
Dose Linearity	Greater than dose proportional exposures up to 1200 mg dose due to increased relative bioavailability		Greater than dose proportional exposures up to 120 mg dose due to increased relative bioavailability	
Differences in Systemic Exposure-Healthy Volunteers vs. Patients	AUC was 18% lower in healthy volunteers compared to patients at a GLE/PIB dose of 300/120 mg based on population PK analysis		AUC was 51% higher in healthy volunteers compared to patients at a GLE/PIB dose of 300/120 mg based on population PK analysis	
Variability in Systemic Exposure in HCV Infected Patients	Inter-individual variability: 80-100%		Inter-individual variability: 40-60%	
Absorption				
Absolute Bioavailability	Not determined		Not determined	
T_{max} (h)[a]	5.0 (4 - 5)		5.0 (5 – 5)	
Effect of Meal (Relative to Fasting)				
Meal Type	AUC[b]	Cmax[b]	AUC[b]	Cmax[b]
Moderate Fat Meal (673 Kcal; 29 % Calories from fat)	2.63 (1.18, 3.17)	3.16 (2.85, 3.87)	1.40 (1.11,1.78)	1.90 (1.49,2.41)
High Fat Meal (849 Kcal; 51 % Calories from fat)	1.83 (1.52-2.21)	2.14 (1.75-2.62)	1.53 (1.20,1.95)	2.05 (1.60,2.62)
Distribution				
Steady-state Apparent Volume of Distribution (L)	170 (CV: not estimated)		3630 (CV: 36%)	
% Bound to Human Plasma Proteins	97.5		>99.9	
Blood-to-Plasma Ratio	0.57		0.62	
Metabolism and Transport				
Metabolism	CYP3A (secondary)		none	
Substrate of Transporters	P-gp, BCRP, OATP1B1, OATP1B3		P-gp, BCRP	

Inhibitor of Transporters	P-gp, BCRP, OATP1B1, OATP1B3	P-gp, BCRP, OATP1B1
Elimination		
Major Route of Elimination	biliary-fecal	biliary-fecal
$t_{1/2}$ (h)[c]	6 (5 to 6.48)	13 (11.5 – 13.6)
% of Dose Excreted in Urine	0.7	Not excreted in urine
% of Dose Excreted in Feces	92.1	96.6

a. Median T_{max} and (range) following single doses of GLE and PIB in healthy subjects.
b. Values represent geometric mean ratio [Fed/Fasted] and (90% confidence interval)
c. Median and (range) of harmonic mean

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The primary evidence of effectiveness for GLE/PIB in the indicated population was provided from 6 Phase 3 studies (Studies M15-464, M13-594, M13-590, M13-583, M14-172, M15-462) and parts of two Phase 2 Studies (Study M14-868 Parts 3 and 4, and Study M15-410 Part 2) in patients infected with HCV genotype 1 to 6 (Table 3.3.1-1).

Supportive evidence of effectiveness was provided by three Phase 2 studies (Studies M14-867 Part 2, M14-868 Parts 1 and 2, and M15-410 Part 1) and a dose-ranging monotherapy study (Study M13-595) to inform dose selection (refer to appendix 4.4). There is no exposure response analysis that provides additional support for the effectiveness of GLE/PIB. A summary of the efficacy results from the pivotal trials is provided below in Table 3.3.1-1.

The results of monotherapy study M13-595 provided supportive evidence of effectiveness for GLE and PIB as increasing anti-viral activity was observed with increasing doses of each drug. The applicant observed that GLE dose ≥ 100 mg QD or PIB dose ≥ 40 mg QD achieved an approximately 4 $\log_{10}$ viral load decline with 3 days of therapy in GT1-infected subjects. GLE exposures at a 300 mg dose and PIB exposures at 120 mg were expected to provide near maximal antiviral effect, and higher doses would not result in further meaningful reductions in HCV RNA.

Table 3.3.1-1. SVR_{12} Rates in Phase 3 Studies and Parts of Phase 2 Studies. All studies evaluated GLE/PIB 300/120 mg regimen.

Study	Genotype	Treatment History	Duration (Weeks)	N	SVR12 (%)
Studies in Subjects without cirrhosis					
M13-590	1	TN+TE	8	351	99.1
			12	332	99.7
M14-868*	2	TN+TE	8	145	97.9
M15-464			12	196	99.5
M13-594	3	TN	8	157	94.9
			12	233	95.3
M14-868*		TE	12	22	90.9
			16	22	95.5
M14-868*	4,5,6	TN+TE	8	58	93.1
M13-583			12	121	99.2
Studies in Subjects with cirrhosis					
M14-172	1,2,4,5,6	TN+TE	12	146	99.3
M14-868*	3	TN	12	40	97.5
		TE	16	47	95.5
Studies in Special Populations (with and without cirrhosis)					
M15-462 (CKD)	1-6	TN+TE	12	104	98.1
M15-410* (DAA-exp.)	1,4	TE-NS5A and/or PI	12	44	88.6
			16	47	91.5
* Phase 2 Study, TN = treatment-naïve; TE = treatment-experienced to peginterferon (or interferon), ribavirin and/or sofosbuvir, CKD = chronic kidney disease stage 4-5; TE-NS5A and /or PI = treatment-experienced to previous NS5A and/or protease inhibitors.					

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen of 300 mg GLE/120 mg PIB QD is acceptable in the general population because high SVR_{12} (> 90%) rates were observed across HCV genotypes 1-6 in both treatment naïve and treatment-experienced patients. Treatment duration will vary depending on patient factors such as cirrhosis, prior treatment experience, and HCV genotype (Table 3.3.1-1).

Exposure Response for Efficacy

The applicant conducted an exposure-SVR_{12} analysis which identified PIB AUC as a significant predictor of SVR12 rates in subjects treated with GLE/PIB. Based on the model, a 50% reduction in PIB AUC will lead to a minimal (0.83%) reduction in SVR_{12} rates in HCV GT1-, GT2-, GT4-, GT5-, or GT6-infected patients who were treatment-naïve or treatment-experienced. In HCV GT3 treatment naïve subjects, a 50% decrease in PIB AUC is predicted to decrease SVR_{12} by 3.3%. The review team had concerns with the developed model as it did not have an independent covariate for GLE exposures, did not have a covariate for individual genotypes, cirrhosis, or prior treatment history, and did not account for treatment duration. In

addition, most of the data (~90%) used in the exposure-SVR_{12} analysis are for GLE/PIB 300/120 mg, which was associated with high SVR_{12} and the model was not capable or predicting the lower response rates observed in Phase 2 studies.

Exposure Response for Safety

The GLE/PIB 300 mg/120 mg dose appears to be generally well tolerated. The adverse events of interest used for exposure-safety analysis were: ALT and bilirubin elevations and diarrhea. These events were selected based on previous experience of adverse events associated with HCV protease inhibitors.

The applicant performed exposure-safety analysis using data from 2660 subjects across 9 clinical studies. The results of the analysis showed no exposure-response relationship for ≥ Grade 3 or ≥ Grade 2 post-nadir ALT elevations with the GLE or PIB. In addition, a minor relationship was observed between GLE exposures and incidences of total bilirubin elevations ≥ Grade 2, which did not result in treatment discontinuation. Overall, the GLE/PIB exposures in Phase 3 studies were not associated with major safety concerns. However, due to the highly variable pharmacokinetics of GLE, substantial intrinsic and extrinsic factor effects on GLE exposure, and as only one dose was evaluated in Phase 3 trials, setting safety margins for GLE or PIB is not feasible.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes, GLE/PIB should be contraindicated in patients with Child-Pugh C cirrhosis and administration is not recommended in patients with Child-Pugh B cirrhosis. No dose adjustments are recommended in patients with Child-Pugh A cirrhosis, patients with renal impairment (mild, moderate, severe, ESRD, or ESRD on dialysis), or based on factors such as race (Han Chinese, Japanese, Caucasian, or Blacks), gender, or transporter (SLCO1B1) polymorphisms.

Hepatic Impairment

Efficacy and safety of GLE/PIB 300/120 mg regimen in 233 HCV subjects with Child-Pugh A cirrhosis was established in Phase 2 and 3 studies. The applicant conducted a dedicated pharmacokinetic study in subjects with hepatic impairment. GLE and PIB AUCs were numerically 2- and 1.3-fold higher in subjects with Child-Pugh Class B cirrhosis relative to healthy subjects (Table 3.3.3-1). GLE/PIB administration in HCV subjects with Child-Pugh B cirrhosis is not recommended because efficacy and safety has not been established in this population. Moreover, post-marketing cases of hepatic decompensation and failure have been reported for regimens containing other HCV protease inhibitors (paritaprevir and simeprevir) in patients with Child-Pugh Class B cirrhosis. GLE and PIB AUC were 11- and 2-fold higher in subjects with Child-Pugh Class C cirrhosis relative to healthy subjects (Table 3.3.3-1). GLE/PIB is contraindicated in subjects with Child-Pugh C cirrhosis due to the significant increase in GLE exposure.

Table 3.3.3-1. GLE and PIB exposure in subjects with hepatic impairment relative to subjects with normal hepatic function

Hepatic Impairment Group	Pharmacokinetic Parameter	GLE		PIB	
		GMR	90% CI	GMR	90% CI
Child-Pugh A	Cmax	**1.01**	0.38 – 2.70	**0.84**	0.58 – 1.21
	AUC_{inf}	**1.33**	0.49 – 3.589	**0.80**	0.48 – 1.34
Child-Pugh B	Cmax	**1.38**	0.53 – 3.59	**1.26**	0.85 – 1.86
	AUC_{inf}	**2.00**	0.76 – 5.25	**1.26**	0.73 – 2.16
Child-Pugh C	Cmax	**4.78**	1.75 – 13.07	**0.59**	0.41 – 0.85
	AUC_{inf}	**11.13**	4.03 – 30.75	**2.14**	1.28 – 3.58

Renal Impairment

The applicant conducted a dedicated pharmacokinetic study in subjects with renal impairment. The highest AUC change was an increase by 45% and 46% of GLE and PIB, respectively (Table 3.3.3-2). Both drugs are not removed by dialysis due to high protein binding. GLE and PIB exposures were similar when administered to subjects with ESRD requiring dialysis prior to hemodialysis or on a non-dialysis day. It should be noted that the applicant conducted a single-arm, open label study (Study M15-462) to evaluate the efficacy and safety of GLE/PIB 300/120 mg in 104 HCV-infected subjects (GT 1-6) with eGFR < 30 mL/min/1.73 m^2 including those on dialysis. SVR_{12} was achieved in 98.1% of the subjects and safety profile was comparable to the safety profile in the overall population.

Table 3.3.3-2. GLE and PIB exposure changes in subjects with renal impairment relative to subjects with normal renal function

Creatinine Clearance (mL/min)	Pharmacokinetic Parameter	GLE		PIB	
		Point Estimate	90% CI	Point Estimate	90% CI
60-89	C_{max}	**1.02**	0.89 -1.17	**1.06**	0.98 -1.15
	AUC_{inf}	**1.13**	1.01 -1.26	**1.11**	1.02 -1.20
30-59	C_{max}	**1.05**	0.77 -1.42	**1.14**	0.95 -1.37
	AUC_{inf}	**1.30**	1.02 -1.66	**1.25**	1.05 -1.50
15-29	C_{max}	**1.07**	0.67 -1.63	**1.20**	0.93 -1.55
	AUC_{inf}	**1.45**	1.03 -2.04	**1.37**	1.07 -1.77
< 15 (ESRD subjects not requiring dialysis)	C_{max}	**1.08**	0.65 -1.80	**1.25**	0.92 -1.69
	AUC_{inf}	**1.56**	1.03 -2.35	**1.46**	1.08 -1.97

Race/Ethnicity

The applicant conducted a dedicated study to evaluate the pharmacokinetics of GLE and PIB (Study M15-432) in healthy Han Chinese, Japanese, and Caucasian adult subjects. At the clinical

dose of GLE/PIB 300/120 mg, GLE and PIB pharmacokinetic parameters were similar in Han Chinese subjects relative to Caucasian subjects. GLE and PIB pharmacokinetic parameters were also similar in Japanese subjects relative to Caucasian subjects. Population PK analysis supports that there are no clinically relevant differences in exposures between patients based on race (Caucasian versus Asian and Caucasian versus Black).

Pharmacogenomics

The in vitro and clinical drug interaction studies indicated that GLE is transported by SLCO1B1. Per applicant's report of pooled data from 12 clinical trials, SLCO1B1 transporter function did not influence GLE AUC. The applicant's assignment of transporter activity based on haplotype is accurate and acceptable. Applicant's analyses failed to show statistical significance between SLCO1B1 function and exposure (AUC) except in two-way interaction between SLCO1B1 function and sex (p=0.017).

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

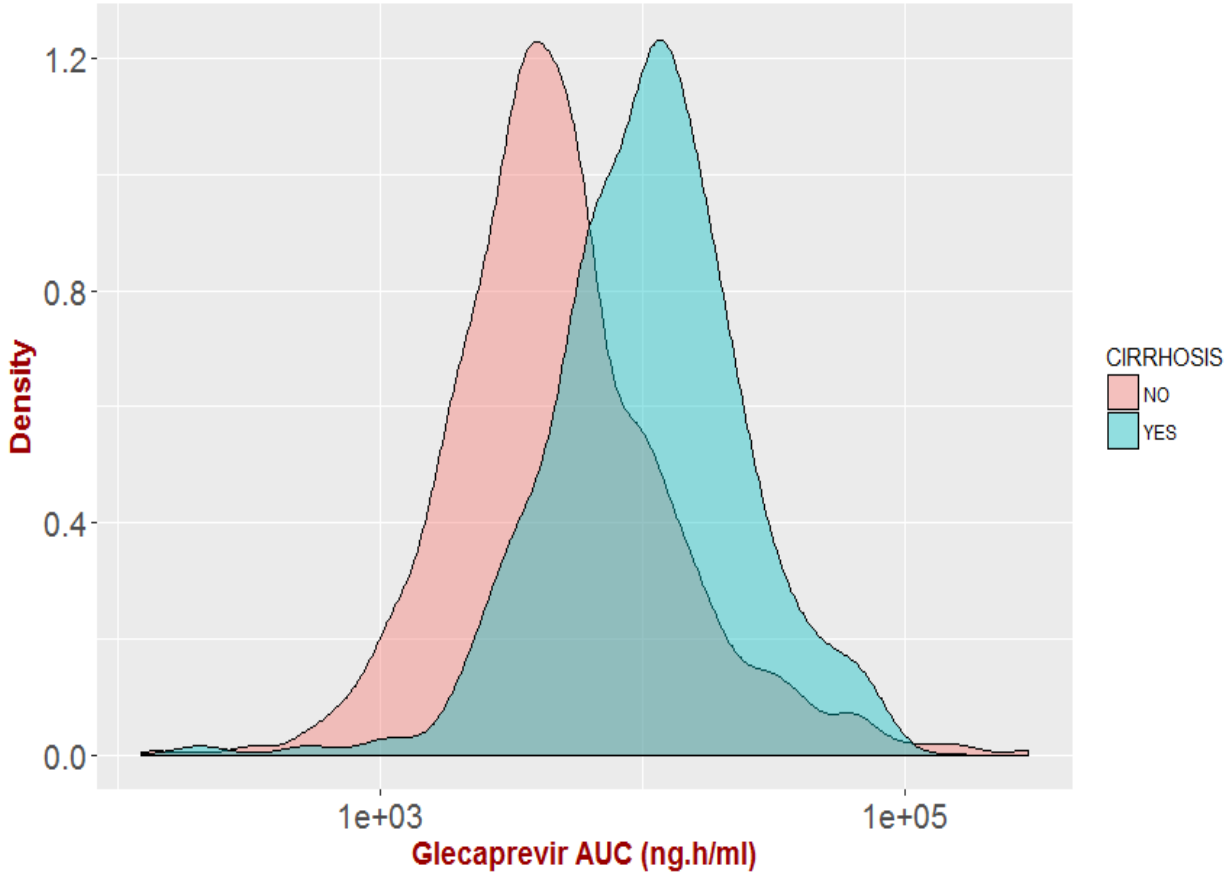
Yes, co-administration of GLE/PIB with certain drugs may be contraindicated, recommended against, or require a dose adjustment due to drug-drug interactions (GLE/PIB as a victim or perpetrator). Drug-drug interactions and the recommended actions are described below. GLE/PIB is recommended to be administered with food as was evaluated in the Phase 3 trials. Food increases the exposure of GLE and PIB (See Section 3.2).

Drug-Drug Interactions

Clinical recommendation for cirrhotic and non-cirrhotic patients

During the pre-NDA meeting, the applicant reported that subjects with Child-Pugh A cirrhosis have GLE AUC that is 2-fold higher than subjects without cirrhosis. This observation prompted the review team to evaluate if the clinical recommendations pertinent to drug-drug interactions should be different for cirrhotic and non-cirrhotic subjects in cases where GLE is a victim or perpetrator of drug-drug interactions. As show in Figure 3.3.4-1, the distribution of AUC is significantly overlapping in cirrhotic and non-cirrhotic subjects, which can be attributed to the high variability in GLE exposure. Therefore, the clinical pharmacology review team proposes that recommendations for drug-drug interactions should not be different for cirrhotic and non-cirrhotic subjects.

Figure 3.3.4-1. Distribution of GLE AUCs in subjects without cirrhosis (N = 1811) and with Child-Pugh A cirrhosis (N = 280). Comparison is based on patients administered the GLE/PIB formulation used in the Phase 3 trials (300/120 mg QD).



Drug-drug interactions that warrant clinical management

Cases where GLE/PIB is a victim for DDI

Table 3.3.4-1 lists DDI evaluations where clinical management is warranted based on changes in GLE or PIB exposure. All of the listed studies were conducted with GLE/PIB 300/120 mg dose.

Cases where GLE and/or PIB exposures were reduced:

Impact of Reduced GLE and/or PIB Exposures on Efficacy

The review team concluded that the applicant's exposure-SVR_{12} analysis cannot be used to inform the impact of reduced GLE and PIB AUC on efficacy (See Appendix 4.4). Instead, the review team based clinical recommendations regarding the impact of reduced GLE and PIB AUC on observed data from Phase 2 studies with a focus on harder to treat subjects, such as those infected with HCV GT-3, where lowest SVR_{12} rates were achieved.

Table 3.3.4-1. Changes in Pharmacokinetic Parameters for PIB and GLE in the Presence of the Listed Co-administered Drug

Co-administered Drug (Regimen)	GLE GMR (90% CI)		PIB GMR (90% CI)		Clinical Management
	C_{max}	AUC	C_{max}	AUC	
Carbamazepine 200 mg BID	0.33 (0.27, 0.41)	0.34 (0.28, 0.40)	0.50 (0.42, 0.59)	0.49 (0.43, 0.55)	Co-administration is contraindicated
Rifampin (600 mg QD MD)	0.17 (0.14, 0.20)	0.13 (0.11, 0.15)	0.14 (0.11, 0.19)	0.12 (0.09, 0.15)	
Cyclosporine (100 mg SD)	1.30 (0.95, 1.78)	1.37 (1.13, 1.66)	1.11 (0.92, 1.33)	1.22 (1.10, 1.36)	Co-administration is not recommended
Cyclosporine (400 mg SD)	4.51 (3.63, 6.05)	5.08 (4.11, 6.29)	1.22 (1.08, 1.38)	1.93 (1.78, 2.09)	
ATV/RTV 300/100 mg	≥4.06* (3.15, 5.23)	≥6.53* (5.24, 8.14)	≥1.29* (1.15, 1.45)	≥1.64* (1.48, 1.82)	Co-administration is contraindicated
DRV/RTV 800/100 mg QD	3.09 (2.26, 4.20)	4.97 (3.62, 6.84)	0.85 (0.75, 0.96)	1.16 (0.981, 1.36)	Co-administration is not recommended
LPV/RTV 400/mg BID	2.55 (1.84, 3.52)	4.38 (3.02, 6.36)	1.40 (1.17, 1.67)	2.46 (2.07, 2.92)	
* Effect of ATV/RTV on single dose GLE/PIB is reported; effect may be greater at steady-state					

As shown in Table 3.3.4-2, treatment of GT-3 subjects for 12 weeks with GLE/PIB 200/40 mg produced a 83% SVR_{12} compared to 96% SVR_{12} following GLE/PIB 300/120 mg. In the GLE/PIB 200/40 mg arm, GLE and PIB AUC were >50% lower relative to mean AUC in Phase 3 studies. It should be noted that increasing treatment duration in GT-3 to 16 weeks was associated with improved $SVR_{12.}$ Nonetheless, reduction in GLE and PIB AUC by > 50% may produce significant reduction in SVR_{12} for this potent regimen.

Table 3.3.4-2. SVR_{12} rate in Genotype 3 Subjects and GLE/PIB AUC for Different Regimens

GLE/PIB dose (mg)	Phase 2			Phase 3
	200/40 (n=30)	200/120 (n=61)	300/120 (n=269)	300/120 (n=390)
Duration (Weeks)	12	12	8 to16	8 to 12
SVR_{12} rates (%)	83.3	93.4	95.5	95.1
PIB GM AUC (CV%)	525.4 (50)	1495 (43)	1572 (56)	1259 (57)
GLE GM AUC (CV%)	1956 (112)	2243 (80)	8767* (130)	3871 (113)
*The higher GLE AUC in Phase 2 compared with Phase 3 studies were largely due to effect of cirrhosis, with some contribution from differences in the GLE/PIB formulation.				

P-gp inducers: Both carbamazepine and rifampin produced a significant reduction in GLE and PIB exposure, which warrants contraindication because of the expected loss of efficacy. Cross-study comparison showed that GLE and PIB exposures were reduced by 50% following co-administration with efavirenz, a P-gp inducer. Other P-gp inducers such as St. John's Wort are expected to produce significant decrease in GLE and PIB exposures (i.e. > 50%); therefore, co-administration with P-gp inducers should be contraindicated.

Omeprazole: The co-administration of GLE/PIB with omeprazole (40 mg) reduces GLE AUC by 50% and does not affect PIB AUC. Dosing recommendation regarding the co-administration of GLE/PIB and omeprazole were not finalized at the time of this review and will be addressed in a review addendum.

Cases where GLE and/or PIB exposures were increased:

Impact of Increased GLE and/or PIB exposures on Safety

As stated in section 3.3.2, safety margins for GLE or PIB exposure could not be established. Because only one GLE/PIB dose was evaluated in most Phase 2 and all Phase 3 trials, the review team agrees with the applicant's approach to not recommend the co-administration of GLE/PIB with drugs that produce > 5-fold increase in GLE and/or PIB exposures. From the Phase 3 studies, approximately 6% of patients had exposures >5-fold of typical (geometric mean) GLE exposures. Adverse event rates (ALT elevations) in patients with higher exposure were only slightly higher than the rest of the population. For PIB, <1% of patients had exposures >5-fold above typical (geometric mean) PIB exposures. Due to the limited patient experience at higher GLE and PIB exposures and due to variability in GLE exposure, the review team considered that the safety of exposures >5-fold was not adequately informed. Therefore, the coadministration of drugs that increase GLE and/or PIB exposure > 5-fold is not recommended. If there are additional concerns, such as observed adverse events when a specific drug is co-administered with GLE/PIB, a contraindication may be warranted.

HIV Protease inhibitors: The co-administration of GLE/PIB with HIV protease inhibitors results in a significant increase in GLE and PIB exposures. ATV/RTV, LPV/RTV, and DRV/RTV increased GLE AUC by 6.35-, 4.97-, and 4.38- fold respectively. As stated above, safety margins for GLE and PIB exposures could not be established due to low rate of adverse events with little or no evidence of a relationship with GLE or PIB exposures from the Phase 3 trial experience (<1% post-nadir Grade 2 elevations in ALT; <1% Grade 2 diarrhea; 2% Grade 2 elevations in bilirubin). However, there remain concerns that safety events may occur with exposures at or exceeding the Phase 3 experience, particularly given post-marketing safety experience with other protease inhibitors. As such, the review team utilized a risk-based assessment in determining the drug-interaction management strategies.

ALT elevations were observed upon co-administration of GLE/PIB and ATV/RTV in healthy subjects. Given that a potential safety signal was identified in healthy subjects with this regimen in addition to the > 6 fold increase in GLE exposure when GLE/PIB is coadministered with ATV/RTV, the co-administration of GLE/PIB and ATV/RTV is contraindicated. Exposures with LPV/RTV and DRV/RTV are also high, but there was no safety signal in healthy subjects. As such, use of GLE/PIB with these regimens is not recommended. These recommendations still

permit the use of various other HIV treatment regimens with GLE/PIB and the HIV regimens mentioned above can be used with one or more approved HCV-treatment regimens.

Cyclosporine: The administration of a single 100 mg and a single 400 mg cyclosporine dose increases GLE AUC by 37% and 5-fold, respectively. The co-administration of GLE/PIB with cyclosporine is not recommended due the increase in GLE exposure.

Cases where GLE/PIB is a perpetrator for DDI

Table 3.3.4-3 lists DDI evaluations that reveal clinical management is needed based on changes in concomitant drug exposure. All studies were conducted with GLE/PIB 300/120 mg dose except for digoxin, pravastatin, rosuvastatin, and atorvastatin which used GLE/PIB 400/120 mg. Note that all clinical recommendations, except for ethinyl estradiol, are made based on observed changes in AUC and are consistent with respective drugs' current labeling.

Ethinyl estradiol containing products: ALT and AST elevations were observed in healthy volunteers following the co-administration of GLE/PIB with oral contraceptives containing ethinyl estradiol. No substantial changes were observed in the exposure of GLE, PIB, or the components of oral contraceptive that would suggest changes in exposure were responsible for ALT and AST elevations. However, given the observed clinical signal in healthy volunteers, the co-administration of GLE/PIB with medications containing ethinyl estradiol is not recommended. No ALT/AST elevations were observed when GLE/PIB was co-administered with the progestin norethindrone only. As such, there are oral contraceptive options available to patients undergoing treatment with GLE/PIB.

Statins: The applicant conducted DDI studies with five statins: pravastatin, rosuvastatin, atorvastatin, lovastatin, and simvastatin. These statins are known substrates of OATP and P-gp and exhibited increases in exposure when co-administered with GLE/PIB as shown in Table 3.3.4-3. Due to increases in the exposure of parent and metabolite concentrations, the co-administration of GLE/PIB with simvastatin, lovastatin, and atorvastatin is not recommended. When co-administered with GLE/PIB, pravastatin dose should be reduced by 50% and rosuvastatin dose should not exceed 10 mg. GLE/PIB may increase, through OATP inhibition, the exposures of fluvastatin and pitavastatin. Therefore, the lowest approved fluvastatin and pitavastatin doses should be used when co-administered with GLE/PIB. If higher doses of fluvastatin or pitavastatin are needed, the lowest necessary dose should be used based on a risk/benefit assessment.

Table 3.3.4-3. Changes in Pharmacokinetic Parameters for Co-administered Drugs in the Presence of PIB and GLE

Co-administered Drug	Central Value Ratio (90% CI)		Clinical Management
	C_{max}	AUC	
Digoxin (0.5 mg SD)	1.72 (1.45, 2.04)	1.48 (1.40, 1.57)	Digoxin dose should be reduced by 50%
Dabigatran (150 md SD)	2.05 (1.72, 2.44)	2.38 (2.11, 2.70)	Dabigatran dose should be reduced to 75 mg BID in subjects with creatinine clearance between 30 and 50 mL/min -The co-administration of GLE/PIB with dabigatran should be avoided in subjects with creatinine clearance < 30 mL/min
Pravastatin (10 mg QD)	2.23 (1.87, 2.65)	2.30 (1.91, 2.76)	Reduce pravastatin dose by 50%
Rosuvastatin (5 mg QD)	5.62 (4.80, 6.59)	2.15 (1.88, 2.46)	Rosuvastatin should do not exceed 10 mg/day
Atorvastatin (10 mg QD)	22.0 (16.4, 29.6)	8.28 (6.06, 11.3)	Co-administration is not recommended
Lovastatin (10 mg QD)	1.17 (0.9, 1.42)	1.70 (1.40, 2.06)	
	lovastatin acid 5.73 (4.65, 7.07)	lovastatin acid 4.10 (3.45, 4.87)	
Simvastatin (5 mg QD)	1.99 (1.60, 2.48)	2.32 (1.93, 2.79)	
	simvastatin acid 10.7 (7.88, 14.6)	simvastatin acid 4.48 (3.11, 6.46)	
Ethinyl estradiol (35 µg)	1.31 (1.24, 1.38)	1.28 (1.23, 1.32)	Co-administration with ethinyl estradiol containing products is not recommended
Ethinyl estradiol (20 µg)	1.30 (1.18, 1.44)	1.40 (1.33, 1.48)	

Cases where dose adjustments are not warranted

The drugs listed below were evaluated in dedicated studies. The changes in exposure of GLE, PIB, or the co-administered drug, if any changes occurred, did not warrant any dose adjustment of GLE, PIB, or the co-administered drug. Refer to appendix 4.2 for detailed description of these studies.

Abacavir, amlodipine, buprenorphine, caffeine, dextromethorphan, dolutegravir, elvitegravir/cobicistat, emtricitabine, felodipine, lamivudine, lamotrigine, losartan, methadone, midazolam, naloxone, norethindrone or other progestin-only contraceptives, raltegravir, rilpivirine, sofosbuvir, tacrolimus, tenofovir alafenamide, tenofovir disoproxil fumarate, tolbutamide, and valsartan.

Food Effect

Mean systemic exposure of GLE and PIB was increased when administered with food. Administration of the GLE/PIB formulation used in the Phase 3 trials under moderate-fat and high-fat conditions increased the mean C_{max} and AUC of GLE and PIB (See Section 3.2). Further, in all Phase 3 trials, patients were instructed to take GLE/PIB with food without regard to fat or calorie content. Overall, based on the available data, GLE/PIB should be taken with food, without regard to calorie or fat content.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Bioanalytical methods used to quantify drugs in clinical and clinical pharmacology studies were reviewed. All methods were validated prior to analyzing plasma samples and validation of all methods is acceptable. Performance of bioanalytical methods during plasma samples analysis is acceptable for all analytes. For calibration ranges for all analytes refer to the individual studies reviews. Of note, the applicant used two calibration curves to quantify GLE and PIB in many of the studies. One calibration curve covers low concentration range and the other covers high concentration range. The two curves overlapped. The slopes and intercepts for the curves were similar and therefore the approach is acceptable, although not ideal. The applicant used one calibration curve (spanning over the two curve concentration range) in later studies. The review team's criteria employed to evaluate the performance of the bioanalytical methods are outlined below.

Validation

- The bioanalytical method was validated according to the criteria outlined in the FDA guidance

Study Samples Analysis

- Sample analysis performed within the established stability period
- Quality control samples concentration range is acceptable
- Chromatograms provided. Analytes and internal standards are measured at reproducible retention times without interference
- Accuracy and precision of the calibration curve samples and quality control samples were within 15% (20% at the lower limit of quantification)
- Incurred sample analysis was performed. Enough samples were analyzed and the reanalysis passed the success criteria.
- Reported bioanalytical protocol deviations do not affect the integrity of the data

4.2 Formulation Development and ADME Summary

Overview

The applicant conducted an extensive development program to characterize the ADME profiles of GLE and PIB and to identify GLE/PIB fixed dose combination tablet (100 mg/40 mg) that was used in the Phase 3 trials and is proposed for commercialization. Considering that comparative bioavailability trials of experimental formulations were conducted throughout clinical development while efforts were ongoing to identify the formulation to be used in Phase 3 trials, the results from some relative bioavailability and pharmacokinetics trials are not clinically relevant. A variety of factors such as the use of either GLE or PIB alone in a trial (not clinically relevant because GLE and PIB will always be administered together using a co-formulated tablet) or the evaluation of GLE and PIB formulations which were not further pursued due to poor bioavailability were considered to determine which trials provide clinically relevant information. For trials from which the results were determined to be clinically relevant and included in this review, the trial design characteristics, bioanalytical methodology (described in the appendix), sample collection for pharmacokinetic assessments, and the conclusions were reviewed in detail and determined to be acceptable for regulatory decision making purposes.

Table 1 provides a summary of trials discussed in this section of the review. Of note, all trials included in the table below were conducted in healthy volunteers.

SUMMARY OF FINDINGS:

Type of Assessment	Overall Conclusions
Formulation Development	• Mean systemic exposures of GLE and PIB with either the Phase 2a or the Phase 2b formulations are expected to be similar. • GLE/PIB film-coated bilayer tablets were used in all registrational trials. • The core composition of the Phase 3 formulation (film coated bilayer tablet) was the same as the (b) (4) bilayer tablet (without the film coating).
Relative Bioavailability Assessment of Food Effect	• Under fasting conditions, the film-coated bilayer FDC tablet had lower exposures for GLE relative to the reference Phase 2b formulation. • Based on cross trial comparisons, under fed conditions, mean AUC of GLE and PIB are higher after administration of GLE and PIB administered individually (Phase 2b tablets) as compared to GLE/PIB Phase 3 formulation. • Differences in systemic exposure of GLE and PIB between the Phase 2b and 3 formulations are not anticipated to alter the efficacy, safety, and drug-drug interaction profiles. • GLE/PIB should be administered with food. Within the range of meals evaluated, alterations in systemic exposure of GLE and PIB are not expected to be clinically relevant.
Assessment of Accumulation	• Observed accumulation of GLE was 1.1-1.2 fold. Accumulation of PIB was 1.27-fold. Based on a half-life of 6 and 13 hours, respectively, the estimated accumulation ratio was 1.1 and 1.38, respectively.
Assessment of the Potential of Drug-Drug Interaction between GLE and PIB	• GLE increased the mean C_{max} and $AUC_{0\text{-}24hrs}$ of PIB by approximately 2.86-fold and 3.1-fold, respectively. • PIB did not have a significant impact on the systemic exposures of GLE.
Mass Balance	• GLE and PIB are primarily cleared through the biliary/fecal route.

*: The conclusions in the table above (except those related to DDI) apply to GLE and PIB administered together.

Table 1. Summary of Trials Discussed in this Review

SUMMARY OF TRIALS REVIEWED		
Trial #	**Type**	**Brief Description of Major Assessments***
M14-714	Relative Bioavailability and Food Effect Assessment	Relative bioavailability Assessment: Single dose of GLE/PIB 300/120 mg (test) compared with single dose of GLE tablets (300 mg; 3 X100 mg tablets) and PIB tablets (120 mg, 3 X 40 mg) under fasting conditions Food Effect Assessment: Single dose of GLE/PIB Phase 3 tablets 300/120 mg (3 X 100/40 mg tablets) under fasting conditions, moderate fat breakfast, and high fat breakfast. Phase 2b (GLE and PIB administered separately) and Phase 3 GLE/PIB fixed dose tablets were used in the trial under fasting and fed conditions as applicable.
M14-716	Pharmacokinetics, Safety, and Tolerability of Single Dose of various GLE and PIB Combinations in Healthy Subjects	Single dose of GLE and PIB (400/120 mg and 800/240 mg) was administered under fed conditions. The applicant used the Phase 2b tablets in the trial.
M13-890	Mass Balance Study	Metabolic Profiles of GLE and PIB. Powder for oral solution delivered as liquid filled capsule and lipid filled capsule for GLE and PIB respectively; [^{14}C] GLE liquid filled capsule and [^{14}C] PIB lipid filled capsule. Drugs were administered under fed conditions to healthy subjects.
M13-586	Drug-Drug Interaction Trial between GLE and PIB	Trial assessed multiple dose pharmacokinetics and safety of the co-administration of various dose combinations of GLE and PIB (shown in Table 12 and Table 13), and co-administration of GLE and ABT-450 with ritonavir. The applicant used the Phase 2a tablets in the trial. Drugs were administered under fed conditions to healthy subjects.
SUMMARY OF TRIALS NOT REVIEWED		
M13-356	Safety, Tolerability, and Pharmacokinetics (including the effect of food) of Single and Multiple Doses of GLE	Results generated in this First-in-Human trial are not relevant to the proposed to-be-marketed formulation. There were multiple formulation changes after the trial was conducted and the proposed to-be-marketed formulation is a fixed dose combination of GLE/PIB. Further, the applicant evaluated GLE alone (without PIB) in the trial.
M13-355	Safety, Tolerability, and Pharmacokinetics (including the effect of food) of Single and Multiple Doses of PIB	Results generated in this First-in-Human trial are not relevant to the proposed to-be-marketed formulation. There were multiple formulation changes after the trial was conducted and the proposed to-be-marketed formulation is a fixed dose combination of GLE/PIB. Further, the applicant evaluated PIB alone (without GLE) in the trial.
M13-601	Relative bioavailability assessment of GLE Phase 2a and Phase 2b test formulation A and PIB Phase 2b test formulation A relative to GLE and PIB formulation used in first-in-human (FIH) trials.	Results generated are not clinically relevant because the applicant did not further develop GLE Phase 2b test formulation A and PIB Phase 2b test formulation A due to poor bioavailability.
M14-214	Relative bioavailability assessment of GLE Phase 2b test formulation relative to the GLE Phase 2a and First-in-Human (FIH) formulation.	Results generated are not clinically relevant because the applicant did not further develop GLE Phase 2b test formulation B.

Source: Prepared by reviewer based on information provided in various trial reports.

The following sections summarize the applicant's formulation development efforts, assessment of the DDI potential between GLE and PIB, effect of food on GLE and PIB and mass balance assessments of GLE and PIB.

Formulation Development:

During the clinical development program, separate formulations of GLE and PIB such as first-in-human (FIH) tablets used in early clinical development and Phase 2a and Phase 2b tablets used in Phase 1 studies and Phase 2 studies (Phase 2a and 2b studies) were evaluated. (b) (4) a variety of co-formulations of GLE/PIB were also developed and evaluated in Phase 1 bioavailability studies.

Table 2 shows the GLE formulations Evaluated in Phase 1 and Phase 2 studies

Table 2. GLE Formulations Evaluated in Phase 1 and Phase 2 Studies

GLE Formulation	Strength	Phase 1 Bioavailability Studies	Additional Phase 1 and Phase 2 Studies
FIH Tablets	2.5 mg, 25 mg	M13-601 M14-214	• FIH Study: M13-356
Phase 2a Tablets[a]	100 mg	M13-580 M13-601 M14-214 M14-611	• Phase 1 Studies: M13-579, M13-582, M13-602, M14-532 (DDI Studies), M14-380 (CYP cocktail study), M13-586 (DAA-interaction study), M14-066 (Asian Pharmacokinetic [PK] study) • Phase 2a Study: M13-595
Phase 2b Tablets[a]	100 mg	M14-711 M14-714 M14-717 M14-719	• Phase 1 Studies: M13-577, M13-578, M13-584, M13-585, M13-587, M13-592, M13-593, M13-597, M13-598, M13-599, M13-603, M13-605, M14-721, M14-723, M14-724, M15-584, (DDI studies), M15-543 (TQT/QTc study), M13-600 (renal impairment study), M13-604 (hepatic impairment study), M15-432 (Asian PK study), M14-716 (PK, Safety and Tolerability study) • Phase 2b Studies: M14-867, M14-868 (Parts 1 and 2), M15-410 (Part 1)

a. GLE Phase 2a and Phase 2b tablets had the same composition.

Source: 2.7 1: Summary of Biopharmaceutic Studies and Associated Analytical Methods. Page 8

Additional GLE formulations (prototype Phase 2b Tablet A [used in trial M13-601], prototype Phase 2b Tablet B [used in trial M14-214], and (b) (4) ablets [used in trial M14-711]) were evaluated in parallel to FIH formulations and Phase 2a and Phase 2b formulations in Phase 1 studies but were not developed further due to lower bioavailability compared to FIH, Phase 2a or Phase 2b tablets. It is important to note that the composition of GLE Phase 2a and Phase 2b tablets was the same.

Table 3 shows the PIB formulations Evaluated in Phase I and Phase 2 studies

Table 3. PIB Formulations Evaluated in Phase 1 and Phase 2 Studies

PIB Formulation	Strength	Phase 1 Bioavailability Studies	Additional Phase 1 and Phase 2 Studies
FIH Tablets	1.5 mg, 15 mg	M13-581, M13-601	M13-355 (FIH)
Phase 2a Tablets	40 mg	M13-580, M14-611	• Phase 1 Studies: M13-579, M13-582, M13-602, M14-532 (DDI Studies), M14-380 (CYP cocktail study), M13-586 (DAA interaction study), M14-066 (Asian PK study) • Phase 2a Study: M13-595
Phase 2b Tablets	40 mg	M14-711, M14-714, M14-717, M14-719	• Phase 1 Studies: M13-577, M13-578, M13-584, M13-585, M13-587, M13-592, M13-593, M13-597, M13-598, M13-599, M13-603, M13-605, M14-721, M14-723, M14-724, M15-584 (DDI studies), M15-543 (TQT study), M13-600 (renal impairment study), M13-604 (hepatic impairment study), M14-716 (PK, Safety and Tolerability study), M15-432 (Asian PK study) • Phase 2b Studies: M14-867, M14-868 (Parts 1 and 2), M15-410 (Part 1)

Source: 2.7 1: Summary of Biopharmaceutics Studies and Associated Analytical Methods. Page 11

PIB Phase 2a tablets were formulated as 40 mg tablets with a [redacted] PIB Phase 2b tablets were also formulated at 40 mg dose strength and differed slightly in composition from the PIB Phase 2a tablets. The PIB Phase 2a tablets were manufactured using [redacted] method while the PIB Phase 2b tablets were manufactured using [redacted] technology. Due to different manufacturing processes, there were slight differences in excipients ([redacted]% increase in SiO_2 and [redacted]% decrease in copovidone) between the two formulations. Table 4 shows the cross study comparison of the m tiple dose pharmacokinetics of GLE and PIB co-administered as Phase 2a or Phase 2b tablets.

Table 4. Multiple Dose Pharmacokinetics of GLE and PIB Co-administered as Phase2a or Phase2b tablets

DAA Regimen	Formulation	Subjects (N)	C_{max}[a] (ng/mL)	T_{max}[b] (h)	AUC_{24}[a] (ng•h/mL)	C_{24}[a] (h)
			GLE			
GLE 400 mg + PIB 120 mg	Ph2a	35	1960 (1020 to 3300)	3.0 (3.0 to 3.0)	6890 (4000 to 10600)	4.81 (4.07 to 5.95)
GLE 300 mg + PIB 120 mg	Ph2b	230	1230 (598 to3550)	4.0 (3.0 to 5.0)	4380 (2380 to 12100)	5.06 (2.57 to 15.2)
			PIB			
GLE 400 mg + PIB 120 mg	Ph2a	35	234 (208 to 262)	4.0 (4.0 to 5.0)	1770 (1670 to 1900)	23.8 (20.5 to 26.8)
GLE 300 mg + PIB 120 mg	Ph2b	230	295 (193 to 457)	5.0 (4.5 to 5.0)	2170 (1450 to 3980)	30.0 (18.0 to 64.7)

a. Overall geometric mean and range of geometric means.

b. Weighted median and range of study medians.

Source: 2.7.1: Summary and Cross Study Comparison of Glecaprevir and Pibrentasvir Pharmacokinetics in Healthy Adult Subjects when administered in Combination (R&D/16/0237), Page 17

After taking into account the inter-study variability and the differences in effect of GLE 300 mg vs GLE 400 mg on PIB 120 mg, the mean PIB exposures were generally similar between the Phase2a and Phase2b tablets. Overall, based on this similarity in PIB exposures between Phase 2a and Phase2b tablets and considering that the composition of GLE was same for Phase2a and Phase2b tablets, the mean systemic exposures of GLE and PIB with either the Phase 2a or the Phase2b formulations are expected to be similar.

Additional PIB formulations evaluated but not developed further included the prototype Phase 2b Tablet formulation A [100 mg; used in trial M13-601], [redacted] tablet [25 mg, 100 mg used in trial M13-581]), and [redacted] tablets [used in trial M14-711].

Development of Coformulated Bilayer Tablets:

Development of the coformulated GLE/PIB was conducted using the [redacted] technology plateform. The earlier bilayer tablets were manufactured as uncoated GLE/PIB HME bilayer tablets and were evaluated in M14-611 (fasting; 300/120 mg), M14-719 (fed; 300/120 mg) and M14-717 (fasting; moderate fat, and high fat; 200/80 mg [cohort 1] and 300/120 mg [cohort 2]).

The core composition for the Phase 3 formulation was the same as the [redacted] bilayer tablet with an additional non-functional coating. **The film-coated bilayer tablet was manufactured and used in all registrational trials**. The Phase 3 formulation was compared to the Phase2b tablets in trial M14-714.

Effect of Food on the Pharmacokinetics of GLE/PIB (Trial M14-714)

Both GLE and PIB show pH dependent solubility in aqueous media, food was anticipated to increase the solubility and bioavailability of GLE and PIB. Trial M14-714 was designed to assess the relative bioavailability of a single dose of GLE/PIB 300/120 mg (test) compared with single dose of GLE tablets (300 mg; 3 X100 mg tablets) and PIB tablets (120 mg, 3 X 40 mg) under fasting conditions. Further, the trial assessed the effect of food on the single dose of GLE/PIB Phase 3 tablets 300/120 mg (3 X 100/40 mg tablets), evaluating exposure

after administration of GLE/PIB under fasting conditions, moderate fat breakfast conditions [673kcal, 29.4 % kcal from fat) and under high fat breakfast[849 kcal; 51.1% kcal from fat]) conditions.

Table 5 shows the relative bioavailability and 90 % confidence intervals for GLE/PIB film coated bilayer tablets compared to phase 2b tablets.

Table 5. Relative Bioavailability and 90 % Confidence Intervals for GLE/PIB Film Coated Bilayer Tablets Compared to Phase 2b Tablets

Regimens (Test vs Reference)	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
		ABT-493			
A vs D	C_{max} (ng/mL)	298	804	0.370	0.302 – 0.453
	AUC_t (ng•h/mL)	1160	2620	0.442	0.366 – 0.533
	AUC_∞ (ng•h/mL)	1160	2620	0.443	0.367 – 0.534
B vs D	C_{max} (ng/mL)	941	804	1.170	0.956 – 1.432
	AUC_t (ng•h/mL)	3040	2620	1.161	1.002 – 1.345
	AUC_∞ (ng•h/mL)	3040	2620	1.162	1.003 – 1.346
C vs D	C_{max} (ng/mL)	638	804	0.793	0.648 – 0.971
	AUC_t (ng•h/mL)	2120	2620	0.809	0.699 – 0.937
	AUC_∞ (ng•h/mL)	2120	2620	0.810	0.700 – 0.937
		ABT-530			
A vs D	C_{max} (ng/mL)	115	174	0.664	0.513 – 0.858
	AUC_t (ng•h/mL)	903	1420	0.638	0.496 – 0.820
	AUC_∞ (ng•h/mL)	952	1480	0.642	0.501 – 0.823
B vs D	C_{max} (ng/mL)	218	174	1.257	1.041 – 1.518
	AUC_t (ng•h/mL)	1270	1420	0.895	0.742 – 1.080
	AUC_∞ (ng•h/mL)	1330	1480	0.900	0.747 – 1.084
C vs D	C_{max} (ng/mL)	236	174	1.360	1.115 – 1.659
	AUC_t (ng•h/mL)	1390	1420	0.979	0.803 – 1.193
	AUC_∞ (ng•h/mL)	1460	1480	0.984	0.808 – 1.198

Regimen A: Single 300 mg/120 mg dose of ABT-493/ABT-530 (3 × 100 mg/40 mg film-coated bilayer tablets) under fasting conditions (Test).
Regimen B: Single 300 mg/120 mg dose of ABT-493/ABT-530 (3 × 100 mg/40 mg film-coated bilayer tablets) following a moderate fat breakfast (Test).
Regimen C: Single 300 mg/120 mg dose of ABT-493/ABT-530 (3 × 100 mg/40 mg film-coated bilayer tablets) following a high fat breakfast (Test).
Regimen D: Single dose of 300 mg ABT-493 (3 × 100 mg tablets) and 120 mg ABT-530 (3 × 40 mg tablets) under fasting conditions (Reference).

Source: M14-714 Clinical Study Report, Page 45

Under fasting conditions, the film-coated bilayer FDC tablet had lower exposures for GLE [63% lower mean C_{max} and 56% lower mean $AUC_{0-\infty}$] relative to the reference Phase 2b formulation (treatment A vs D); however, the exposures of GLE after administration of film-coated bilayer tablet under fed conditions were similar [17% higher C_{max} and 16% higher mean $AUC_{0-\infty}$ with moderate fat [treatment B vs D]; 21% lower mean C_{max} and 19% lower mean $AUC_{0-\infty}$ with high fat breakfast [treatment C vs D]) to the reference Phase 2b formulation under fasting conditions.

Because numerous DDI trials were conducted using individual GLE and PIB Phase 2b tablets under fed conditions, the applicant summarized the multiple dose pharmacokinetic parameters of 300 mg GLE and 120 mg PIB (administered as the Phase2b individual products) under fed conditions. Table 6 shows the summary.

Table 6. GLE 300 mg once daily and PIB 120 mg once daily Multiple Dose Pharmacokinetics in Healthy Volunteers (Phase 2b tablets, administered under fed conditions)

DAA	Subjects (N)	C_{max}[a] (ng/mL)	T_{max}[b] (h)	AUC_{24}[a] (ng•h/mL)	C_{24}[a] (h)
GLE	230	1230 (598 to 3550)	4.0 (3.0 to 5.0)	4380 (2380 to 12100)	5.06 (2.57 to 15.2)
PIB	230	295 (193 to 457)	5.0 (4.5 to 5.0)	2170 (1450 to 3980)	30.0 (18.0 to 64.7)

a. Overall geometric mean and range of geometric means.
b. Median and range of study medians.

Source: 2.7 2: Summary and Clinical Pharmacology Studies, Page 84

Multiple doses of GLE/PIB Phase 3 co-formulated bilayer tablets were not evaluated in healthy subjects, therefore, the applicant provided a summary (Table 7) of the pharmacokinetic parameters of GLE and PIB after single dose administration of GLE/PIB under fed conditions.

Table 7. GLE/PIB 300/120 mg Single Dose Pharmacokinetic Parameters in Healthy Subjects (Phase 3 tablets) under fed conditions.

DAA	Subjects (n)	C_{max}[a] (ng/mL)	T_{max}[b] (h)	AUC_{inf}[a] (ng•h/mL)	$t_{1/2}$[c] (h)
GLE	79	772 (592 to 1090)	5.0 (4.0 to 5.0)	2610 (2110 to 3720)	6.14 (5.00 to 6.48)
PIB	79	204 (159 to 237)	5.0 (5.0 to 5.0)	1250 (950 to 1460)	13.1 (11.5 to 13.6)

a. Overall geometric mean and range of geometric means.

b. Median and range of study medians.

c. Median and range of study harmonic means.

Source: 2.7 2: Summary of Clinical Pharmacology Studies, Page 84

Based on comparison of the mean PK parameters of GLE and PIB shown in the tables above, it appears that the mean AUC of GLE and PIB are higher after multiple dose administration of individual Phase2b formulations vs Phase 3 formulation. Of note, comparing the mean PK parameters of GLE and PIB after single dose administration of GLE/PIB Phase 3 formulation with multiple dose administration of GLE and PIB Phase 2b formulations is a reasonable approach considering that minimal accumulation of GLE and PIB is anticipated after multiple dose administration of GLE/PIB Phase 3 formulation.

Even though the systemic exposure of GLE and PIB is higher after administration of GLE and PIB individual products (Phase 2b formulation) as compared to GLE/PIB FDC (Phase 3 formulation), such differences are not expected to have any impact on overall interpretation of efficacy (because efficacy data was generated using the FDC product), safety (because the FDC product will be administered to patients for which safety data was generated in registrational trials using the FDC) or drug-drug interactions (because most of the DDI trials were evaluated at the higher exposures from the individual Phase2b products (thus maximizing the potential to observe a DDI) and the results can be extrapolated to the Phase 3 FDC tablets (to be administered under fed conditions). Considering that GLE and PIB administered individually (as Phase 2b tablets) showed higher mean GLE and PIB exposures as compared with GLE/PIB Phase 3 FDC tablets, extrapolating the clinical recommendations based on results from DDI trials conducted using the individually administered Phase 2b tablets to the Phase 3 FDC tablets is a conservative approach.

As part of End of Phase 2 meeting discussions in October 2015, the applicant was asked to consider administering GLE/PIB without regards to food in Phase 3 trials in order to simplify the dosing instructions for patients. The recommendation was based on available SVR data for the various genotypes, non-linear increase of GLE exposures between the 200 mg and 300 mg doses, and the dose (exposure)-response relationships. Further, trials M14-867 and M14-868 (which formed the basis of dose selection for Phase 3 trials and used GLE and PIB individual products) were also conducted without regard to food. Although the applicant agreed that the impact of food on the SVR is minimal for GT1 and GT2 patients, dosing without food may reduce the SVR in more difficult to treat populations (for example GT3 patients or patients with compensated cirrhosis). Hence, in order to have one recommendation (w.r.t food intake) for the Phase 3 patient population, the applicant decided to recommend GLE and PIB to be taken with food in all Phase 3 trials without regard to fat or calorie content.

Table 8 shows the relative bioavailability and 90 % confidence intervals for GLE/PIB film-coated bilayer tablets under fasting and fed (moderate fat and high fat) conditions.

Table 8. Relative Bioavailability and 90 % Confidence Intervals for GLE/PIB Film Coated Bilayer Tablets under Fasting and Fed (moderate fat and high fat) conditions

Regimens (Test vs Reference)	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
		ABT-493			
B vs A	C_{max} (ng/mL)	941	298	3.161	2.584 – 3.868
	AUC_t (ng•h/mL)	3040	1160	2.630	2.178 – 3.176
	AUC_∞ (ng•h/mL)	3040	1160	2.625	2.175 – 3.168
C vs A	C_{max} (ng/mL)	638	298	2.143	1.751 – 2.622
	AUC_t (ng•h/mL)	2120	1160	1.833	1.518 – 2.213
	AUC_∞ (ng•h/mL)	2120	1160	1.829	1.516 – 2.207
		ABT-530			
B vs A	C_{max} (ng/mL)	218	115	1.895	1.487 – 2.414
	AUC_t (ng•h/mL)	1270	903	1.404	1.106 – 1.783
	AUC_∞ (ng•h/mL)	1330	952	1.402	1.106 – 1.775
C vs A	C_{max} (ng/mL)	236	115	2.050	1.602 – 2.623
	AUC_t (ng•h/mL)	1390	903	1.535	1.203 – 1.958
	AUC_∞ (ng•h/mL)	1460	952	1.532	1.204 – 1.950

Regimen A: Single 300 mg/120 mg dose of ABT-493/ABT-530 (3 × 100 mg/40 mg film-coated bilayer tablets) under fasting conditions (Reference).
Regimen B: Single 300 mg/120 mg dose of ABT-493/ABT-530 (3 × 100 mg/40 mg film-coated bilayer tablets) following a moderate fat breakfast (Test).
Regimen C: Single 300 mg/120 mg dose of ABT-493/ABT-530 (3 × 100 mg/40 mg film-coated bilayer tablets) following a high fat breakfast (Test).

Source: M14-714 Clinical Study Report, Page 47

Food increased bioavailability of co-formulated GLE/PIB FDC tablets. Following moderate and high-fat breakfast, GLE exposure ranged from 1.8- to 3.2-fold, and PIB exposure ranged from 1.4- to 2.1-fold of those under fasting conditions.

Assessment of Accumulation of GLE and PIB when Co-Administered

The applicant assessed the accumulation of GLE and PIB when each drug was administered alone in trials M13-356 and M13-355, respectively.

Table 9. Multiple Dose Pharmacokinetics of GLE (trial M13-356)

Pharmacokinetic Parameters (units)	GLE Regimens, Day 10 Geometric Mean (Mean, %CV)		
	200 mg QD (N = 8)	400 mg QD (N = 8)	800 mg QD (N = 8)
C_{max} (ng/mL)	137 (148, 44)	1810 (2610, 100)	14100 (17200, 52)
T_{max}[a] (h)	3.0 (1.0 – 5.0)	4.0 (3.0 – 5.0)	4.0 (3.0 – 5.0)
C_{trough} (ng/mL)	1.04 (1.14, 39)	4.98 (7.88, 130)	40.9 (58.2, 80)
AUC_{24} (ng•h/mL)	556 (565, 19)	5980 (8840, 113)	64100 (80400, 54)
C_{max}/Dose (ng/mL/mg)	0.68 (0.74, 44)	4.53 (6.52, 100)	17.6 (21.5, 52)
AUC_{24}/Dose (ng•h/mL/mg)	2.78 (2.83, 19)	15.0 (22.1, 113)	80.1 (100, 54)
AUC R_{ac}[b]	0.95 [0.88 – 1.30]	1.14 [0.76 – 1.31]	1.81 [0.72 – 3.66]

a. Median (minimum through maximum).
b. R_{ac} = Accumulation ratio (calculated as the ratio of AUC_{24} on Study Day 10 to Study Day 1). Median and range are presented.

Source: Summary of Clinical Pharmacology Studies, Page 18

Table 10. Multiple Dose Pharmacokinetics of PIB (trial M13-355)

Pharmacokinetic Parameters (units)	PIB Regimens, Day 10 Geometric Mean (Mean, %CV)			
	30 mg QD (N = 7)	60 mg QD (N = 7)	180 mg QD (N = 8)	600 mg QD (N = 8)
C_{max} (ng/mL)	9.17 (9.68, 34)	27.0 (31.0, 56)	115 (123, 38)	312 (324, 26)
T_{max}[a] (h)	5.0 (1.0 – 5.0)	5.0 (2.0 – 5.0)	5.0 (3.0 – 5.0)	5.0 (4.0 – 5.0)
C_{trough} (ng/mL)	0.64 (0.68, 32)	2.31 (2.47, 40)	9.97 (12.9, 84)	26.5 (27.6, 28)
AUC_{24} (ng•h/mL)	52.1 (54.5, 33)	162 (180, 49)	786 (881, 52)	2090 (2170, 27)
C_{max}/Dose (ng/mL/mg)	0.31 (0.32, 34)	0.45 (0.52, 56)	0.64 (0.69, 38)	0.52 (0.54, 26)
AUC_{24}/Dose (ng•h/mL/mg)	1.74 (1.82, 33)	2.70 (3.00, 49)	4.37 (4.89, 52)	3.48 (3.61, 27)
AUC R_{ac}[b]	1.53 [0.98 – 2.46]	1.32 [0.73 – 2.61]	1.38 [1.15 – 1.98]	1.33 [1.11 – 1.68]

a. Median (minimum through maximum).

b. R_{ac} = Accumulation ratio (calculated as the ratio on Study Day 10 to Study Day 1); mean and range (minimum to maximum) are presented.

Source: Summary of Clinical Pharmacology Studies, Page 21

Considering that GLE and PIB will be [redacted](b) (4) as a fixed dose combination and GLE affects the systemic exposure of PIB at the clinically recommended dose (see Table 12), estimating accumulation of GLE and PIB when GLE and PIB are co-administered is more clinically relevant.

In trial M14-532 (DDI trial with sofosbuvir), GLE and PIB were co-administered and the pharmacokinetic parameters were assessed after single and multiple dose. Based on mean C_{max} and mean AUC_{24hrs} (data taken from table 7 on page 79 of clinical study report) on day 1 in period 1 and day 7 in period 1, the accumulation of GLE was 1.11-fold and 1.22-fold, respectively. For PIB, based on mean C_{max} and AUC_{24hrs} (data taken from table 9 on page 82 of clinical study report) on day 1 in period 1 and day 7 in period 1, there was no accumulation based on comparison of mean C_{max} whereas the accumulation of PIB was 1.27-fold based on comparison of AUC_{24hrs}.

The applicant also summarized the single dose pharmacokinetic data of GLE and PIB after co-administration of GLE and PIB in various trials. Table 11 shows the comparison.

As shown in the table above, the half-life of GLE and PIB was estimated to be approximately 6 hours and 13 hours, respectively. It is important to note that in the DDI trial with omeprazole which used GLE/PIB FDC tablet (trial M14-715), the half-life of GLE and PIB after single dose administration was 5.3 hours and 11.5 hours, respectively in Arm 1 and 5.3 hours and 12.3 hours in Arm 2, respectively. Using an estimate of 6 hours for GLE half-life and 13 hours for PIB half-life, the calculated accumulation ratio R ($R=1/1-exp^{(-ke*\tau)}$) for GLE and PIB was approximately 1.1 and 1.38, respectively. Of note, the estimated accumulation ratio is similar to the accumulation ratio based on observed data from trial M14-532.

Table 11. Single Dose Pharmacokinetics of GLE and PIB co-administered as Phase 2b or Phase 2a/2b tablets

DAA Regimen	Formulation	Food Status	Subjects (N)	C_{max}[a] (ng/mL)	T_{max}[b] (h)	AUC_{inf}[a] (ng•h/mL)	$t_{1/2}$[c] (h)
GLE							
GLE 400 mg + PIB 120 mg	Ph2b	Non-fasting	59	3490 (3330 to 4190)	4.0 (4.0 to 4.0)	11000 (10900 to 11700)	4.18 (4.18 to 6.18)
GLE 300 mg + PIB 120 mg	Ph2b	Non-fasting	60	935 (652 to 1050)	3.5 (3.0 to 4.0)	3340 (2650 to 3900)	5.82 (5.16 to 7.11)
GLE 300 mg + PIB 120 mg	Ph2a/b	Fasting	126	654 (388 to 950)	2.0 (2.0 to 2.0)	2340 (1710 to 3180)	6.03 (5.54 to 6.75)
PIB							
GLE 400 mg + PIB 120 mg	Ph2b	Non-fasting	59	304 (302 to 313)	5.0 (5.0 to 5.0)	2250 (2230 to 2260)	19.1 (19.1 to 20.7)
GLE 300 mg + PIB 120 mg	Ph2b	Non-Fasting	60	239 (181 to 302)	5.0 (4.0 to 6.0)	1690 (1400 to 2090)	13.4 (11.2 to 39.5)
GLE 300 mg + PIB 120 mg	Ph2a/b	Fasting	125	155 (125 to 175)	4.0 (3.0 to 5.0)	1340 (1170 to 1490)	13.2 (12.6 to 13.5)

a. Overall geometric mean and range of geometric means.
b. Weighted median and range of study medians.
c. Weighted median and range of study harmonic means.
Cross reference: Appendix 3.1.1, Appendix 3.1.2, Appendix 3.2.1, Appendix 3.2.2, Appendix 4.1, Appendix 4.2

Source: 2.7.1: Summary and Cross Study Comparison of Glecaprevir and Pibrentasvir Pharmacokinetics in Healthy Adult Subjects when administered in Combination (R&D/16/0237), Page 16

Assessment of the Potential of Drug-Drug Interaction between GLE and PIB (Trial M13-586)

Trial M13-586 was designed to assess the potential of DDI between GLE and PIB. This multi- arm trial evaluated various doses and dose combinations of GLE and PIB. The trial did not include a group of healthy volunteers who were administered GLE 300 mg and PIB 120 mg. In order to assess the impact of GLE on PIB at the clinically relevant dose (and other dose combinations), the applicant conducted a cross trial comparison. Table 12 shows the results of the cross trial comparison.

Table 12. Effect of Multiple GLE Doses on the Pharmacokinetics of Multiple PIB Doses

			PIB C_{max} Central Value Ratio		PIB AUC_{24} Central Value Ratio	
GLE Dose (mg)	PIB Dose (mg)	Study	Point Estimate	90% CI	Point Estimate	90% CI
1200[a]	200	M13-586	2.870	(2.459 to 3.350)	3.967	(3.430 to 4.588)
700[b]	160[b]	M13-586	4.846	(4.185 to 5.611)	7.046	(5.366 to 9.250)
700[b]	160[b]	M14-066	4.651	(3.695 to 5.855)	6.825	(5.543 to 8.405)
400	120	M13-586	2.856	(2.296 to 3.554)	3.506	(2.679 to 4.588)
400	40	M13-586	6.158	(4.317 to 8.785)	6.307	(5.063 to 7.857)
300	120	M15-432	2.866	(2.593 to 3.168)	3.142	(2.912 to 3.391)
200	80	M15-432	3.025	(2.541 to 3.601)	2.910	(2.539 to 3.335)
100	40	M13-586	1.455	(1.045 to 2.024)	1.455	(1.133 to 1.869)

a. Coadministration of GLE 1200 mg QD with PIB 120 mg QD was prematurely discontinued in Study M13-586, results are shown for the effect of a single PIB 120 mg dose on GLE 1200 mg QD.
b. The GLE 700 mg + PIB 160 mg combination was evaluated in Studies M13-586 and M14-066. Results for each study are listed independently.
Cross reference: Studies M13-586,[8] M14-066,[9] M15-432[10]

Source: 2.7 1: Summary and Cross Study Comparison of Glecaprevir and Pibrentasvir Pharmacokinetics in Healthy Adult Subjects when administered in Combination (R&D/16/0237), Page 19

Note: footnote "a" does not apply because the table primarily describes the effect of GLE on PIB. Further, the footnote refers to the 120 mg dose of PIB whereas the table indicates a 200 mg dose.

Based on the results of trial M15-432, at the clinically relevant dose of GLE and PIB (300 mg and 120 mg, respectively), GLE increased the mean C_{max} and $AUC_{0\text{-}24hrs}$ of PIB by approximately 2.86-fold and 3.1-fold, respectively. Table 13 shows the effect of multiple PIB doses on the pharmacokinetics of multiple GLE doses (based on cross trial comparison).

Table 13. Effect of Multiple PIB Doses on the Pharmacokinetics of Multiple GLE Doses

			GLE C_{max} Central Value Ratio		GLE AUC_{24} Central Value Ratio	
GLE Dose (mg)	PIB Dose (mg)	Study	Point Estimate	90% CI	Point Estimate	90% CI
1200[a]	200	M13-586	1.178	(0.924 to 1.501)	1.265	(0.919 to 1.741)
700[b]	160[b]	M13-586	1.717	(1.275 to 2.312)	1.829	(1.445 to 2.314)
700[b]	160[b]	M14-066	1.301	(1.069 to 1.583)	1.298	(1.064 to 1.583)
400	120	M13-586	1.406	(1.010 to 1.959)	1.451	(1.093 to 1.927)
300	120	M15-432	1.167	(1.004 to 1.356)	1.174	(1.053 to 1.309)
200	120	M15-432	1.171	(0.978 to 1.403)	1.197	(1.036 to 1.383)
100	120	M15-432	1.233	(1.082 to 1.406)	1.567	(1.404 to 1.748)

a. Coadministration of GLE 1200 mg QD with PIB 120 mg QD was prematurely discontinued in Study M13-586, results are shown for the effect of a single PIB 120 mg dose on GLE 1200 mg QD.

b. The GLE 700 mg + PIB 160 mg combination was evaluated in Studies M13-586 and M14-066. Results for from each study are listed independently.

Cross reference: Studies M13-586,[8] M14-066,[9] M15-432[10]

Source: 2.7 1: Summary and Cross Study Comparison of Glecaprevir and Pibrentasvir Pharmacokinetics in Healthy Adult Subjects when administered in Combination (R&D/16/0237), Page 20

Based on the results of trial M15-432, at the clinically relevant dose of GLE and PIB (300 mg and 120 mg, respectively), PIB increased the mean C_{max} and $AUC_{0\text{-}24hrs}$ of GLE by 16 % and 17 %, respectively.

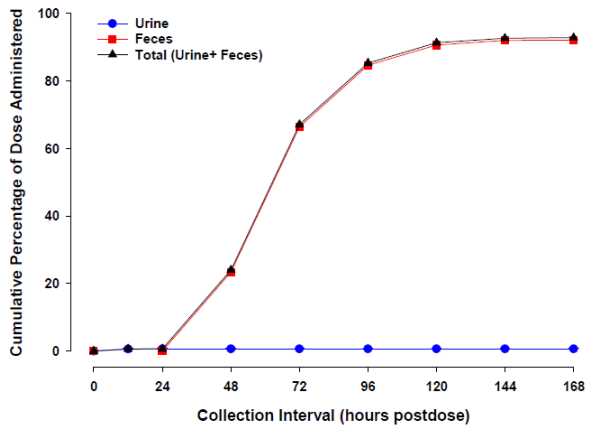
Mass Balance (Trial M13-890)

The mass balance trial was designed to assess the ADME of [redacted] (b) (4) formulation of GLE and [redacted] (b) (4) formulation of PIB. Of note, these formulations are not discussed in this review because they were not further developed by the applicant.

GLE

Figure 1 shows the mean cumulative percent of total radioactivity recovered in the urine and feces after a single dose of GLE 400 mg containing 125 µCi [^{14}C].

Figure 1. Mean Cumulative Percent of Total Radioactivity Recovered in Urine and Feces after a Single Dose of GLE 400 mg Containing 125 µCi [^{14}C]



Total radioactivity was determined for urine and feces of each subject. The mean values from the six subjects are plotted in the above figure.

Cross reference: R&D/15/0355

Source: M13-890 Clinical Study Report, Page 54

The overall mean recovery of radioactivity in urine and feces was 92.8% ± 0.9 % up to 168-hour post dose, with recovery in individual subjects ranging from 91.2% to 93.9%. The majority of the radioactivity was excreted in the feces (92.1 % ± 0.9 %) with limited radioactivity (0.66 %) found in urine. Table 14 shows the percent recovery of radioactive dose for [^{14}C] GLE and metabolites in pooled feces.

Table 14. Percent Recovery of Radioactive Dose for [^{14}C] GLE and Metabolites in Pooled Feces

	Percent Recovery of Radioactive Dose								
	ABT-493	M2	M4	M5	M6	M24	M23	M22	UFL
Feces[a]	22.6	1.52	0.27	1.76	41.7	2.02	12.3	8.30	1.67

UFL = Unidentified fecal metabolite

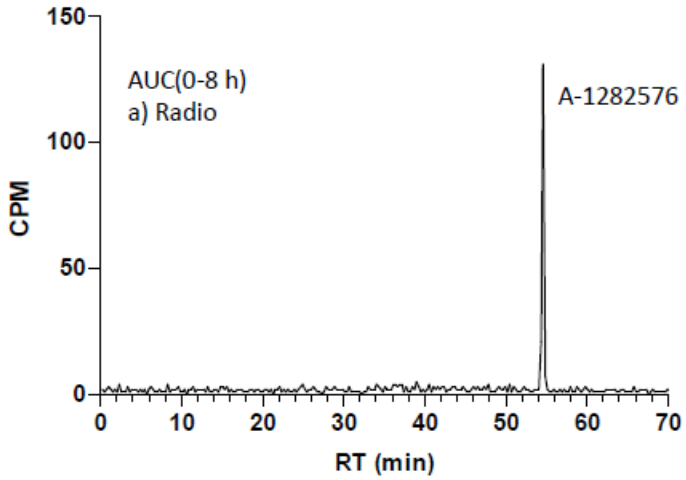
a. Sum of radioactivity dose recovered from 0 – 168 hours in feces pooled across subjects.

Cross reference: R&D/15/0355

Source: M13-890 Clinical Study Report, Page 55

Figure 2 shows the representative chromatogram of the global time-point weighted AUC pooled plasma (0-8 hour) from 6 subjects.

Figure 2. Representative radiochromatogram of global time-point weighted AUC pooled plasma (0-8 hour) from 6 subjects.



Source: R&D/15/0355 Drug Metabolism Report. Page 21 (A-1282576 refers to GLE)

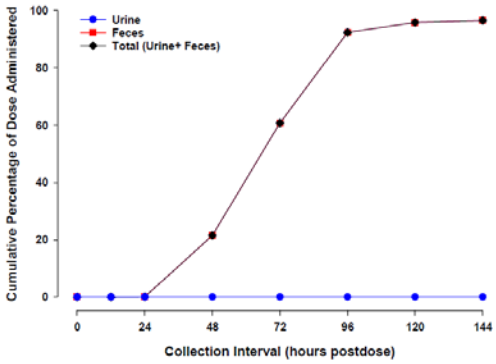
Unchanged GLE accounted for 22.6% of the administered dose recovered in feces. The most abundant metabolite in the feces was the sulfonamide hydrolysis product M6. In vitro incubation of [^{14}C] GLE in fresh human fecal homogenate indicated that sulfonamide hydrolysis to form M6 is mediated by human intestinal microflora and occurs primarily in the gut. Considering that GLE was the only component detected in plasma (as shown in Figure 2) and four metabolites (M2, M4, M5 and M13) were only detected in plasma at trace levels, it is very unlikely that metabolite M6 will have any efficacy or safety related implications.

Due to the low radioactivity recovered from human urine, metabolite profiling of GLE in urine was not conducted. Overall, GLE is primarily cleared through the biliary/fecal route.

PIB

Figure 3 shows the mean cumulative percent of total radioactivity recovered in the urine and feces after a single dose of PIB 120 mg containing 125 µCi [^{14}C].

Figure 3. Mean Cumulative Percent of Total Radioactivity Recovered in Urine and Feces after a Single Dose of PIB 120 mg Containing 125 µCi [^{14}C]



Total radioactivity was determined in urine and feces for each subject. The mean values from the six subjects are plotted in the above figure.
Cross reference: R&D/15/0353

Source: M13-890 Clinical Study Report, Page 58

The overall mean recovery of radioactivity was 96.6% over the 144-hour study, with recovery in individual subjects ranging from 94.9% to 100 %. The administered radioactivity was found entirely in the feces, with no measurable radioactivity found in urine (because of which metabolite profiling was not performed in the urine). Overall, PIB is primarily cleared through the biliary/fecal route as unchanged parent drug (based on the fecal metabolite profiling of PIB)

The results from the mass balance trial also help with further explaining the results from dedicated trials conducted in subjects with renal impairment (M13-600). The results from trial M13-600 suggest that there is no need for dose adjustment of GLE and PIB in subjects with different degrees of renal impairment which may be explained by the very limited excretion of GLE in urine and absence of urinary excretion of PIB. Because GLE and PIB are primarily cleared through the biliary/fecal route, different degrees of hepatic impairment can lead to altered exposures of GLE and PIB as observed in the hepatic impairment trial (M13-604).

APPENDIX

Trial #	Bioanalytical Methods
M14-714	Link to Report: GLE and PIB Method Type: Liquid-Liquid Extraction with LC-MS/MS Matrix: Plasma Analytes: GLE and PIB Range for GLE: 0.205-105 ng/mL (low); 85.9 ng/mL -10,100 ng/mL (high) Range for PIB: 0.205-105 ng/mL (low); 85.9 ng/mL -1030 ng/mL (high)
M14-716	Link to Report: GLE and PIB Method Type: Liquid-Liquid Extraction with LC-MS/MS Matrix: Plasma Analytes: GLE and PIB Range for GLE: 0.199-106 ng/mL (low); 87.1-9850 ng/mL (high) Range for PIB: 0.193-103 ng/mL (low); 84.3 ng/mL -1030 ng/mL (high)
M13-890	Link to Report: GLE and PIB Method Type: Liquid-Liquid Extraction with LC-MS/MS Matrix: Plasma Analytes: GLE and PIB Range for GLE: 0.2-100 ng/mL (low); 85.2-10400 ng/mL (high) Range for PIB: 0.197-98.6 ng/mL (low); 83.8 ng/mL -985 ng/mL (high) Note: Total radioactivity, blood, plasma, urine, feces, fecal homogenate samples, and bulk fecal homogenate were determined using liquid scintillation counting.
M13-586	Link to Report (only information pertaining to GLE and PIB presented below): GLE and PIB Method Type: Liquid-Liquid Extraction with LC-MS/MS Matrix: Plasma Analytes: GLE and PIB Range for GLE: 0.0978 – 249 ng/mL Range for PIB: 0.0987 – 251 ng/mL

4.3 Population PK and/or PD Analyses

4.3.1 Population PK Analysis objectives

The applicant performed popPK analysis of GLE and PIB using the data collected from 10 clinical studies to:

- Characterize the population pharmacokinetics of GLE and PIB when administered alone and in combination in HCV infected subjects
- Identify demographic, pathophysiologic and treatment factors that may contribute to the variability in the pharmacokinetics of GLE and PIB

4.3.2 Methods

The popPK analysis was based on concentration data from four Phase 2 studies (Studies M13-595, M14-867, M14-868 and M15-410) and six Phase 3 studies (Studies M13-583, M13-590, M13-594, M14-172, M15-462, and M15-464). A brief overview of studies included is summarized in Table 4.3.1 (Phase 2 studies) and Table 4.3.2 (Phase 3 studies). The lower limit of quantification in each study is shown in Table 4.3.1.

Table 4.3.1. Summary of Phase 2 studies included in popPK analysis dataset *(Source: Applicant's popPK analysis report, Table 2, Page 29-32)*

STUDY (N)	POPULATION	Dose ranges	PK sampling
M13-595 (N = 84) 3-day monotherapy	Randomised, treatment naïve adult Subjects; chronic HCV GT1; with or without cirrhosis	GLE (N=45): 100, 200, 300, 400 and 700 mg; and 200 mg QD in cirrhotics PIB : 100, 200, 300, 400 and 700 mg; and 200 mg QD in cirrhotics	**Intensive PK sampling:** Study Days 1, 2 and 3: 0 hour (immediately prior to the morning dose), 2, 4, 6, 8, 12 and 16 hours post dose. Study Day 4: 0 and 2 hours post-dose
M14-867 (N = 174) (SURVEYOR-I)	An Open-Label, GLE and PIB with and without ribavirin GT1, 4-6)	GLE: 200, 300 mg QD PIB: 40, 120 mg QD	Day 1: 2, 4 and 6 hours post dose; Week 4 visit at 0, 2, and 4 hours post; Week 1, 2, 6, 8, 10, 12b, 14b and 16b: single samples during the visit without regard to the time since the last dose
M14-868 (N = 691) (SURVEYOR-II)	Randomized, Open-Label, GLE and PIB With and Without RBV in GT2-6	GLE: 200, 300 QD PIB : 40, 120 mg QD	Day 1: 2, 4 and 6 hours post-dose; Week 4: 0, 2, and 4 hours post. Week 1, 2, 6, 8, 10, 12b, 14b and 16b: single samples during the visit without regard to the time since the last dose
M15-410 (N = 141) (MAGELLAN-1)	A Randomized, Open-Label, GLE/PIB With and Without RBV in Adults who Failed a Prior DAA-Containing Therapy	GLE: 200, 300 QD PIB : 80, 120 mg QD	Day 1: 2, 4 and 6 hours post-dose; Week 4: 0, 2, and 4 hours post; Week 1, 2, 6, 8, 10c, 12c, 14c and 16c: single samples during the visit without regard to the time since the last dose.

The available data were from a total of 2710 subjects who received GLE and 2704 subjects who received PIB. Subjects who had at least one measurable GLE or PIB concentration were included in the population pharmacokinetic analyses. The applicant excluded data from five subjects in Study M13-595 citing that these subjects had unusual GLE and PIB pharmacokinetic-profiles. The applicant highlighted that these subjects were from the same study site and had measurable concentrations before dosing and unchanged plasma concentrations measured at different sampling times, suggesting their PK sample collections were misconducted. In total, 21866 plasma concentrations for GLE and 22013 plasma concentrations for PIB were

included in the popPK analysis. The majority of the subjects (89%) included in the pharmacokinetic analysis received GLE 300 mg and PIB 120 mg dose. The lower limit of quantification (LLOQ) results for both GLE and PIB are shown in Table 4.3.3; the intra-run assay results are acceptable due to low percent bias and %CV.

Table 4.3.2. Summary of Phase 3 studies included in popPK analysis dataset *(Source: Applicant's popPK analysis report, Table 2, Page 33-35)*

STUDY (N)	POPULATION	Dose ranges	PK sampling
M13-590 (N = 702) (ENDURANCE-1)	A Randomized, Open-Label, GLE/PIB in Adults with Chronic HCV GT1	GLE: 300 QD PIB : 120 mg QD	**Optional Intensive PK sampling** Day 1: 2, 4 and 6 hours post-dose ; Week 4 : 0, 2 and 4 hours post-dose **Sparse PK sampling**: Week 1, 2, 4, 8/12e: single samples during the visit
M15-464 (N = 202) (ENDURANCE-2)	A Randomized, Double-Blind, GLE/PIB in Adults with Chronic HCV GT2	GLE: 300 QD PIB : 120 mg QD	Sparse PK sampling only: Week 1, 2, 4, 8, and 12: single samples during the visit without regard to the time since the last dose
M13-594 (N = 384) (ENDURANCE-3)	A Randomized, Open-Label, Safety of GLE/PIB to Sofosbuvir+ Daclatasvir in HCV GT3	GLE: 300 QD PIB : 120 mg QD	Week 1, 2, 4, 8/12e: single samples during the visit without regard to the time since the last dose
M13-583 (N = 121) (ENDURANCE-4)	A Single-Arm, Open-Label, Evaluate the Efficacy and Safety in HCV GT4-6	GLE: 300 QD PIB : 120 mg QD	**Optional Intensive PK sampling:** Day 1: 2, 4 and 6 hours post-dose; Week 4: 0, 2 and 4 hours post-dose **Sparse PK sampling:** Week 1, 2, 4, 8, and 12: single samples during the visit
M14-172 (N = 146) (EXPEDITION-1)	A Single Arm, Open-label, HCV GT1-2,4-6 with compensated cirrhosis	GLE: 300 QD PIB : 120 mg QD	Day 1: 2, 4 and 6 hours post-dose; Week 4: 0, 2 and 4 hours post-dose **Sparse PK sampling:** Week 1, 2, 4, 8, and 12: single samples during the visit
M15-462 (N = 104) (EXPEDITION-4)	A Single-Arm, Open-Label, Renally-Impaired Adults HCV GT1, 6	GLE: 300 QD PIB : 120 mg QD	**Optional Intensive PK sampling:** Week 4: 0, and 2, 3, 4, 5 and 6 hours post-dose (Additional intensive PK data were collected for subjects on hemodialysis at Week 4 + 1 Day Visit. GLE/PIB dose was given 2 hour prior to hemodialysis. PK samples 0, 2, 3, 4, and 5 hours post-dose and at the end of dialysis) **Sparse PK sampling:** Week 1, 2, 4, 8, and 12/16f: single samples during the visit without regard to the time since the last dose.

Table 4.3.3. Bioanalytical assay method lower limit of quantification (LLOQ) values *(Source: Applicant's popPK analysis report, Table 3, Page 42)*

	LLOQ (ng/mL)	
Study	**Glecaprevir**	**Pibrentasvir**
M13-595	0.0976 ng/mL	0.0996 ng/mL
M15-410	0.202 ng/mL	0.205 ng/mL
M14-867 M14-868	0.200 ng/mL	0.197 ng/mL
M13-590 M15-464 M13-594 M13-583 M14-172 M15-462	1.00 ng/mL	1.00 ng/mL

Model Development

The applicant developed popPK models using nonlinear mixed effects modeling based on NONMEM 7.3 compiled with the GNU Fortran compiler (Version 4.5.1). The first-order conditional estimation method with η-

ε interaction (FOCE-INT) was employed for all model runs within NONMEM. Base model development included testing of one-, two- and three-compartment models. Based on the observed PK data from GLE and PIB monotherapy Study M13-595 and first-in-human (FIH) Study M13-356, the applicant observed nonlinear PK due to difference in relative bioavailability across doses for both study drugs. Nonlinearity was incorporated on relative bioavailability in the base models. The applicant also incorporated a cirrhosis effect in the base model for GLE. Different covariates were evaluated; continuous covariates were normalized to a reference value (general typical value of the study population) and included in the model with a power function. Categorical covariates were tested with a multiplicative model in order to obtain the fractional difference of pharmacokinetic parameters between the tested categorical groups. The methods used in model evaluation by the applicant included goodness-of-fit plots, visual and numeric predictive checks, and bootstrap evaluation. A summary of intrinsic and extrinsic factors evaluated are provided in Table 4.3.4 and Table 4.3.5 below.

Table 4.3.4. Summary of intrinsic factors included in popPK analysis *(Source: Applicant's popPK analysis report, Table 6, Page 60)*

Characteristic		All Subjects GLE	All Subjects PIB
Sex	Male, N (%)	1532 (57%)	1529 (57%)
	Female, N (%)	1178 (43%)	1175 (43%)
Body Mass Index (kg/m^2)	Mean (SD)	26.8 (5.00)	26.8 (5.02)
	Median	26.1	26.1
	Min – Max	17.3 – 65.7	17.3 – 65.7
Body Surface Area (m^2)	Mean (SD)	1.9 (0.23)	1.9 (0.23)
	Median	1.88	1.88
	Min – Max	1.3 – 2.7	1.3 – 2.7
Treatment experience	Naive, N (%)	1902 (70%)	1896 (70%)
	Experienced, N (%)	808 (30%)	808 (30%)
Cirrhosis	Without cirrhosis, N (%)	2340 (86%)	2335 (86%)
	With cirrhosis, N (%)	370 (14%)	369 (14%)
Renal Function	Normal, N (%)	1293 (48%)	1292 (48%)
	Mild impairment, N (%)	1262 (47%)	1257 (47%)
	Moderate impairment, N (%)	51 (2%)	51 (2%)
	Severe impairment, N (%)	11 (0.4%)	12 (0.4%)
	End stage impairment, N (%)	92 (3%)	92 (3%)

SD = standard deviation; Min = minimum; Max = maximum

Table 4.3.5. Summary of extrinsic factors included in popPK analysis *(Source: Applicant's popPK analysis report, Table 6, Page 60)*

Comedication	Comedication Sub-Category	Number of Subjects (%) GLE (N=2710)	Number of Subjects (%) PIB (N =
Acid Reducing	--	239 (9%)	244 (9%)
Anti-depressants	--	697 (26%)	698 (26%)
Anti-diabetics	--	194 (7%)	197 (7%)
Anti-epileptics	--	189 (7%)	191 (7%)
Anti-hypertensives	--	884 (31%)	845 (31%)
Anti-infectives	--	436 (16%)	435 (16%)
Anti-psychotics	--	116 (4%)	117 (4%)
Antihistamines	--	547 (20%)	551 (20%)
CYP3A Inducer	Moderate	2 (0.07%)	2 (0.07%)
	Strong	2 (0.07%)	2 (0.07%)
	Weak	447 (16%)	446 (16%)
CYP3A Inhibitor	Moderate	64 (2%)	64 (2%)
	Strong	7 (0.3%)	6 (0.2%)
Corticosteroids	-	265 (10%)	270 (10%)
Hormonal	-	56 (2%)	56 (2%)
Hormonal Replacement	-	227 (8%)	229 (8%)
Non-opioid	-	1061 (39%)	1059 (39%)
OATP1B1/B3	Weak	10 (0.4%)	10 (0.4%)
Opioids	--	571 (21%)	569 (21%)
P-gp Inducer	Weak	47 (2%)	48 (2%)
P-gp Inhibitor		131 (5%)	136 (5%)
PDE5 inhibitors	-	43 (2%)	44 (2%)
Proton Pump	-	319 (12%)	318 (12%)
Proton Pump Inhibitors	-	77 (3%)	76 (3%)
Ribavirin	-	105 (4%)	105 (4%)
Statins	-	120 (4%)	121 (5%)

4.3.3 Results

4.3.3.1 GLE Structural and final models

The applicant found a two-compartment PK model with first-order absorption and elimination adequately described the GLE concentration-time data. The two compartment model was parameterized in terms of clearance (CL/F), apparent volume of distribution (V2/F), apparent volume of distribution of the peripheral

compartment (V3/F), inter compartmental clearance (Q/F) and absorption rate constant (KA). High inter-individual variability (IIV) in bioavailability was observed.

There was dose-nonlinearity observed for GLE from the FIH single ascending dose (SAD) and multiple ascending dose (MAD) analyses in study M13-356, GLE exposures increased in a greater than dose-proportional manner across the dose range of 25 mg to 1200 mg with similar observed half-life. The applicant modelled the nonlinearity in GLE pharmacokinetics outside of NONMEM. In this analysis, a non-compartmental analysis (NCA) was used to derive their area under the curve $(AUC)_{0\text{-}6}$ and fit a nonlinear function to the log-transformed $AUC_{0\text{-}6}$ values in SAS. Higher GLE exposures were observed in subjects with cirrhosis when compared to subjects without cirrhosis (Studies M13-595 and M13-604). In order to account for the observed exposure difference between subjects with cirrhosis and those without cirrhosis, a factor for subjects with cirrhosis was added to the nonlinear function (a cubic polynomial function). Figure 4.3.1 shows the relationship between log-transformed $AUC_{0\text{-}6}$ and dose and different functions tested. The selected cubic function is shown below:

$$\log(AUC_{0-6}) = a + b \cdot Dose + c \cdot Dose^2 + d \cdot Dose^3 + e \cdot Cir$$

$$\xrightarrow{yields} \quad \frac{AUC_{0-6}}{Dose} = \frac{\exp(a + b \cdot Dose + c \cdot Dose^2 + d \cdot Dose^3) \cdot (\exp(e) \cdot Cir)}{Dose}$$

where *a, b, c* and *d* are the coefficients of the polynomial function, *Dose* is the GLE dose and *e* is the factor for the difference between with or without cirrhosis.

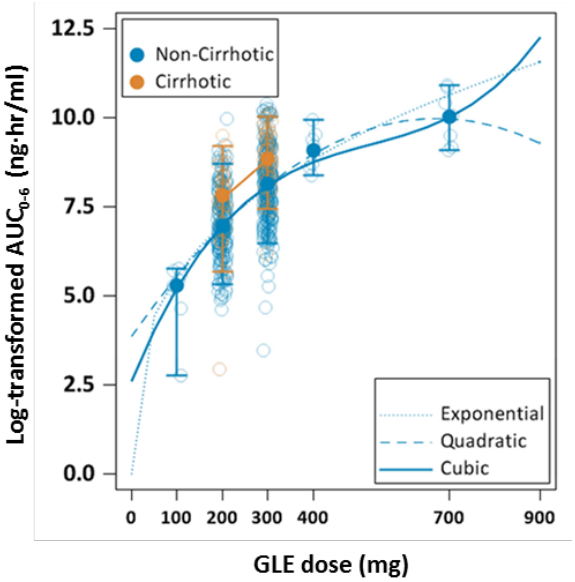


Figure 4.3.1. Dose-Nonlinearity Comparison of GLE *(Source: Applicant's popPK report, Figure 1, Page 65)*

The estimates of coefficients for the polynomial function were obtained using a nonlinear regression model by nonlinear least squares (PROC NLIN in SAS 9.4). The parameter values are shown in Table 4.3.6 and the applicant fixed these estimates when performing NONMEM models. For reference, a dose of 300 mg was selected as the bioavailability reference value (F=1) with bioavailability values for all other doses normalized to this reference.

Table 4.3.6. Parameter estimates for nonlinear polynomial function of GLE bioavailability

Parameter	Estimate
a	2.61
b	3.11E-2
c	5.26E-5
d	3.34E-8
e[a]	7.17

a. The effect of cirrhosis on GLE pharmacokinetics were re-evaluated in subsequent NONMEM Pop PK analysis.

(Source: Applicant's popPK analysis report, Table 9, Page 66)

Reviewer's Comments: The reviewer agrees with the applicant's approach to select cubic function which was developed in SAS and outside NONMEM, to cater for GLE nonlinearity. The approach is sound. However, there was a bias in fixing the cirrhosis effect of bioavailability without considering other factors. The applicant did not provide scientific justification and mechanistic basis for testing cirrhosis effect on bioavailability.

GLE Final Model

The applicant used a step-wise covariate model building strategy and the covariates were tested on CL/F, V2/F and F1. The covariates that gave statistically significant ($P < 0.001$) drop of the objective function in the univariate forward inclusion process are listed in Table 4.3.7 below.

Table 4.3.7. GLE covariate effects based on univariate analysis *(Source: Applicant's popPK analysis report, Table 11, Page 66)*

Covariate	Parameter	Step	Change in OFV	DF	P-value
Renal Function	CL/F	1	–59.2	4	< 0.001
Female Sex	CL/F	2	–31.9	1	< 0.001
Age	CL/F	3	–43.6	1	< 0.001
Phase 3 Formulation	F1	4	–29.5	1	< 0.001
PPI High Dose	F1	5	–20.6	1	< 0.001
Cirrhosis	CL/F	6	–32.5	1	< 0.001
Opioid Comedication	CL/F	7	–13.4	1	< 0.001

OFV = Objective Function Value; DF = Degree of Freedom; PPI = Protein Pump Inhibitor

The final structure of the GLE PK model was a two-compartment model with first order absorption. Inter-individual variability on CL/F and F1 was modeled using a full variance-covariance matrix. A proportional error model was found to be most appropriate for explaining the intra-subject residual variability. The estimated pharmacokinetic parameter values, the effect of the covariates, and their associated variability for the final GLE pharmacokinetic model are listed in Table 4.3.8.

SEE = Standard Error of Estimate; IIV = interindividual variability; PPI = Proton Pump Inhibitor % Relative Standard Error (RSE) was estimated as the SEE divided by the population estimate multiplied by 100. The 95%

confidence interval (CI) was approximated as the point estimate ± 1.96 × SEE. Note: Due to parameter estimation in logarithmic space, estimated effect on F1 may be obtained by exp (estimate).

The goodness of fit plots and visual predictive check for GLE final model are shown in Figure 4.3.2 and Figure 4.3.3, respectively.

Table 4.3.8. Parameter estimates for the Final GLE model *(Source: Applicant's popPK analysis report, Table 13, Page 77)*

Parameter	Estimate (SEE)	%RSE	95% CI	IIV (%) [%RSE]
CL/F (L/day)	1150 (62.6)	5.44	1030, 1270	118 (4.09)
V2/F (L)	130 (8.06)	6.20	114, 146	
Q/F (L/day)	68.0 (4.84)	7.12	58.5, 77.5	
V3/F (L)	39.6 (2.46)	6.21	34.8, 44.4	
KA (1/day)	8.63 (0.139)	1.61	8.36, 8.90	
F1 (300 mg)	1			230 (3.76)
Dose nonlinearity	Fix (Table 9)			
Cirrhosis on F1	1.5 (0.107)	24.9	0.220, 0.640	
Mild Renal Impairment on CL/F	1.03 (0.032)	3.07	0.968, 1.09	
Moderate + Severe Renal Impairment on CL/F	0.706 (0.062)	8.82	0.584, 0.828	
End Stage Impairment on CL/F	0.530 (0.038)	7.13	0.456, 0.604	
Female Sex on CL/F	0.814 (0.024)	2.99	0.766, 0.862	
Age on CL/F	–0.330 (0.061)	18.5	–0.450, –0.210	
Phase 3 Formulation on F1	–0.302 (0.055)		–0.300	
PPI High Dose on F1	–0.541(0.076)			
Cirrhosis on CL/F	0.763 (0.049)	6.36	0.668, 0.858	
Opioids on CL/F	0.900 (0.018)	2.02	0.864, 0.936	
Proportional error (%)	56.6 (0.0088)	1.56	0.545,0.579	

Reviewer's Comments: The model characterized the PK profile of glecapevir (300 mg) in the presence of pibrentasvir (120 mg). The inter-individual variabilities were large for both apparent oral clearance at GLE 300 mg (CL/F), estimated to be 94%, and for relative bioavailability (F) it was 136%. Even though the presence of cirrhosis was a significant model covariate on relative bioavailability, it is unclear how cirrhosis would impact overall bioavailability of the drug. There are various hypotheses for such an effect (i.e., altered liver blood flow), but given that this has not been observed in previous population PK modeling exercises with HCV drugs, the reviewer considers this parameterization to lack physiological justification and is a numeric result from the covariate selection process. Hence the reviewer removed this covariate effect on bioavailability but included it on clearance in the reviewer's independent assessment below. In addition, the reviewer disagrees with the identified renal effect on CL/F given that the results of the dedicated renal impairment study suggest only a marginal impact of renal function on GLE exposure.

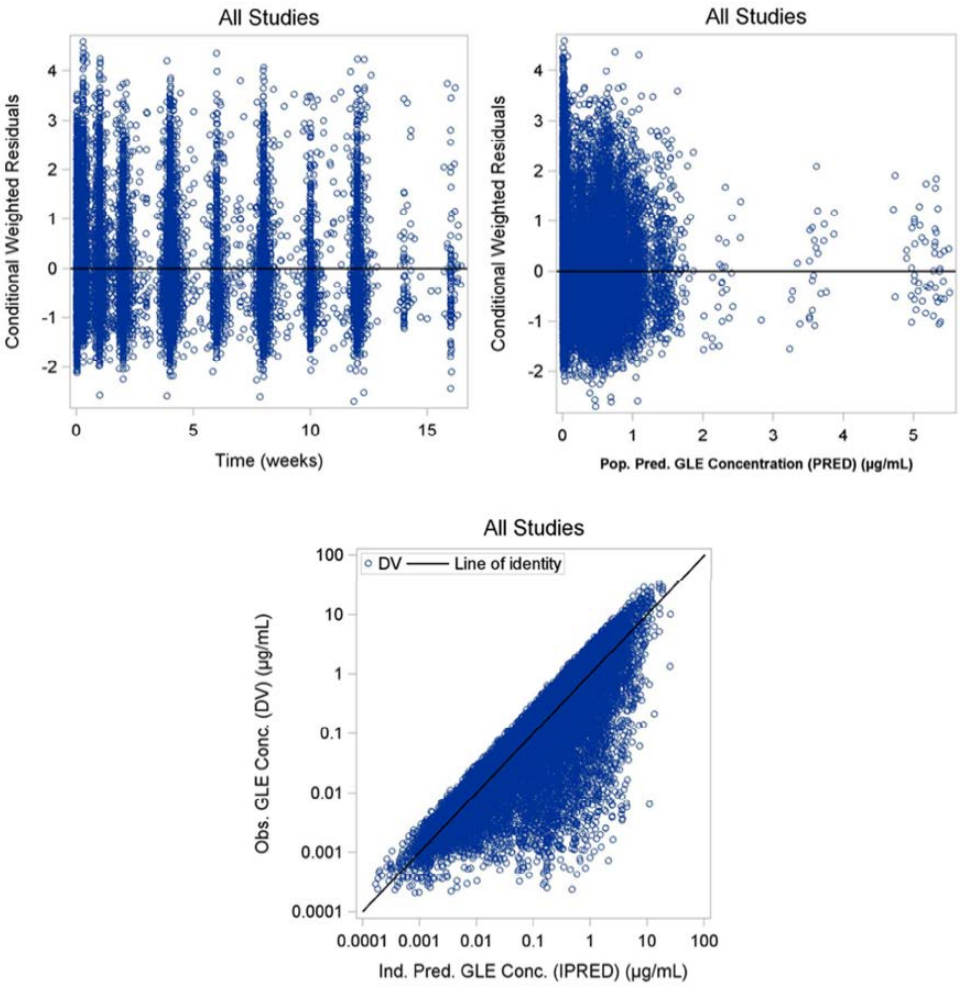


Figure 4.3.2. Goodness-of-fit plots for the final GLE PK model. Goodness-of-fit plots for the conditional weighted residuals versus population predicted (top right) and time (top left) and observed versus individual subject predicted concentrations on log scale (bottom). *(Source: Applicant's popPK analysis report, Figure 2, Page 74)*

The final GLE model was used to obtain estimates of peak plasma concentrations (Cmax) and area under concentration-time curve (AUC) for patients included in the popPK analysis. The majority of the population was patients without cirrhosis (86%) (shown in Table 4.3.4). The applicant's prior information from two Phase 2 studies (studies M13-595 and M13-604) indicated that, for the same GLE dose, patients with compensated cirrhosis had higher exposures when compared to subjects without cirrhosis. The presence of cirrhosis was tested as a covariate on CL/F (24% lower) and F1 (54% higher) in the stepwise model building procedure. The difference between (geometric mean) exposures of subjects with cirrhosis and subjects without cirrhosis was estimated to be 2.2-fold as shown in Table 4.3.9.

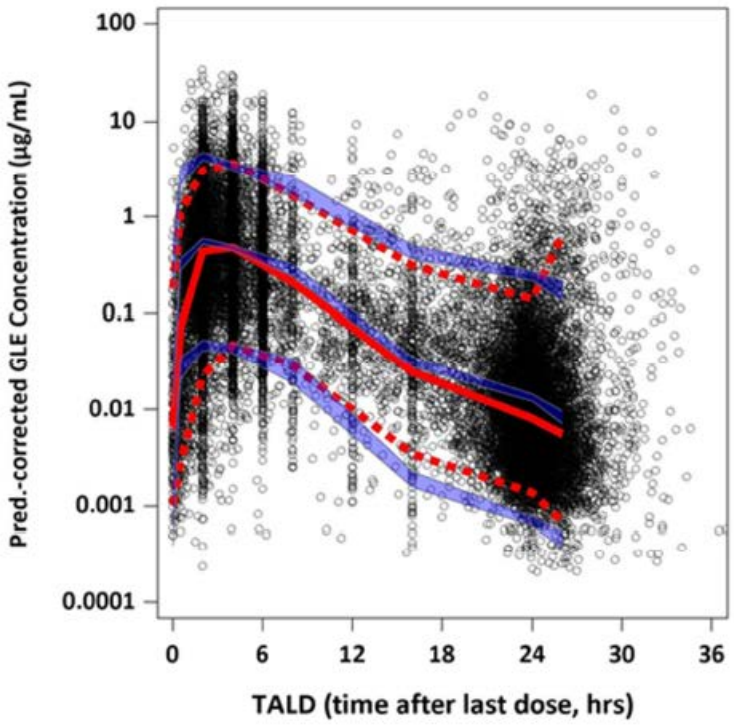


Figure 4.3.3. Visual Predictive Check of Final GLE PK Model. The shaded blue areas represent the 90% prediction interval of the 5th, 50th and 95th percentiles of prediction corrected simulated GLE concentrations, the solid red line represents median of prediction corrected observed GLE concentrations and dashed red lines represent the 5th and 95th percentile of the prediction corrected observed GLE concentrations. The open circles represent prediction corrected observed GLE concentrations. *(Source: Applicant's popPK analysis report, Figure 3, Page 75).*

Reviewer's Comments: The diagnostic plot of observed versus individual predicted concentrations presented in Figure 4.3.2 shows that a subset of concentrations was over-predicted compared to observations. This was predominantly for concentrations less than 0.1 µg/ml, represents a small percentage of the overall data, and may reflect situations where the patient was non-adherent relative to the sampling day (i.e., the dataset is coded with the assumption that the previous doses were administered). . Also, as shown in the visual predictive check plot (Figure 4.3.3), there was a slight under prediction of observed concentrations before peak concentrations were reached.

Table 4.3.9. Model predicted GLE exposures for subjects with or without cirrhosis for GLE/PIB at 300 mg/120 mg QD (Phase 3 Formulation) *(Source: Applicant's popPK analysis report, Table 14, Page 81)*

Parameter	Without Cirrhosis Geometric Mean (%CV)	With Cirrhosis Geometric Mean (%CV)	Overall Geometric Mean (%CV)
$AUC_{24,ss}$ (ng•hr/mL)	4800 (122%)	10473 (101%)	5332 (126%)
$C_{max,ss}$ (ng/mL)	597 (114%)	1109 (91%)	649 (115%)

Overall GLE Comments: The model characterized the PK profile of glecapevir (300 mg) in the presence of pibrentasvir (120 mg). The inter-individual variabilities were large for both apparent oral clearance at GLE 300 mg (CL/F), estimated to be 94%, and relative bioavailability (F), estimated to be 136%. The reviewer agrees with the following identified covariate effects:

- *10-year increase in age (65 years versus 55 years) is associated 32% higher exposures;*
- *Gender: 39% higher exposures in females compared to male;*
- *PPI usage: 5% lower exposure in subjects who took high dose PPIs (omeprazole 40 mg QD equivalent or higher);*
- *Opioid usage: 16% higher exposure in subjects who took opioid medications.*

The reviewer disagrees with the following include covariate effects:

- *The renal function effect does not seem to be supported by the model;*
- *As stated above, there is no mechanistic justification for cirrhosis effect on relative bioavailability, though it is expected that cirrhosis can alter CL/F.*

Even though the effect of cirrhosis on relative bioavailability is not supported, the 2.2-fold effect of cirrhosis on GLE exposure identified using popPK model could still exist.

The applicant suggested a 6- to 10-fold safety margin for GLE relative to typical exposures since a subset of patients had high GLE exposures. These higher exposures appeared to be due to variability in the drug that is not attributed to any of the covariates tested. Thus, the risk of taking various concomitant medications that increase GLE exposure could be additive on this variability. As a result, for any drug/transporter interaction there may be a subset of patients who have exposure increases 6- to 10-fold greater than the mean effect from the drug/transporter interaction. As such, we do not consider it appropriate to justify the safety margin of GLE based on a subset of patients with exposure >6-fold the typical exposure in phase 3 trials.

4.3.3.2 PIB Structural and Final model

A two-compartment PK model with first-order absorption and elimination was found to adequately describe the PIB concentration-time data. The two compartment model was parameterized in terms of CL/F, V2/F, V3/F, Q/F and KA. Inter-individual variability was initially modeled using a variance term only on F1. Similar to GLE, high inter-individual variability in bioavailability was observed for PIB.

The non-linearity in PIB bioavailability was observed in the applicant's first-in-human SAD and MAD studies. The PIB exposures increased in a greater than dose-proportional manner over the 1.5 to 120 mg dose range and were approximately dose-proportional (linear) from 120 to 600 mg. The non-linearity was modelled through derivation AUC_{0-6} of intensive PK samples and fit a maximum efficacy response (E_{max})-type function to the log-transformed AUC_{0-6} values.

The coadministration of GLE with PIB has been observed to increase PIB exposures dose-dependently with comparable half-lives, hence the drug interaction when co-administered with GLE was incorporated on F1. The

effect of GLE on PIB exposure (drug interaction) was estimated to be similar for the GLE 200 mg and GLE 300 mg doses (exponential 1.145 [95% CI: 0.927, 1.364] and 1.172 [95% CI: 0.950, 1.394]) and therefore the same covariate was used for both doses of GLE. The Figure 4.3.4 below shows the relationship between log-transformed AUC_{0-6} and dose of PIB.

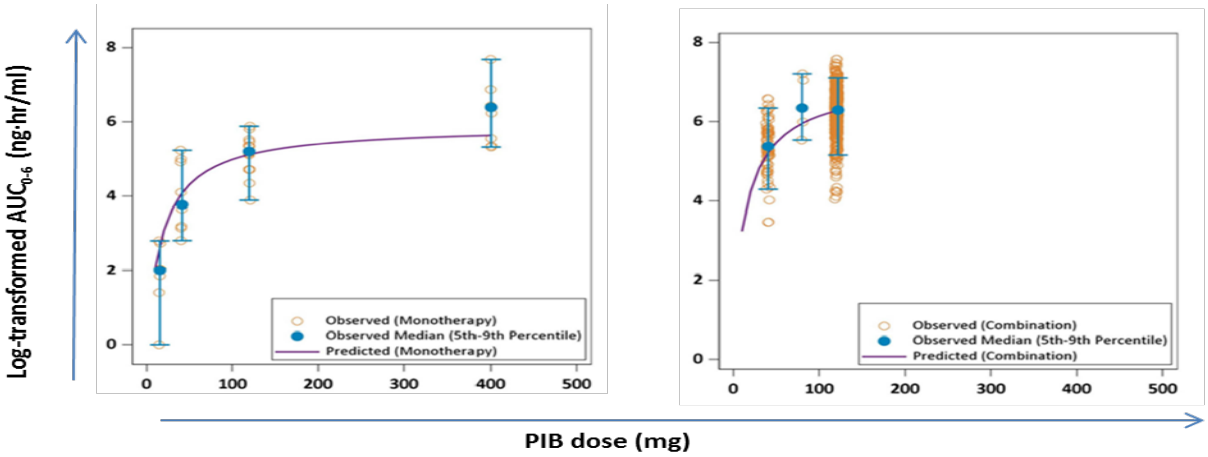


Figure 4.3.4. Log-transformed AUC0-6 versus dose for PIB monotherapy (feft) and combination therapy (right) *(Source: Applicant's popPK report, Figure 8, Page 87)*

The following E_{max}-type functions were used to describe the relationship between GLE and PIB doses:

$$\log(AUC_{0-6}) = \left(Dose_{max} \cdot \frac{Dose}{Dose + Dose_{50}}\right) + boost \cdot GLE$$

$$\xrightarrow{yields} \quad \frac{AUC_{0-6}}{Dose} = \frac{exp\left(Dose_{max} \cdot \frac{Dose}{Dose + Dose_{50}}\right) \cdot \exp(boost \cdot GLE)}{Dose}$$

where $Dose_{max}$ is the dose where the relative bioavailability reaches its maximum, $Dose_{50}$ is the "Dose" where the relative bioavailability reaches half its maximum and "boost" describes the drug interaction effect of GLE 200 and 300 mg doses on the relative bioavailability of PIB.

The parameter estimates for the PIB E_{max}-type function are shown in Table 4.3.10 below.

Table 4.3.10. Parameter estimates for the PIB E_{max}-type function *(Source: Applicant's popPK analysis report, Table 16, Page 86)*

Parameter	Estimate
$Dose_{max}$	5.889
$Dose_{50}$	18.244
boost	1.157

PIB Final Model

The applicant used a step-wise covariate model building approach and covariates were tested on CL/F, V2/F and F1. The covariates that resulted in a statistically significant (P < 0.001) drop of the objective function in the univariate forward inclusion process are listed in Table 4.3.11 below.

The final structure of the PIB PK model was a two-compartment model with first order absorption. A proportional error model was found to be most appropriate for explaining the intra-subject residual variability. The final PIB model parameter estimates are shown in Table 4.3.12.

Table 4.3.11. GLE covariate effects based on univariate analysis *(Source: Applicant's popPK analysis report, Table 18, Page 91)*

Covariate	Parameter	Step	Change in OFV	DF	P-value
Female Sex	CL/F	1	–139	1	< 0.001
Renal function	CL/F	2	–66.2	4	< 0.001
Phase 3 formulation	F1	3	–29.7	1	< 0.001
Asian race	CL/F	4	–32.8	1	< 0.001
Bodyweight	V2/F	5	–5.27	1	0.02
BMI[a]	V2/F		–12.6	1	< 0.001
Age	CL/F	6	–39.1	1	< 0.001
BCRP Inhibitors	F1	7	–24.9	1	< 0.001
Cirrhosis	CL/F	8	–16.2	1	< 0.001

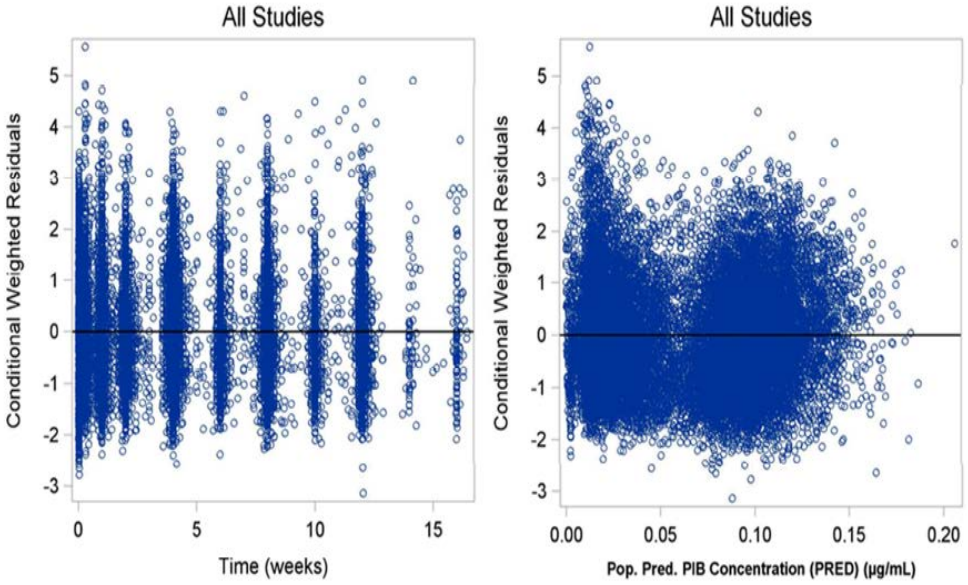
OFV = Objective Function Value; DF = Degree of Freedom; BMI = Body Mass Index; BCRP = Breast Cancer Resistance Protein

Table 4.3.12 Parameter estimates for the final PIB model *(Source: Applicant's popPK analysis report, Table 20, Page 99)*

Parameter	Estimate (SEE)	%RSE	95% CI	IIV (%) [%RSE]
CL/F (L/day)	6340 (171)	2.70	6000, 6680	28.9 (7.84)
V2/F (L)	1380 (63.3)	4.59	1260, 1500	57.8 (5.90)
Q/F (L/day)	1660 (49.9)	3.01	1560, 1760	
V3/F (L)	2250 (111)	4.93	2030, 2470	
KA (1/day)	6.13 (0.186)	3.03	5.77, 6.50	
F1 (120 mg)	1			44.5 (5.10)
Dose nonlinearity	Fix (Table 16)			
Female Sex on CL/F	0.778 (0.014)	1.80	0.751, 0.805	
Mild Renal Impairment on CL/F	0.988 (0.018)	1.84	0.952, 1.02	
Moderate + Severe Renal Impairment on CL/F	0.918 (0.045)	4.92	0.829, 1.01	
End Stage Impairment on CL/F	0.646 (0.025)	3.90	0.597, 0.695	
Phase 3 Formulation on F1	–0.180 (0.027)	15.1	–0.233, –0.127	
Asian Race on CL/F	0.810 (0.024)	2.93	0.764, 0.856	
Bodyweight on V2/F	0.538 (0.083)	15.2	0.378, 0.698	
Age on CL/F	–0.148 (0.036)	24.0	–0.218, –0.078	
BCRP Inhibitors on F1a	0.122 (0.025	20.4	0.073, 0.171	
Cirrhosis on CL/F	0.912 (0.023)	2.51	0.867, 0.957	
Proportional error (%)	25.2 (0.0025)	1.00	0.247, 0.257	

SEE = Standard Error of Estimate; IIV = interindividual variability; PPI = Proton Pump Inhibitor % Relative Standard Error (RSE) was estimated as the SEE divided by the population estimate multiplied by 100. The 95% confidence interval (CI) was approximated as the point estimate ± 1.96 × SEE. Note: Due to parameter estimation in logarithmic space, estimated effect on F1 may be obtained by exp(estimate).

The goodness of fit plots and visual predictive check for the PIB final model are shown below in Figure 4.3.5 and Figure 4.3.6, respectively.



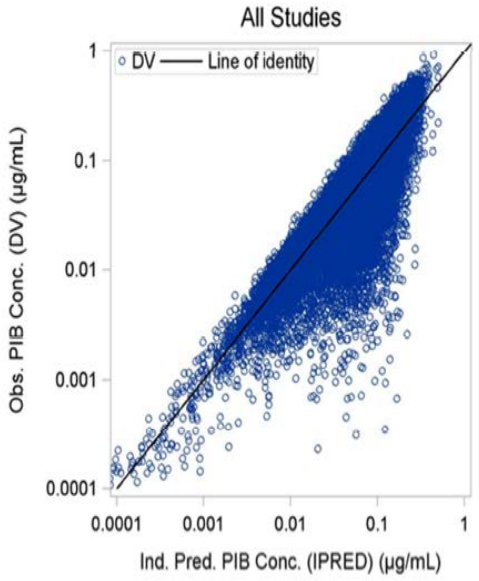


Figure 4.3.5. Goodness-of-fit plots of final PIB PK model. Goodness-of-fit plots for the conditional weighted residuals versus population predicted (top right) and time (top left) and observed versus individual subject predicted concentrations on log scale (bottom). *(Source: Applicant's popPK analysis report, Figure 9, Page 96)*

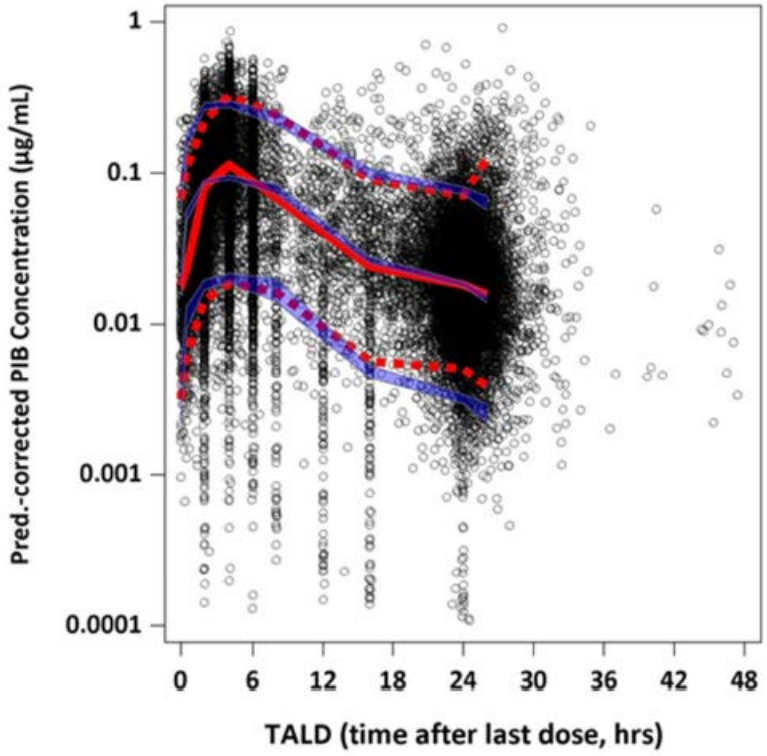


Figure 4.3.6. Visual predictive check of the final PIB PK model. The shaded blue areas represent the 90% prediction interval of the 5th, 50th and 95th percentiles of prediction corrected simulated PIB concentrations, the solid red line represents median of prediction corrected observed PIB concentrations and dashed red lines represent the 5th and 95th percentile of the prediction corrected observed PIB concentrations. The open circles represent prediction corrected observed PIB concentrations. *(Source: Applicant's popPK analysis report, Figure 10, Page 97).*

The final PIB model was used to get the estimates of peak plasma concentrations (Cmax) and area under concentration-time curve (AUC). The majority of the population was patients without cirrhosis (86%) (shown in Table 4.3.4). Subjects with compensated cirrhosis had approximately 9% lower apparent clearance. The differences in the model-predicted exposures (AUC24,ss and maximum plasma concentration at steady state (Cmax,ss)) for subjects with or without cirrhosis administered 300 mg/120 mg GLE/PIB QD of the Phase 3 formulation is shown in Table 4.3.12.

Table 4.3.12. Model predicted GLE exposures for subjects with or without cirrhosis for GLE/PIB at 300 mg/120 mg QD (Phase 3 formulation) *(Source: Applicant's popPK analysis report, Table 21, Page 105).*

Parameter	Without Cirrhosis Geometric Mean (%CV)	With Cirrhosis Geometric Mean (%CV)	Overall Geometric Mean (%CV)
$AUC_{24,ss}$ (ng•hr/mL)	1430 (63)	1530 (54)	1440 (62)
$C_{max,ss}$ (ng/mL)	110 (49)	111 (44)	110 (49)

Reviewer's Comments: The model was appropriate for characterizing the PK profile of PIB (120 mg) in the presence of GLE (300 mg). The inter-individual variabilities for PIB were modest, 29%, 58% and 45% on CL/F, volume of distribution in central compartment (V2/F) and F, respectively. The reviewer agrees with the identified covariates which are: body weight; age; gender; race; BCRP inhibitor usage; cirrhosis Status; except: renal impairment on CL/F.

Conclusions:

Generally the GLE models and PIB models are acceptable. However, independent analysis to evaluate the relevance of renal function as a covariate on GLE and PIB PK was performed by the reviewer given the dedicated renal impairment study results (the study results showed limited impact on PK).

4.3.4 Reviewer's Analysis

4.3.4.1 Introduction

PopPK analysis for GLE and PIB were included in this application to identify covariates that influence GLE and PIB exposure and to use those exposures in subsequent exposure-response efficacy and safety analyses. Therefore, it is of interest to know the adequacy of the GLE and PIB popPK models in describing the observed data. Therefore, the reviewer performed independent analysis to verify the sponsor's analysis. The primary objective was to evaluate whether the results from population PK analysis will support the applicant's claims in the label regarding the impact of various covariates (sex, cirrhosis, body weight, and age) on GLE and PIB exposures.

4.3.4.2 Objectives

Analysis objectives are to:

Evaluate the adequacy of the applicant's final model in describing the observed GLE and PIB concentrations after the proposed dosing regimen.

Evaluate the effect of covariates of interest, such as age, race, renal effect, body weight and cirrhosis, and other factors, on GLE and PIB exposures (steady state AUC).

4.3.4.3 Methods

4.3.4.3.1 Data Sets

The data sets used in the analyses are summarized in Table 4.3.1 and Table 4.4.2. The Table 4.3.13 below shows the link to the lists the link to the dataset.

Table 4.3.13. Link to analysis datasets

Study Number	Name	Link to EDR
Report Number rd160234	pk493.xpt; pk530.xpt	\\cdsesub1\evsprod\NDA209394\0000\m5\datasets\rd160234\analysis\legacy\datasets

4.3.4.3.2 Software

NONMEM (Version 7.3) installed on a 48-core Linux cluster was used for the population PK analysis. An R package in Pirana® was used for graphical diagnostics; R version 3.3.2 was used for all other graphing and statistical analyses.

4.3.4.3.2 Models

The applicant's population PK datasets, final model GLE model (run pk493_run4m_FULL_8-ctl) and final PIB model (pk530-run3b-full-9-ctl) were used for testing the adequacy of the submitted final model and estimating PK parameters. The dataset name and its location are summarized in Table 4.3.13

4.3.4.3 Results

4.3.4.4.1 Population PK estimates

The reviewer conducted population PK analysis with the applicant's models. The results of the applicant's population PK analysis can be repeated. The GLE PK parameter estimates from the reviewer's model were similar to those of the applicant's analysis as shown in Table 4.3.14. In addition, Table 4.3.14 shows the parameter estimates after removing the renal function covariate on GLE CL/F. Table 4.3.15 show the effect of removing the renal function covariate on PIB exposures. Interestingly, after removing the renal function covariate from the GLE popPK model, there was a 64 point increase in objective function value. At the same time there was only a marginal change in parameter estimates of both drugs suggesting the renal function covariate is not clinically significant. For PIB there was marginal change in parameters estimates but the objective function value increased by 73 points.

4.3.4.4.2 Goodness-of-fit plots for the final model

The final models were evaluated by assessing the goodness-of-fit plots as shown in Figure 4.3.7 for GLE and Figure 4.3.8 for PIB, which shows the concentrations for all subjects. The plots show that the model describes the observed data adequately. For both drugs, there was a slight under-prediction of higher exposures as shown in the respective population prediction versus observed concentration figures. This under-prediction was worse for GLE and could be attributed to its overall high variability (>80% CV).

4.3.4.4.3 Visual predictive check

The final models were also evaluated by assessing the visual predictive checks, which were stratified by dose and cirrhosis status, as shown in Figure 4.3.9 for GLE and Figure 4.3.10 for PIB. In general, the GLE model is acceptable and describes the data fairly well; however there is under-prediction in the absorption phase. For

PIB, there was under-estimation of doses above 120 mg. Based on parameter estimates and goodness of fit plots, no significant impact on model performance are expected with removal of a covariate for renal function.

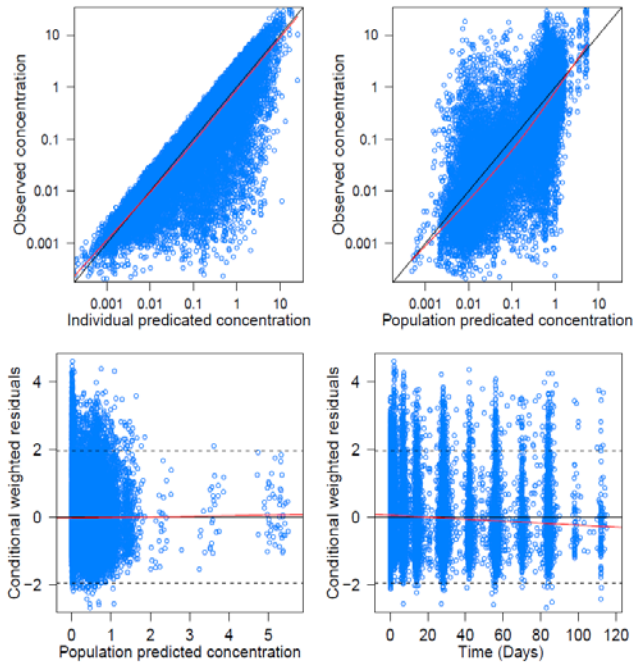
Table 4.3.14. Parameter Estimates for GLE final model

Description	Applicant's final model with a covariate for renal function		Reviewer's model, no covariate for renal function
Objective function value	-73490.462		-73426.689
OFV diff with run4938	0		63.773
CL/F (L/day)	1150		1150
V2/F (L)	130		130
Q (L/day)	68		70.1
V3/F (L)	39.6		40.9
KA (1/day)	8.62		8.56
Dose nonlinearity	Fix (Table 4.3.6)		Fix (Table 4.3.6)
Cirrhosis on F1	0.433		0.437
Mild renal impairment on CL/F	1.03		-
Moderate and severe renal impairment on CL/F	0.707		-
End stage renal impairment on CL/F	0.532		-
Female sex on CL/F	0.815		0.83
Age on CL/F	-0.33		-0.369
Phase 3 formulation on F1	-0.3		-0.266
PPI high dose on F1	-0.541		-0.505
Cirrhosis on CL/F	0.767		0.762
Opioids on CL/F	0.901		0.904
IIV_CL	93.60%		95.80%
IIV_F1	135.60%		137.10%
Proportional error (%)	75%		75%

Table 4.3.15. Parameter Estimates for PIB final model

Description	Applicant's final model with a covariate for renal function		Reviewer's model, no covariate for renal function
Objective function value	-136721		-136648
OFV diff with run5310	0		73.051
CL/F (L/day)	6340		6240
V2/F (L)	1380		1400
Q (L/day)	1660		1660
V3/F (L)	2250		2260
KA (1/day)	6.13		6.11
Dose nonlinearity	Fix (Table 4.3.10)		Fix (Table 4.3.10)
Female sex on CL/F	0.778		0.785
Mild renal impairment on CL/F	0.988		-
Moderate and severe renal impairment on CL/F	0.925		-
End stage Impairment on CL/F	0.647		-
Phase 3 formulation on F1	-0.18		-0.162
Asian race on CL/F	0.811		0.819
Body weight on V2/F	0.535		0.514
Age on CL/F	-0.147		-0.176
BCRP inhibitors on F1	0.122		0.145
Cirrhosis on CL/F	0.912		0.913
IIV _CL	28.90%		29.30%
IIV _V2	57.80%		58.70%
IIV _F1	44.50%		44.70%
Proportional error (%)	25.2		25.2

Applicant's model



Reviewer's model without a covariate for renal function

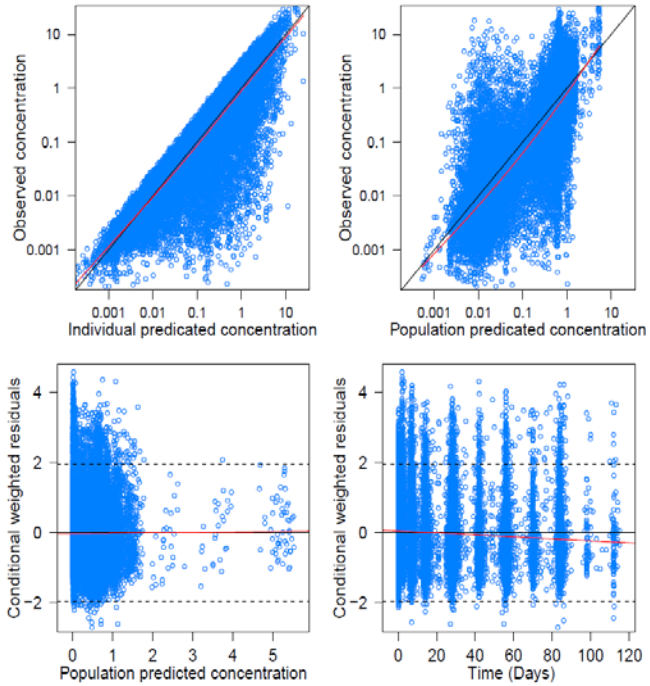
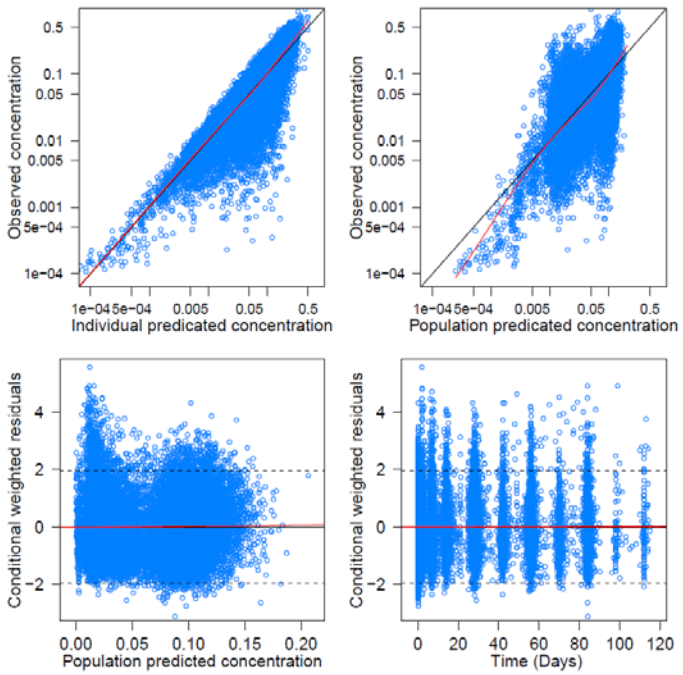


Figure 4.3.7. Goodness of fit plots for GLE models

Applicant's model



Reviewer's model without a covariate for renal function

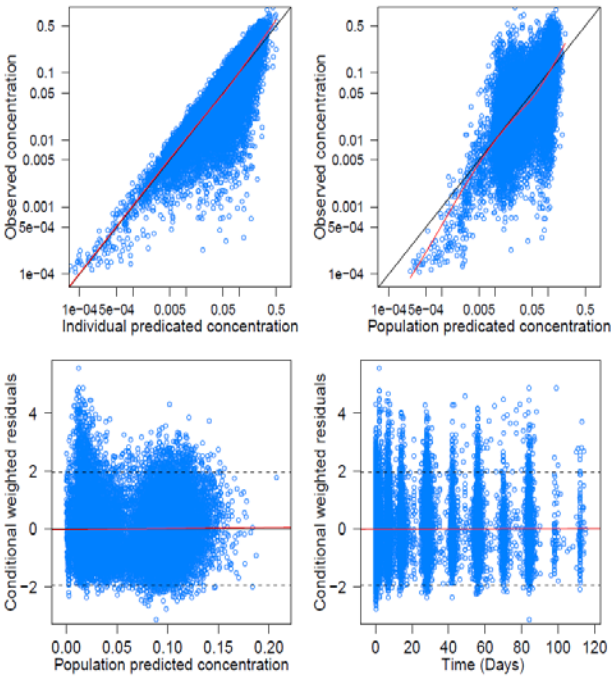


Figure 4.3.8. Goodness of fit plots for PIB models

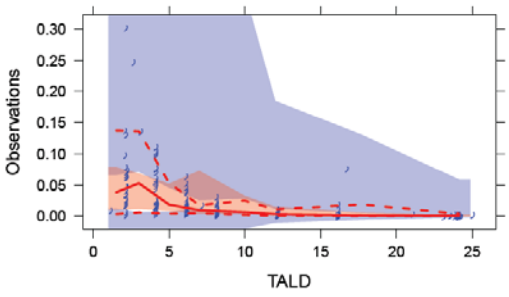
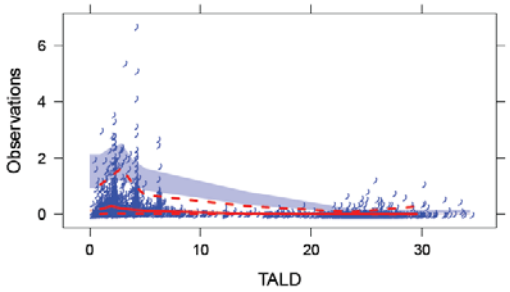
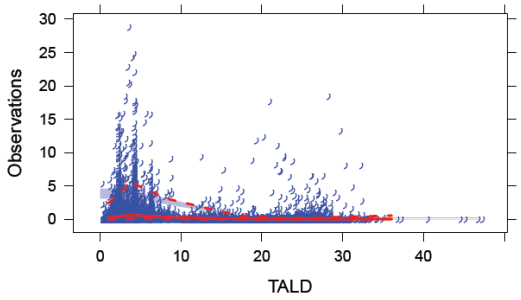
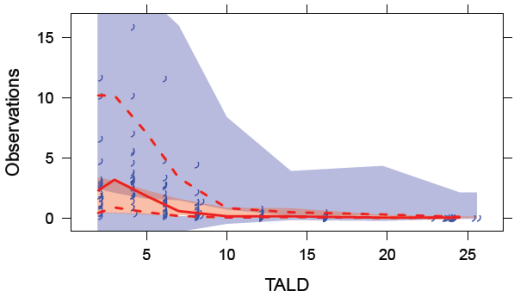
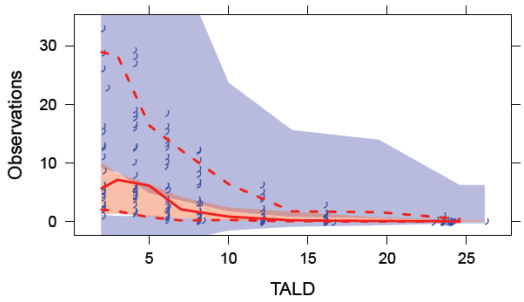
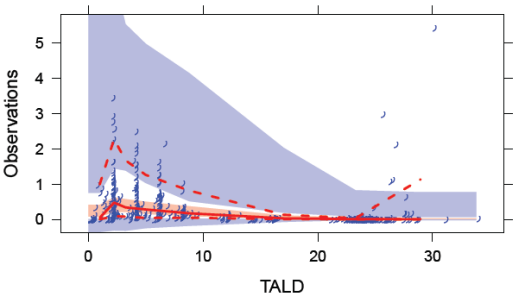
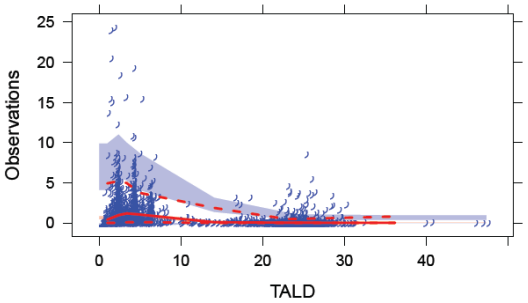
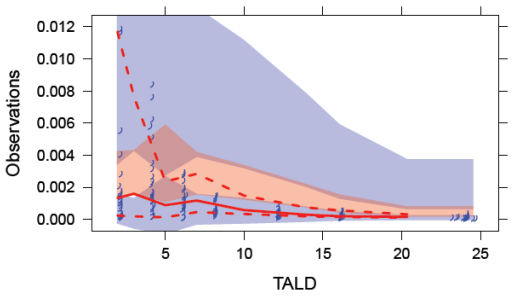
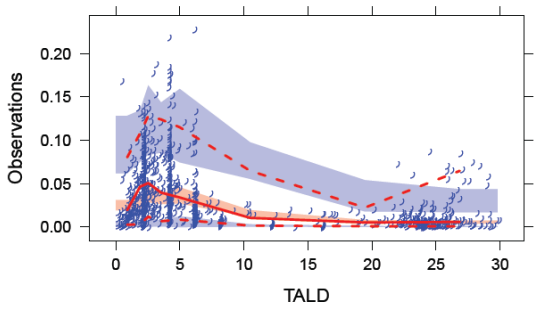
Subjects without cirrhosis , GLE dose 100 mg 	Subjects without cirrhosis, GLE dose 200 mg 
Subjects without cirrhosis , GLE dose 300 mg 	Subjects without cirrhosis, GLE dose 400 mg 
Subjects without cirrhosis , GLE dose 700 mg 	Subjects cirrhosis, GLE dose 200 mg 
Subjects cirrhosis, GLE dose 300 mg 	***Key***: Observations – GLE concentrations (µg/ml); TALD- time after last dose in hours. The shaded areas represent the 90% prediction interval of the 5th, 50th and 95th percentiles of simulated GLE concentrations, the solid red line represents median of prediction corrected observed GLE concentrations and dashed red lines represent the 5th and 95th percentile of the observed GLE concentrations. The open blue circles represent prediction corrected observed PIB concentrations

Figure 4.3.9. Visual predictive check for GLE stratified by cirrhosis status and dose

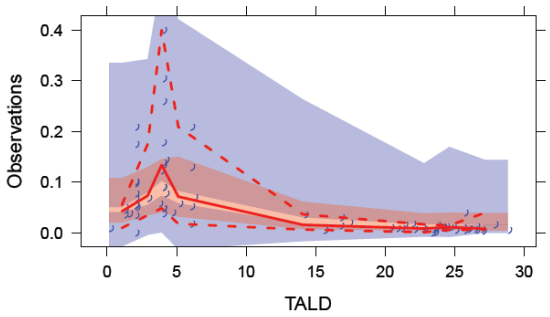
Subjects without cirrhosis , PIB dose 15 mg



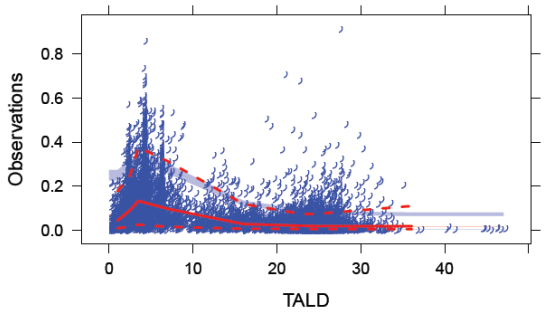
Subjects without cirrhosis, PIB dose 40 mg



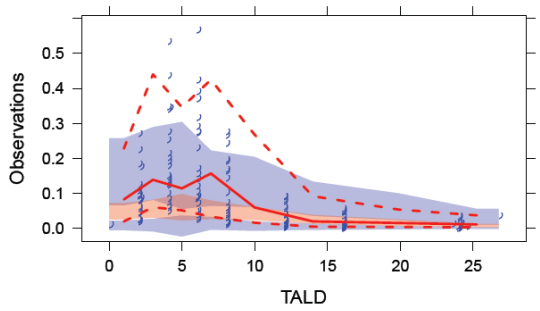
Subjects without cirrhosis , PIB dose 80 mg



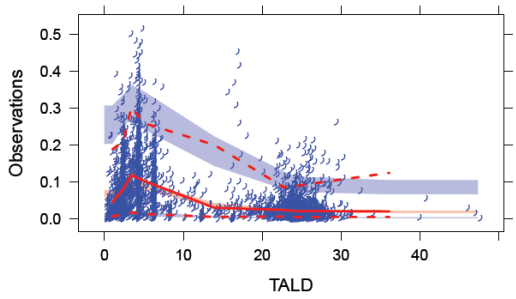
Subjects without cirrhosis, PIB dose 120 mg



Subjects without cirrhosis , PIB dose 400 mg



Subjects cirrhosis, PIB dose 120 mg



Key: Observations – PIB concentrations (µg/ml); TALD- time after last dose in hours. The shaded areas represent the 90% prediction interval of the 5th, 50th and 95th percentiles of simulated PIB concentrations, the solid red line represents median of prediction corrected observed PIB concentrations and dashed red lines represent the 5th and 95th percentile of the observed PIB concentrations. The open blue circles represent prediction corrected observed PIB concentrations

Figure 4.3.10. Visual predictive check for PIB stratified by cirrhosis status and dose

4.4.4.4 Cirrhosis effect on GLE exposures

The applicant tested the effect of cirrhosis on the relative bioavailability for GLE. However, as stated above, the reviewer considers inclusion of such a covariate on this parameter as lacking appropriate physiological justification. Instead, we suggest that this effect should have been tested as an effect of clearance of GLE. The reviewer performed an analysis using the applicant's final model where:

1. The cirrhosis effect was removed on relative bioavailability but kept on clearance
2. Covariates for cirrhosis were included on volume and clearance terms

Table 4.3.16 below lists estimates from the different GLE models evaluated, focusing on the Phase 3 formulation and 300 mg GLE dose. The estimates of Cmax and $AUC_{24,ss}$ were estimated in NONMEM and are close to the estimates reported by the applicant.

Table 4.3.16. Estimates of Cmax and AUCss of 300 mg GLE for Phase 3 formulation

Model structure	OFV	HCV-infected patients without cirrhosis	HCV-infected patients with cirrhosis
1) Original final model (N=2708)	-73490		
Cmax (ng/mL)		605 (160%)	924 (155%)
$AUC_{24,ss}$(ng·h/mL)		5282 (139%)	9839 (128%)
2) Original model without cirrhosis effect on F	-73468		
Cmax (ng/mL)		642 (162%)	692 (162%)
$AUC_{24,ss}$(ng·h/mL)		5502 (140%)	8105 (129%)
3): Cirrhosis on V and CL terms	-73498		
Cmax (ng/mL)		604 (159%)	918 (155%)
$AUC_{24,ss}$(ng·h/mL)		5269 (139%)	9852 (128%)

The results of this analysis showed that subjects with cirrhosis may have approximately 2-fold higher exposures compared with subjects without cirrhosis. However, based on the observed data, there was an overlap in concentrations between cirrhotic and non-cirrhotics, hence making clinical recommendations based on cirrhosis is difficult.

Conclusion. A 2-fold difference in mean exposures between cirrhotic and non-cirrhotic subjects was confirmed; however the overlap in exposures for those subjects without cirrhosis and those with cirrhosis limit the clinical significance of the observed difference.

4.4 Exposure-Response Analyses

4.4.1 Methods

The outcome variables for the exposure-response efficacy analysis were SVR_{12} and RVR collected from HCV GT1- to GT6-infected subjects following treatment with GLE and PIB with or without RBV. These data came from supportive Phase 2 studies (Studies M14-867, M14-868 and M15-410) and registrational Phase 3 studies (Studies M13-590, M15-464, M13-594, M13-583, M14-172, M15-462). The applicant analyzed the relationships between SVR12 or RVR and drug exposure (GLE or PIB) through graphical and multiple linear regression analyses.

A similar analytical approach was done for safety. The applicant performed the exposure-response safety analysis utilizing data from Phase 2 (Studies M14-867 [Parts 1 and 2], M14-868 [Parts 1 and 2] and M15-410 [Part 1]) and registrational studies (Studies M15-410 [Part 2], M13-590, M15-464, M13-594, M13-583, M14-172, M15-462, and M14-868 [Parts 3 and 4]). All subjects who received the GLE/PIB regimens (without RBV) or placebo in the Phase 2 and registrational studies, who had data for safety variables of interest, and who had population pharmacokinetic model predicted exposure values (subjects who received placebo were treated as concentrations of zero) were included in the exposure-response safety dataset.

The applicant used steady state AUC and maximum observed plasma concentration (Cmax) that were estimated based on the predicted individual pharmacokinetic profiles from the population pharmacokinetic models. The adverse events evaluated in the exposure-safety report were post-nadir ALT elevation, post-baseline total bilirubin elevation and diarrhea. ALT/bilirubin elevations and diarrhea were selected as exposure/dose related events as elevations in these laboratory measures have been observed with other protease inhibitors.

Specific definitions used for the analysis were:

1. Maximum post-nadir ALT elevation by Common Terminology Criteria for Adverse Events (CTCAE) grade, where the post-nadir elevation must be an increase in grade from the nadir grade
2. Maximum post baseline total bilirubin elevation by CTCAE grade, where the post-baseline elevation must be an increase in grade from the baseline grade
3. Treatment-emergent diarrhea based on the Medical Dictionary for Regulatory Activities (MedDRA) preferred term by CTCAE grade, where the event must be considered to have a reasonable possibility of being related to study drug by the investigator. The list of Laboratory Abnormalities of Special interest is in Table 4.4.1 below.

Table 4.4.1. Summary of laboratory abnormalities of special interest *(Source: Applicant's rd160 exposure-response analysis page 37, Table 5)*

Laboratory Abnormalities	Treatment	CTCAE Grade, N (%)				
		Grade 1	Grade 2	Grade 3	Grade 4	Total
Post-nadir ALT elevation	Active (N = 2560)	109 (4.3%)	9 (0.4%)	3 (0.1%)	0 (0%)	121 (4.7%)
	Placebo (N = 100)	13 (13%)	9 (9%)	3 (3%)	0 (0%)	25 (25%)
Post-baseline total bilirubin elevation	Active (N = 2560)	172 (6.7%)	52 (2.0%)	9 (0.4%)	0 (0%)	233 (9.1%)
	Placebo (N = 100)	4 (4%)	0 (0%)	0 (0%)	0 (0%)	4 (4%)

For the summary of elevation from nadir by grade in ALT, the post-nadir grade must represent an increase in grade from the grade of the first nadir (including baseline) to be counted. For summary of elevation from baseline by grade in total bilirubin, the maximum post-baseline elevation in grade must represent an increase in grade from the grade of baseline to be counted.

Logistic Regression Exposure-Safety Response Analyses

Exposure –efficacy

The applicant investigated the impact of exposure changes in GLE and PIB on binary efficacy variables, SVR_{12} or RVR, using multiple linear logistic regression. The steady-state GLE and PIB steady-state AUC and C_{trough} were logarithmically transformed and their relationship with $\%SVR_{12}$ or %RVR explored while accounting for the covariates effects. In the multiple linear logistic regressions, probability of SVR_{12} or RVR was modeled via the logit function as follows:

$$logit\left(p\left(Y_i=1\right)\right)=\ln\left(\frac{p\left(Y_i=1\right)}{1-p\left(Y_i=1\right)}\right)=\ln\left(odds\left(Y_i=1\right)\right)=\alpha+\beta_1 x_{1i}+\ldots+\beta_k x_{ki}$$

where Y_i represents the response variable, SVR_{12} or RVR, in the i^{th} subject. $p(Y_i=1)$ represents the probability of achieving SVR_{12} or RVR (SVR_{12} = 1 or RVR = 1) given the explanatory variables $x_{1i},\ldots,x_{ki}$. *Odds* $(Y_i=1) = p(Y_i=1)/\ p(Y_i=0)$ represents the odds of achieving SVR_{12} or RVR (SVR_{12} = 1 or RVR = 1) given the explanatory variables $x_{1i},\ldots,x_{ki}$. The applicant estimated the regression coefficients α and βs using a maximum likelihood method with PROC LOGISTIC in SAS 9.4 implemented using a Unix operating system. A positive regression coefficient means that the explanatory variable increases the odds and the probability of the outcome, while a negative regression coefficient means that the variable decreases the odds/probability of that outcome. Parameter estimates with p-value <0.05 were determined to be significant predictors of SVR_{12} or RVR. The association between SVR12 or RVR and covariates was evaluated in the model at an alpha level of 0.05.

Exposure-safety

The applicant performed logistic regression analyses to evaluate the relationships between exposures (logarithmic exposure values) and safety events, and the effects of selected covariates and baseline status were

also taken into account. The grouping of the categories of response variables in the logistic regression analyses was dichotomized as follows:

1. Maximum post-nadir ALT elevation level: (< Grade 2 versus ≥ Grade 2) and (< Grade 3 versus ≥ Grade 3)
2. Maximum post-baseline total bilirubin elevation level: (< Grade 2 versus ≥ Grade 2) and (< Grade 3 versus ≥ Grade 3)
3. Diarrhea, according to the MedDRA preferred term, and considered to have a reasonable possibility of being related to study drug by the investigator: Any event(s) of any grade (≥ Grade 1) versus No event

The logistic regression model was modelled as follows:

$$logit\left(p(Y_i \geq level)\right) = \ln\left(\frac{p(Y_i \geq level)}{1 - p(Y_i \geq level)}\right) = \ln\left(odds\left(Y_i \geq level\right)\right) = \alpha + \beta_1 x_{1i} + \ldots + \beta_k x_{ki}$$

and

$$p(Y_i < level) + p(Y_i \geq level) = 1$$

where $p(Y_i \geq level)$ represents the probability of obtaining a safety event higher than or equal to certain level (e.g., ≥ Grade 3 laboratory abnormality event) given certain explanatory variables $x_{1i}, x_{2i}, \ldots,$ *and* x_{ki}; $odds(Y_i \geq level)$ represents the odds of obtaining a safety event higher than or equal to a certain level (e.g., ≥ Grade 3 laboratory abnormality event) given certain explanatory variables $x_{1i}, x_{2i}, \ldots,$ *and* x_{ki}. Regression coefficients, α and βs, were estimated using SAS Version 9.2 PROC LOGISTIC procedure.

4.4.2 Results

Exposure-efficacy

The predictor variables for the SVR_{12} are shown in Table 4.4.2.

Table 4.4.2. Predictor variables for SVR_{12} *(Source: Applicant's rd160 exposure-response analysis Table 8, page 46)*

Predictor Variable (Unit)	β	SE	p-value
Treatment-Naïve and PRS-Experienced GT1, GT2, GT4, GT5, and GT6 (Non-GT3) Subjects			
Intercept	−7.1974	4.7936	0.1332
Ln PIB AUC (ng•hr/mL)	1.8276	0.7060	0.0096
Treatment-Naïve GT3 Subjects			
Intercept	−6.7969	3.2964	0.0392
Ln PIB AUC (ng•hr/mL)	1.5361	0.4879	0.0016
PRS-Experienced GT3 Subjects who Received GLE/PIB for 16 Weeks			
Intercept	2.8478	0.5143	< 0.0001
NS5A Inhibitor-Experienced GT1 and GT4 Subjects who Received GLE/PIB for 16 Weeks			
Intercept	1.7729	0.6367	0.0054
Presence of Cirrhosis	−1.4852	0.6367	0.0197

SE = Standard error

The only identified statistically significant predictor of SVR_{12} ($p < 0.05$) in treatment-naïve and PRS-experienced GT1, GT2, GT4, GT5, and GT6 subjects (non-GT3 subjects) and treatment-naïve GT3 subjects was PIB exposure. The identified covariate suggests that an increase in PIB exposures was positively associated with percent SVR_{12} as shown in Table 4.4.2. No tested predictors were found to be significantly associated with SVR_{12} rate in PRS-experienced GT3 subjects who received GLE/PIB for 16 weeks. Presence of cirrhosis was the only predictor which was associated with SVR_{12} rate in NS5A inhibitor-experienced subjects. No significant GLE/PIB exposure-RVR relationship was identified within the GLE and PIB exposure ranges evaluated in the analyses.

Since PIB exposures were associated with SVR_{12}, further analysis was conducted by the applicant to determine the effect of low PIB exposures on treatment outcomes. A subset of data with only subjects who were on Phase 3 formulation in this analysis was used to predict SVR_{12} associated with decreased PIB exposures. The impact lower PIB AUC on SVR_{12} predictions was estimated using the regression model. A 50% decrease in PIB AUC resulted in a 0.8% decrease in SVR_{12} (from 99.7% to 98.9%) for treatment-naïve and PRS-experienced non-GT3 subjects, and a 3.3% decrease in SVR_{12} (from 98.1 to 94.8%) for treatment-naïve GT3 subjects; these results are shown in Figure 4.4.1 below. The high efficacy rates, shallow trends observed even with some lower doses and low sample sizes, limit the model performance to predict efficacy rates outside observed data. GLE and PIB exposures were highly correlated. Efforts to find lower efficacy bounds for GLE were inconclusive since no clear trend was observed.

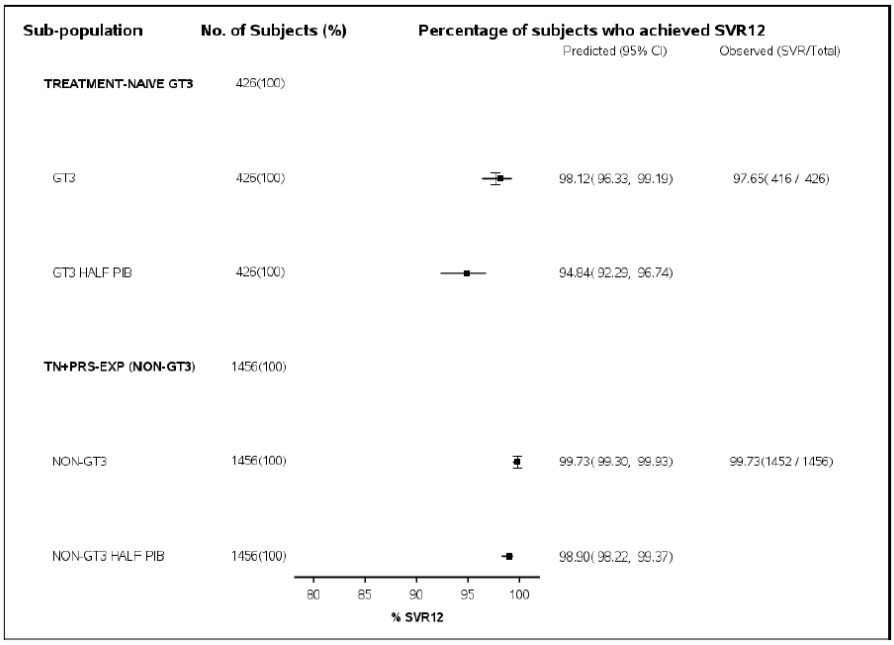


Figure 4.4.1. Summary of the impacts of lower PIB exposure on SVR_{12} rates based on the logistics regression analysis (*Source: Applicant's rd160 exposure-response analysis Figure 9, page 49)*

Exposure- Safety

The results of logistic regression model are summarized in Table 4.4.3. In general, relatively flat relationships with low event rates were identified between ALT elevations ((≥ Grade 2 or ≥ Grade 3) and GLE or PIB exposures. However, based on this analysis, higher GLE AUCs (unlike PIB) correlated with higher odds of post-baseline total bilirubin elevation ≥ Grade 2.

Table 4.4.3. Summary of final models in logistic regression analyses for exposure-safety *(Source: Applicant's rd160 exposure-response analysis page 37, Table 5)*

Response Variable	Predictor Variable	Estimate	Standard Error	p-value
Maximum Post-nadir ALT Elevation (≥ Grade 2)	Intercept	–4.17	0.256	< 0.0001
	Active vs. Placebo	–1.79	0.223	< 0.0001
	Baseline ALT Value	0.00562	0.00117	< 0.0001
Maximum Post-nadir ALT Elevation (≥ Grade 3)	Intercept	–5.11	0.412	< 0.0001
	Active vs. Placebo	–1.64	0.412	< 0.0001
Maximum Post-baseline Total Bilirubin Elevation (≥ Grade 2)	Intercept	–13.2	1.30	< 0.0001
	log AUC of GLE	0.809	0.132	< 0.0001
	Baseline Bilirubin Value	0.168	0.0174	< 0.0001
Maximum Post-baseline Total Bilirubin Elevation (≥ Grade 3)	Intercept	–9.18	0.910	< 0.0001
	Baseline Bilirubin Value	0.208	0.0309	< 0.0001
Diarrhea[a] (Any event)	Intercept	–3.26	0.103	< 0.0001

The applicant used the Hosmer-Lemeshow test to assess the goodness of fit of the logistic regression models, except for models for ≥ Grade 3 post-nadir ALT elevation and diarrhea, where there were no or only one binary predictor in the model. The estimates of the corresponding probability of post-baseline total bilirubin elevation by the predictor variables and covariates in the final regression model are presented in Figure 4.4.1. These

results show that subjects with GLE AUC at the 4th quartile had higher probability (5.9%) of experiencing ≥ Grade 2 events compared to the probability (0.63%) in subjects with GLE AUC in the 1st quartile. Based on these predictions, increasing GLE exposure by 2-fold is predicted to increase the odds of post-baseline total bilirubin elevation ≥ Grade 2 to 1.6-fold.

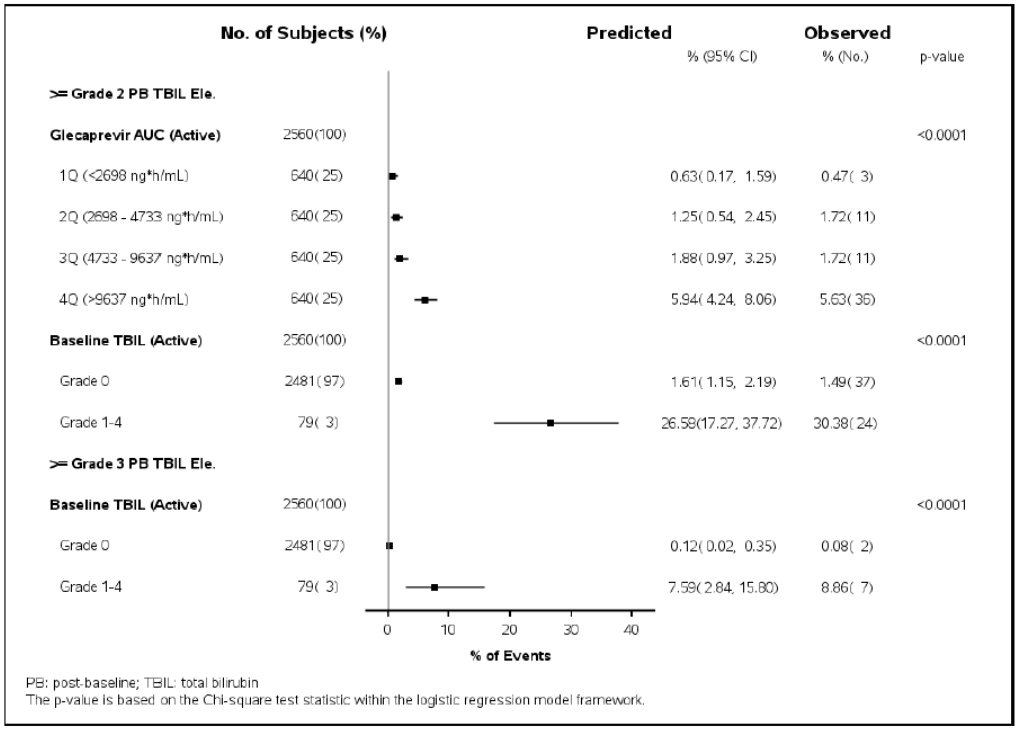


Figure 4.4.2. Summary of the impact of covariates on the rate of post-nadir ALT elevations based on the logistics regression analysis *(Source: Applicant's rd160 exposure-response analysis Figure 8, Page 52).*

Reviewer's comments:

The reviewer agrees with the approach taken by the applicant in assessing the exposure-response. In general, treatment with 300/120 mg GLE/PIB was highly efficacious across all genotypes and patient demographics. However, it should be noted that applicant evaluated pooled data across different treatment durations and genotypes, such that the overall results could be driven by finding in certain subgroups. For example, if the data is stratified by genotype and duration of treatment, then there is limited data on patients with genotype 5-6 treated for 8-weeks versus 12-weeks. Similarly, the results for 16-weeks of treatment for PRS-experienced GT3 subjects who received GLE/PIB and NS5A inhibitor-experienced subjects who received GLE/PIB for 16–weeks was not explored due to minimal predictors.

To evaluate the impact of lower exposures on treatment response, the applicant utilized Phase 2 and Phase 3 data involving various doses, treatment durations, and patient demographics (cirrhosis/non-cirrhosis; genotypes 1-6). Even though, the reviewer agrees with covariate search, the model developed by the applicant could not identify cirrhosis, HCV genotype, and treatment duration as important covariates on treatment, a result that could be due to limited amount of data in the 16-week duration, and high efficacy results observed in subjects with cirrhosis. In general, the regression model adequately described the observed data. Model predictions outside observed data could be associated with in inaccuracy since SRV_{12} lowest doses were not well predicted compared to higher doses. Overall, there was no clear evidence to show the relationship between

GLE exposures and response rate of SVR_{12} or RVR. This conclusion was reached based on graphical assessment and results from the multiple logistic regression analysis. . For PIB, a decrease of 50% in exposures is acceptable based on multiple regression analysis. Comparison of AUCs and corresponding efficacy results obtained in dose ranging studies and those from Phase 3 studies can be utilized to inform the extent of decrease in GLE exposures that would be expected to have minimal impact on efficacy. The 300 mg GLE and 120 mg PIB generally gave high efficacy results of at least 98% in treatment naïve subjects. The respective SVR_{12} rates of more than 93% and 91% in harder to treat GT3 infected treatment naïve and PRS-experienced subjects were observed. Subjects with cirrhosis had generally higher SVR_{12} rates compared with subjects without cirrhosis. However, the SVR_{12} rates as low as 83% were observed in treatment naïve, PR experienced GT3 infected subjects without cirrhosis following 200 mg GLE and 40 mg PIB.

The reviewer agrees with the findings and conclusion reached by the applicant, there was no conclusive evidence of association between PIB exposures and safety signals such as ALT and bilirubin elevations. Higher GLE AUCs (unlike PIB) were correlated with higher odds of post-baseline total bilirubin elevation ≥ Grade 2. The results from dose ranging studies show no major safety signals associated with higher GLE or PIB doses. GLE had highly variable exposures, with some subjects experiencing very high GLE exposure (6- to 10-fold higher than the median value); hence caution should be taken when setting up safety margins.

4.5 Individual Studies Review

Study #	M13-578	**Study Period**	June 25, 2015-October 13, 2015	EDR Link
Title	A Phase 1, Open-Label Study to Assess the Pharmacokinetics, Safety and Tolerability of the Co-Administration of Felodipine or Amlodipine with the Combination of ABT-493 and ABT-530 in Healthy Adult Subjects			

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives:

- Evaluate the effect of GLE and PIB at steady state on the pharmacokinetics of felodipine or amlodipine administered as a single dose.
- Evaluate the effect of felodipine or amlodipine administered as a single dose on the pharmacokinetics of GLE and PIB at steady state.
- To evaluate the safety and tolerability of GLE and PIB when co-administered with felodipine or amlodipine.

Rationale:

Coadministration with GLE (700 mg) and PIB (160 mg) led to an increase in the exposure of CYP3A substrates. Because felodipine and amlodipine are both metabolized by CYP3A, the applicant conducted a DDI trial to assess the potential for a DDI between amlodipine, felodipine and GLE/PIB.

Dose Selection:

GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase 3 trials and proposed for marketing.
Felodipine: Recommended starting dose is 5 mg once daily with titrated doses of 2.5 or 10 mg once daily.
Amlodipine: Recommended starting dose is 5 mg once daily with a maximum dose of 10 mg once daily.

Design and PK Assessments:

Arm	Number of Subjects	Period 1	Washout	Period 2
1	12	Felodipine 2.5 mg on day 1	9 days	GLE 300 mg once daily (days 1-10) + PIB 120 mg once daily (days 1-10); Felodipine 2.5 mg on day 8
2	12	Amlodipine 5 mg on day 1	10 days	GLE 300 mg once daily (days 1-10) + PIB 120 mg once daily (days 1-10); Amlodipine 5 mg on day 8

Source: Table prepared by reviewer based on information provided in the study report.

Serial blood samples for determination of plasma concentrations of GLE and PIB were collected for 24 hours on days 7 and 8; for felodipine or amlodipine, PK samples were collected for 72 hours after dosing.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed

Formulations

GLE (100 mg tablet); PIB (40 mg tablet) [Phase 2b tablets]; Felodipine (2.5 mg tablet); and Amlodipine (5 mg tablet)

RESULTS

Enrolled	24	Completed	24	Discontinued Due to AE	0	PK Population	23*	Safety Population	24

*: One subject in arm 1 was excluded from the statistical analysis. For this subject, there were no (or minimally) detectable DAA and felodipine concentrations on Period 2, Day 7 and Period 2, day 8.

Bioanalytical Method: Link to reports (GLE and PIB) and Amlodipine and Felodipine

Method Name	Liquid/Liquid Extraction with LC-MS/MS		
Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE, PIB, Amlodipine, Felodipine		
Range	GLE: 0.2-100 ng/mL 80-10,300 ng/mL PIB: 0.2-102 ng/mL 81.4-1030 ng/mL Amlodipine: 50 pg/mL -10,000 pg/mL		

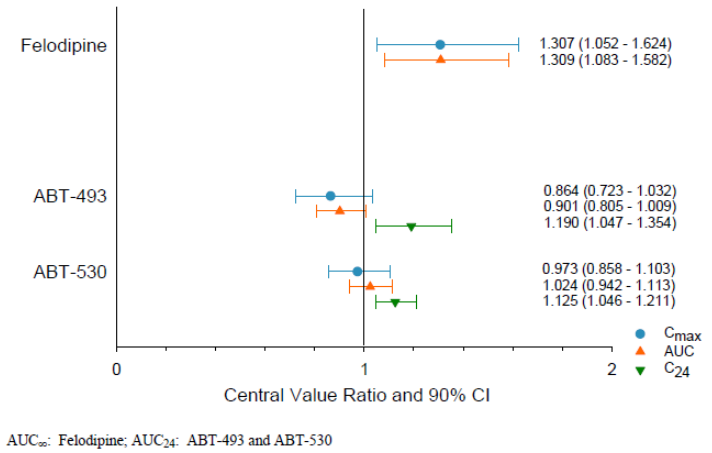
		Felodipine:20 pg/mL -10,000 pg/mL

Protocol Deviations During the intensive pharmacokinetic sampling days, one subject did not consume the entire breakfast on Days 7 and 8 of Period 2. In addition, a few other subjects did not consume their entire lunch or dinner. These deviations are not anticipated to affect the overall outcome of the study results.

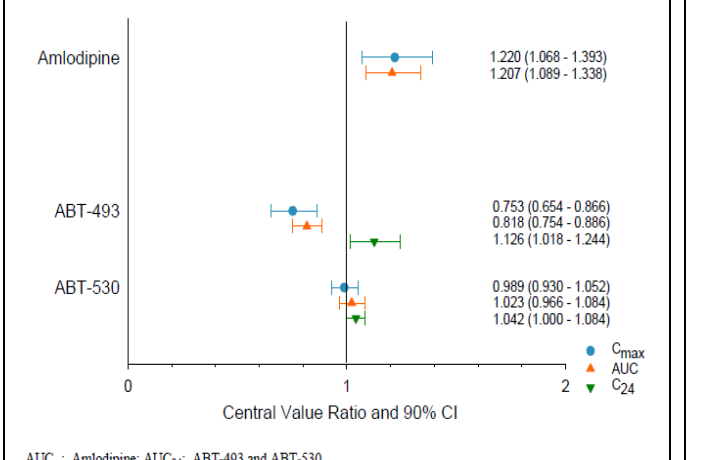
Pharmacokinetics

For felodipine and amlodipine, PK parameters in period 2, day 8 ("test treatment") were compared with Period 1, day 1 ("reference treatment"). For GLE and PIB, PK parameters in period 2, day 8 ("test treatment") were compared with Period 2, day 7 ("reference treatment").

Arm 1



Arm 2



Source: Study Report, Pages 71-72

Safety

No deaths or adverse events leading to discontinuation were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:

Both amlodipine and felodipine are extensively metabolized by the liver. Per the approved prescribing information of NORVASC™ (amlodipine), patients with hepatic impairment have decreased clearance of amlodipine and a lower initial dose may be required. The clearance of felodipine is reduced by 60 % in patients with liver disease as compared with healthy volunteers (Facts and Comparisons® eAnswers, Wolters Kluver). Considering that the DDI trial was conducted in healthy subjects with normal hepatic function, it is challenging to determine if the magnitude ("fold-change") of DDI and the systemic exposures of amlodipine and felodipine (as a result of DDI) would be similar between healthy subjects and Hepatitis C infected patients. Dose titration of amlodipine or felodipine when amlodipine or felodipine is combined with GLE/PIB is a cautious approach to address potential differences in magnitude of DDI between healthy subjects and HCV infected patients and is not expected to deviate from routine clinical practice.

The mean systemic exposure of GLE decreased by 19 % when co-administered with amlodipine. Of note, there is , no available data to assess whether GLE exposures may further decrease in case amlodipine is titrated to a

dose higher than the amlodipine dose evaluated in this DDI trial. Based on the non-linear increase in GLE exposures between GLE 200 mg and 300 mg doses and the observed high SVR rates (when GLE [200 mg or 300 mg] was combined with PIB) observed in Phase 2 and Phase 3 trials, the observed decrease (or potentially further reductions) in GLE exposures when co-administered with amlodipine are not anticipated to be clinically relevant.

Applicant's Proposed Recommendation:

Include amlodipine and felodipine in Section 7.4 (Drugs with No Observed Clinically Significant Interactions with TRADENAME)

Review Team's Recommendation:

GLE/PIB can be co-administered with amlodipine or felodipine without any dose adjustments. Monitor for increased amlodipine or felodipine effects (for example hypotension) and dose titrate based on clinical response.

Study #	M13-593	Study Period	July 30, 2014- September 22, 2014	EDR Link
Title	A Phase 1, Open-Label Study to Assess the Pharmacokinetics, Safety, and Tolerability of the Co-administration of Raltegravir with the Combination of ABT-493 and ABT-530 in Healthy Adult Subjects.			

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the effect of raltegravir (RAL) on the pharmacokinetics of GLE and PIB and the effect of GLE and PIB on the pharmacokinetics of RAL in healthy subjects.

Rationale:
The trial was conducted to obtain quantitative drug-drug interaction information for the safe and effective use of RAL with GLE/PIB.

Dose Selection:
GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase 3 trials and proposed for marketing.
RAL(400 mg twice daily): Approved dosing regimen of RAL (in combination with other antiretroviral drugs)

Design and PK Assessments:

Number of Subjects	Period 1	Period 2		
	Days 1-3	Day 1	Day 2-7	Day 8-10
12	RAL twice daily	GLE once daily +PIB once daily + RAL twice daily*	GLE once daily +PIB once daily	GLE once daily +PIB once daily + RAL twice daily

*:two doses
Source: Table prepared by reviewer based on information provided in the study report.

Subjects received a standardized diet providing approximately 40 % of the daily calories from fat and no more than 45 % of calories from carbohydrates. For once daily dosing of GLE and PIB and the morning dose of RAL, drugs was administered 30 minutes after start of breakfast; evening administration of RAL occurred 30 minutes after start of evening snack. Of note, GLE and PIB were given under fed conditions in the Phase 3 trials and RAL is approved for administration with or without food.

Serial blood samples for determination of plasma concentrations of GLE and PIB were collected pre-dose and up to 24 hours after period 2, day 1; period 2, day 7; and period 2, day 10 (48-hour sample was also collected after period 2, day 10 dosing) with additional sampling prior to morning dose on days 6 and 9 of period 2. For RAL, samples were collected on period 1, day 3 (up to 12 hours); period 2, day 1 (up to 24 hours); and period 2, day 10 (up to 24 hours). PK parameters were computed using non-compartmental analysis.

Population: ☑ Healthy Subjects ☐ Patients | Administration: ☐ Fasted ☑ Fed

Formulations Phase 2b tablet formulations of GLE (100 mg tablet) and PIB (40 mg tablet); RAL (400 mg tablet)

RESULTS

Enrolled	12	Completed	12	Discontinued Due to AE	0	PK Population	12	Safety Population	12

Bioanalytical Method: Link to reports: GLE and PIB and Raltegravir

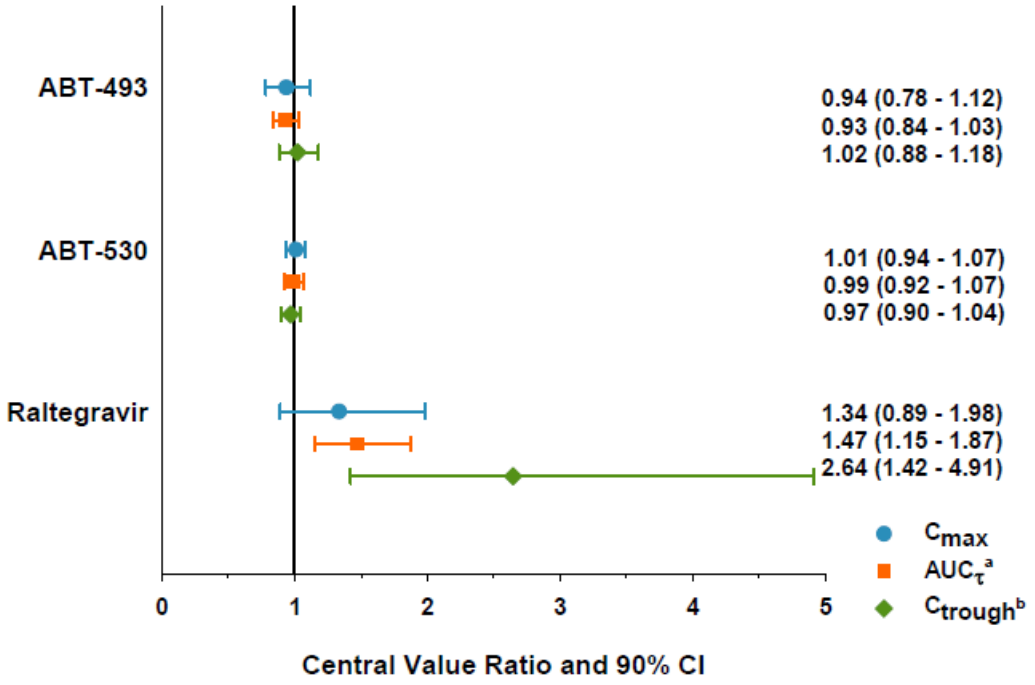
Method Name	Liquid/Liquid Extraction with LC-MS/MS (for GLE and PIB) and HPLC with MS/MS for RAL		
Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE, PIB, RAL		
Range	GLE: 0.2-10000 ng/mL PIB: 0.2-1000 ng/mL RAL: 10 ng/mL -10,000 ng/mL		

Protocol Deviations

No protocol deviations were reported in the trial.

Pharmacokinetics

For raltegravir: PK parameters in period 2, day 10 ("test treatment") were compared with Period 1, day 3 ("reference treatment"). For GLE and PIB, PK parameters in period 2, day 10 ("test treatment") were compared with Period 2, day 7 ("reference treatment")



a. $AUC_\tau = AUC_{24}$ for ABT-493 and ABT-530. $AUC_\tau = AUC_{12}$ for raltegravir.
b. $C_{trough} = C_{24}$ for ABT-493 and ABT-530. $C_{trough} = C_{12}$ for raltegravir.

Source: M13-593 Clinical Study Report, Pages 80

Safety
No deaths, serious adverse events or other significant adverse events were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct
- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Study Results
The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:

GLE is a substrate and inhibitor of P-gp and BCRP. GLE is also a substrate and inhibitor OATP1B1 and OATP1B3. PIB is a substrate of P-gp and/or BCRP and an inhibitor of P-gp, BCRP and OATP1B1. Both GLE and PIB show limited metabolism *in vivo*. Per a publication from Rizk et al, RAL has a low propensity to cause clinical DDIs through inhibition of major drug transporters (Rizk ML et al, *Antimicrob Agents Chemother*, 2014, 58 (3), 1294-1301). Hence, a pharmacokinetic interaction was not expected and the results

from the trial (w.r.t effect of RAL on GLE and PIB) are consistent with predictions based on *in vitro* data.

RAL is primarily metabolized by UGT1A1. The IC_{50} of GLE and PIB for UGT1A1 is 17.2 µM and 2.54 µM respectively, and based on "R" value predictions using the mechanistic static model (R =1.01 for GLE and R=1 for PIB), there is low potential for GLE or PIB to interact with co-administered drugs that are substrates of UGT1A1 (R&D/15/1004 (Link to Report); Pages 7-8). PIB shows potential to inhibit UGT1A4 in vitro (R-value: 1.45), however, co-administration of GLE and PIB with lamotrigine (UGT1A4 substrate) did not significantly affect lamotrigine exposure (trial M13-585). Moreover, there is no available data in the literature to suggest that RAL is a UGT1A4 substrate. Overall, it does not appear that inhibition of UGT enzymes by GLE/PIB can explain increase in RAL exposures observed in the trial.

Another plausible explanation for increase in RAL exposures observed in this trial could be that RAL is a substrate of transporters and GLE/PIB inhibits those transporters leading to increase in RAL exposures. Based on *in vitro* studies, RAL has been suggested to be a P-gp substrate by Hoque et al (Hoque MT et al, *Antimicrob Agents Chemother*, 2015, 59 (5), 2572-2582) and Moss et al. (Moss et al, *Antimicrob Agents Chemother*, 2011, 55 (2), 879-887). Further, Hoque et al. have also shown that RAL is a substrate of BCRP. Overall, inhibition of P-gp and BCRP by GLE and PIB may explain the increase in mean RAL exposures observed in the trial.

The increase in RAL exposures observed in the trial is not anticipated to be clinically relevant. When administered with a strong UGT1A1 inhibitor, atazanavir (400 mg daily), raltegravir (100 mg single dose) exposures (C_{max} and AUC_{τ}) increased by 1.53-fold and 1.72-fold, respectively and C_{min} increased by 1.95-fold (RAL prescribing information). No dose adjustment of RAL is recommended for the concomitant use of raltegravir with atazanavir. In the current study, raltegravir C_{max} and AUC_{τ} increased by 34% and 47% and C_{12} increased by 164 % (2.64-fold).

Applicant's Proposed Recommendation:

Include raltegravir in Section 7.4 (Drugs with No Observed Clinically Significant Interactions with TRADENAME)

Review Team's Recommendation

GLE/PIB can be co-administered with RAL without any dose adjustments. Applicant's proposal to include RAL in Section 7.4 is acceptable.

Study #	M13-597	Study Period	December 15, 2014- June 18, 2015	EDR Link
Title	A Phase 1, Open-Label Study to Assess the Pharmacokinetics, Safety, and Tolerability of the Co-administration of Atripla® (efavirenz, emtricitabine, and tenofovir disoproxil fumarate) tablets with ABT-493 and ABT-530 in HIV-Mono-Infected Adult Subjects			

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives:

Evaluate the effect of GLE and PIB on the pharmacokinetics of efavirenz, emtricitabine, and tenofovir (administered as Atripla®) and to characterize the pharmacokinetics of GLE and PIB when administered with Atripla® in HIV-mono-infected subjects

Rationale:

The trial was conducted to obtain quantitative drug-drug interaction information for the safe and effective use of GLE/PIB with Atripla®. The trial was conducted in subjects with virologically suppressed HIV-1 mono-infection

Dose Selection:

GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase 3 trials and proposed for marketing.
Atripla® (600/200/300 efavirenz/emtricitabine/tenofovir) once daily: approved dosing regimen

Design and PK Assessments:

Number of Subjects	Period 1		Period 2	
	Days -7 to Day -1	Day 1 to Day 7	Day 1 to Day 7	Day 8 to Day 9
15	Atripla once daily	Atripla once daily	Atripla once daily + GLE once daily + PIB once daily	Atripla once daily

Source: Table prepared by reviewer based on information provided in the study report.

All doses of study drug administered from Period 1 Day 1 through Period 2 Day 8 were taken orally with approximately 240 mL of water at approximately 2 hours after starting a standardized breakfast. Atripla is typically administered under fasting conditions (primarily because of increase in efavirenz when given with food), however, presumably in order to determine the clinical recommendation pertaining to co-administration of Atripla with GLE/PIB, the applicant administered Atripla with GLE/PIB under fed conditions. Blood samples for determining the concentration of GLE and PIB were collected in period 2, day 1 (prior to dosing and up to 24 hours after dosing of GLE and PIB), period 2, day 7 (prior to dosing and up to 48 hours after dosing of GLE and PIB). Additional PK samples were collected prior to morning dose on day 6 of period 2. Blood samples for determining the plasma concentration of efavirenz, emtricitabine, and tenofovir were collected in period 1, day 7 (prior to dosing and up to 16 hours after dosing), period 2, day 1 (prior to dosing and up to 24 hours after dosing), period 2, day 7 (prior to dosing and up to 24 hours after dosing). Additional PK samples were collected prior to morning dose on day 6 of periods 1 and 2.

Population: ☐ Healthy Subjects ☑ Patients (HIV-1 mono-infected)	Administration: ☐ Fasted ☑ Fed (all doses of the study drug were taken 2 hours after starting a standardized breakfast) Note- an altered definition of "fed" was used in this study because of the effect of food on efavirenz concentrations.

Formulations

Phase 2b tablet formulations of GLE (100 mg tablet) and PIB (40 mg tablet) were used. Atripla (600/200/300 mg tablets) was not provided by the applicant; the study site requested the existing prescribed Atripla from the subjects and dispensed the drug to the subjects during study confinement.

RESULTS

Enrolled	15	Completed	12*	Discontinued Due to AE	0	PK Population	12	Safety Population	12

*Nine subjects received incorrect doses of GLE (100 mg once daily instead of 300 mg once daily) and PIB (40 mg once daily instead of 120 mg once daily) during Period 2. Six of these 9 subjects were re-enrolled in the study and received GLE 300 mg once daily + PIB 120 mg once daily as initially planned. Three replacement subjects were enrolled. Thus, a total of 15 subjects were enrolled in the study: 12 subjects received GLE and PIB at correct doses (including 6 subjects that were re-enrolled after initially receiving incorrect doses) and 3 subjects received incorrect doses (but were not re-enrolled).

Bioanalytical Method: Link to reports (GLE and PIB; Efavirenz; Emtricitabine and Tenofovir)

Method Name	Liquid Chromatographic Method with Mass Spectrometric Detection		
Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE, PIB, Efavirenz, Emtricitabine, Tenofovir		
Range	GLE: 0.205-101 ng/mL; 86.5-10,200 ng/mL PIB: 0.205-101 ng/mL; 86.4-1020 ng/mL Efavirenz: 0.1-25 µg/mL Emtricitabine: 20-4000 ng/mL Tenofovir: 5-1000 ng/mL		

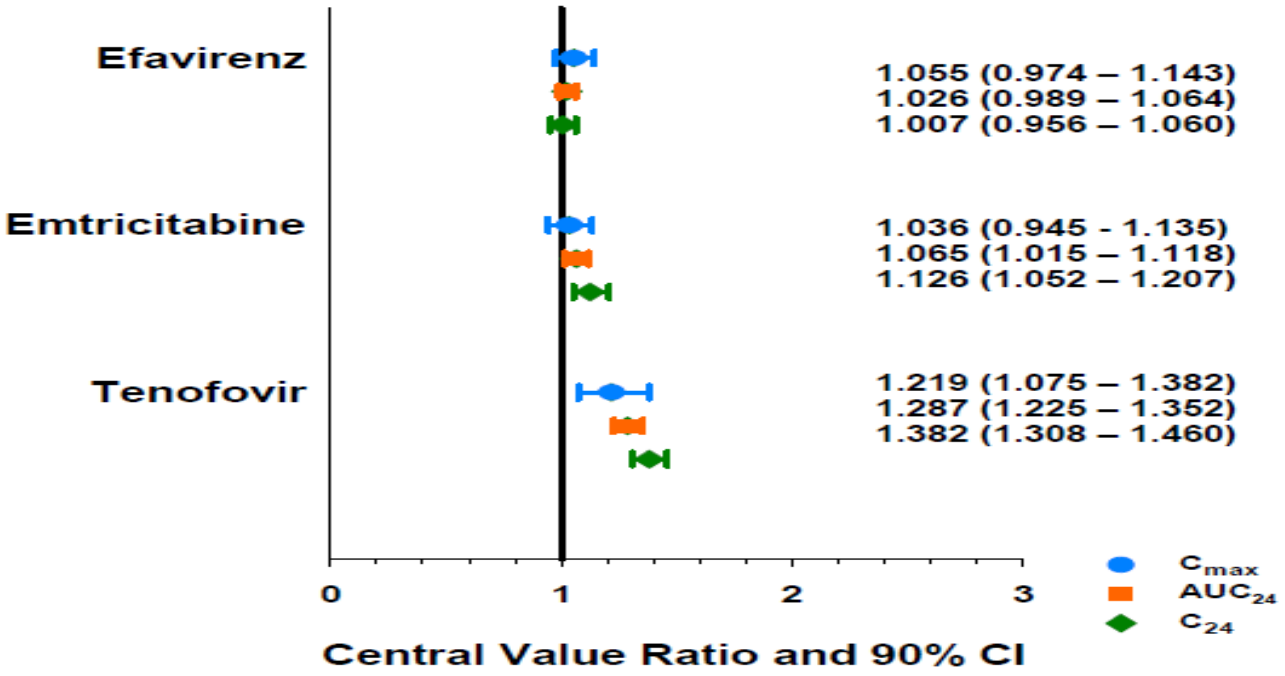
Protocol Deviations

As previously described, there were dosing errors in the trial (9 subjects received incorrect doses of GLE and PIB); however, the dosing errors do not impact the conclusions because the pharmacokinetic and statistical analysis is based on only those subjects who received the correct dose of GLE and PIB.

One subject (subject # 105) tested positive for amphetamines (subject claimed the positive result was due to taking Nyquil). Because of incorrect dosing, this subject was re-enrolled as subject # 205 and tested negative for amphetamines during drug screening. Of note, a pregnancy test was performed in error for subject 205 (male subject). Subject 112 took Advil for lower back pain. There were some additional deviations such as unscheduled sample collection for hematology assessments and non-conduct of ECG for one subject. Overall, the aforementioned protocol deviations are not expected to impact the outcome of the trial.

Pharmacokinetics

For efavirenz, emtricitabine, and tenofovir, PK parameters in period 2, day 7 (“test treatment”) were compared with PK parameters in Period 1, day 7 (“reference treatment”)



Source: M13-597 Clinical Study Report, Pages 67

Table below shows the geometric mean (Mean, CV %) pharmacokinetic parameters of GLE and PIB.

Pharmacokinetic Parameters (Units)	Period 2/Day 1 ABT-493 300 mg + ABT-530 120 mg + Atripla[a] QD (N = 12)	Period 2/Day 7 ABT-493 300 mg QD + ABT-530 120 mg QD + Atripla[a] QD (N = 12)
	ABT-493	
C_{max} (ng/mL)	331 (404, 84)	383 (451, 67)
T_{max}[b] (h)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)
AUC_{24} (ng•h/mL)	1265 (1411, 60)	1262 (1395, 56)
C_{24} (ng•h/mL)	0.94 (1.07, 55)	0.91 (1.14, 87)
	ABT-530	
C_{max} (ng/mL)	93.9 (98.2, 32)	102 (108, 38)
T_{max}[b] (h)	5.0 (3.0 to 6.0)	5.0 (3.0 to 5.0)
AUC_{24} (ng•h/mL)	636 (667, 31)	708 (731, 27)
C_{24} (ng/mL)	4.92 (5.23, 35)	7.04 (7.30, 26)

a. Atripla: efavirenz/emtricitabine/tenofovir DF 600/200/300 mg.

b. Median (minimum to maximum).

Source: M13-597 Clinical Study Report, Pages 60

Safety

No deaths, serious adverse events or other significant adverse events were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:

When co-administered with GLE 300 mg once daily and PIB 120 mg once daily, efavirenz and emtricitabine exposures were similar (≤ 13% difference), however, tenofovir exposures were higher compared to efavirenz/emtricitabine/tenofovir alone. The increase in mean tenofovir exposures is most likely driven by the P-gp inhibitory effect of GLE and PIB. Of note, a similar increase in tenofovir exposures is also observed when tenofovir is combined with some antiretroviral protease inhibitors co-administered with ritonavir (German et al., 2015 CROI Meeting, Abstract # 82).

Exposures of GLE and PIB with EFV/FTC/TDF relative to GLE and PIB alone were not evaluated in subjects participating in this trial because the trial enrolled HIV-1 infected subjects who were virologically suppressed and receiving Atripla®. Therefore, GLE +PIB "alone" arm could not be enrolled in the trial.

Comparison of the mean systemic exposures of GLE and PIB observed in this trial with GLE and PIB exposures observed in other trials (data shown in the table below) suggested that the mean GLE and PIB exposures were 69 % to 71 % lower than mean exposures for healthy subjects enrolled in other Phase 1 trials. The decrease in GLE and PIB exposures was most likely driven by the induction of P-gp transporters by efavirenz. GLE and PIB exposures observed in this trial were similar to the GLE and PIB exposures observed when GLE and PIB was co-administered with another P-gp inducer, carbamazepine (trial M14-724). It is important to note that some of these differences in GLE exposures across trials can be attributed to inter-subject variability of GLE. Despite high inter-study variability, the decrease in GLE exposures when co-administered with Atripla appears to be "real" considering a similar magnitude of decrease with carbamazepine in trial M14-724.

Table below shows the single dose pharmacokinetics of GLE and PIB 300 mg/120 mg as co-formulated Phase 3 Film-Coated Bilayer Tablets

	Subjects (N)	C_{max}[a] (ng/mL)	T_{max}[b] (h)	AUC_{inf}[a] (ng•h/mL)	$t_{1/2}$[c] (h)
GLE	79	772 (592 to 1090)	5.0 (4.0 to 5.0)	2610 (2110 to 3720)	6.14 (5.00 to 6.48)
PIB	79	204 (159 to 237)	5.0 (5.0 to 5.0)	1250 (950 to 1460)	13.1 (11.5 to 13.6)

a. Overall geometric mean and range of geometric means.
b. Weighted median and range of study medians.
c. Weighted median and range of study harmonic means.

Source: Summary of Phase 1 studies (R&D/16/0237), Page 14.

Because the DDI trial with Carbamazepine (P-gp inducer), Rifampin (P-gp inducer), and Atripla® (P-gp inducer) used the same formulation of GLE ([(b) (4)] Bulk Product Lot # [14-001033]) and PIB ([(b) (4)] Bulk Product Lot # [14-001596]), the review team conduced an additional analysis using the reference arms from the carbamazepine DDI trial and rifampin DDI trial to calculate the % decrease in GLE and PIB exposures. Table below shows the % decrease in GLE and PIB exposures in the rifampin DDI trial, carbamazepine DDI trial, and in the Atripla® DDI trial (using various reference treatments as previously described).

Perpetrator	Decrease in mean C_{max} (%)		Decrease in mean AUC (%)		Applicant's Proposed Clinical Recommendation
	GLE	PIB	GLE	PIB	
Rifampin	86	83	88	87	Contraindicate
Carbamazepine	67	50	67	51	Not recommended
Atripla	57 *	54*	51 *	49*	Not recommended
	68 **	69**	66 **	70**	
	66 ***	65 %	63***	66 ***	

*: Using data from single dose PK of GLE and PIB presented above
**: Using the reference arm from the carbamazepine trial (trial M14-724)
***Using the reference arm from the rifampin trial (trial M14-723)
Source: Prepared by the reviewer based on single dose PK data (from report R&D/16/0237, page 14) and clinical study reports of trials M14-723 and M14-724.

The magnitude of decrease in mean GLE and PIB exposures is lower when GLE/PIB is co-administered with Atripla® as compared with when GLE/PIB is co-administered with rifampin. Considering the high variability in GLE and PIB exposures (especially GLE exposures) and the potential co-administration of GLE/PIB and Atripla® across various HCV genotypes (including the harder-to-treat populations where it is important to maximize GLE and PIB exposures), the decrease in GLE and PIB exposures is clinically significant.

The review team also discussed the following:

1) **Should GLE/PIB be contraindicated with all efavirenz containing products based on the significant decrease in GLE exposures observed in the DDI trial with ATRIPLA®?** Considering that emtricitabine and tenofovir have not been shown to play a significant role in mediating DDIs, the significant decrease in GLE exposure is most likely driven by the induction of P-gp transporters by efavirenz. Therefore, a similar magnitude of DDI can be expected when SUSTIVA® (efavirenz) is given with GLE/PIB. Further, there are other EFV containing products (in addition to SUSTIVA® and ATRIPLA®) approved under the PEPFAR program (not currently marketed in the US) and those products may be subsequently marketed in the US, hence extending the recommendation to efavirenz containing products (instead of only restricting the recommendation to ATRIPLA®) will also address the possible combination of those efavirenz containing PEPFAR products with GLE/PIB.

2) **Should GLE/PIB be contraindicated with all P-gp inducers?** Data from DDI trials with drugs that are known to induce P-gp such as rifampin, carbamazepine and ATRIPLA® and other available information such as minimal metabolism (based on results from mass balance trial) and less than 2-fold increase in the systemic exposure of GLE when co-administered with ritonavir (suggesting a limited role of metabolism especially considering that ritonavir also impact inhibits P-gp and BCRP) underscores the importance of transporters in the overall disposition of GLE and PIB. The review team decided to extend the contraindication to all P-gp inducers and suggested the following language, **"P-gp inducers that are known or expected to significantly decrease GLE exposures are contraindicated with GLE/PIB".**

3) **Should St. John's Wort be included in the list of contraindicated drugs?** The review team decided to include St. John's Wort in the contraindication section considering that St. John's wort is a known P-gp inducer and is commonly available and used by the Hepatitis C infected population.

Applicant's Proposed Labeling Recommendation:

Co-administration may lead to reduced therapeutic effect of [TRADENAME] and is not recommended.
Review Team's Recommendation:

1) **Co-administration of GLE/PIB with EFV containing products is contraindicated due to the potential for significant decrease in systemic exposure of GLE and PIB.**
2) **GLE/PIB is contraindicated with P-gp inducers that are known or expected to significantly decrease GLE and PIB exposures.**
3) **GLE/PIB is contraindicated with St. John's wort due to potential for significant decrease in GLE and PIB exposures.**

Study #	M13-599	**Study Period**	July 24, 2015-September 21, 2015	EDR Link
Title	A Phase 1, Open-Label Study to Assess the Pharmacokinetics, Safety and Tolerability of the Co-Administration of Losartan or Valsartan with ABT-493 and ABT-530 in Healthy Adult Subjects			

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives:

- Evaluate the effect of GLE and PIB at steady state on the pharmacokinetics of losartan or valsartan.
- Evaluate the effect of losartan or valsartan on the pharmacokinetics of GLE and PIB.
- To evaluate the safety and tolerability of GLE and PIB when co-administered with losartan or valsartan.

Rationale:

Losartan (Cozaar®) and valsartan (Diovan®) are angiotensin 2 receptor blockers indicated for the treatment of hypertension. Losartan is a substrate of CYP2C9 and CYP3A. CYP2C9 is the primary enzyme responsible for conversion of losartan to an active carboxylic acid metabolite which is responsible for angiotensin II receptor antagonism. Per the prescribing information of Cozaar, losartan carboxylic acid is 10- to 40-fold more potent as an AT1 receptor antagonist than the parent losartan. Losartan has been reported to be a substrate of OATP transporters (Flynn CA. Fexofenadine and organic anion transporting polypeptides (OATPs): transport and drug-drug interactions [Dissertation]. University of Kansas. 2011.). Valsartan is a substrate of OATP transporters and is mainly eliminated unchanged in the bile. Only 20% of valsartan is metabolized, possibly by non-CYP enzymes, with the primary metabolite accounting for 9% of the administered dose.

The systemic exposure of losartan or valsartan may increase when co-administered with CYP3A and OATP inhibitors such as the combination of GLE and PIB.

Dose Selection:

GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase 3 trials and proposed for marketing.
Losartan: Recommended starting dose is 50 mg once daily with a maximum dose of 100 mg once daily.
Valsartan: Recommended starting dose is 80 mg once daily with a maximum dose of 320 mg once daily.

Design and PK Assessments:

Arm	Number of Subjects	Day 1 and Day 10	Days 3 through 11
1	12	Losartan 50 mg single dose	GLE (300 mg) + PIB (120 mg) once daily
2	12	Valsartan 80 mg single dose	GLE (300 mg) + PIB (120 mg) once daily

Source: Table prepared by reviewer based on information provided in the study report.

Serial blood samples for determination of plasma concentrations of GLE and PIB were collected for 24 hours on days 9 and 10; for losartan and valsartan, PK samples were collected for 48 hours after dosing on days 1 and 10. PK parameters were computed using non-compartmental analysis.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed

Formulations

Phase 2b formulations of GLE (100 mg tablet) and PIB (40 mg tablet); Losartan (50 mg tablet); and Valsartan (80 mg tablet)

RESULTS

Enrolled	24	Completed	24	Discontinued Due to AE	0	PK Population	24	Safety Population	24

Bioanalytical Method: Link to Reports (GLE and PIB and Valsartan and Losartan)

Method Name	Liquid Chromatographic Method with Tandem Mass Spectrometric Detection		
Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE, PIB, Losartan, Valsartan		
Range	GLE: 0.2-100 ng/mL; 80-10,300 ng/mL PIB: 0.2-102 ng/mL; 81.4-1030 ng/mL Losartan: 1-1000 ng/mL (for losartan and its carboxylic acid metabolite) Valsartan: 20-10,000 ng/mL		

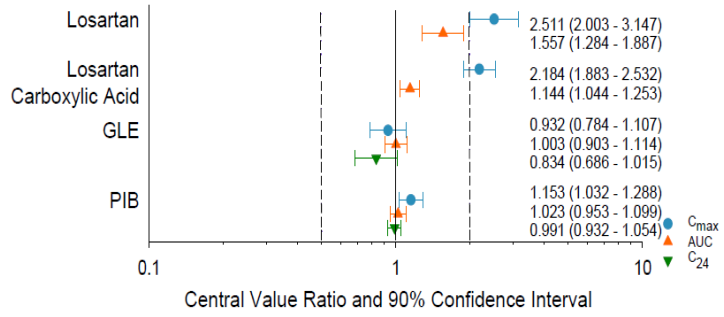
Protocol Deviations

There were several deviations from the protocol during the study; however, none of the deviations are expected to affect the overall outcome of the trial. Deviations reported were as follows:

- One subject reported taking cough drops during the study.
- One subject did not consume the entire breakfast on the two non-intensive pharmacokinetic sampling days.
- One subject in Arm 2 consumed more than 240 mL of water (i.e., 295, 480, 720 mL on 4 dosing days, respectively) for study drug administration.
- Three subjects had follow-up visits outside of the protocol allowed time.

Pharmacokinetic

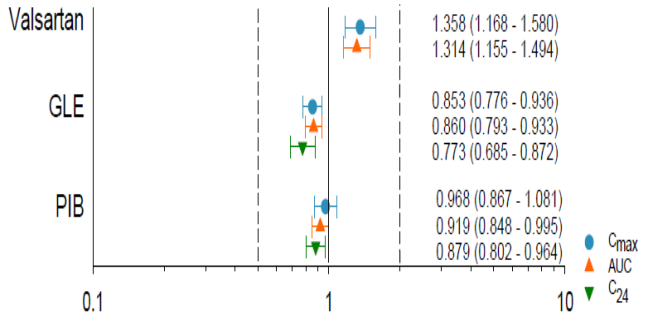
Arm 1



AUC_{inf} = Losartan and losartan carboxylic acid; AUC_{24} = GLE and PIB

Losartan: Day 10/Day 1; GLE and PIB: Day 10/Day 9

Arm 2



AUC_{inf} = Valsartan; AUC_{24} = GLE and PIB

Valsartan: Day 10/Day 1; GLE and PIB: Day 10/Day 9

Source: Summary of Clinical Pharmacology Studies, Pages 44-45

Safety

No deaths, serious adverse events or other significant adverse events were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:
Losartan + GLE/PIB:

The mean systemic exposure of losartan and its carboxylic acid metabolite increased when losartan was co-administered with GLE/PIB as compared to administration of losartan alone. There is at least one report in the literature that suggests that losartan is a substrate of P-gp (Soldner et al, British Journal of Pharmacology, 2000, 129, 1235-1243), hence the inhibitory effect of GLE/PIB on P-gp and OATP may be have contributed to the higher losartan exposures upon co-administration with GLE/PIB.

According to the prescribing information of Cozaar®, following oral administration of losartan to subjects with renal impairment, plasma concentrations and AUCs of losartan and its carboxylic acid metabolite are increased by 50-90% in patients with mild (creatinine clearance of 50 to 74 mL/min) or moderate (creatinine clearance 30 to 49 mL/min) renal insufficiency. Losartan can be administered to subjects with renal impairment without the need for dose adjustments. Therefore, the magnitude of increase in losartan and its carboxylic acid metabolite observed when co-administered with GLE/PIB in this trial does not warrant an initial dose adjustment. Of note, losartan 100 mg once daily can be given to subjects with any degree of renal impairment and the exposures of losartan under this scenario are anticipated to be significantly higher that losartan exposures under "losartan 50 mg once daily + GLE/PIB once daily" scenario.

Valsartan + GLE/PIB:

The mean C_{max} and AUC of valsartan increased by 36 % and 32 %, respectively, when valsartan was co-administered with GLE/PIB as compared with when valsartan was given alone. This increase in mean valsartan exposure is not expected to be clinically relevant, especially considering that the highest approved dose of valsartan is 320 mg once daily and valsartan follows linear pharmacokinetics over the clinical dosing range (per the prescribing information of valsartan).

Applicant's Proposed Recommendation:

Include losartan and valsartan in Section 7.4 (Drugs with No Observed Clinically Significant Interactions with TRADENAME)

Review Team's Recommendation

GLE/PIB can be co-administered with losartan or valsartan without any dose adjustments. Applicant's proposal to include losartan and valsartan in Section 7.4 is acceptable.

Study #	M14-715	Study Period	November 12, 2015- May 26, 2016	EDR Link
Title	A Phase 1, Open-Label Study to Assess the Effect of Acid Reducing Agent on the Pharmacokinetics, Safety and Tolerability of ABT-493/ABT-530 in Healthy Adult Subjects			

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives:

The objective of this study was to evaluate the effect of an acid-reducing agent such as omeprazole, a proton pump inhibitor and potent gastric-pH altering agent, on the pharmacokinetics, safety and tolerability of GLE/PIB in healthy subjects.

Rationale:

Omeprazole is a proton pump inhibitor indicated for treatment of duodenal ulcer and gastric ulcer in adults and treatment of symptomatic gastroesophageal reflux disease (GERD) in patients 1 year of age or older. Omeprazole could affect absorption or bioavailability of drugs that are susceptible to increase in gastric pH such as GLE.

Dose Selection:

GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase 3 trials and proposed for marketing.

Omeprazole: The recommended starting dose of omeprazole is 20 mg once daily. Omeprazole 40 mg once daily is approved for treatment of gastric ulcer and omeprazole 60 mg once daily is approved for pathological hypersecretory conditions.

Design and PK Assessments:

Arm	Number of Subjects	Period 1	Washout	Period 2	
		Day 1		Day 1-5	Day 6
1	12	GLE (300 mg) + PIB (120 mg) single dose in the morning (fed conditions)	7 days	Omeprazole **20 mg once daily in the morning** (fasting conditions)	Omeprazole 20 mg once daily in the morning (fasting conditions) + GLE (300 mg) + PIB (120 mg) single dose in the morning (fed conditions)
2	12	GLE (300 mg) + PIB (120 mg) single dose in the morning (fed conditions)	6 days	Omeprazole **40 mg once daily in the morning** (fasting conditions)	Omeprazole 40 mg once daily in the morning (fasting conditions) + GLE (300 mg) + PIB (120 mg) single dose in the morning (fed conditions)
3	12	GLE (300 mg) + PIB (120 mg) single dose in the morning (fed conditions)	4 days	Omeprazole **40 mg once daily in the evening** (fasting conditions)	GLE (300 mg) + PIB (120 mg) single dose in the morning (fed conditions)

Source: Table prepared by reviewer based on information provided in the study report.

	Period 1 Day 1	Period 2 Days 1 to 5	Period 2 Day 6
Arm 1 N = 12		Omeprazole 20 mg QD	
	GLE 300 mg + PIB 120 mg		GLE 300 mg + PIB 120 mg
Arm 2 N = 12		Omeprazole 40 mg QD	
	GLE 300 mg + PIB 120 mg		GLE 300 mg + PIB 120 mg
Arm 3 N = 12		Omeprazole 40 mg QPM	
	GLE 300 mg + PIB 120 mg		GLE 300 mg + PIB 120 mg

Formulation: GLE/PIB Film-coated Bilayer tablets

QPM = once daily, in the evening

Each dose of study drug was taken orally with approximately 240 mL of water. In all 3 arms, GLE/PIB was administered approximately 30 minutes after the start of breakfast on Period 1 Day 1 and Period 2 Day 6. In Arms 1 and 2, each dose of omeprazole was administered after a minimum 10-hour fast and approximately 1 hour before the start of breakfast for Period 2 Days 1 through 6. In Arm 3, each dose of omeprazole was administered approximately 1 hour before the evening snack for Period 2 Days 1 – 5. Serial blood samples for determination of plasma concentrations of GLE, PIB and omeprazole were collected after dosing in each period (for omeprazole, samples were only collected in arms 1 [period 2, day 5] and 2 [period 2, day 5 and period 2, day 6]). PK parameters were computed using non-compartmental analysis.

Population: ☑ Healthy subjects ☐ Patients	Administration: ☑ Fasted ☑ Fed (omeprazole was administered under fasting conditions and GLE/PIB was administered under fed conditions)

Formulations

GLE/PIB film coated tablet (100 mg/40 mg) Phase 3 Fixed Dose Combination tablet; Omeprazole 20 mg delayed release tablets (Perrigo, Allegan, MI)

RESULTS

Enrolled	36	Completed	36	Discontinued Due to AE	0	PK Population	33*	Safety Population	36

*: Per the applicant, in arm 1, three subjects (subjects 103, 105, and 107) had atypical omeprazole pharmacokinetic profiles (for subjects 103 and 105, omeprazole concentrations were reported as "0" for the majority of the time points and for subject 107, after omeprazole administration, the 12 hour concentration was higher than the concentrations reported at earlier time points. Subjects 103, 105, and 107 were excluded from the summary statistics and statistical analysis of pharmacokinetic parameters.

Bioanalytical Method: Link to Reports (GLE and PIB and Omeprazole)

Method Name	Liquid Chromatographic Method with Tandem Mass Spectrometric Detection		
Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE, PIB, Omeprazole		
Range	GLE: 0.205-105 ng/mL (low); 85.9-10,100 ng/mL (high) PIB: 0.205-105 ng/mL (low); 85.9-1030 ng/mL (high) Omeprazole: 1.02 ng/mL -502 ng/mL		

Protocol Deviations

No protocol deviations were reported in the trial.

Pharmacokinetic
Geometric mean ratios and 90% confidence interval

Arm (Omeprazole Dose)	**GLE**		**PIB**	
	AUC Ratio	**Cmax Ratio**	**AUC Ratio**	**Cmax Ratio**
Arm 1 (OME 20 mg QD AM)	**0.71** (0.58-0.86)	**0.78** (0.6-1.0)	**0.97** (0.80-1.18)	**1.0** (0.83-1.22)
Arm 2 (OME 40 mg QD AM)	**0.49** (0.35-0.68)	**0.36** (0.21-0.59)	**1.15** (0.94-1.40)	**0.85** (0.7-1.03)
Arm 3 (OME 40 mg QD PM)	**0.51** (0.45-0.59)	**0.54** (0.44-0.65)	**1.01** (0.85-1.20)	**0.93** (0.79-1.09)

Source: Prepared by reviewer utilizing study data

The mean C_{max} and AUC_{24} of omeprazole in Arm 1 was 485 ng/mL and 887 ng*hr/mL, respectively. Because PK samples for determination of omeprazole were only collected on day 5 in period 2, a comparison of omeprazole PK with and without co-administration with GLE/PIB cannot be made. In Arm 2, PK parameters of omeprazole were determined on period 2, day 5 and period 2, day 6. Table below shows the comparison of PK parameters.

Pharmacokinetic Parameters (units)	**Period 2/Day 5 Omeprazole 40 mg QD (fasting) (N = 12)**	**Period 2/Day 6 Omeprazole 40 mg QD (fasting) (N = 12)**
C_{max} (ng/mL)	1290 (1540, 60)	1850 (1950, 33)
AUC_t (ng•h/mL)[a]	3640 (4710, 78)	4110 (5000, 69)

ND = Not determined

a. $AUC_t = AUC_{24}$ for Period 2 Day 5 and $AUC_{25.5}$ for Period 2 Day 6.

Source: M14-715 Clinical Study Report, Pages 76

PK samples for the determination of omeprazole concentrations in Period 3 were not collected.

Safety
No deaths, serious adverse events or other significant adverse events were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No

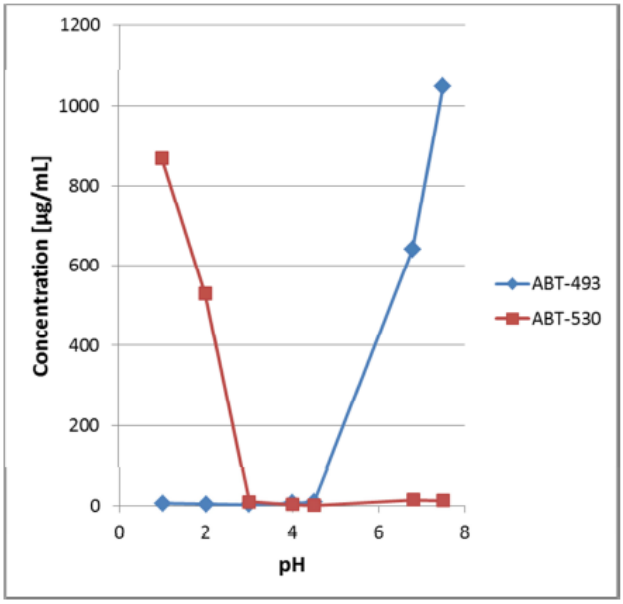
Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion: (please note that the discussion outlined below and proposed recommendation summarizes some preliminary ideas about the potential mechanism(s) of interaction between GLE/PIB and omeprazole. The review team will prepare an addendum to summarize the labeling discussions with the applicant on this topic and the final recommendation related to use of GLE/PIB with omeprazole).

Based on the review of protocol for trial M14-715, the review team asked the applicant to assess the effect of omeprazole 40 mg once daily (instead of the 20 mg once daily as proposed by the applicant) because the solubility of both GLE and PIB appear to be low in the pH range anticipated after administration of omeprazole and the prescribing information of Prilosec suggests that omeprazole 40 mg once daily may show a greater increase in pH than omeprazole 20 mg once daily.

Figure below shows the pH dependent aqueous solubility of GLE and PIB at 37°C



Source: Section 3.2.P.2.2 (Drug Product) Page 72

Gan KH et al (*Dig Dis Sci*, 1997, 42 (11); 2304-2309; PMID 9398810) showed that the median intragastric pH on day 7 after once daily administration of 40 mg omeprazole for 8 days was 4.93. Based on the figure above, at this pH, the solubility of GLE is expected to significantly decrease which may explain the decrease in GLE exposures observed in the trial. On the other hand, PIB exposures were not significantly affected by omeprazole which may be because the solubility of PIB appears to be pH-independent in the pH range anticipated after administration of omeprazole. Staggering the dosing of GLE/PIB and omeprazole by 12 hours (panel C) did not attenuate the magnitude of DDI, most likely due to the prolonged binding of omeprazole to the parietal H^+/K^+ ATPase enzyme.

As opposed to proton pump inhibitors such as omeprazole, H_2 blockers (such as cimetidine, famotidine and ranitidine) primarily act by competitive inhibition of H_2 receptors located on the parietal cells in the stomach. Both PPIs and H_2 blockers reduce the intragastric pH to a similar extent, however, H_2 blockers have a rapid onset of action and duration of effect of less than 12 hours whereas PPIs have a delayed onset of action and a prolonged duration of effect. It is possible that staggering the dose of GLE/PIB with an H_2 blocker may mitigate the concerns associated with decreased exposures of GLE observed with omeprazole; however, there is no pharmacokinetic data available to make a recommendation regarding administration of GLE/PIB with H_2 blockers.

Applicant's Proposed Recommendation:

Include omeprazole in Section 7.4 (Drugs with No Observed Clinically Significant Interactions with TRADENAME)

Review Team's Recommendation (incorporates the feedback received from the clinical pharmacology team leader of Liver/PPI/In Born Error team): (Note- the recommendation was under discussion at the time this review was finalized. An addendum will be written.)

Co-administration of GLE/PIB with omeprazole **20 mg** once daily:

GLE/PIB can be co-administered with omeprazole 20 mg once daily without any dose adjustments.

Co-administration of GLE/PIB with omeprazole **40 mg** once daily:

Co-administration of GLE/PIB with omeprazole 40 mg once daily is not recommended.

Staggered administration (by 12 hours) of GLE/PIB with omeprazole **40 mg** once daily:

Staggered administration (by 12 hours) of GLE/PIB with omeprazole 40 mg once daily is not recommended.

The administration of omeprazole 40 mg dose and GLE/PIB resulted in 50% reduction in GLE exposure. The impact of this reduction in GLE exposure on the efficacy of the regimen is unknown. The co-administration of omeprazole and GLE/PIB should be considered if the benefit outweighs the risk.

Study #	M13-582	Study Period	03 March 2014 - 17 April 2014	EDR Link
Title	A Phase 1, open-label study to assess potential pharmacokinetic interaction between GLE and PIB combination and digoxin in healthy adult subjects			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the effect of GLE/PIB on the pharmacokinetics of digoxin.

Rationale: Digoxin is a probe P-gp substrate and both GLE and PIB are P-gp inhibitors. Data from this study can be used to guide dose adjustment recommendations for P-gp substrates when co-administered with GLE/PIB.

Dose Selection:

GLE (400 mg) and PIB (120 mg): GLE dose is higher than the dose evaluated in Phase 3 trials while PIB dose is the clinical dose proposed for marketing. At the time of study conduct, the applicant was considering evaluating GLE 400 mg dose in Phase 3 trials.

Digoxin: The digoxin labeling recommends 0.75 to 1.25 mg digoxin as a loading dose in a 70 kg patient. The maintenance dose of digoxin ranges from 0.125 to 0.5 mg once daily. The 0.5 mg digoxin dose provides > 2 fold safety margin to the maximum recommended loading dose.

Design and PK Assessment

Period 1		Period 2		
Day 1	10-day Washout	Days 1 to 7	Day 8	Days 9 to 12
Digoxin 0.5 mg			Digoxin 0.5 mg	
		GLE 400 mg QD + PIB 120 mg QD		

Serial blood samples for the determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE and PIB: for 24 hours on Day 7 and Day 8.
2. Digoxin: for 120 hours on Day 1 and Day 8.

Urine samples for assay of digoxin were collected over 5 intervals (24 hours each) following dosing on Day 1and Day 8.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulation: Phase 2b formulation of GLE (100 mg tablet) and PIB (40 mg tablet). Commercially available formulation of digoxin (Lanoxin® 0.25 mg tablet).

RESULTS

Enrolled	12	Completed	12	Discontinued due to AE	0	PK Population	12	Safety Population	12

Bioanalytical Method: Link to reports GLE and PIB/ Digoxin (Plasma)/ Digoxin (Urine)

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE, PIB, Digoxin		
Range	GLE: 0.107 ng/mL - 270 ng/mL PIB: 0.101 ng/mL - 255 ng/mL Digoxin: 10.0 pg/mL - 10000 pg/mL		

Protocol Deviations No protocol deviations were reported in this study.

Pharmacokinetics

PK Parameter	Digoxin	
	GMR	**90% CI**
Cmax	**1.721**	1.453 – 2.038
$AUC_{0\text{-inf}}$	**1.480**	1.399 – 1.566
% Fraction excreted in urine	**1.18**	1.088 – 1.271
CLr	**0.822**	0.761 - 0.889

Digoxin mean $t_{1/2}$ was slightly increased (increase of only 15%) in the presence of GLE/PIB.
Safety There were no reported deaths or serious adverse events in the study.

REVIEWER ASSESSMENT
The study design is acceptable ☑ Yes ☐ No
Study Conduct ▪ Bioanalytical method performance in acceptable ☑ Yes ☐ No ▪ Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ NA
Study Results The study results are acceptable as reported by the sponsor ☑ Yes ☐ No
Discussion The study results confirm that GLE/PIB combination inhibits P-gp *in vivo* in a manner that leads to significant changes in exposure especially for drugs with narrow therapeutic index. GLE dose used (400 mg) is higher than the clinically recommended dose (300 mg). Due to nonlinearity in GLE pharmacokinetics, it is not feasible to estimate the P-gp inhibitory effect of the clinical dose of GLE/PIB on digoxin exposure. Study results represent an exaggerated scenario and can be used for labeling. The results of the study can be applied to higher digoxin doses because digoxin exhibits linear pharmacokinetics. These results may not apply to IV digoxin.
Labeling Recommendations The applicant's proposed labeling recommendation is to reduce digoxin dose by 50% when co-administered with GLE/PIB. We recommend making the recommendation consistent with Lanoxin® labeling as follows: "Measure serum digoxin concentrations before initiating concomitant drugs. Reduce digoxin concentrations by decreasing the dose by approximately 50% or by modifying the dosing frequency and continue monitoring". We agree with the applicant's proposal to include the following statement in the labeling in Section 7.1: "*glecaprevir and pibrentasvir are inhibitors of P-glycoprotein (P-gp). Co-administration with TRADENAME may increase plasma concentration of drugs that are substrates of P-gp*"

Study #	M13-585	Study Period	24 August 2015 - 29 October 2015	EDR Link
Title	A Phase 1, open-label study to assess the pharmacokinetics, safety and tolerability of the co-administration of dabigatran or lamotrigine with the combination of GLE and PIB in healthy adult subjects			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the effect of GLE/PIB on the pharmacokinetics of dabigatran and lamotrigine.

Rationale: Dabigatran is a substrate for the P-gp efflux transporter which is inhibited by both GLE and PIB. Lamotrigine is predominantly metabolized via UGT1A4. PIB shows *in vitro* potential to inhibit UGT1A4 (R-value: 1.45).

Dose Selection:

GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase 3 trials and proposed for marketing.

Dabigatran (150 mg): The recommended starting dose of dabigatran etexilate is 150 mg BID in patients with CrCl > 30 mL/min.

Lamotrigine: The recommended starting dose of lamotrigine is 25 mg QOD and the maximum therapeutic dose is 500 mg/day for lamotrigine monotherapy.

Design and PK Assessment

	Day 1	Days 2 to 3	Days 4 to 10	Day 11	Days 12 to 13
Arm 1	Dabigatran etexilate 150 mg			Dabigatran etexilate 150 mg	
			GLE 300 mg QD + PIB 120 mg QD		
	Day 1	**Days 2 to 7**	**Days 8 to 14**	**Day 15**	**Days 16 to 20**
Arm 2	Lamotrigine 50 mg			Lamotrigine 50 mg	
			GLE 300 mg QD + PIB 120 mg QD		

Each arm enrolled 12 subjects.

Serial blood sample for the determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE and PIB: for 24 hours on Day 10 and Day 11 (Arm 1) and Day 14 and Day 15 (Arm 2).
2. Dabigatran: for 72 hours on Day 1 and Day 11.
3. Lamotrigine: for 144 hours on Day 1 and Day 15.

Urine samples for assay of dabigatran (Arm 1) were collected over 4 intervals on Day 1 and Day11.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulation: Phase 2b formulation of GLE (100 mg tablet) and PIB (40 mg tablet). Commercially available formulations for dabigatran (150 mg capsule) and lamotrigine (25 mg tablet).

RESULTS

Enrolled	24	Completed	22	Discontinued due to AE	0	PK Population	23*	Safety Population	24

* In Arm 1, Subject 102 withdrew consent and was excluded.

Bioanalytical Method: Link to reports GLE and PIB/ Dabigatran & Lamotrigine

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE, PIB, dabigatran, lamotrigine		
Range	GLE: Low (0.205 to 105 ng/mL)/ High (85.9 to 10100 ng/mL) PIB: Low (0.205 to 105 ng/mL)/ High (85.9 to 1030 ng/mL) Dabigatran: 1 to 400 ng/mL Lamotrigine: 10 to 10000 ng/mL		

Protocol Deviations Three subjects did not consume their entire meals on non-intensive PK sampling days; two subjects in Arm 2 had follow-up visits outside the protocol specified time.

In Arm 1, Subject 112 discontinued GLE/PIB dose on Day 12 and was not excluded from the PK analysis.

Pharmacokinetics: N= 11 for dabigatran and N=12 for lamotrigine

PK Parameter	Dabigatran		Lamotrigine	
	GMR	**90 % CI**	**GMR**	**90 % CI**
Cmax	**2.046**	1.717 - 2.438	**0.979**	0.939 - 1.019
AUC_{inf}	**2.384**	2.109 - 2.695	**0.956**	0.878 - 1.041
Fe (%)	**2.531**	2.066 - 3.101		
CLr	**1.059**	0.938 - 1.196		

Safety

There were no reported deaths or serious adverse events in the study. Three Grade 1 AEs were reported in each arm with no pattern in the proportion of subjects who reported them, and were considered as having "no reasonable possibility" of being related to study drugs.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance is acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No

- Incurred sample reproducibility was not performed for GLE/PIB. This is not considered an issue because the reproducibility of the assay has been established during the analysis of multiple studies.

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion

The results from Arm 1 confirm the inhibitory effect of GLE/PIB on P-gp. The results from Arm 2 suggest that GLE/PIB is not an inhibitor of UGT1A4. Although lamotrigine dose is not the maximum approved lamotrigine monotherapy dose, the absence of significant interaction at low dose can be extrapolated to higher doses.

Labeling Recommendations

Dabigatran: The applicant proposes [redacted] (b) (4) We disagree with the proposal and recommend making the clinical recommendations consistent with dabigatran labeling.

Per dabigatran labeling, the following recommendations apply to GLE/PIB

- No dose adjustment is needed when dabigatran is co-administered with GLE/PIB in subjects with creatinine clearance ≥ 50 mL/min.
- Dabigatran dose should be reduced to 75 mg BID in subjects with creatinine clearance between 30 and 50 mL/min.
- The co-administration of GLE/PIB with dabigatran should be avoided in subjects with creatinine clearance < 30 mL/min.

Lamotrigine: We agree with the applicant's labeling recommendations; no dose adjustment is needed when GLE/PIB is co-administered with lamotrigine.

Study #	M13-584	Study Period	24 July 2014 - 03 October 2014	EDR Link
Title	A Phase 1, open-label study to assess the pharmacokinetics, safety and tolerability of the co-administration of cyclosporine with the combination of GLE and PIB in healthy adult subjects			

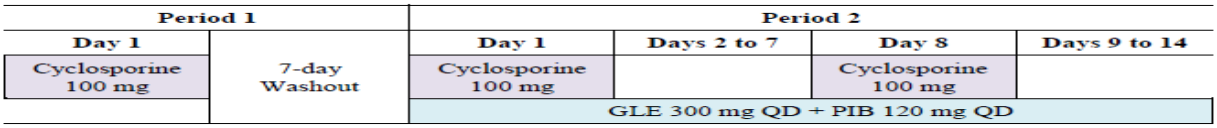
STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the effect of GLE/PIB on the pharmacokinetics of cyclosporine.

Rationale: Cyclosporine is a substrate of CYP3A4. A clinical drug-drug interaction study showed that GLE (700 mg) and PIB (160 mg) had moderate inhibition of CYP3A4 (2.2-fold increase in exposure for midazolam)
Dose Selection:
GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase 3 trials and proposed for marketing.
Cyclosporine: Per the applicant, the recommended dose used in transplant patients in order to maintain a trough concentration of 75 to 125 ng/mL is 75 to 150 mg twice daily.

Design and PK Assessment



Serial blood sample for determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE and PIB: for 24 hours on Day 1, Day 7, and Day 8 (Period 2).
2. Cyclosporine: for 48 hours on Day 1 (Period 1) and 144 hours on Day 1 and Day 8 (Period 2).

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulation: Phase 2b formulation of GLE (100 mg tablet) and PIB (40 mg tablet). Commercially available cyclosporine (Neoral® 100 mg capsule).

RESULTS

Enrolled	12	Completed	12	Discontinued Due to AE	0	PK Population	12	Safety Population	12

Bioanalytical Method: Link to reports GLE and PIB / Cyclosporine

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE	PIB	Cyclosporine
Range	Low: 0.202 - 100 ng/mL High: 85.2 - 10000 ng/mL	Low: 0.202 - 100 ng/mL High: 85.1 - 1000 ng/mL	5 - 2500 ng/mL

Protocol Deviations No protocol deviations were reported in this study.

Pharmacokinetics

Drug	Regimens	PK Parameter	GMR	90% CI
Cyclosporine	Period 2 Day 1 vs. Period 1 Day 1	Cmax	**1.09**	0.952 - 1.24
		$AUC_{0\text{-}inf}$	**1.13**	1.07 - 1.20
	Period 2 Day 8 vs. Period 1 Day 1	Cmax	**1.11**	0.876 - 1.40
		$AUC_{0\text{-}inf}$	**1.14**	1.02 - 1.27
GLE	Period 2 Day 8 vs. Period 2 Day 7	$AUC_{0\text{-}24}$	**1.37**	1.13 - 1.66
		Cmax	**1.30**	0.950 - 1.78
		C_{24}	**1.34**	1.12 - 1.60
PIB	Period 2 Day 8 vs. Period 2 Day 7	$AUC_{0\text{-}24}$	**1.22**	1.10 - 1.36
		Cmax	**1.11**	0.922 - 1.33
		C_{24}	**1.26**	1.15 - 1.37

Safety
There were no reported deaths or serious adverse events in the study. Two (2/12, 17%) subjects reported a single Grade 1 AE in Period 2 after cyclosporine was co-administered with GLE and PIB (gastroesophageal reflux, and increased blood creatine phosphokinase). The AEs were assessed as having “no reasonable possibility" of being related to study drugs.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No
According to Neoral® labeling, the recommended daily dose of cyclosporine is:

- Newly transplanted patients: the initial dose range is 7±3 (renal transplant), 8±4 (liver transplant), 9±3 (heart transplant) mg/kg/day divided into two doses.
- Rheumatoid arthritis & psoriasis: 2.5 mg/Kg/day (1.25 mg/Kg/day BID), maximum dose is 4 mg/Kg/day

The cyclosporine dose evaluated in this study is lower than the recommended clinical dose in transplant patients (8-12 mg/kg/day in two divided doses ~ 280 to 420 mg BID for a 70 Kg subject). However, the study design is acceptable because the objective is to assess the effect of GLE and PIB on cyclosporine pharmacokinetics and a lower cyclosporine dose was selected as a safety precaution because up to 2-fold increases in cyclosporine exposure were expected.

Study Conduct

- Bioanalytical method performance is acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion

The objective of the study was to assess the effect of GLE/PIB on the pharmacokinetics of cyclosporine. The results indicated that the pharmacokinetics of cyclosporine is not altered following single and multiple dose administrations of GLE/PIB. Of note, the single dose administration of cyclosporine increased both GLE and PIB AUC.

Labeling Recommendations

The study was designed to assess the effect of multiple dose administration of GLE/PIB on the pharmacokinetics of cyclosporine. GLE/PIB at steady state does not affect cyclosporine exposure which is consistent with the observed effect of GLE/PIB on midazolam at the clinical proposed GLE/PIB dose (26% increase in AUC), cyclosporine is a substrate of CYP3A4.

The study results cannot be used to inform labeling recommendations regarding the co-administration of GLE/PIB and cyclosporine because cyclosporine dose used in the trial is not the recommended clinical dose in transplant patients although the applicant states that it is the clinically recommended dose in dose selection rationale. In the study, single dose administration of cyclosporine increased GLE and PIB exposures and therefore it is possible that further increases in GLE and PIB exposures can occur when co-administered with the clinically recommended cyclosporine dose in transplant patients (7-9 mg/kg/day divided in two doses ~ 245 – 315 mg BID for a 70 Kg subject).

Study #	M13-592	Study Period	18 August 2014 - 19 November 2014	EDR Link
Title	A Phase 1, open-label study to assess the pharmacokinetics, safety and tolerability of the co-administration of tacrolimus with the combination of GLE and PIB in healthy adult subjects			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the effect of GLE/PIB on the pharmacokinetics of tacrolimus

Rationale: Tacrolimus is principally metabolized by CYP3A4 and is a P-gp substrate. GLE/PIB combination is a weak CYP3A4 inhibitor and both GLE and PIB are P-gp inhibitors.

Dose Selection:

GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase 3 trials and proposed for marketing.

Tacrolimus: The recommended dosing in transplant patients is 0.075 to 0.2 mg/kg/day. A sub-therapeutic tacrolimus dose was selected to reduce the risks of potential nephrotoxicity or other toxicity related to tacrolimus exposure.

Design and PK Assessment

<table>
<tr><th colspan="2">Period 1</th><th colspan="3">Period 2</th></tr>
<tr><th>Day 1</th><th>Days 2 to 7</th><th>Days 1 to 7</th><th>Day 8</th><th>Day 9 to 21</th></tr>
<tr><td>Tacrolimus 1 mg</td><td rowspan="2">Washout</td><td></td><td>Tacrolimus 1 mg</td><td></td></tr>
<tr><td></td><td colspan="3">GLE 300 mg QD + PIB 120 mg QD</td></tr>
</table>

Serial blood sample for determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE and PIB: for 24 hours on Day 1, Day 7, and Day 8 (Period 2)
2. Tacrolimus: for 144 hours on Day 1 (Period 1) and 312 hours on Day 1 (Period 1) and Day 8 (Period 2)

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulations: Phase 2b formulation of GLE (100 mg Tablet) and PIB (40 mg Tablet). Commercially available tacrolimus (Prograf® 1 mg Capsule).

RESULTS

Enrolled	12	Completed	10	Discontinued Due to AE	1	PK Population	10*	Safety Population	12

*Subjects 102 discontinued from the study due to a family emergency, after he received a single 1 mg tacrolimus dose in Period 1. Subject 106, discontinued from the study due to a haematoma, after receiving a single 1 mg tacrolimus dose in Period 1.

Bioanalytical Method: Link to reports GLE and PIB / Tacrolimus

Method Type	LC-MS/MS	Matrix	Plasma (GLE/PIB), Whole Blood (Tacrolimus)
Analytes	GLE	PIB	Tacrolimus
Range	Low: 0.202 - 100 (ng/mL) High: 85.2 -10000 (ng/mL)	Low: 0.202 - 100 (ng/mL) High: 85.1 -1000 (ng/mL)	0.25 – 25 (ng/mL)

Protocol Deviations No protocol deviations were reported in this study

Pharmacokinetics

Drug	PK Parameter	GMR	90% CI
Tacrolimus	Cmax	1.50	1.24 – 1.81
	AUC_{0-t}	1.53	1.30 – 1.80
	AUC_{0-inf}	1.45	1.24 – 1.69

GLE and PIB exposures did not change following the administration of a single dose of tacrolimus

Safety
- There were no reported deaths or serious adverse events in the study.
- **S**ubject 106 (1/12, %) in Period 1 reported a treatment-emergent haematoma and discontinued from the study.

REVIEWER ASSESSMENT
The study design is acceptable ☑ Yes ☐ No
Study Conduct ▪ Bioanalytical method performance in acceptable ☑ Yes ☐ No ▪ Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A
Study Results The study results are acceptable as reported by the sponsor ☑ Yes ☐ No
Discussion As expected, following multiple dose administrations of GLE/PIB, tacrolimus exposure increased by ~ 50%. The study used a sub-therapeutic dose of tacrolimus; however, the results can be used to guide tacrolimus dosing because tacrolimus has linear PK in the dose range 3 to 10 mg and its blood levels are monitored frequently as part of clinical practice.
Labeling Recommendations The Applicant recommends no dosage adjustment of tacrolimus when co-administered with GLE/PIB and lists tacrolimus as a drug with no observed clinically significant interaction in Section 7.4 The following statements were found in tacrolimus labeling: 1. ENVARSUS XR® label: in reference to mild and moderate CYP3A inhibitors in Section 7.2: *May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) [see Warnings and Precautions (5.6, 5.10)]"* 2. PROGRAF® label: contains the following statement in the drug interactions section: "*Frequent monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when concomitant use of the following drugs with tacrolimus is initiated or discontinued [see Drug Interactions (7)]"* including magnesium-aluminum-hydroxide which causes a 21% increase in tacrolimus AUC. We recommend the following clinical recommendation for the co-administration of GLE/PIB and tacrolimus "Monitor whole blood concentration of tacrolimus frequently and adjust the tacrolimus dose if needed because GLE/PIB may increase the risk of adverse events associated with tacrolimus"

Study #	M14-724	Study Period	06 March 2015- 10 June 2015	EDR Link
Title	A Phase 1, open-label study to assess the pharmacokinetics, safety and tolerability of the co-administration of carbamazepine with the combination of GLE and PIB in healthy adult subjects			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the effect of carbamazepine on the pharmacokinetics of GLE and PIB.

Rationale: Carbamazepine is a strong inducer of CYP3A4 and is also a P-gp inducer. Both GLE and PIB are P-gp substrates

Dose Selection:

GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase 3 trials and proposed for marketing.

Carbamazepine: The recommended initial oral dosing in adult subjects is 200 mg BID for epilepsy or 100 mg BID for trigeminal neuralgia. The total maximum daily dose of 400 mg in this study was selected to minimize risk to healthy subjects while providing maximal CYP3A induction.

Design and PK Assessment

Period 1		Period 2			
Day 1	7-day Washout	Days 1 to 3	Days 4 to 20	Day 21	Day 22
		Carbamazepine 200 mg QD	Carbamazepine 200 mg BID		
GLE 300 mg + PIB 120 mg				GLE 300 mg + PIB 120 mg	

Serial blood sample for determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE and PIB: for 48 hours on Day 1 (Period 1) and Day 21 (Period 2)
2. Carbamazepine and carbamazepine-10, 11-epoxide(CBZE, active metabolite): for 24 hours on Day 20 and Day 21 (Period 2)

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulations: Phase 2b formulation of GLE (100 mg Tablet) and PIB (40 mg Tablet). Commercially available carbamazepine (Tegratol® 200 mg Tablet).

RESULTS

Enrolled	12	Completed	10	Discontinued Due to AE	2	PK Population	10*	Safety Population	12

* Subject 107 was discontinued on Period 2 Day 16 due to pyrexia and Subject 110 was discontinued on Period 1 Day 7 due to nausea, abdominal pain and vomiting during the washout period

Bioanalytical Method: Link to reports GLE and PIB / Carbamazepine

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE	PIB	Carbamazepine & CBZE
Range	Low: 0.205 - 101 (ng/mL) High: 86.5 - 10200 (ng/mL)	Low: 0.205 - 101 (ng/mL) High: 86.4 -1020 (ng/mL)	0.05 – 50 (µg/mL)

Protocol Deviations One subject did not have an 8-hour fasting blood sample for a serum chemistry sample time. Subject 108's Period 1 Day 2 serum chemistry sample hemolyzed after it was drawn, it was disposed of and an additional serum chemistry sample was drawn after only a 2-hour fasting period.

Subjects 102, 103, 105, 107, 110, and 111 did not finish their dinner meals on Day 1 (did not eat dessert)

Pharmacokinetics

PK Parameter	GLE		PIB	
	GMR	90 % CI	GMR	90 % CI
Cmax	**0.331**	0.266 – 0.411	**0.500**	0.423 – 0.591
AUC_{inf}	**0.336**	0.283 – 0.399	**0.490**	0.434 – 0.552

Carbamazepine and CBZE pharmacokinetics were not changed following the administration of a single dose of GLE/PIB

Safety

There were no reported deaths or serious adverse events in the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No

- Incurred sample reproducibility for GLE and PIB was not performed in this study. Ideally this should have been performed; however, given the experience with using the assay across multiple studies, study results can be accepted.

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion

Carbamazepine significantly reduced the exposure of both GLE and PIB. The decrease in GLE exposure is more than that of PIB. The range of AUC reduction for GLE was 50% to 80% (individual AUC ratios range = 0.2 – 0.5) and the range of AUC reduction for PIB was 42% to 31% (individual AUC ratios range = 0.29 – 0.58). The decrease can be mainly attributed to P-gp induction by carbamazepine.

Labeling Recommendations

The applicant is proposing not to recommend the co-administration of GLE/PIB and carbamazepine. We have to evaluate exposure-efficacy data to determine whether the observed reduction in exposure warrants contraindicating the co-administration of GLE/PIB and carbamazepine or any P-gp inducer.

Study #	M13-602	Study Period	22 July 2014 - 12 November 2014	EDR Link
Title	An open-label Phase 1 study to assess pharmacokinetics, pharmacodynamics, safety and tolerability of co-administration of methadone or buprenorphine/naloxone in combination with GLE and PIB in subjects on stable maintenance therapy			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the effect of GLE and PIB on the pharmacokinetics and pharmacodynamics of methadone and buprenorphine/naloxone

Rationale: Opioid replacement therapies may be commonly coadministered with GLE/PIB.
Dose Selection:
- GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase 3 trials and proposed for marketing.
- Methadone: Subjects were on individualized methadone doses (20 to 120 mg daily dose). Doses of methadone did not change in the study.
- Buprenorphine/Naloxone: Subjects were on individualized buprenorphine/naloxone doses up to 24 mg/6 mg QD. Doses of buprenorphine/naloxone did not change in the study.

Design and PK/PD Assessment

	Period 1 Days 1 to 9	Period 2 Days 1 to 7	Period 2 Days 8 to 10
Arm 1 N = 12	Methadone QD		
		GLE 300 mg QD + PIB 120 mg QD	
Arm 2 N = 12	Buprenorphine/Naloxone QD		
		GLE 300 mg QD + PIB 120 mg QD	

PK assessment: Serial blood sample for determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE and PIB: for 24 hours on Day 1 (Period 2) and 48 hours on Day 7 (Period 2)
2. Methadone and buprenorphine/naloxone: for 24 hours on Day 6 and Day 9 (Period 1) and Day 1 and 7 (Period 2)

PD assessment: Short Opiate Withdrawal (SOWS) Scale, Desire for Drugs Questionnaire (DDQ) Heroin Questionnaire, and Pupillometry instruments were evaluated on Day 9 (Period 1) and Days 1, 2 ,3, 5, 7, 8, 9 , and 10 (Period 2)

Population: ☑ Healthy Subjects ☐ Patients Adult male and female subjects on a stable methadone or buprenorphine/naloxone maintenance program for at least 14 days and in general good health	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulation: Phase 2b formulation of GLE (100 mg Tablet) and PIB (40 mg Tablet). The identity of methadone and buprenorphine/naloxone products is not documented in the clinical study report.

RESULTS

Enrolled	24	Completed	23	Discontinued Due to AE	0	PK Population	23	Safety Population	24

* Subject 112 (Arm 1) withdrew consent on Study Day 5 of Period 2

Bioanalytical Method: Link to reports GLE and PIB / Buprenorphine/Nalaxone/Methadone

Method Type	LC-MS/MS	Matrix		Plasma	
Analytes	GLE	PIB	Methadone	Buprenorphine Norbuprenorphine	Naloxone
Range	Low: 0.202 – 100 (ng/mL) High: 85.2 – 1000 (ng/mL)	Low: 0.202 – 100 (ng/mL) High: 85.1 – 1000 (ng/mL)	1.00 - 1000 (ng/mL)	100 - 25000 (pg/mL)	20.0 - 5000 (pg/mL)

Protocol Deviations
No protocol deviations were reported in this study

Pharmacokinetic Results

Drug	PK Parameter (Unit)	GMR	90% CI
(R)-Methadone	C_{max}/Dose	**0.963**	0.908 – 1.021
	AUC_{0-24}/Dose	**1.018**	0.980 – 1.058
	C_{24}/Dose	**0.983**	0.929 – 1.041
(S)-Methadone	C_{max}/Dose	**0.976**	0.926 – 1.029
	AUC_{0-24}/Dose	**1.046**	1.008 – 1.086
	C_{24}/Dose	**1.015**	0.956 – 1.078
Buprenorphine	C_{max}/Dose	**1.076**	0.972 – 1.192
	AUC_{0-24}/Dose	**1.171**	1.082 – 1.268
	C_{24}/Dose	**1.237**	1.094 – 1.399
Norbuprenorphine*	C_{max}/Dose	**1.254**	1.172 – 1.341
	AUC_{0-24}/Dose	**1.299**	1.190 – 1.419
	C_{24}/Dose	**1.210**	1.055 – 1.389
Naloxone	C_{max}/Dose	**0.882**	0.737 – 1.055
	AUC_{0-24}/Dose	**1.069**	0.895 – 1.276

* Normalized to buprenorphine dose

Pharmacodynamic Results
No changes in pupil response, (SOWS) scale, or DDQ Heroin were observed when GLE and PIB were co-administered with methadone or buprenorphine/naloxone.

Safety
There were no reported deaths or serious adverse events in the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct
- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Study Results
The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Labeling Recommendations
We agree with the Applicant's recommendation that no dose adjustment is recommended when GLE/PIB is co-administered with methadone or buprenorphine/naloxone.

Study #	M13-603	Study Period	05 November 2014 - 02 April 2015	EDR Link
Title	A Phase 1, open-label study to assess the pharmacokinetics, safety and tolerability of the co-administration of atazanavir with the combination therapy of GLE and PIB in healthy adult subjects.			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the effect of GLE/PIB on the pharmacokinetics of atazanavir (ATV)/ritonavir(RTV) and the effect ATV/RTV on the pharmacokinetics of GLE/PIB.

Rationale: ATV/RTV may be commonly co-administered with GLE and PIB in subjects co-infected with HIV. ATV is a substrate and inhibitor of CYP3A and an inhibitor of UGT1A1. ATV is also an inhibitor of OATP1B1 and OATP1B3. RTV is a substrate of CYP3A4, and an inhibitor of CYP3A, P-gp and BCRP. GLE is a substrate and inhibitor of OATP1B1/3 and both GLE and PIB are substrates and inhibitors of P-gp and BCRP and PIB is an inhibitor of OATP1B1.

Dose Selection:

GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase 3 trials and proposed for marketing.

ATV/RTV (300 mg/ 100 mg): This is the recommended clinical dose for both treatment-naïve and treatment-experienced adult patients.

Design and PK Assessment

<table>
<tr><td rowspan="3">Cohort I
N = 12</td><td>Period 1, Days 1 to 7</td><td colspan="2">Period 2, Days 1 to 14</td></tr>
<tr><td></td><td colspan="2">Atazanavir 300 mg QD + Ritonavir 100 mg QD</td></tr>
<tr><td colspan="3">GLE 300 mg QD + PIB 120 mg QD</td></tr>
<tr><td rowspan="3">Cohort II
N = 12</td><td colspan="2">Period 1, Days 1 to 14</td><td>Period 2, Days 1 to 7</td></tr>
<tr><td colspan="3">Atazanavir 300 mg QD + Ritonavir 100 mg QD</td></tr>
<tr><td colspan="2"></td><td>GLE 300 mg QD + PIB 120 mg QD</td></tr>
</table>

Serial blood sample for determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE/PIB:
   - Cohort I: For 16 hours on Day 7 (Period 1) and 24 hours on Day1 (Period 2). Pre-dose samples were collected on Day 14 (Period 2); Cohort I was terminated after dosing on Period 2 Day 13
   - Cohort II: For 24 hours on Day 1 (Period 2) and Day 7 (Period 2)
2. ATV/RTV
   - Cohort I: For 24 hours on Day 1 (Period 2) and pre-dose on Day 14 (Period 2)
   - Cohort II: For 16 hours on Day 14 (Period 1) and for 24 hours on Day 1 and Day 7 (Period 2)

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulation: Phase 2b formulation of GLE (100 mg Tablet) and PIB (40 mg Tablet). Commercially available formulation of ATV (Reytaz® 300 mg Capsule) and RTV (100 mg Tablet).

RESULT

Enrolled	24	Completed	19	Discontinued Due to AE	5	PK Population	23	Safety Population	24

Bioanalytical Method: links to reports GLE and PIB ATV/RTV

Method Type	LC-MS/MS	Matrix		Plasma
Analyte	GLE	PIB	ATV	RTV
Range (ng/mL)	Low:0.200 to 100 High:85.2 to 10400	Low:0.197 to 98.6 High: 83.8 to 985	10 - 10000	10 - 10000

Protocol Deviations

No protocol deviations were reported in this study.

Pharmacokinetic: Note that Study drug administration was discontinued for Cohort I after dosing on Day 13 of

Period 2.

Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of **GLE**

Pharmacokinetic Parameters (Units)	Cohort I[a]		Cohort II	
	Period 1/Day 7 (N = 12)	Period 2/Day 1 (N = 12)	Period 2/Day 1 (N = 11)	Period 2/Day 7 (N = 11)
C_{max} (ng/mL)	1720 (2290, 77)	6970 (7600, 43)	3430 (3810, 48)	6640 (9160, 87)
T_{max}[b] (h)	4.0 [3.0 to 6.0]	4.0 [3.0 to 5.0]	4.0 [3.0 to 6.0]	4.0 [3.0 to 6.0]
AUC_{24} (ng•h/mL)	5300 (6990, 81)	34600 (39400, 53)	18200 (20200, 55)	44500 (75700, 122)
C_{24} (ng/mL)	6.60 (11.5, 129)	94.4 (185, 157)	44.1 (88.8, 158)	163 (1030, 185)

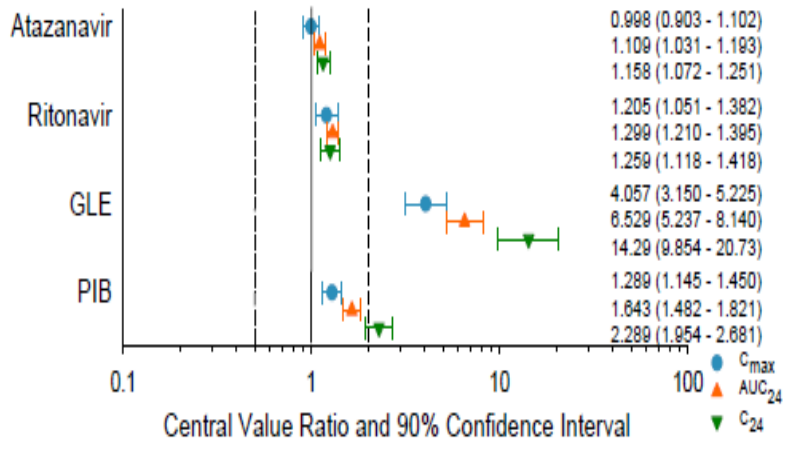
Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of **PIB**

Pharmacokinetic Parameters (Units)	Cohort I[a]		Cohort II	
	Period 1/Day 7 (N = 12)	Period 2/Day 1 (N = 12)	Period 2/Day 1 (N = 11)	Period 2/Day 7 (N = 11)
C_{max} (ng/mL)	356 (396, 50)	458 (482, 33)	310 (321, 27)	462 (476, 25)
T_{max}[b] (h)	5.0 [4.0 to 5.0]	5.0 [5.0 to 6.0]	6.0 [4.0 to 6.0]	5.0 [4.0 to 6.0]
AUC_{24} (ng•h/mL)	2780 (3240, 63)	4570 (5010, 47)	3030 (3150, 29)	6060 (6450, 39)
C_{24} (ng/mL)	44.3 (53.5, 73)	101 (116, 57)	58.4 (63.3, 42)	154 (175, 57)

Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of **ATV**

Pharmacokinetic Parameters (Units)	Cohort I[a]	Cohort II		
	Period 2/Day 1 (N = 12)	Period 1/Day 14 (N = 11)	Period 2/Day 1 (N = 11)	Period 2/Day 7 (N = 11)
C_{max} (ng/mL)	4210 (4310, 23)	6630 (6870, 27)	6890 (7110, 26)	6610 (6790, 22)
T_{max}[b] (h)	3.0 [2.0 to 4.0]	3.0 [2.0 to 4.0]	3.0 [2.0 to 5.0]	3.0 [2.0 to 5.0]
AUC_{24} (ng•h/mL)	36700 (37900, 27)	74200 (80400, 39)	82000 (88500, 37)	82300 (87700, 33)
C_{24} (ng/mL)	752 (834, 52)	1740 (2190, 65)	1950 (2480, 61)	2020 (2460, 54)

Satistical Comparison of PK Parameters (GMR and 90% CI)



ATV: Day 7 Period 2 vs. Day 14 Period 1 (Cohort II)
RTV: Day 7 Period 2 vs. Day 14 Period 1 (Cohort II)
GLE: Day1 Period 2 vs. Day 7 Period 1 (Cohort I)
PIB: Day1 Period 2 vs. Day 7 Period 1 (Cohort I)

Notes:

For GLE and PIB: ratios represent the effect of a single dose ATV/RTV on GLE or PIB steady state exposure (because dosing was terminated early)

For ATV/RTV: ratios represent the effect of GLE/PIB at steady state on the exposure of steady state ATV/RTV

Safety

- There were no deaths or serious adverse events reported in the study.
- All subjects in both cohorts developed hyperbilirubinemia following ATV/RTV administration, a known effect due to UGT inhibition.
- Five subject discontinued the study due to adverse events as shown in the table below:

Subject	Age/Sex	Cohort	Day of Onset	Adverse Event	Severity Grade	Relationship to GLE/PIB	Relationship to ATV
101	39/M	I	Period 2, Day 1	Ventricular Extrasystoles	1	RP*	RP
106	40/M	I	Period 2, Day 13	ALT Increased	2	RP	RP
110	30/F	I	Period 2, Day 7	ALT Increased	1	RP	RP
			Period 2, Day 7	AST Increased	1	RP	RP
111	46/F	I	Period 2, Day 10	ALT Increased	1	RP	RP
			Period 2, Day 12	AST Increased	1	RP	RP
			Period 2, Day 13	ALT Increased	2	RP	RP
208	26/F	II	Period 2, Day 6	ALT Increased	1	RP	RP
			Period 2, Day 6	AST Increased	1	RP	RP

*RP = Reasonable possibility

Source: page 68 of CSR.

The applicant suspended the study in Cohort I and subsequently terminated it after dosing on Period 2 Day 13 for the remaining eight subjects. Cohort II was completed as planned.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance is acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion

Due to early discontinuation of study drug administration in Cohort I, the effect of multiple doses of atazanavir/ritonavir on GLE/PIB was not measured. Cross-cohort comparison indicates the following:

1. Effect of multiple dose administration of ATV/RTV on GLE exposure is higher (AUC ratio [Day7 Period 2 (Cogort II) vs. Day 7 Period 1 (Cohort I)] = 8.4) compared to the effect of a single dose administration of ATV/RTV on GLE exposure (AUC ratio=6.53)
2. Effect of multiple dose administration of ATV/RTV on PIB exposure is slightly higher (AUC ratio = 2.18) compared to the effect of a single dose administration of ATV/RTV on GLE exposure (AUC ratio=1.64)
3. Single and multiple dose administration of GLE/PIB produced the same change in steady state exposure of ATV/RTV.

It is not clear why more subjects I in Cohort I had ALT/AST elevation compared to Cohort II. The exposure of GLE/PIB should be similar toward the end of Period 2 of both cohorts because both ATV/RTV and GLE/PIB should have reached steady state.

Labeling Recommendations

We agree with the applicant that co-administration of GLE/PIB with atazanavir (b) (4) is contraindicated based

on the safety observation in the study. A question is whether this contraindication should be extended to all OAT1P1 inhibitors. This should be discussed in QBR once studies with other OAT1P1 inhibitors have been reviewed in addition to exposure-safety relationship for GLE/PIB.

Study #	M13-577	Study Period	12 November 2014 - 27 January 2015	EDR Link
Title	Phase 1, open-label study to assess the pharmacokinetics, safety and tolerability of the co administration of darunavir and ritonavir with the combination of GLE and PIB or the co-administration of rilpivirine with the combination of GLE and PIB in healthy adult subjects			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the effect of GLE/PIB on the pharmacokinetics of darunavir (DRV)/ritonavir (RTV) or rilpivirine (RPV) and the effect DRV/RTV or RPV on the pharmacokinetics of GLE/PIB.

Rationale:

DRV/RTV may be commonly co-administered with GLE and PIB in cases of HIV-HCV co-infection. DRV is an inhibitor of OATP1B1/3 and an inducer of P-gp. RTV is an inhibitor of CYP3A, P-gp, and BCRP, and a substrate of CYP3A. GLE is a substrate and inhibitor of OATP1B1/3 and both GLE and PIB are substrates and inhibitors of P-gp and BCRP and PIB is an inhibitor of OATP1B1.

RPV: RPV may be commonly co-administered with GLE and PIB in cases of HIV-HCV co-infection. It is metabolized extensively by CYP3A and it is not an inducer or inhibitor of CYP enzymes at the recommended 25 mg QD dose. It is not significantly transported by P-gp.

Dose Selection:

GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase 3 trials and proposed for marketing.

DRV/RTV (800 mg/100 mg): This is the recommended clinical regimen for treatment-naïve adult patients and treatment-experienced adult patients with no darunavir resistance-associated substitutions.

RPV (25 mg): This is the recommended therapeutic dose of rilpivirine in combination with other antiretroviral agents for the treatment of HIV-1 infection in antiretroviral treatment-naïve adult patients.

Design and PK Assessment

Arm 1, Cohort I N = 12	**Period 1, Days 1 to 7**	**Period 2, Days 1 to 14**
		Darunavir 800 mg QD + Ritonavir 100 mg QD
	GLE 300 mg QD + PIB 120 mg QD	
Arm 1, Cohort II N = 12	**Period 1, Days 1 to 14**	**Period 2, Days 1 to 7**
	Darunavir 800 mg QD + Ritonavir 100 mg QD	
		GLE 300 mg QD + PIB 120 mg QD
Arm 2, Cohort I N = 12	**Period 1, Days 1 to 7**	**Period 2, Days 1 to 14**
		Rilpivirine 25 mg QD
	GLE 300 mg QD + PIB 120 mg QD	
Arm 2, Cohort II N = 12	**Period 1, Days 1 to 14**	**Period 2, Days 1 to 7**
	Rilpivirine 25 mg QD	
		GLE 300 mg QD + PIB 120 mg QD

The interaction between the DAAs with rilpivirine was studied in a separate arm due to its long half-life (50 hr)
Serial blood sample for determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE/PIB (Arms 1 & 2):
   - Cohort I: For 24 hours on Day 7 (Period 1) and Day1 and Day 14 (Period 2)
   - Cohort II: For 24 hours on Day 1 (Period 2) and Day 7 (Period 2)
2. DRV/RTV & RPV (Arms 1 & 2):
   - Cohort I: For 24 hours on Day 1 (Period 2) and on Day 14 (Period 2)
   - Cohort II: For 24 hours on Day 14 (Period 1) and Day 1 and Day 7 (Period 2)

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulation: Phase 2b formulation of GLE (100 mg Tablet) and PIB (40 mg Tablet). Commercially available

formulation of DRV (Prezista® 800 mg Capsule), RTV (100 mg Tablet), and RPV (Edurant® 25 mg).

RESULT

Enrolled	48	Completed	46	Discontinued Due to AE	2	PK Population	41(GLE/PIB) 46 (RPV and DRV/RTV)	Safety Population	48

Bioanalytical Method GLE/PIB, DRV/RTV, RPV

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE, PIB, darunavir, ritonavir, rilpivirine		
Range	GLE, Low: 0.200 ng/mL to 100 ng/mL High: 85.2 ng/mL to 10400 ng/mL PIB, Low 0.197 ng/mL to 98.6 ng/mL High 83.8 ng/mL to 985 ng/mL RTV: 10- 1000 ng/mL DRV: 10 - 1000 ng/mL RPV: 0.5 - 250 ng/mL		

Protocol Deviations

No significant protocol deviations were reported in this study.

Pharmacokinetic – Arm 1

Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of **GLE**

Pharmacokinetic Parameters (Units)	Cohort I (N = 8)			Cohort II (N = 10)	
	Per 1 Day 7	Per 2 Day 1	Per 2 Day 14	Per 2 Day 1	Per 2 Day 7
C_{max} (ng/mL)	1056 (1838, 115)	2962 (3897, 74)	3258 (4981, 99)	2743 (3062, 55)	4995 (5963, 69)
T_{max}[a] (h)	4.0 [2.0 to 5.0]	4.0 [3.0 to 5.0]	4.5 [3.0 to 9.0]	4.0 [3.0 to 5.0]	4.0 [3.0 to 6.0]
AUC_{24} (ng•h/mL)	4009 (6495, 109)	16845 (22737, 88)	19940 (31518, 115)	10948 (11648, 40)	21440 (27038, 77)
C_{24} (ng/mL)	5.66 (8.26, 91)	44.8 (68.3, 105)	46.6 (115, 161)	14.1 (18.2, 81)	33.7 (85.1, 141)

Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of **PIB**

Pharmacokinetic Parameters (Units)	Cohort I (N = 8)			Cohort II (N = 10)	
	Per 1 Day 7	Per 2 Day 1	Per 2 Day 14	Per 2 Day 1	Per 2 Day 7
C_{max} (ng/mL)	301 (318, 36)	333 (349, 34)	255 (283, 58)	261 (273, 30)	319 (330, 27)
T_{max}[a] (h)	5.0 [4.0 to 5.0]	5.0 [5.0 to 6.0]	5.0 [3.0 to 6.0]	5.0 [4.0 to 5.0]	5.0 [5.0 to 5.0]
AUC_{24} (ng•h/mL)	2366 (2521, 41)	3089 (3290, 41)	2732 (3226, 72)	1719 (1781, 29)	2851 (2970, 28)
C_{24} (ng/mL)	32.8 (35.8, 49)	50.0 (56.3, 59)	54.5 (75.1, 98)	18.1 (19.6, 45)	46.3 (54.0, 53)

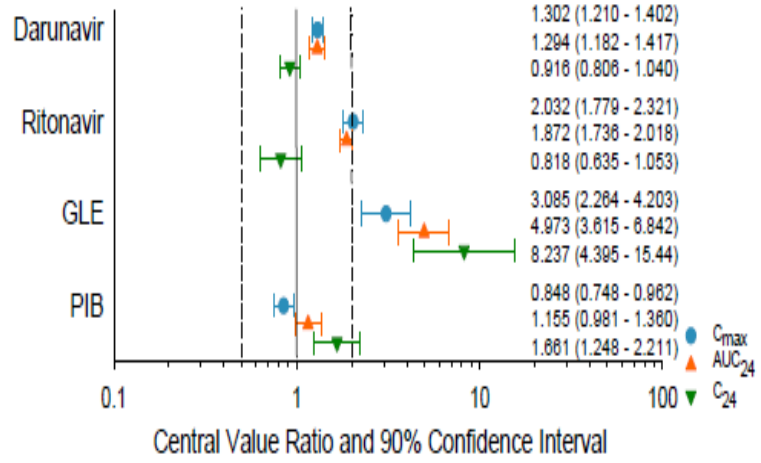
Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of **DRV**

Pharmacokinetic Parameters (Units)	Cohort I (N = 10)		Cohort II (N = 12)		
	Per 2 Day 1	Per 2 Day 14	Per 1 Day 14	Per 2 Day 1	Per 2 Day 7
C_{max} (µg/mL)	8.97 (9.21, 26)	9.11 (9.26, 18)	7.02 (7.06, 11)	9.06 (9.10, 10)	9.14 (9.20, 13)
T_{max}[a] (h)	4.0 [3.0 to 6.0]	4.0 [3.0 to 6.0]	4.0 [2.0 to 5.0]	4.0 [2.0 to 6.0]	4.0 [4.0 to 9.0]
AUC_{24} (µg•h/mL)	103 (111, 41)	103 (106, 22)	76.4 (78.6, 23)	99.5 (102, 25)	98.9 (101, 24)
C_{24} (µg/mL)	1.76 (2.09, 64)	1.86 (2.03, 39)	2.22 (2.28, 25)	2.26 (2.45, 45)	2.03 (2.18, 40)

Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of **RTV**

Pharmacokinetic Parameters (Units)	Cohort I (N = 10)		Cohort II (N = 12)		
	Per 2 Day 1	Per 2 Day 14	Per 1 Day 14	Per 2 Day 1	Per 2 Day 7
C_{max} (ng/mL)	1131 (1143, 15)	1205 (1236, 23)	635 (667, 34.3)	1608 (1655, 27)	1290 (1311, 19)
T_{max}[a] (h)	4.0 [3.0 to 5.0]	4.0 [3.0 to 5.0]	4.0 [4.0 to 5.0]	4.0 [2.0 to 5.0]	4.0 [4.0 to 9.0]
AUC_{24} (ng•h/mL)	6586 (6997, 40)	8136 (8667, 42)	4275 (4356, 20)	8526 (8688, 20)	8003 (8214, 25)
C_{24} (ng/mL)	30.0 (37.1, 94)	34.4 (50.7, 117)	39.7 (45.4, 55)	34.1 (45.7, 94)	32.5 (47.5, 104)

Statistical Comparison of PK Parameters (GMR and 90% CI)



DRV: Day 7 Period 2 vs. Day 14 Period 1 (Cohort II)
RTV: Day 7 Period 2 vs. Day 14 Period 1 (Cohort II)
GLE: Day14 Period 2 vs. Day 7 Period 1 (Cohort I)
PIB: Day14 Period 2 vs. Day 7 Period 1 (Cohort I)
Notes:
For GLE and PIB: ratios represent the effect of multiple doses of DRV/RTV on GLE or PIB exposure at steady state
For DRV and RTV: ratios represent the effect of GLE/PIB at steady state on the exposure of DRV/RTV at steady state

Pharmacokinetic – Arm 2

Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of **GLE**

Pharmacokinetic Parameters (Units)	Cohort I (N = 11)			Cohort II (N = 12)	
	Per 1 Day 7	Per 2 Day 1	Per 2 Day 14	Per 2 Day 1	Per 2 Day 7
C_{max} (ng/mL)	1520 (2015, 77)	1548 (2172, 79)	1326 (1754, 84)	1486 (1687, 50)	2104 (2525, 61)
T_{max}[a] (h)	3.0 [3.0 to 5.0]	3.0 [3.0 to 5.0]	4.0 [3.0 to 5.0]	4.0 [2.0 to 6.0]	4.0 [3.0 to 5.0]
AUC_{24} (ng•h/mL)	4894 (5987, 61)	5076 (6500, 68)	4386 (5500, 75)	4554 (4956, 39)	6515 (7771, 71)
C_{24} (ng/mL)	5.19 (6.79, 79)	5.45 (7.72, 98)	4.78 (6.06, 72)	3.99 (4.81, 66)	6.25 (9.09, 97)

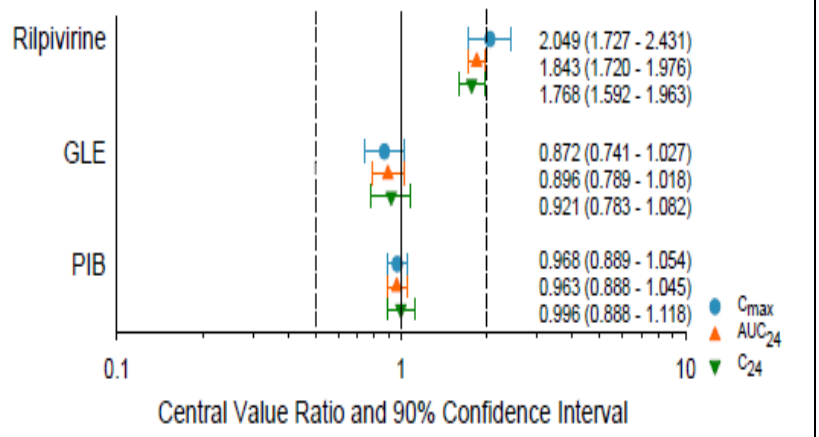
Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of **PIB**

Pharmacokinetic Parameters (Units)	Cohort I (N = 11)			Cohort II (N = 12)	
	Per 1 Day 7	Per 2 Day 1	Per 2 Day 14	Per 2 Day 1	Per 2 Day 7
C_{max} (ng/mL)	345	337	334	276	334
	(370, 38)	(364, 39)	(365, 47)	(289, 32)	(341, 21)
T_{max}[a] (h)	5.0	5.0	5.0	5.0	5.0
	[3.0 to 5.0]	[4.0 to 5.0]	[3.0 to 5.0]	[3.0 to 6.0]	[4.0 to 5.0]
AUC_{24} (ng•h/mL)	2519	2532	2426	1716	2471
	(2807, 48)	(2819, 46)	(2717, 51)	(1782, 30)	(2568, 29)
C_{24} (ng/mL)	32.8	32.3	32.6	16.5	33.4
	(37.7, 53)	(37.7, 53)	(37.4, 55)	(17.3, 31)	(36.1, 41)

Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of **RPV**

Pharmacokinetic Parameters (Units)	Cohort I (N = 12)		Cohort II (N = 12)		
	Per 2 Day 1	Per 2 Day 14	Per 1 Day 14	Per 2 Day 1	Per 2 Day 7
C_{max} (ng/mL)	195	400	234	284	479
	(201, 30)	(416, 28)	(242, 31)	(289, 20)	(488, 20)
T_{max}[a] (h)	4.0	4.0	4.0	4.0	4.0
	[3.0 to 4.0]	[2.0 to 4.0]	[3.0 to 5.0]	[3.0 to 9.0]	[3.0 to 6.0]
AUC_{24} (ng•h/mL)	1812	5053	3148	3742	5802
	(1833, 16)	(5230, 28)	(3195, 19)	(3792, 18)	(5919, 21)
C_{24} (ng/mL)	52.1	150	103	116	182
	(53.6, 25)	(158, 35)	(106, 24)	(119, 22)	(191, 34)

Statistical Comparison of PK Parameters (GMR and 90% CI)



RPV: Day 7 Period 2 vs. Day 14 Period 1 (Cohort II)
GLE: Day14 Period 2 vs. Day 7 Period 1 (Cohort I)
PIB: Day14 Period 2 vs. Day 7 Period 1 (Cohort I)
Notes:
For GLE and PIB: ratios represent the effect of multiple doses of DRV/RTV on GLE or PIB exposure at steady state
For RPV: ratios represent the effect of GLE/PIB at steady state on the exposure of DRV/RTV at steady state

Safety

- There were no deaths or serious adverse events reported in the study.
- Two subjects (113 and 119) , in Arm 1 Cohort I, were discontinued due to Grade 2 AE of rash during dosing with of GLE., PIB, DRV/RTV; the rashes resolved at follow-up. Rash is a known adverse reaction observed with administration of DRV (sulfonamide moiety) as per Prezista® labeling.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance is acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ N/A

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No
Five subjects displayed atypical plasma concentration-time profiles for GLE/PIB. Those were four subjects in Arm 1 (Subjects 110 and 114 in Cohort 1; Subjects 109 and 112 in Cohort 2), and one subject in Arm 2 (Subject 224 in Cohort 1). A sensitivity statistical analysis was performed with the inclusion of the five subjects and the magnitude of GLE and PIB exposure increases was similar when all subjects who completed the study were included in the analysis.

Discussion

The co-administration of DRV/RTV significantly increases the exposure of GLE. This can be attributed to transporter mediated interaction as explained under study rationale. Unlike the study with ATV where ALT/AST elevations were observed, no ALT/AST elevations were observed in this. The applicant is recommending against the co-administration of DRV/RTV and GLE/PIB. The decision to change this recommendation to a contraindication should be based on the exposure-safety analysis.

The increase in RPV exposure can be attributed to the ability of GLE/PIB to weakly inhibit CYP3A4. The increase is not considered clinically significant.

Labeling Recommendations

The applicant's recommendation regarding DRV/RPV co-administration needs further assessment based on the results of the exposure-safety analysis. We agree with the Applicant's recommendation of no dosage adjustment when co-administered with rilpivirine.

Study #	M13-587	Study Period	17 December 2014 - 09 March 2015	EDR Link
Title	A Phase 1, open-label study to assess the pharmacokinetics, safety and tolerability of the co-administration of lopinavir/ritonavir (LPV/r) with the combination of GLE and PIB in healthy adult subjects			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the effect of GLE/PIB on the pharmacokinetics of lopinavir (LPV)/ritonavir (RTV) and the effect LPV/RTV on the pharmacokinetics of GLE/PIB.

Rationale: LPV/RTV may be commonly co-administered with GLE and PIB in subjects co-infected with HIV. LPV/RTV can inhibit OATP, P-gp, and BCRP transporters. RTV a substrate of CYP3A4, and an inhibitor of CYP3A and P-gp and BCRP. GLE is a substrate and inhibitor of OATP1B1/3 and both GLE and PIB are substrates and inhibitors of P-gp and BCRP and PIB is an inhibitor of OATP1B1.

Dose Selection:

GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase 3 trials and proposed for marketing.

LPV/RTV (400 mg/100 mg): This is the recommended clinical dose (800/200 mg given once daily or in two equally divided doses).

General Study Design

Cohort I N = 11	**Period 1, Days 1 to 7**	**Period 2, Days 1 to 14**
		Lopinavir/ritonavir 400 mg/100 mg BID
	GLE 300 mg QD + PIB 120 mg QD	
Cohort II N = 10	**Period 1, Days 1 to 14**	**Period 2, Days 1 to 7**
	Lopinavir/ritonavir 400 mg/100 mg BID	
		GLE 300 mg QD + PIB 120 mg QD

Serial blood sample for determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE/PIB:
- Cohort I: For 24 hours on Day 7 (Period 1) and Day1and Day 14 (Period 2)
- Cohort II: For 24 hours on Day 1 (Period 2) and Day 7 (Period 2)

2. LPV/RTV
- Cohort I: For 24 hours on Day 1 (Period 2) and on Day 14 (Period 2)
- Cohort II: For 24 hours on Day 14 (Period 1) and Day 1 and Day 7 (Period 2)

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulation: Phase 2b formulation of GLE (100 mg Tablet) and PIB (40 mg Tablet). Commercially available formulation of LPV/RTV (200/50 mg Tablet).

RESULTS

Enrolled	21	Completed	18	Discontinued Due to AE	3	PK Population	18	Safety Population	21

Bioanalytical Method: links to reports GLE and PIB LPV/RTV

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE, PIB, lopinavir, ritonavir		
Range	GLE: 85.2 ng/mL to 10400 ng/mL 0.200 ng/mL to 101 ng/mL PIB: 0.197 ng/mL to 101 ng/mL 83.8 ng/mL to 985 ng/mL Lopinavir and ritonavir: 10 - 1000 ng/mL		

Protocol Deviations

No protocol deviations were reported in this study.

Pharmacokinetic

Cohort I

Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of **GLE and PIB**

Pharmacokinetic Parameters (Units)	Regimen A Period 1, Day 7 (N = 9)	Regimen B Period 2, Day 1 (N = 9)	Regimen B Period 2, Day 14 (N = 9)
		ABT-493	
C_{max} (ng/mL)	764 (1170, 107)	3470 (4160, 60)	1940 (2340, 67)
T_{max}[a] (h)	3.0 (2.0, 6.0)	5.0 (3.0, 9.0)	4.0 (3.0, 36)
AUC_{0-24} (ng•h/mL)	2810 (3740, 82)	26800 (32100, 70)	12300 (15600, 90)
C_{24} (ng/mL)	4.75 (6.78, 118)	384 (597, 140)	88.4 (184, 125)
		ABT-530	
C_{max} (ng/mL)	236 (253, 46)	351 (366, 31)	331 (351, 37)
T_{max}[a] (h)	5.0 (3.0, 6.0)	5.0 (4.0, 6.0)	5.0 (5.0, 6.0)
AUC_{0-24} (ng•h/mL)	1670 (1810, 55)	3670 (3840, 36)	4100 (4490, 49)
C_{24} (ng/mL)	23.0 (26.7, 76)	101 (107, 45)	121 (136, 55)

Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of **LPV and RTV**

Pharmacokinetic Parameters (Units)	Regimen B Period 2, Day 1 (N = 9)	Regimen B Period 2, Day 14 (N = 9)
	Lopinavir	
C_{max} (ng/mL)	7620 (7700, 15)	12100 (12400, 23)
T_{max}[a] (h)	5.0 (3.0, 9.0)	4.0 (3.0, 6.0)
AUC_{0-12} (ng•h/mL)	67700 (69200, 22)	112000 (115000, 24)
C_{12} (ng/mL)	5710 (5939, 29)	6950 (7210, 29)
	Ritonavir	
C_{max} (ng/mL)	788 (810, 25)	1140 (1190, 29)
T_{max}[a] (h)	5.0 (3.0, 5.0)	4.0 (3.0, 6.0)
AUC_{0-12} (ng•h/mL)	4770 (5020, 36)	5960 (6200, 29)
C_{12} (ng/mL)	157 (204, 92)	151 (170, 58)

Cohort II

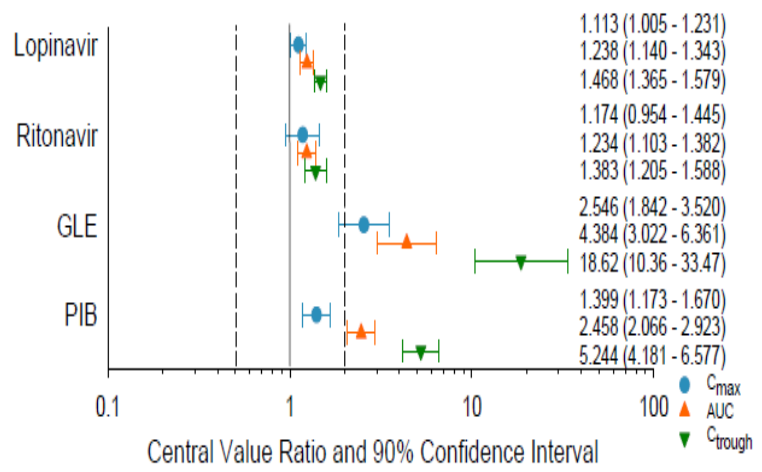
Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of **GLE and PIB**

Pharmacokinetic Parameters (Units)	Regimen D Period 2, Day 1 (N = 9)	Regimen D Period 2, Day 7 (N = 9)
	ABT-493	
C_{max} (ng/mL)	730 (1080, 101)	2460 (3750, 103)
T_{max}[a] (h)	3.0 (2.0, 5.0)	4.0 (3.0, 5.0)
AUC_{24} (ng•h/mL)	4060 (6230, 91)	16900 (28400, 114)
C_{24} (ng/mL)	26.0 (147, 233)	92.6 (267, 153)
	ABT-530	
C_{max} (ng/mL)	132 (175, 59)	314 (330, 39)
T_{max}[a] (h)	5.0 (2.0, 6.0)	5.0 (3.0, 6.0)
AUC_{24} (ng•h/mL)	1170 (1600, 59)	3740 (4040, 47)
C_{24} (ng/mL)	24.4 (43.4, 102)	100 (117, 73)

Geometric Mean (Mean, CV%) Pharmacokinetic Parameters of **LPV and RTV**

Pharmacokinetic Parameters (Units)	Regimen C Period 1, Day 14 (N = 9)	Regimen D Period 2, Day 1 (N = 9)	Regimen D Period 2, Day 7 (N = 9)
	Lopinavir		
C_{max} (ng/mL)	11200 (11400, 24)	10900 (11100, 21)	12400 (12600, 17)
T_{max}[a] (h)	4.0 (3.0, 5.0)	4.0 (0.0, 9.0)	4.0 (2.0, 9.0)
AUC_{0-12} (ng•h/mL)	93600 (95900, 22)	90200 (93500, 27)	116000 (118000, 20)
C_{12} (ng/mL)	4670 (4940, 31)	3810 (4850, 49)	6860 (7280, 34)
	Ritonavir		
C_{max} (ng/mL)	984 (1130, 62)	1040 (1140, 40)	1160 (1250, 48)
T_{max}[a] (h)	4.0 (2.0, 5.0)	4.0 (3.0, 9.0)	4.0 (2.0, 9.0)
AUC_{0-12} (ng•h/mL)	5250 (5630, 38)	4910 (5480, 43)	6480 (6870, 35)
C_{12} (ng/mL)	118 (128, 41)	88.7 (115, 66)	164 (188, 54)

Statistical Comparison of PK Parameters (GMR and 90% CI)



LPV: Day 7 Period 2 vs. Day 14 Period 1 (Cohort II)
RTV: Day 7 Period 2 vs. Day 14 Period 1 (Cohort II)
GLE: Day 14 Period 2 vs. Day 7 Period 1 (Cohort I)
PIB: Day 14 Period 2 vs. Day 7 Period 1 (Cohort I)

Notes:
For GLE and PIB: ratios represent the effect of multiple doses of LPV/RTV on GLE or PIB exposure at steady state
For LPV/RTV: ratios represent the effect of GLE/PIB at steady state on the exposure of LPV/RTV at steady state

Safety

- There were no deaths or serious adverse events reported in the study.
- Three subjects discontinued from study due to AEs that were deemed drug related:

ID	Cohort	Day of Discontinuation	AE	Regimen
104	I	Day 12	Dizziness and abdominal pain	GLE,PIB, LPV/RTV
108	I	Day 11	Non-cardiac chest pain	GLE,PIB, LPV/RTV
207	II	Day 9	Rash maculo-papular	LPV/RTV

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance is acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion

GLE exposure increased significantly following the administration of LPV/RTV. It appears that the effect on GLE exposure decreases with time as shown in the Table below suggesting an induction of transporters involved in GLE disposition. PIB exposure increases by the same magnitude following single and multiple dose

administration of LPV/RTV. The study results are applicable to the LPV/RTV 800/200 mg QD regimen because LPV exposure is comparable following QD and BID administration. According to Kaletra® labeling, Cmax is slightly lower following the BID administration (9.8±3.7 µg/mL) compared to QD administration (11.8±3.7 µg/mL) while AUC is higher for the BID ($AUC_{ss,0-12}$=92.6±36.7 µg h/mL) compared to the QD administration ($AUC_{ss,0-24}$=154±61.4 µg h/mL).
The applicant is recommending against the co-administration of LPV/RTV and GLE/PIB. The decision to change this recommendation to a contraindication should be based on the exposure-safety analysis

Drug	PK Parameter	Duration of LPV/RTV Administration (Reference is Day 7 Period 1[Cohort I])		
		One Day (Day 1 Period 2 [Cohort I])	7 Days (Day 7 Period 2 [Cohort II])	14 Days (Day 14 Period 2 [Cohort I])
GLE	Cmax	4.54	3.22	2.54
	AUC	9.54	6.01	4.38
	C24	80.84	19.49	18.61
PIB	Cmax	1.49	1.33	1.40
	AUC	2.20	2.24	2.46
	C24	4.39	4.35	5.26

Labeling Recommendations
The applicant's recommendation needs further assessment based on the results of the exposure-safety analysis.

Study #	M15-584	Study Period	12 February 2016 - 19 May 2016	EDR Link
Title	A Phase 1, open-label study to assess potential pharmacokinetic interaction between GLE and PIB combination and Genvoya® (Elvitegravir (EVG)/Cobicistat (COBI)/Emtricitabine (FTC)/Tenofovir Alafenamide (TAF)) or Triumeq® (Abacavir (ABC)/Dolutegravir (DTG)/Lamivudine (3TC)) in healthy adult subjects			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the effect of EVG/COBI/FTC/TAF and ABC/DTG/3TC on the pharmacokinetics of GLE/PIB, and vice versa.

Rationale: EVG/COBI/FTC/TAF and ABC/DTG/3TC may be commonly co-administered with GLE and PIB in subjects co-infected with HIV and HCV.

Dose Selection:

GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase III trials and proposed for marketing.

Genvoya®: EVG 150 mg, COBI 150 mg, FTC 200 mg, TAF 10 mg QD; the recommended daily regimen.

Triumeq®: ABC 600 mg, DTG 50 mg, 3TC 300 mg QD; the recommended daily regimen.

Design and PK Assessment

Arm 1, Cohort I N = 12	Period 1, Days 1 to 7	Period 2, Days 1 to 14
		EVG/c/FTC/TAF 150 mg/150 mg/200 mg/10 mg QD
	GLE 300 mg QD + PIB 120 mg QD	
Arm 1, Cohort II N = 12	Period 1, Days 1 to 14	Period 2, Days 1 to 7
	EVG/c/FTC/TAF 150 mg/150 mg/200 mg/10 mg QD	
		GLE 300 mg QD + PIB 120 mg QD
Arm 2, Cohort I N = 12	Period 1, Days 1 to 7	Period 2, Days 1 to 7
		ABC/DTG/3TC 600 mg/50 mg/300 mg QD
	GLE 300 mg QD + PIB 120 mg QD	
Arm 2, Cohort II N = 12	Period 1, Days 1 to 7	Period 2, Days 1 to 7
	ABC/DTG/3TC 600 mg/50 mg/300 mg QD	
		GLE 300 mg QD + PIB 120 mg QD

Serial blood samples for the determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE and PIB:
- Arms 1 and 2, Cohort I: for 24 hours on Day 7 (Period 1) and Day 1 and Day 14 (Period 2)
- Arms 1 and 2, Cohort II: for 24 hours on Days 1 and Day 7 (Period 2).
2. EVG/COBI/FTC/TAF:
- Cohort I: for 24 hours on Day 1 and Day 14 (Period 2)
- Cohort II: for 24 hours on Day 14 (Period 1) and on Day 1 and Day 7 (Period 2)
3. ABC/DTG/3TC:
- Cohort I: for 24 hours on Day 1 and Day 7 (Period 2)
- Cohort II: for 24 hours on Day 7 (Period 1) and Day 1 and Day 7 (Period 2)

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulation: Phase 2b formulation of GLE (100 mg Tablet) and PIB (40 mg Tablet). Commercially available tablet formulations of Genvoya® and Triumeq®.

RESULTS

Enrolled	48	Completed	47	Discontinued Due to AE	1	PK Population	47	Safety Population	48

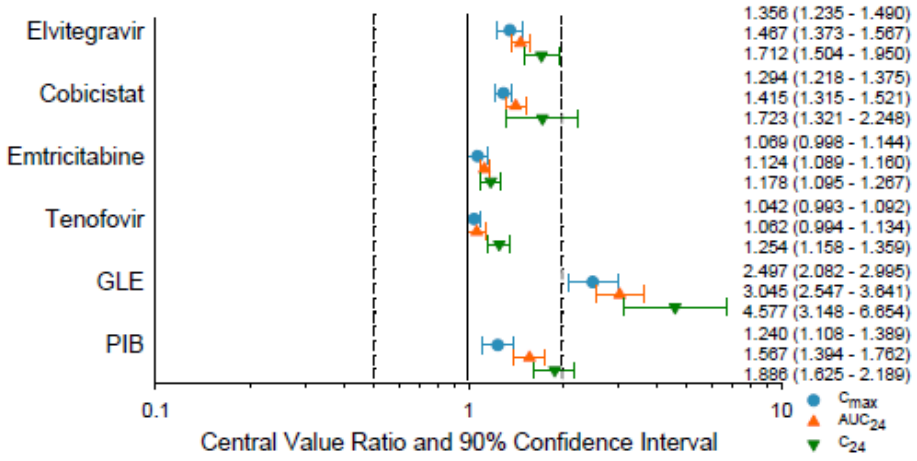
Bioanalytical Method: Link to reports GLE and PIB/ FTC, TFV /EVG/ ABC, 3TC/DTG/COBI

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE, PIB, FTC, TFV, EVG, ABC, 3TC, DTG, COBI		
Range	GLE: 1.00 ng/mL - 5000 ng/mL PIB: 1.00 ng/mL - 751 ng/mL FTC: 20.0 ng/mL - 4000 ng/mL TFV: 5.00 ng/mL - 1000 ng/mL EVG: 0.5 ng/mL - 500 ng/mL ABC: 2.50 ng/mL - 2500 ng/mL 3TC: 2.50 ng/mL - 2500 ng/mL DTG: 20.0 ng/mL - 20000 ng/mL COBI: 10.0 ng/mL - 10000 ng/mL		

Protocol Deviations No protocol deviations were reported in this study

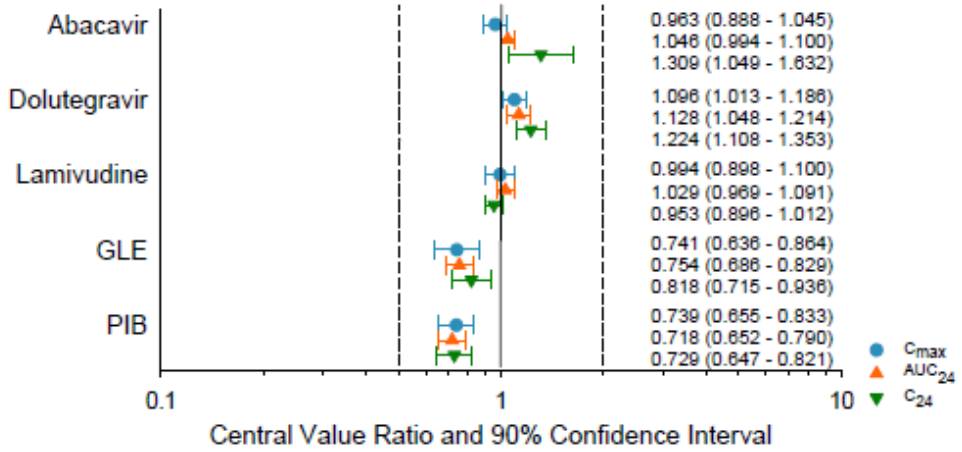
Pharmacokinetics: Statistical Comparison of steady state PK Parameters

Arm 1: EVG/COBI/FTC/TAF (Cohort II): Period 2 Day 7/Period 1 Day 14; GLE and PIB (Cohort I): Period 2 Day 14/Period 1 Day 7



Pharmacokinetics

Arm 2: ABC/DTG/3TC (Cohort II): Period 2 Day 7/Period 1 Day 7; GLE and PIB (Cohort I): Period 2 Day 7/Period 1 Day 7



Safety

There were no reported deaths or serious adverse events in the study. One subject was discontinued from the study due to a Grade 3 decrease in neutrophil count.

REVIEWER ASSESSMENT
The study design is acceptable ☑ Yes ☐ No
Study Conduct ▪ Bioanalytical method performance in acceptable ☑ Yes ☐ No ▪ Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ NA The applicant should have quantified TAF in addition to tenofovir.
Study Results The study results are acceptable as reported by the sponsor ☑ Yes ☐ No
Discussion - <u>Genvoya® (EVG/COBI/FTC/TAF):</u> The increase in GLE and PIB exposures can be attributed to the ability of COBI to inhibit P-gp, BCRP, and OATP1B1/3 and EVG ability to inhibit OATP1B1/3. GLE is a substrate of OATP1B1/3, P-gp, and BCRP and PIB is a substrate of P-gp and BCRP. EVG and COBI exposures were higher; 47% and 42%, respectively, whereas FTC and tenofovir exposures changed minimally, when administered with GLE/PIB. It should be noted that TAF is a P-gp substrate and its exposure is expected to increase in the presence of GLE/PIB. The applicant did not quantify TAF. <u>Triumeq® (ABC/DTG/3TC):</u> GLE and PIB AUC values decreased to 75% and 72%, respectively, when administered with Triumeq®. Such decreases in exposure are not anticipated to cause loss of efficacy. Exposures of ABC, DTG, and 3TC were similar with and without GLE/PIB.
Labeling Recommendations We agree with the applicant's proposal of no dosage adjustment is needed when GLE/PIB is co-administered with Triumeq®. The clinical sequence and dosing recommendations for the co-administration of Genvoya® with GLE/PIB should be based on the exposure-safety analysis.

Study #	M13-598	Study Period	21 August 2014 - 08 July 2015	EDR Link
Title	A Phase 1, open-label study to assess the pharmacokinetics, safety and tolerability of the co-administration of an oral contraceptive with combination therapy of GLE and PIB in healthy premenopausal female subjects			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the pharmacokinetics, safety, and tolerability of multiple dose regimens of GLE/PIB with multiple doses of ethinyl estradiol (EE)/norgestimate (NGM), norethindrone (NET), and EE/levonorgestrel (LNG) oral contraceptive regimens.

Rationale: Oral contraceptives may be commonly co-administered with GLE and PIB including EE/NGM, NET, or EE/LNG.

Dose Selection:

GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase III trials and proposed for marketing.

Ortho-Cyclen®: 35 µg/250 µg EE/NGM; the only marketed strength.

Jolivette®: 0.35 mg NET, the maximum safe dose considering an anticipated increase in NET exposures (< 2-fold).

Aviane®: 20 µg /100 µg EE/LNG was selected as it contains a commonly prescribed dose of both EE and LNG.

Design and PK Assessment

In all three arms subjects were receiving the oral contraceptive for at least 3 months prior to start of the study.

Arm 1	Days 1 to 14	Days 15 to 21	Days 22 to 28
N = 12	EE/NGM 35/250 µg QD		
		GLE 300 mg QD + PIB 120 mg QD	
Arm 2	Days 1 to 3	Days 4 to 10	Days 11 to 17
N = 12	NET 0.35 mg QD		
		GLE 300 mg QD + PIB 120 mg QD	
Arm 3	Days 1 to 10	Days 11 to 21	Days 22 to 28
N = 14	EE/LNG 20/100 µg QD		
		GLE 300 mg QD + PIB 120 mg QD	

Serial blood samples for the determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE and PIB: for 24 hours on:
   - Arm 1: Day 15, Day 21 and Day 28.
   - Arm 2: Days 4, Day 10 and Day 17.
   - Arm 3: Day 11, Day 21 and Day 28.

2. Norelgestromin (NGMN), EE, and NG (Arm 1): for 24 hours on Day 14, Day 15, and Day 21.

4. NET (Arm 2): for 24 hours on Day 3, Day 4, and Day 10.

3. EE and NG (Arm 3): for 24 hours on Day 10, Day 11, and Day 21.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulation: Phase 2b formulation of GLE (100 mg Tablet) and PIB (40 mg Tablet). Commercially available tablet formulations of Ortho-Cyclen® (35 mg/250 µg EE/NGM), Jolivette® (0.35 mg NET), and Aviane® (20/100 µg EE/LNG).

RESULTS

Enrolled	38	Completed	33	Discontinued Due to AE	3	PK Population	33*	Safety Population	33

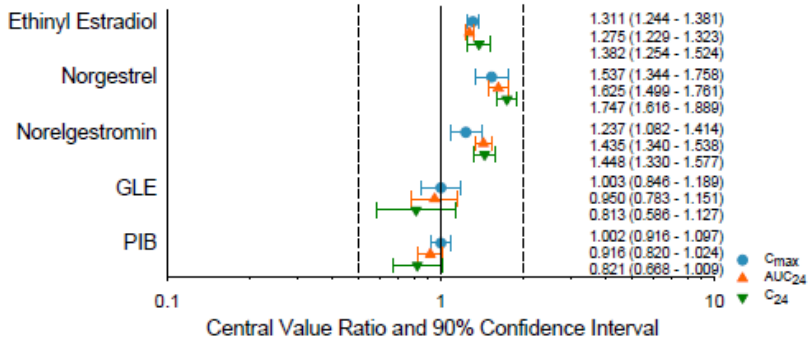
Bioanalytical Method: Link to reports GLE and PIB EE and NG - Arm 1 NGMN - Arm 1 Norethindrone EE and NG

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE, PIB, EE, NG, NGMN, NET		
Range	GLE: Low: 0.202 to 100 ng/mL/ High:80.0 to 10300 ng/mL PIB: Low: 0.206 to 102 ng/mL/ High: 81.4 to 1030 ng/mL EE: 0.002 to 0.5 ng/mL NG: 0.05 to 25 ng/mL NGMN: 0.0200 to 10.0 ng/mL NET: 0.05 to 25 ng/mL		

Protocol Deviations: Subject 308 entered the study but did not meet the inclusion criteria. Several subjects did not consume their entire breakfast (18 subjects on intensive and 10 subjects on the non-intensive pharmacokinetic sampling days).

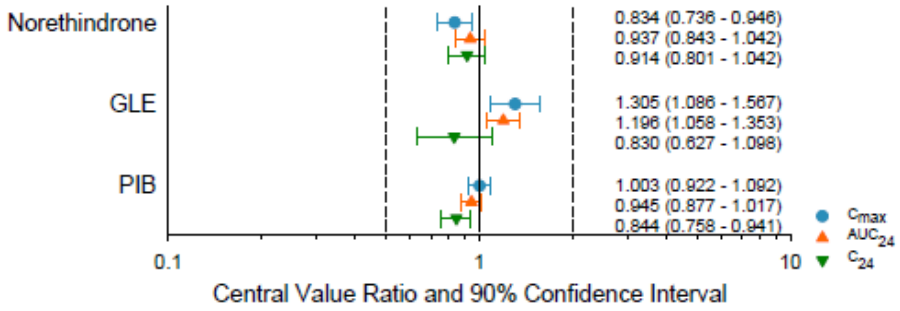
Pharmacokinetics:

Arm 1: EE, NGMN and NG: Day 21/Day 14; GLE and PIB: Day 21/Day 28

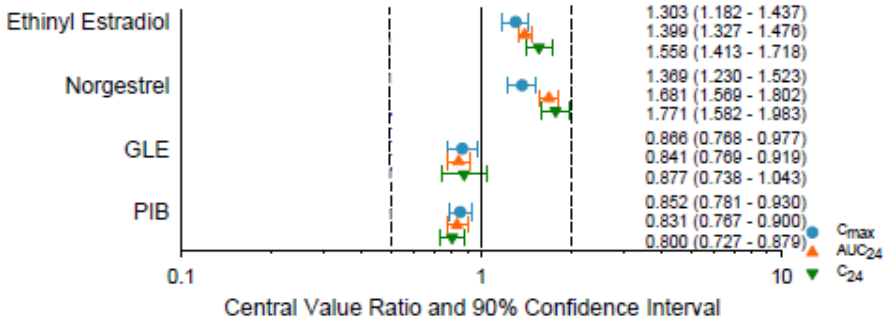


- Single dose GLE/PIB administration does not affect NG, NGM, and EE pharmacokinetics (see Table 6, page 77 of CSR)

Arm 2: NET: Day 10/Day 3; GLE and PIB: Day 10/Day 17



Arm 3: EE and NG: Day 21/Day 10; GLE and PIB: Day 10/Day 17



- Single dose GLE/PIB administration does not affect NG and EE pharmacokinetics (see Table 14, page 92 of CSR)

Safety

- No deaths or serious adverse events were reported during the study

- Three subjects discontinued from the study in Arm 1:
  - Two subjects discontinued from the study due to urinary tract infection (Subject 101) and breast abscess along with ALT/AST elevations (Subject 107). These AEs were not considered related to GLE/PIB or oral contraceptive. Subject 107 had elevations in ALT and AST that occurred 7 days after the last dose of the GLE/PIB while the subject was being treated for breast abscess with oral antibiotic and analgesic/anti-inflammatory medications.
  - Subject 103 developed Grade 3 ALT elevations on Day 21 and was discontinued from the study on Day 23. The AE was considered related to study drug.
- The Table below lists observed ALT elevation while on study drug

Maximum ALT Elevations (per NCI CTCAE)[8]	Arm 1 (ABT-493 + ABT-530 + EE/NGM 35/250 µg)	Arm 2 (ABT-493 + ABT-530 + NET 0.35 mg)	Arm 3 (ABT-493 + ABT-530 + EE/LNG 20/100 µg)
Grade 1	0	0	3
Grade 2	1	0	0
Grade 3	1	0	0
Grade 4	0	0	0

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No ☐ NA

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion

Asymptomatic Liver enzyme elevations were observed when oral contraceptive regimens containing 35 µg and 20 µg of EE were co-administered with the DAAs in Arms 1 and 3, respectively. The more significant elevations were in Arm 1, where two subjects (103 and 112) developed ALT (Grade 3 in Subject 103, and Grade 2 in Subject 112) and AST (Grade 2 in Subject 103, Grade 1 in Subject 112) elevations that were considered clinically significant by the investigator. Although oral contraceptive products containing EE, NGM, LNG or NET had minimal impact (≤ 31%) on GLE and PIB exposures, the pattern of the associated laboratory abnormalities observed suggests that administration of GLE/PIB with EE-containing contraceptives may be associated with risk of liver enzyme elevations. The mechanism for these interactions is unknown, and, notably, administration of the GLE/PIB with progestin-only contraceptives is not associated with such elevations.

It should be noted that 91 subjects (3.8% of subjects enrolled in Phase 2 and 3 trials, 2 of which had cirrhosis) of Phase 2 and 3 studies subjects used either a concomitant contraceptive (n=53) or hormone replacement therapy (n=38); the most common were estradiol (n = 18), norethisterone (n = 12), desogestrel (n = 11), and levonorgestrel (n = 11). Only 2 subjects of Phase 2 used an EE containing contraceptive (1 oral and 1 transdermal).). ALT/AST elevations in these subjects were comparable to what was observed in the overall population.

Labeling Recommendations

We agree with the applicant's proposal to:

1. Not recommend co-administration of GLE and PIB with EE containing contraceptives.
2. Allow the co-administration of GLE/PIB and norethindrone without dose adjustment.

We agree with the applicant's proposal to allow the co-administration of progestin only oral contraceptives in the absence of DDI data.

Study #	M13-579	Study Period	08 April 2014 - 25 September 2014	EDR Link
Title	A Phase 1, open-label study to assess the pharmacokinetics, safety and tolerability of the co-administration of pravastatin, rosuvastatin, and atorvastatin in combination with GLE and PIB in healthy adult subjects.			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the pharmacokinetics, safety, and tolerability of multiple dose regimens of GLE/PIB when co-administered with multiple doses of pravastatin, rosuvastatin, and atorvastatin.

Rationale: Pravastatin is a substrate of OATP1B1 and OATP1B3. Rosuvastatin is a substrate of BCRP and OATP1B1/3.Atorvastatin is a substrate of OATP1B1 and OATP1B3, and is significantly metabolized by CYP3A4. GLE/PIB inhibits BCRP and OATP1B1/3.

Dose Selection: GLE (400 mg) and PIB (120 mg): PIB doses evaluated in Phase 3 trials and proposed for marketing. GLE dose. GLE dose is based on Phase 2a trials and is higher than the 300 mg dose proposed for marketing.

Pravastatin, rosuvastatin and atorvastatin doses were 10 mg, 5 mg and 10 mg respectively, which are the lowest available strengths. The doses were selected to minimize the risk of any adverse effects that could have occurred because of the expected increase in statin's exposure when co-administered with GLE/PIB.

Design and PK Assessment

	Period 1 Day 1		Period 2 Days 1 to 3	Period 3 Days 1 to 7
Arm 1 N = 12		8-day Washout	Pravastatin 10 mg QD	
	GLE 400 mg + PIB 120 mg			GLE 400 mg QD + PIB 120 mg QD
	Period 1 Day 1		Period 2 Days 1 to 7	Period 3 Days 1 to 7
Arm 2 N = 12		6-day Washout	Rosuvastatin 5 mg QD	
	GLE 400 mg + PIB 120 mg			GLE 400 mg QD + PIB 120 mg QD
	Period 1 Day 1		Period 2 Days 1 to 7	Period 3 Days 1 to 7
Arm 3 N = 12		7-day Washout	Atorvastatin 10 mg QD	
	GLE 400 mg + PIB 120 mg			GLE 400 mg QD + PIB 120 mg QD

Serial blood samples for the determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE and PIB (All arms): for 48 hours on Day1 (Period1), and for 24 hours on Day 1 and Day 7 (Period 3).
2. Pravastatin: for 24 hours on Day 1and Day 3 (Period 2), Day 1 and 7 (Period 3)
3. Rosuvastatin and atorvastatin: for 24 hours on Day 1and Day 7 (Period 2), Day 1 and 7 (Period 3)

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulation: Phase 2a formulation of GLE (100 mg Tablet) and PIB (40 mg Tablet). Commercially available tablet formulations of rosuvastatin (Crestor® 5 mg Tablet), atorvastatin (Lipitor® 10 mg Tablet), and pravastatin (generic; Glenmark Generics 10 mg Tablet)

RESULTS

Enrolled	36	Completed	34	Discontinued Due to AE	2	PK Population	34	Safety Population	36

Bioanalytical Method: Link to reports GLE and PIB Atorvastatin Pravastatin Rosuvastatin

Method Type	LC-MS/MS	Matrix		Plasma	
Analytes	GLE	PIB	Atorvastatin	Pravastatin	Rosuvastatin
Range (ng/mL)	Low: 0.204 - 101 High: 86.2 - 10100	Low: 0.202 - 100 High: 85.1 - 1000	0.100 - 75.0	0.50 - 250	0.100 - 100

Protocol Deviations No protocol deviations were reported in this study

Pharmacokinetics:

Effect of multiple doses administration of GLE/PIB on statins steady state PK parameters

Statin	Comparison	Cmax		AUC_{0-24}	
		GMR	90% CI	GMR	90% CI
Pravastatin	Day 7 (Period 3) vs. Day 3 (Period 2)	**2.23**	1.87-2.65	**2.30**	1.91-2.76
Rosuvastatin	Day 7 (Period 3) vs. Day 7 (Period 2)	**5.62**	4.80-6.59	**2.15**	1.88-2.46
Atorvastatin*	Day 7 (Period 3) vs. Day 7 (Period 2)	**22.0**	16.4-29.5	**8.28**	6.06-11.3

*Ortho-hydroxy atorvastatin AUC and Cmax ratios are 5.42 and 15.5 and para-hydroxy atorvastatin AUC and Cmax ratios are 12.7 and 42.0.

- Rosuvastatin and atorvastatin AUC and Cmax are similar on Day 7 (Period 3) relative to Day 1(Period 3)
- Pravastatin AUC and Cmax are 30% and 25% higher in Day 7 (Period 3) relative to Day 1 (Period 3)

Effect of multiple dose administration of statins on GLE and PIB PK parameters following single dose administration

GLE

Statin	Comparison	Cmax		AUC_{0-24}	
		GMR	90% CI	GMR	90% CI
Pravastatin	Day 1 (Period 3) vs. Day 1 (Period 1)	**1.59**	1.25-2.03	**1.44**	1.25-1.67
Rosuvastatin	Day 1 (Period 3) vs. Day 1 (Period 1)	**1.25**	0.93-1.67	**1.21**	0.98-1.49
Atorvastatin	Day 1 (Period 3) vs. Day 1 (Period 1)	**0.90**	0.70-1.15	**0.97**	0.83-1.14

PIB

Statin	Comparison	Cmax		AUC_{0-24}	
		GMR	90% CI	GMR	90% CI
Pravastatin	Day 1 (Period 3) vs. Day 1 (Period 2)	**1.24**	1.13-1.37	**1.23**	1.13-1.35
Rosuvastatin	Day 1 (Period 3) vs. Day 1 (Period 2)	**1.23**	1.11-1.37	**1.20**	1.12-1.29
Atorvastatin	Day 1 (Period 3) vs. Day 1 (Period 2)	**1.05**	0.91-1.21	**1.09**	0.96-1.23

Safety

-No death or serious adverse events were reported during the study.

- Two subjects discontinued from the study due to adverse events and were excluded from the PK analysis:
  - Subject 208 was discontinued from the study due to a panic attack on Period 1/Day 1.
  - Subject 309 was discontinued from the study due to pseudothrombocytopenia on Period 1/Day.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ NA

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion

Pravastatin is a substrate of OATP1B1 and OATP1B, rosuvastatin is a substrate of BCRP and OATP1B1/3, and atorvastatin is a substrate of OATP1B1/3, BCRP and CYP3A. GLE/PIB inhibits OATP1B1/3 and BCRP, and is a weak inhibitor of CYP3A. Fold increases in Cmax and AUC24 precipitated by the aforementioned interactions were 2.2- and 2.3-fold, for pravastatin; 5.6- and 2.2-fold for rosuvastatin, and 22- and 8.3-fold for atorvastatin, respectively. To minimize the risk of adverse events associated with increased exposures of statins, the dose of pravastatin should be reduced by 50%, rosuvastatin dose should be limited to 10 mg, and co-administration of atorvastatin should not be recommended concomitantly with GLE/PIB. Note that statin dose adjustment recommendations are typically based on AUC changes.

Labeling Recommendations

We agree with the Applicant to reduce the dose of pravastatin by 50%, limit the rosuvastatin dose to 10 mg, and not recommend the co-administration with atorvastatin.

Study #	M14-721	Study Period	14 May 2015 - 17 July 2015	EDR Link
Title	A Phase 1, open-label study to assess the pharmacokinetics, safety and tolerability of the co-administration of simvastatin or lovastatin with ABT-493 and ABT-530 in healthy adult subjects			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the pharmacokinetics, safety, and tolerability of multiple dose regimens of GLE/PIB with multiple doses of simvastatin and lovastatin.

Rationale: Simvastatin and simvastatin hydroxy acid are substrates of OATP1B1/3, and simvastatin is also a substrate of CYP3A and OATP1B1/3. Lovastatin and lovastatin acid are substrates of OATP1B1/3, and lovastatin is a substrate of CYP3A. GLE/PIB inhibits OATP1B1/3 and weakly inhibits CYP3A, potentially causing increased statin exposures and their associated rhabdomyolysis.

Dose Selection:

GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase III trials and proposed for marketing.

Simvastatin and lovastatin doses were 5 mg and 10 mg once daily, respectively, as the lowest available doses to minimize the risk of any adverse effects that could have occurred after co-administration with DAAs due to potentially increased exposures.

Design and PK Assessment

Arm 1 N = 12	Period 1 Day 1	5-day Washout	Period 2 Days 1 to 3	Period 3 Days 1 to 7
			Simvastatin 5 mg QD	
	GLE 300 mg + PIB 120 mg			GLE 300 mg QD + PIB 120 mg QD
Arm 2 N = 12	Period 1 Day 1	5-day Washout	Period 2 Days 1 to 3	Period 3 Days 1 to 7
			Lovastatin 10 mg QD	
	GLE 300 mg + PIB 120 mg			GLE 300 mg QD + PIB 120 mg QD

Serial blood samples for the determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE and PIB: for 48 hours on Day 1 (Period 1) and for 24 hours on Day 1 and Day 7(Period 3).
2. Simvastatin, simvastatin hydroxy acid, lovastatin and lovastatin acid: for 24 hours on Day 1 and Day 3 (Period 2) and for 48 hours on Day1 and Day 7 (Period 3).

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulation: Phase 2a formulation of GLE (100 mg Tablet) and PIB (40 mg Tablet). Commercially available tablet formulations of simvastatin (Zocor®, 5 mg Tablet), and lovastatin (10 mg Tablet, Teva Pharmaceuticals Inc.)

RESULTS

Enrolled	24	Completed	24	Discontinued Due to AE	0	PK Population	24	Safety Population	24

Bioanalytical Method: Link to reports GLE and PIB Lovastatin Simvastatin

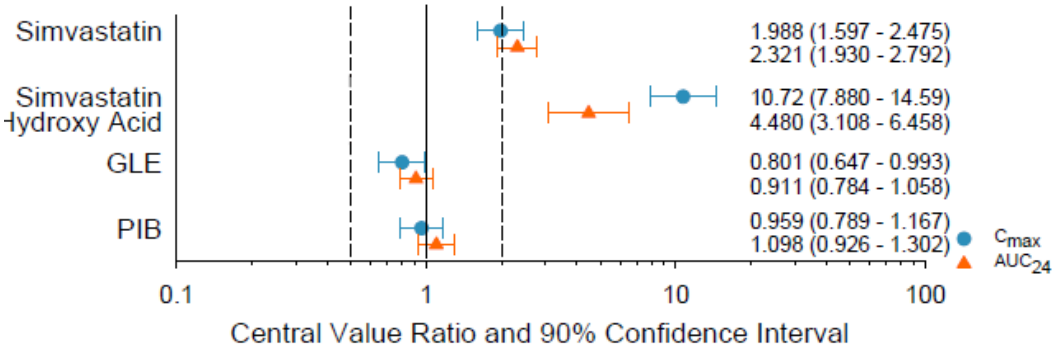
Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE, PIB, Atorvastatin, Pravastatin, Rosuvastatin		
Range	GLE: Low: 0.202 ng/mL - 100 ng/mL / High: 80.0 ng/mL - 10300 ng/mL PIB: Low: 0.206 ng/mL - 102 ng/mL/ High: 81.4 ng/mL - 1030 ng/mL Lovastatin and lovastatin acid: 0.0500 to 50.0 ng/mL Simvastatin and simvastatin hydroxyacid: 50.0 - 50,000 pg/mL		

Protocol Deviations Several subjects in both arms did not finish their meals on days where there was no intensive pharmacokinetic sampling. No significant protocol deviations were reported in this study.

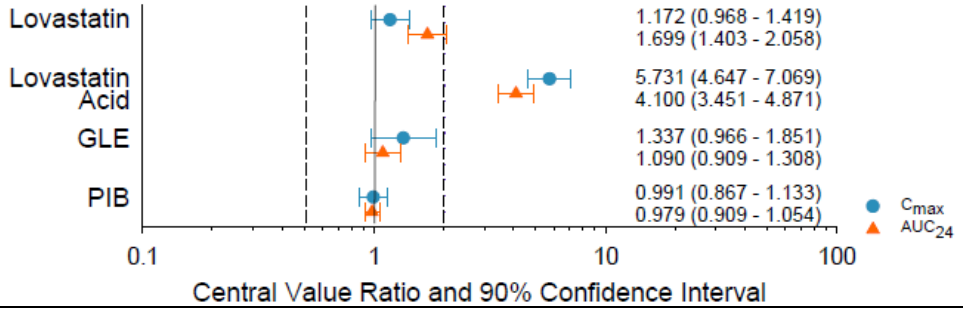
Pharmacokinetics: Statistical comparison of PK parameters

- GLE/PIB: Day 1 (Period 3) vs. Day 1 (Period 1)
- Simvastatin and lovastatin: Day 7 (Period 3) vs. Day 3 (Period 2)

Arm 1:



Arm 2:



Safety

No death or serious adverse events were reported during the study.

REVIEWER ASSESSMENT
The study design is acceptable ☑ Yes ☐ No
Study Conduct ▪ Bioanalytical method performance in acceptable ☑ Yes ☐ No ▪ Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No ☐ NA
Study Results The study results are acceptable as reported by the sponsor ☑ Yes ☐ No
Discussion Simvastatin and simvastatin hydroxy acid are substrates of OATP1B1/3, and simvastatin is also a substrate of CYP3A and OATP1B1/3. Lovastatin and lovastatin acid are substrates of OATP1B1/3, and lovastatin is a substrate of CYP3A. GLE/PIB inhibits OATP1B1/3 and weakly inhibits CYP3A potentially causing statin exposures to increase. In this study, Cmax and AUC24 increased to 2.0- and 2.3- fold, and 11- and 4.5-fold for simvastatin and simvastatin hydroxyl acid, respectively. Lovastatin Cmax and AUC24 increased to 1.17- and 1.7- fold, respectively, and lovastatin acid Cmax and AUC24 were increased to 5.7-fold and 4.1-fold, respectively. To minimize the risk of adverse events associated with increased exposures of statins, co-administration of simvastatin and lovastatin with GLE/PIB is not recommended.
Labeling Recommendations We agree with the Applicant that co-administration of simvastatin and lovastatin with GLE/PIB is not recommended.

Study #	M13-723	Study Period	26 March 2015- 19 May 2015	EDR Link
Title	A Phase 1, open-label study to assess the pharmacokinetics, safety and tolerability of the co-Administration of rifampin with the combination of GLE and PIB in healthy subjects			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the effect rifampin administered as a single dose and at steady state on the pharmacokinetics of GLE and PIB in healthy subjects, and to evaluate the effect of GLE and PIB administered as a single dose on the pharmacokinetics of rifampin at steady-state.

Rationale: To evaluate the effect of OATP inhibition of rifampin as a single dose, the net effect of OATP inhibition and P-gp induction at on Day 14, and the more durable effect of P-gp induction 24 hours after the last rifampin dose.

Dose Selection:

GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase 3 trials and proposed for marketing.

Rifampin: recommended dose is 10 mg/kg up to a maximum of 600 mg/day for treatment of tuberculosis or 600 mg twice daily (BID) for 2 days for meningococcal carrier state. For DDI studies, doses of 600 mg rifampin QD are utilized.

Design and PK Assessment

Period 1		Period 2				
Day 1	7-day Washout	Day 1	Days 2 to 13	Day 14	Days 15 to 17	Day 18
		Rifampin 600 mg QD				
GLE 300 mg + PIB 120 mg		GLE 300 mg + PIB 120 mg		GLE 300 mg + PIB 120 mg		GLE 300 mg + PIB 120 mg

Serial blood samples for the determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE/PIB: for 48 hours on Day 1 (Period 1) and Day 1, Day 14, and Day 18 (Period 2).
2. Rifampin: for 24 hours Day 1, Day 13, and Day 14.

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulation: Phase 2b formulation of GLE (100 mg Tablet) and PIB (40 mg Tablet) and commercially available rifampin (Rifadin®, 300 mg Capsule).

RESULTS

Enrolled	12	Completed	12	Discontinued Due to AE	0	PK Population	12	Safety Population	12

Bioanalytical Method: **Link to reports** GLE and PIB Rifampin

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE, PIB, rifampin		
Range	GLE: 0.205 ng/mL - 101 ng/mL 86.5 ng/mL - 10200 ng/mL PIB: 0.205 ng/mL - 101 ng/mL 86.4 ng/mL - 1020 ng/mL Rifampin: 50.0 ng/mL - 35000 ng/mL		

Protocol Deviations Protocol deviations related to the timing of ECG tests and urinalysis samples (subjects 104, 108, 109, and 112) occurred, and a few subjects did not finish their meals but do not impact the pharmacokinetic analyses and data reported throughout the study.

Pharmacokinetics

Statistical comparison of PK parameters

	Pharmacokinetic Parameter	Cmax		AUC	
	Comparison	**GMR**	**90% CI**	**GMR**	**90% CI**
GLE	Period 2 Day 1 vs. Period 1 Day 1 (OATP inhibition)	**6.521**	5.056 – 8.410	**8.554**	7.006 – 10.443
	Period 2 Day 14 vs. Period 1 Day 1 (Net effect of OATP inhibition and P-gp induction)	**1.402**	0.954 – 2.059	**1.046**	0.752 – 1.457
	Period 2 Day 18 vs. Period 1 Day 1 (P-gp induction)	**0.142**	0.105 – 0.191	**0.115**	0.088 – 0.151
PIB	Period 2 Day 1 vs. Period 1 Day 1 (OATP inhibition)	**0.912**	0.760 – 1.095	**1.042**	0.887 – 1.223
	Period 2 Day 14 vs. Period 1 Day 1 (Net effect of OATP inhibition and P-gp induction)	**0.209**	0.162 – 0.271	**0.169**	0.137 – 0.208
	Period 2 Day 18 vs. Period 1 Day 1 (P-gp induction)	**0.168**	0.140 – 0.202	**0.128**	0.109 – 0.151
Rifampin	Period 2 Day 14 vs. Period 2 Day 13	**1.175**	1.046-1.319	**1.130**	1.054-1.212

Safety
No death or serious adverse events were reported in this study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ NA

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion

A single dose of rifampin increased GLE C_{max} by 6.5 fold and AUC_{inf} by 8.6 fold with almost no effect (≤ 9% change) on PIB. This is due to OATP inhibition effects of rifampin; GLE is a substrate of OATP1B1/3 and PIB is not a substrate of OATP.

Multiple doses of rifampin displayed the net effect of OATP inhibition and P-gp induction. GLE exposure did not change whereas PIB exposure decreased. With continued dosing of rifampin, P-gp induction dominates OATP inhibition and the net effect is significant reduction in GLE and PIB exposures.

Labeling Recommendations

We agree with the applicant's recommendation of contraindication the co-administration of rifampin with GLE and PIB due to potential loss of activity caused by decreased exposures of GLE and PIB.

Study #	M13-605	Study Period	23 April 2015 - 12 September 2015	EDR Link
Title	Phase 1, open-label study to assess the pharmacokinetics, safety and tolerability of the co-administration of CYP substrates: caffeine, midazolam, tolbutamide, omeprazole and dextromethorphan or the co-administration of cyclosporine with the combination of GLE and PIB in healthy adult subjects			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives:

Arm 1: To evaluate the effect of multiple doses of GLE/PIB on the pharmacokinetics of a single-dose cocktail of CYP substrates

Arm 2: To evaluate the effects of GLE/PIB on the pharmacokinetics of single dose cyclosporine and the effects of cyclosporine on the pharmacokinetics of GLE/PIB administered as a single dose.

Rationale:

- Arm 1: Study M14-380 showed that GLE/PIB 700/160 mg (higher dose) is a weak inhibitor of CYP1A2 and a moderate inhibitor of CYP3A4.
- Arm 2: Cyclosporine may be commonly administered with GLE/PIB in kidney, liver, or heart transplant patients. Study M13-584 utilized 100 mg cyclosporine doses which are below the clinically recommended doses. The study was also designed to only evaluate the effect of GLE/PIB on cyclosporine .. Evaluating the effect of 400 mg doses of cyclosporine on GLE/PIB is warranted.

Dose Selection:

- GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase III trials and proposed for marketing.
- Arm 1: Standard doses typically used in CYP probe substrates studies(see Table below)
- Arm 2: Cyclosporine: According to Neoral® labeling, the recommended daily dose of cyclosporine is:
  - Newly transplanted patients: The initial dose range is 7±3 (renal transplant), 8±4 (liver transplant), 9±3 (heart transplant) mg/kg/day divided into two doses.
  - Rheumatoid arthritis & psoriasis: 2.5 mg/kg/day (1.25 mg/kg/day BID), maximum dose is 4 mg/kg/day

The cyclosporine dose evaluated in this study is in the range of the recommended clinical dose in transplant patients (8-12 mg/kg/day in two divided doses ~ 280 to 420 mg BID for a 70 Kg subject) but administered as a single dose.

Design and PK Assessment: Each arm enrolled 12 subjects

Arm 1

Day 1	Days 4 to 10	Day 11	Days 12 to 13
CYP Cocktail[a]		CYP Cocktail[a]	
	GLE 300 mg QD + PIB 120 mg QD		

Serial blood samples for the determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE and PIB: for 24 hours on Day 10
2. Probe substrates: for 72 hours on Day 1 and Day 11

Arm 2

Period 1		Period 2		
Day 1		Day 1		Day 4
Cyclosporine 400 mg	7-day Washout		2-day Washout	Cyclosporine 400 mg
		GLE 300 mg + PIB 120 mg		GLE 300 mg + PIB 120 mg

Serial blood samples for the determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE and PIB: for 48 hours on Day 1 (Period 2) and 144 hours on Day 4 (Period 2)
2. Cyclosporine: for 72 hours on Day 1 (Period 1) and 144 hours on Day 4 (Period 2)

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulation: Phase 2b formulation of GLE (100 mg tablet) and PIB (40 mg tablet). Commercially available of caffeine (40 mg tablet, Pro Plus®), midazolam HCl (2 mg/mL syrup), tolbutamide (500 mg tablet), omeprazole (20 mg capsule), dextromethorphan HBr (10 mg/mL syrup), and cyclosporine (100 mg soft gelatin capsule, Neoral®).

RESULTS

Enrolled	24	Completed	23	Discontinued Due to AE	0	PK Population	23	Safety Population	24

Subject 204 was discontinued after failing to return for Period 2 and was excluded from the statistical analyses of PK parameters.

Bioanalytical Method:

Analyte	Type	Matrix	Range	Link to Report
GLE	LC-MS/MS	Plasma	Low: 0.202 - 100 ng/mL High: 80.0 - 10,300 ng/mL	GLE and PIB
PIB	LC-MS/MS	Plasma	Low: 0.206 - 102 ng/mL High: 81.4 - 1,030 ng/mL	
Caffeine	LC-MS/MS	Plasma	25 - 25,000 ng/mL	Caffeine
Omeprazole	LC-MS/MS	Plasma	1.00 - 502 ng/mL	Link
5-Hydroxy-Omeprazole	LC-MS/MS	Plasma	1.01 - 503 ng/mL	
Midazolam 1-hydroxymidazolam	LC-MS/MS	Plasma	0.050 - 20.0 ng/mL	
Dextromethorphan	LC-MS/MS	Plasma	0.050 -10.2 ng/mL	
Dextrophan	LC-MS/MS	Plasma	0.10 - 20.4 ng/mL	
Cyclosporine	LC-MS/MS	Plasma	5.00 - 2500 ng/mL	Cyclosporine

Protocol Deviations: None in arm 1. Two subjects in Arm 2 returned for the Follow-Up visits outside the protocol-specified + 2 days window. This protocol deviation did not affect the study outcome or interpretation of the study results.

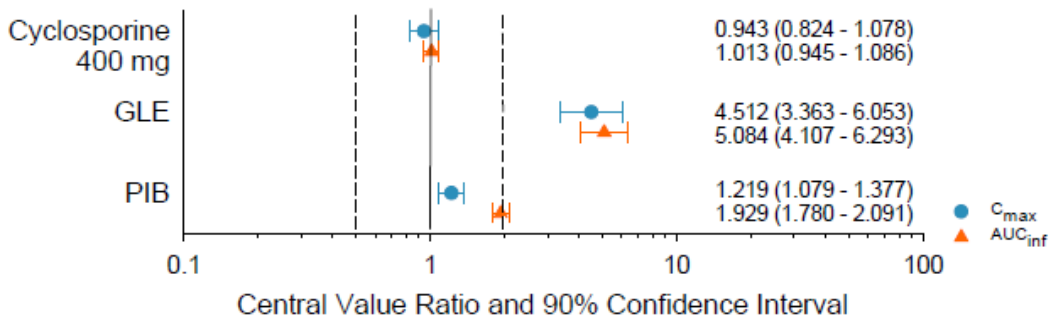
Pharmacokinetics:

Arm 1: Effect of multiple doses of GLE/PIB on PK of CYP probe substrates.

Caffeine, dextromethorphan, midazolam, tolbutamide, and omeprazole: Day 11/Day 1

- In case of omeprazole ratio of metabolite to parent (AUC_{0-t}) is 1.44 on Day 1 and 1.66 on Day 11.

Arm 2: Effect of GLE/PIB single dose on cyclosporine pharmacokinetics and vice versa.



Safety

- No deaths or serious adverse events were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☑ Yes ☑ No ☐ NA

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion

Arm 1:

- GLE/PIB combination, at the clinical dose, is a weak inhibitor of CYP1A2 and CYP3A4 evident by the increase in AUC of probe substrates.
- GLE/PIB combination, at the clinical dose, decreased omeprazole AUC by 21%. The metabolite to parent ratio increased by 15% suggesting that the effect is not solely due to CYP2C19 induction, but also due to effect on omeprazole absorption given that omeprazole Cmax was reduced by 43%.
- GLE/PIB combination, at the clinical dose, does not affect CYP2C9 and CYP2D6, and CYP2C19. Therefore, it is expected that the combination will not alter the pharmacokinetics of drugs that are metabolized by these enzymes.

Arm 2:

Cyclosporine is an inhibitor of multiple drug transporters, including P-gp, BCRP, and OATP1B1/3. GLE is a substrate of OATP1B1/3, and both GLE and PIB are substrates of P-gp and/or BCRP. At the expected cyclosporine clinical dose, GLE and PIB exposures were significantly changed with more pronounced effect on GLE exposure. The observed increase in GLE exposure is comparable to what has been observed when LPV/RTV and DRV/RTV were co-administered with GLE/PIB. It should be noted that study was conducted using a single dose of cyclosporine and it is possible that at steady state cyclosporine, GLE exposure can be increased more than what has been observed in this study.

The applicant recommends against the administration of GLE/PIB in subjects requiring stable cyclosporine doses> 100 mg per day, (b) (4)

Labeling Recommendations

The co-administration of GLE/PIB should not be recommended with cyclosporine.

Study #	M14-532	Study Period	19 May 2014 - 30 June 2014	EDR link
Title	A Phase I Open-Label study to Assess the Pharmacokinetics, Safety and Tolerability of the Co-Administration of Sofosbuvir in Combination with ABT-493 and ABT-530 in Healthy Adult Subjects.			

STUDY SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To evaluate the effect of GLE/PIB on the pharmacokinetics of sofosbuvir (SOF) at steady state and vice versa.

Rationale: SOF is a P-gp and BCRP substrate. Both GLE and PIB are substrates and inhibitors of P-gp and BCRP. SOF can be administered with GLE/PIB to treat HCV subjects who failed HCV therapy.
Dose Selection:
- GLE (300 mg) and PIB (120 mg): Doses evaluated in Phase III trials and proposed for marketing.
- SOF (400 mg) dose is the approved dose.

Design and PK Assessment: Each arm enrolled 12 subjects

	Period 1 Days 1 to 7	Period 2 Days 1 to 7
Cohort I N = 8		Sofosbuvir 400 mg QD
	GLE 400 mg QD + PIB 120 mg QD	
Cohort II N = 8	Sofosbuvir 400 mg QD	
		GLE 400 mg QD + PIB 120 mg QD

Serial blood samples for the determination of plasma concentrations were collected, post-dosing, as follows:

1. GLE and PIB:
- Cohort I: for 24 hours on Day 1 (Period 1), Day 7(Period 1), Day 1 (Period 2), and for 72 hours on Day 7 (Period 2).
- Cohort II: for 24 hours on Day 1 (Period 2) and for 72 hours on Day 7 (Period 2)

2. SOF & GS-331007:
- Cohort I: for 24 hours on Day 7 (Period 2) and for 72 hours on Day 7 (Period 2)
- Cohort II: for 24 hours on Day 1 (Period 1), Day 7(Period 1), Day 1 (Period 2), and for 72 hours on Day 7 (Period 2).

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast)

Formulation: Phase 2b formulation of GLE (100 mg tablet) and PIB (40 mg tablet). Commercially available SOF (400 mg tablet, Sovaldi®).

RESULTS

Enrolled	16	Completed	16	Discontinued Due to AE	0	PK Population	16	Safety Population	16

Bioanalytical Method:

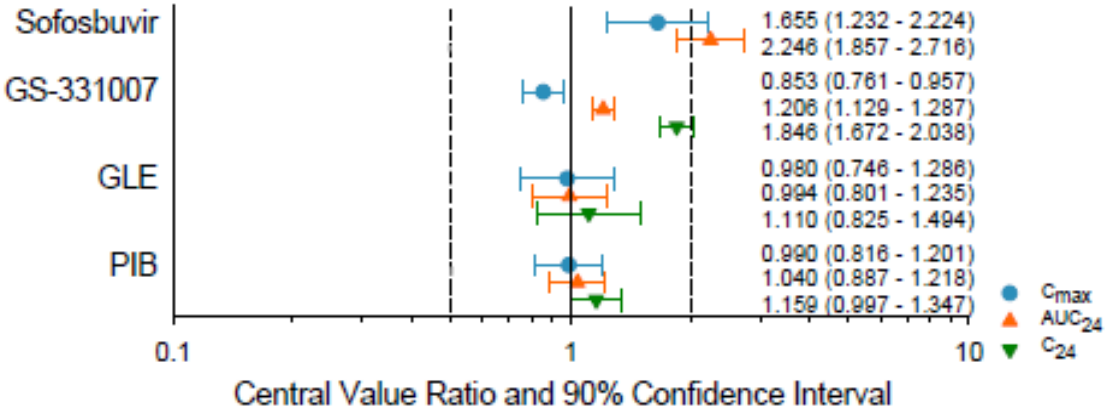
Analyte	Type	Matrix	Range	Link to Report
GLE	LC-MS/MS	Plasma	Low: 0.204 - 101 ng/mL High: 86.2 - 10,100 ng/mL	GLE and PIB
PIB	LC-MS/MS	Plasma	Low: 0.204 - 101 ng/mL High: 86.2 - 1,030 ng/mL	
SOF	LC-MS/MS	Plasma	5 - 5,000 ng/mL	EDR Link
GS-331007	LC-MS/MS	Plasma	10 - 10,000 ng/mL	

Protocol Deviations: No protocol deviations were reported in this study.

Pharmacokinetics:

- GLE PK parameters were similar on Day 7 of period 2 in Cohort I and Cohort II (page 79 of CSR).
- PIB PK parameters were similar on Day 7 of period 2 in Cohort I and Cohort II (page 82 of CSR).
- Single dose and multiple dose effect of GLE/PIB on SOF PK parameters is similar (page 865 CSR).
- GS-331007 AUC was 34% higher following multiple doses of GLE/PIB compared to single dose of GLE/PIB (Page 85 CSR)

Effect of GLE/PIB on SOF PK at steady state and effect of SOF on GLE/PIB PK at steady sate



- SOF and GS-331007: Ratio is from cohort II Day 7 Period 2 vs. Day 7 Period 1
- GLE and PIB: Ratio is from cohort I (Day 7 Period 2 vs. Day 7 Period 1)

Safety

- No deaths or serious adverse events were reported during the study.

REVIEWER ASSESSMENT
The study design is acceptable ☑ Yes ☐ No
Study Conduct ▪ Bioanalytical method performance in acceptable ☑ Yes ☐ No ▪ Protocol deviations do not affect the integrity of the study ☐ Yes ☐ No ☑ NA
Study Results The study results are acceptable as reported by the sponsor ☑ Yes ☐ No
Discussion GLE/PIB significantly increases SOF exposure, which can be attributed to GLE/PIB inhibition of P-gp and BCRP. The observed increase in SOF AUC (increase by ~ 125%) is not considered clinically significant according to SOF labeling. Similar increases in SOF exposures were observed in subject with Child-Pugh B and C hepatic impairment and did not warrant any dose adjustment. SOF does not affect the exposures of GLE or PIB.
Labeling Recommendations The co-administration of GLE/PIB and SOF does not require any dose adjustment.

CLINICAL PHARMACOLOGY RENAL IMPAIRMENT STUDY REVIEW				
Study #	M13-600	**Study Period**	16 March 2015 – 16 December 2015	EDR Link
Title	Evaluation of the Pharmacokinetics and Safety of ABT-493 and ABT-530 in Subjects with Normal and Impaired Renal Function			

STUDY DESIGN

- Sub-study 1 consisted of five groups (normal, mild, moderate, and severe renal impairment and subjects with ESRD not on dialysis). All subjects received a single GLE and PIB dose on Day 1
- In Sub-study 2 (Group 6; subjects with ESRD and on dialysis), subjects received a single GLE and PIB dose on:

1. Day 1 of Period 1 **(dialysis day)**: hemodialysis started 3 hours post-dose
2. Day 1 of Period 2 **(non-dialysis day)**: hemodialysis 24 hours post-dose

There was a washout period of at least 7 days between period 1 and period 2

Population	Male or female healthy subjects between 18 and 75 years old						
	Renal Impairment Groups	☑ Normal	☑ Mild	☑ Moderate	☑ Severe	☑ ESRD no dialysis	☑ ESRD dialysis
	GFR (Range)	≥ 90	60-89	30-59	15-29	< 15	--
	Group No	5	1	2	3	4	6
Renal Function Classification Method ☐ C-G ☑ MDRD							
Renal function assessed at ☑ Screening ☑ Baseline							
Groups Matching Criteria	Age, sex, and weight.						
Study Rationale	The renal elimination of GLE and PIB is minimal (< 1% of the dose). The applicant conducted this study prior to efficacy and safety studies of the combination in HCV infected subject with ESRD.						
Treatments	Co-administered GLE and PIB tablets; 300 mg GLE, 120 mg PIB						
Dose Selection Rationale	The clinical dose evaluated in phase 3 studies.						
Drug Administration	☐ Fasted ☑ Fed *30 minutes after the start of a standardized breakfast.						
Formulation	Phase 2b formulation was used: GLE (100 mg tablet) and PIB (40 mg tablet)						
Interfering Substances Excluded	Use of known inhibitors or inducers of CYP3A, P-gp or OATP1B1 was prohibited .within 30 days of the initial dose of study drug through the end of the study. The following subjects were excluded from the study: - followed strictly a vegetarian diet. - used creatine supplements within 2 weeks prior to screening through the end of the study.						
Sampling Times	**Plasma** Sub-Study 1: 0, 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, 72, 96 and 144 hours post dose. Sub-Study 2: Day 1 of Period 1: 0, 1, 2, 3, 9, 12, 16 and 24 hours post dose. Day 1 of Period 2: 0, 1, 2, 3, 4, 5, 6, 9, 12, 16 and 24 hours post dose Additional arterial, venous, and dialysate samples (interval samples) were taken at 0.25, 1, 2, and 3 on Period 1 Day 1 and prior to the end of dialysis. **Urine** Sub-Study 1: urine was collected during the intervals of 0 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, and 120 to 144 hours post dose.						
PK Parameters	Sub-study 1: Cmax. Tmax, β, half-life, AUC0-t, AUC0-inf, CL/F, V/F, fu (mean unbound fraction of drug), fe (fraction excreted in urine), CLr (renal clearance)..						

	Sub-study 2: Cmax. Tmax, C24, AUC0-t, AUC arterial, AUC venous, the mean pre-dialysis unbound fraction (fu, pre-dialysis), mean post-dialysis unbound fraction (fu, post-dialysis).
PK Analysis	Non-compartmental.
Statistical Analysis	**Sub-study 1:** A linear regression analysis on the logarithms of Cmax and AUC_{inf} against eGFR, the calculated CLcr and $CLcr_{24}$, with weight, sex, and age as possible covariates. Ratios of the predicted Cmax and AUC values of a typical subject from each impaired group to the predicted Cmax and AUC values of a typical subject from the normal group and their 90% confidence intervals (CI) were calculated. **Sub-study 2:** Repeated measures analysis for each analyte on the logarithms of Cmax, AUC0-t, with Period as a fixed effect. The 90% CI of Cmax and AUC of each analyte when subjects were on dialysis (Period 1 Day 1) to when subjects were not on dialysis (Period 2 Day 1) was assessed
Protein Binding	☐ ex vivo ☐ in vitro / ☐ Equilibrium Dialysis ☐ Ultrafiltration ☑ Flux Dialysis Blood samples for protein binding assay were collected at 0 hour on Day 1 of sub-study 1, and prior to and after hemodialysis on Period 1 Day 1 of Sub-study 2

Is the study design acceptable? ☑ Yes ☐ No

Reviewer Notes: *A multiple-dose study is desirable when the drug is known to exhibit nonlinear PK. Renal impairment is not expected to affect the exposure of GLE and PIB because of limited renal elimination of both drugs. A single dose study design is acceptable in this case to confirm the prediction and guide initial dose selection for efficacy and safety study. Use of the Phase 2b formulation as opposed to the to-be-marketed (Phase 3) formulation does not confound the study results; the two formulations have similar relative bioavailability when administered with food..*

STUDY CONDUCT

Bioanalytical Method: Report Link

Method Name	Liquid/Liquid Extraction HPLC Tandem Mass Spectrometric Method		
Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE (ABT 493), PIB (ABT530)		

Range	GLE Low Range	GLE High Range	PIB Low Range	PIB High Range
	0.202 to 105 ng/mL	80.0 to 10300 ng/mL	0.205 to 101 ng/mL	81.4 to 1020 ng/mL

Validation	▪ Method validated prior to use	☑ Yes ☐ No ☐ NA
	▪ Method validation acceptable	☑ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No
Inspection	▪ Will the bioanalytical site be inspected	☐ Yes ☑ No

Reviewer Notes:

- 51.1% of the total samples were repeated for GLE and PIB. The applicant utilized two calibration ranges for

the assays; for low and high concentrations. This caused the concentration values to fall above and below the limit of quantitation for each calibration range and contributed to the high rate of re-assays.
- The applicant used two calibration curves for each analyte (low range and high range). While this approach is not optimal, the similarity in slopes and intercepts of the two calibration curves for each analyte renders the approach acceptable.
- Samples were stored for a maximum of 354 days, and stability data provided at the time of assay support storage for at least 282 days at~ -20°C. Long-term stability experiments were ongoing at the time of study samples analysis. The applicant submitted additional long term storage stability testing results (R&D/16/0743) with established stability of 618 days stored at ~ -20°C.

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☑ Yes ☐ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☑ No ☐ NA

Subject 107 was enrolled and tested positive for alcohol on Day -2

STUDY RESULTS

Study Population

Planned: up to 48, enrolled: 46, completed: 45, evaluated for safety: 46, evaluated for pharmacokinetics and safety: 46, discontinued due to AE: none

	Normal	Mild	Moderate	Severe	ESRD No Dialysis	ESRD Dialysis
Completed	8	8	8	8	6	8
Age [Mean (range)]	57 (52-62)	61 (40-74)	64 (56-73)	65 (59-69)	53 (30-62)	57 (47-73)
Male/Female	6/2	6/2	6/2	8/0	2/4	6/2
Race (Caucasian/ Black/Asian/Other)	7/1/0/0	7/0/0/1	5/2/1/0	5/1/0/2	3/2/0/1	0/8/0/0

Did any of the subjects change renal impairment group between screening and baseline? ☐ Yes ☑ No

Pharmacokinetics

- [Ratios of the regression model estimated GLE and PIB Cmax and AUCinf for each renal impairment group relative to the normal group and their respective 90% confidence intervals

Renal Impairment Group	Pharmacokinetic Parameter (units)	GLE		PIB	
		Point Estimate	90% CI	Point Estimate	90% CI
Mild	C_{max} (ng/mL)	**1.021**	0.890-1.172	**1.062**	0.978-1.152
	AUC_{inf} (ng•h/mL)	**1.127**	1.008-1.259	**1.108**	1.021-1.202
Moderate	C_{max} (ng/mL)	**1.047**	0.774-1.417	**1.141**	0.953-1.366
	AUC_{inf} (ng•h/mL)	**1.301**	1.019-1.661	**1.253**	1.048-1.498
Severe	C_{max} (ng/mL)	**1.068**	0.697-1.635	**1.204**	0.934-1.552
	AUC_{inf} (ng•h/mL)	**1.449**	1.026-2.044	**1.374**	1.068-1.767
ESRD (non-Dialysis)	C_{max} (ng/mL)	**1.081**	0.650-1.798	**1.248**	0.922-1.690
	AUC_{inf} (ng•h/mL)	**1.556**	1.032-2.348	**1.461**	1.081-1.973
ESRD on Dialysis (Dialysis day/ Non-dialysis day)	C_{max} (ng/mL)	**0.928**	0.576-1.496	**0.817**	0.633-1.054
	AUC_t (ng•h/mL)	**1.060**	0.7909-1.585	**0.909**	0.726-1.139

- Fraction excreted in urine was less than 1% in groups 1 to 5
- In groups 1 to 5, percent fraction unbound was ~ 1.7% for GLE and ~ 0.06% for PIB and was similar in subjects with renal impairment when compared to subjects with normal renal function.
- In group 6, mean percent fraction unbound was < 3% for GLE (2.5% on dialysis day and 2.9% on non-dialysis day) and < 0.03 % for PIB (0.029% on dialysis day and 0.019% on non-dialysis day).
- Exposure of GLE and PIB in arterial (pre-dialyzer) and venous (post-dialyzer) plasma was similar and indicated limited removal of either drug by hemodialysis.
- Dialysate concentrations of both drugs were not determined because of limited removal by dialysis.

Reviewer Notes:

- Were there any outliers or excluded data from analysis? ☐ Yes ☐ No ☑ NA
- Are the study results acceptable? ☑ Yes ☐ No

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No

Subject 406 (ESRD not yet on dialysis) experienced renal colic and renal impairment (progressive renal dysfunction) on study Day 13. These events were considered by the investigator to be Grade 2 in severity and as having no reasonable possibility of being related to study drug. We agree with the assessment.

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

Conclusions

Does the study finding warrant dose adjustment in patients with renal impairment? ☐ Yes ☑ No

We agree with the applicant that no dosage adjustment of 300 mg GLE co-administered with 120 mg PIB is needed in subjects with renal impairment including those subjects on dialysis. Of note, the applicant conducted an efficacy and safety study in HCV infected subjects with ESRD.

CLINICAL PHARMACOLOGY HEPATIC IMPAIRMENT STUDY REVIEW				
Study #	M13-604	**Study Period**	17 October 2014– 24 September 2015	EDR Link
Title	Pharmacokinetics and Safety of GLE and/or PIB in Subjects with Normal and Impaired Hepatic Function			

STUDY DESIGN

Study Schema

Group	Child-Pugh Class	Regimens (Single Dose Administration)		
		Period 1	Period 2	Period 3
I	A (Mild)	120 mg PIB	120 mg PIB + 200 mg GLE	120 mg PIB + 300 mg GLE
II	B (Moderate)	120 mg PIB	120 mg PIB + 200 mg GLE	120 mg PIB + 300 mg GLE
III	C (Severe)	120 mg PIB	120 mg PIB + 300 mg GLE	[redacted]
IV	---	120 mg PIB	120 mg PIB + 200 mg GLE	120 mg PIB + 300 mg GLE

*A minimum washout interval of 14 days separated the doses of the three periods

Population	Male and female volunteers whose ages were between 18 and 55 years
Hepatic Impairment Groups ☑ Normal ☑ Mild ☑ Moderate ☑ Severe	
Hepatic Function Classification Method ☑ Child-Pugh ☐ NCI ☐ MELD	
Hepatic function assessed at ☑ Screening ☑ Baseline	
Group Matching Criteria	Age, weight and sex
Study Rationale	Both GLE and PIB are mainly eliminated through the hepatobiliary route; therefore, hepatic impairment can alter their exposure. The objective of this study is to evaluate the impact of the level hepatic impairment on GLE and PIB exposure.
Dose Selection Rationale	The 200 mg GLE dose was evaluated in Phase 2 trials. GLE 300 mg and PIB 120 doses were evaluated in Phase 3 trials and are proposed for marketing.
Drug Administration	☐ Fasted ☑ Fed (30 minutes after the start of a standardized breakfast.)
Formulation	Phase 2b formulation was used: GLE (100 mg tablet) and PIB (40 mg tablet)
Interfering Substances Excluded	Use of any medications (prescription and over-the-counter), vitamins and/or herbal supplements, treatment of concomitant stable medical, and hormonal replacement therapies for females from 2 weeks or within 10 half-lives, prior to study drug administration through the end of the study was prohibited. Exclusion criteria included use of known strong inhibitors or strong inducers of CYP3A, BCRP, P-gp or OATP1B1 and 1B3 within 1 month prior to study drug administration.
Sampling Times	Pre-dose and 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, 72, 96 and 144 hours post-dose.
PK Parameters	Cmax. Tmax, β (apparent terminal elimination rate constant), half-life, AUC_{0-t} , AUC_{inf}, Vd/F, CL/F, and fu (mean unbound fraction).
PK Analysis	Non-compartmental.
Statistical Analysis	For each analyte and each regimen, a regression analysis was performed on the logarithms of AUC, Cmax, Vd/F, Tmax and β. The factor of primary interest was hepatic function category. Body weight, sex, age, and other variables were considered as covariates at the significance level of 0.1. The effect of each hepatic impairment group was estimated and compared to the normal category at the significance level of 0.05. For AUC and Cmax, 90% confidence intervals were provided for the ratio of the central value of each impaired group to that of the normal group.
Protein Binding	☑ ex vivo ☐ in vitro / ☐ Equilibrium Dialysis ☐ Ultrafiltration ☑ Flux Dialysis A sample for determination of protein binding was withdrawn immediately prior to

	dosing

Is the study design acceptable? ☑ Yes ☐ No

Reviewer Notes: *A multiple-dose study is desirable when the drug is known to exhibit nonlinear PK. The current study design is not optimal given that both drugs exhibit non-linear PK; however, because efficacy and safety data are available in subjects with cirrhotic Child-Pugh A and drug administration will not be allowed in subjects with decompensated cirrhosis unless efficacy and safety data are available, the current design is sufficient to inform dose selection for efficacy and safety trials.*

Use of the Phase 2b formulation in this study compared to the to-be-marketed (Phase 3) formulation does not confound the study results; the two formulations have similar relative bioavailability when administered with food.

STUDY CONDUCT

Bioanalytical Method: Link to bioanalytical report for GLE and PIB and Updated Stability Report

Method Name	Liquid/Liquid Extraction HPLC Tandem Mass Spectrometric Method			
Method Type	LC-MS/MS	Matrix	Plasma	
Analytes/ Range	GLE Low Range	GLE High Range	PIB Low Range	PIB High Range
	0.200 to 100 ng/mL	85.2 to 10400 ng/mL	0.205 to 101 ng/mL	81.4 to 1020 ng/mL

Validation	▪ Method validated prior to use	☑ Yes ☐ No ☐ NA
	▪ Method validation acceptable	☑ Yes ☐ No ☐ NA
Study Samples Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Incurred samples analysis is acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No

Reviewer Notes:

- Samples were stored for a maximum of 354 days, and the stability data at the time of assay support storage for at least 282 days at~ -20°C. Long-term stability experiments were ongoing at the time of study samples analysis. The Applicant submitted additional long term storage stability testing results (R&D/16/0743) with established stability of 618 days stored at ~ -20°C.

-During the course of the study, 80.2% and 71% of the total samples analyzed were repeated for GLE and PIB, respectively, due to rejected runs. The re-analysis of these samples is considered acceptable based on the review of the performance (QC samples) of the analytical run.

the Applicant used two calibration curves for each analyte (low range and high range). While this approach is not optimal, the similarity in slopes and intercepts of the two calibration curves for each analyte renders the approach acceptable.

Protocol Deviations

- Are there any protocol deviations listed in the study report? ☑ Yes ☐ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☑ No ☐ NA

List of reported protocol deviations

1. Subject 309 had a prolonged QT interval at screening
2. Subject 207 had a body mass index (BMI) of 41.18
3. Subjects 305, 113, 201, and 206 tested positive for drugs (opiates, benzodiazepines, etc.)
4. Subject 311 was administered an incorrect dose in Period 2 and was excluded from the calculation of the

pharmacokinetic parameters in Period 2, and Subject 316 was enrolled as a replacement subject.
5. Multiple subjects did not consume their entire meals on intensive blood sampling days. This was mainly related to the dessert part of the meals.

STUDY RESULTS

Study Population

Enrolled: 27, completed:22, discontinued due to AE: none; evaluated for PK: 24; evaluated for safety: 27

	Normal	Mild	Moderate	Severe
Evaluated for Safety	7	7	6	7
Evaluated for PK*	6	6	6	6
Age [Mean (range)]	57 (54-60)	55 (49-58)	56 (47-64)	54 (46-64)
Male/Female	3/4	6/1	4/2	3/4
Race (Caucasian/Black/Asian/Hispanic)	6/1/0/0	7/0/0/0	5/0/0/1	7/0/0/0

One subject was dismissed on Day –1 of Period 3 due to a positive urine drug screen and another discontinued on Day 2 of Period 2 after withdrawing consent; both were replaced.
*Due to replacement occurrence, the pharmacokinetic summary and statistical analyses for each regimen included data from only 6 subjects in each group.

Distribution of Child-Pugh Scores

Score	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
N-Screening	2	5	4	2	0	4	3	0	0	0	0
N-Baseline	3	4	3	2	1	2	2	2	1	0	0

Etiology of Liver Disease: These etiologies are not mutually exclusive; a subject may fall under more than one etiology.

Group	Cirrhosis	Hepatitis	Portal HTN
Mild	4 (2 alcoholic)	4 (HCV)	0
Moderate	7 (1 alcoholic)	1 (HCV), 2 (HBV)	0
Severe	7 (1 alcoholic)	2 (HCV)	3

Pharmacokinetics

- Geometric Mean Ratios (GMRs; hepatic impairment/ normal hepatic function) & 90% confidence intervals (90% CIs) following the administration of GLE 300 mg and PIB 120 mg doses

Hepatic Impairment Group	Pharmacokinetic Parameter (units)	GLE		PIB	
		GMR	90%CI	GMR	90%CI
Mild	Cmax (ng/mL)	**1.011**	0.379 – 2.695	**0.836**	0.577 – 1.212
	AUCinf (ng•h/mL)	**1.329**	0.493 – 3.579	**0.799**	0.478 – 1.335
Moderate	Cmax (ng/mL)	**1.381**	0.532 – 3.588	**1.257**	0.851 – 1.858
	AUCinf (ng•h/mL)	**2.002**	0.763 – 5.251	**1.259**	0.734 – 2.161
Severe	Cmax (ng/mL)	**4.782**	1.749 – 13.071	**0.587**	0.405 – 0.852
	AUCinf (ng•h/mL)	**11.134**	4.031 – 30.750	**2.139**	1.278 – 3.580

Hepatic impairment had a greater impact on GLE exposure when GLE 200 mg was administered (Mild AUCR=1.797 and CmaxR=1.688, moderate AUCR=2.816 and CmaxR=2.704). PIB exposure changes were comparable in subjects with mild and moderate hepatic impairment following the administration of PIB 120 mg dose with either GLE 200 mg dose or 300 mg dose.

- Mean percent fraction unbound fraction of GLE and PIB.

Hepatic Impairment Group	GLE	PIB
Normal	2.7%	0.0096%
Mild	2.2%	0.0103%
Moderate	3.1%	0.0095%
Severe	4.7%	00129%

The mean unbound fraction (fu) of GLE in subjects with mild or moderate hepatic impairment was not significantly different from subjects with normal hepatic function ($p > 0.05$), but was significantly higher in subjects with severe hepatic impairment. Whereas for PIB, the mean fraction unbound was comparable for all hepatic impairment groups.

- Were there any outliers or excluded data from analysis? ☑ Yes ☐ No ☐ NA
- Are the study results acceptable? ☑ Yes ☐ No

Subject 311 was administered an incorrect dose in Period 2 and was excluded from the calculations of the PK analysis in Period 2, and Subject 316 was enrolled as a replacement subject, therefore, this does not affect the results of the study

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No

CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS

- Does the study finding warrant dose adjustment in patients with hepatic impairment? ☑ Yes ☐ No

Hepatic impairment had a greater impact on GLE PK parameters compared to PIB. Based on the observed exposure changes of GLE in the severe hepatic impairment group and the significant increase in its unbound fraction, we agree with the applicant's proposal to contraindicate the combination with Child-Pugh class C subjects.

We agree with the applicant's proposal to not recommend use in Child-Pugh class B subjects. Although GLE and PIB exposures in subjects with moderate hepatic impairment were ≤ 2-fold of healthy subjects, the upper limit of the 90% CI for GLE AUC extends to 5.3-fold. Exposure changes from single dose alone may not be predictive of exposure changes following multiple doses. Efficacy and safety of the combination in subjects with Child-Pugh B cirrhosis should be established in clinical efficacy and safety study. Moreover, HCV protease inhibitors have been associated with post-marketing safety issues which led to restricting their use in HCV infected subjects with Child-Pugh class B cirrhosis.

Of note, the Child-Pugh class A group included a mix of non-cirrhotic and cirrhotic subjects; therefore, the observed exposure changes from this group does not represent the exposure changes in subjects with Child Pugh A cirrhosis. Dosing recommendation of no dosage adjustment in this category is based on Phase 2 and Phase 3 efficacy and safety data in HCV patient with Child-Pugh A cirrhosis.

Study #	M14-066	Study Period	November 19, 2013- February 26, 2014	EDR Link
Title	Assessment of Multiple Dose Pharmacokinetics and Safety of the Co-administration of GLE and PIB in Healthy Han Chinese, Japanese, and Caucasian Adult Subjects			

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To assess the pharmacokinetics and safety of multiple oral doses of GLE and PIB given alone and in combination under non-fasting conditions in healthy Han Chinese, Japanese, and Caucasian adult subjects.

Rationale: The trial was conducted to determine if there are differences in the systemic exposure of GLE and PIB in healthy Han Chinese, Japanese, and Caucasian adult subjects.
Dose Selection: Doses used were higher than those evaluated in Phase 3.

Design and PK Assessments:

	Days 1 to 7	Days 8 to 14
Cohort I	GLE 700 mg QD	GLE 700 mg QD + PIB 160 mg QD
Cohort II	PIB 160 mg QD	GLE 700 mg QD + PIB 160 mg QD

Note that the original study design included an optional second arm that was supposed to evaluate lower doses (not specified) of GLE and PIB. **Based on the review of available pharmacokinetic and safety data from Arm 1, the applicant made a decision not to conduct Arm 2.**

Blood samples for determining the concentration of GLE and PIB were collected on day 1 (prior to dosing and up to 24 hours after dosing), days 5 and 6 (prior to dosing), day 7 (prior to dosing and up to 16 hours after dosing), day 8 (prior to dosing and up to 24 hours after dosing), day 12 and 13 (prior to dosing), day 14 (prior to dosing and up to 72 hours after dosing).

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized breakfast.)

Formulations
Phase 2a tablet formulations of GLE (100 mg tablet), PIB (40 mg tablet).

RESULTS

Enrolled	35	Completed	34*	Discontinued Due to AE	0	PK Population	35	Safety Population	35

*: One subject (subject # 1204) withdrew consent and was lost to follow up.

Bioanalytical Method: Link to Reports ABT-493 and ABT-530

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE		PIB
Range	0.105-268 ng/mL 0.0978-249 ng/mL		0.0997-253 ng/mL 0.0987-251 ng/mL

Protocol Deviations
There were no protocol deviations reported in the trial.

Pharmacokinetics:
Note: Because treatments on day 14 were identical in Cohorts 1 and 2, the applicant combined the Day 14 results from Cohort 1 and Cohort 2 in the tables above.

GLE: Geometric Mean (Mean, CV %) Pharmacokinetic Parameters of GLE on Day 7 and 14

Pharmacokinetic Parameters	Units	Han Chinese GeoMean (Mean, %CV)	Japanese GeoMean (Mean, %CV)	Caucasian GeoMean (Mean, %CV)
		Cohort 1, Day 7 (700 mg ABT-493 QD)		
		(N = 6)	(N = 6)	(N = 6)
C_{max}	ng/mL	10400 (12400, 53)	13700 (16800, 64)	10600 (13200, 70)
C_{24}	ng/mL	27.0 (33.7, 64)	47.5 (69.6, 101)	41.6 (107, 126)
AUC_{24}	ng•h/mL	36900 (45800, 61)	46500 (62000, 80)	43900 (66100, 96)
		Cohorts 1 and 2, Day 14 (700 mg ABT-493 QD + 160 mg ABT-530 QD)		
		(N = 11)	(N = 12)	(N = 12)
C_{max}	ng/mL	13900 (16290, 51)	16700 (19000, 48)	15300 (18800, 59)
C_{24}	ng/mL	32.4 (47.8, 88)	71.6 (127, 121)	60.8 (253, 194)
AUC_{24}	ng•h/mL	49400 (62500, 63)	67500 (83900, 68)	66000 (101000, 85)

Source: M14-066 Clinical Study Report, Pages 106

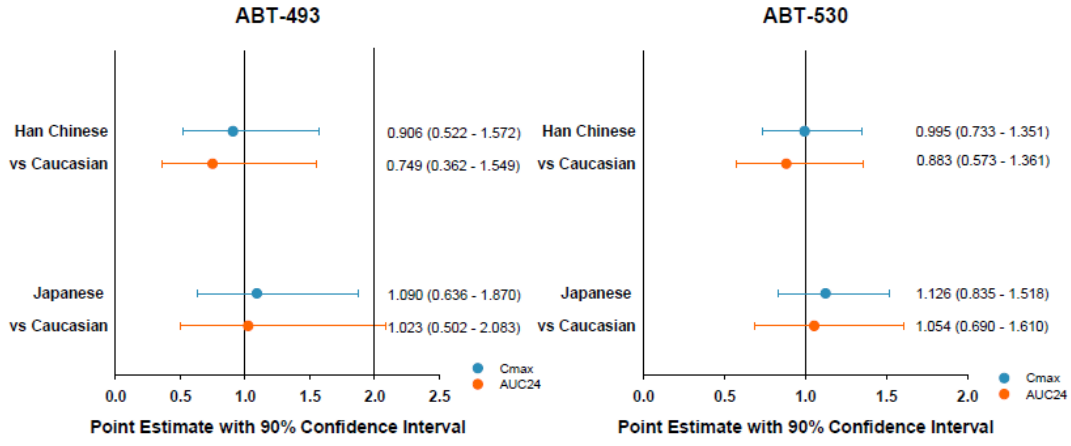
PIB: Geometric Mean (Mean, CV %) Pharmacokinetic Parameters of PIB on Day 7 and 14

Pharmacokinetic Parameters	Units	Han Chinese GeoMean (Mean, %CV)	Japanese GeoMean (Mean, %CV)	Caucasian GeoMean (Mean, %CV)
		Cohort 2, Day 7 (160 mg ABT-530 QD)		
		(N = 5)	(N = 6)	(N = 6)
C_{max}	ng/mL	96.6 (101, 32)	63.5 (73.6, 51)	61.1 (81.9, 69)
C_{24}	ng/mL	7.43 (8.18, 51.6)	4.81 (6.00, 71)	6.02 (8.03, 79)
AUC_{24}	ng•h/mL	587 (624, 39)	382 (460, 62)	424 (550, 65)
		Cohorts 1 and 2, Day 14 (160 mg ABT-530 QD + 700 mg ABT-493 QD)		
		(N = 11)	(N = 12)	(N = 12)
C_{max}	ng/mL	288 (298, 29)	326 (345, 34)	289 (311, 37)
C_{24}	ng/mL	43.2 (49.9, 60)	54.1 (67.2, 66)	60.3 (76.3, 60)
AUC_{24}	ng•h/mL	2570 (2760, 42)	3070 (3480, 50)	2910 (3310, 47)

Source: M14-066 Clinical Study Report, Pages 106

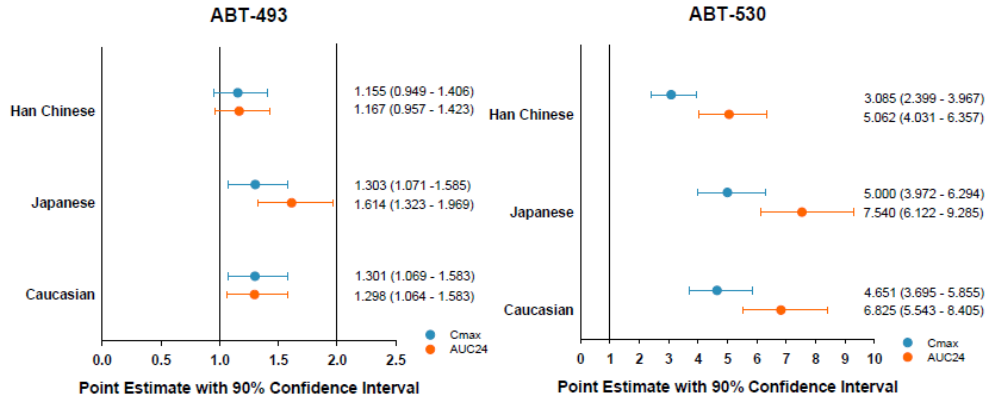
Ethnicity Effect:

Statistical comparison of pharmacokinetic parameters in Asians Vs Caucasians for day 14



Source: M14-066 Clinical Study Report, Pages 108

Statistical comparison of **GLE and PIB** pharmacokinetic parameters **for day 14 vs day 7**



Source: M14-066 Clinical Study Report, Page109

Safety
No deaths, serious adverse events or other significant adverse events were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:

Mean C_{max} and AUC of GLE and PIB in Han Chinese and Japanese subjects were similar to the values observed in Caucasian subjects.

PIB increased the mean AUC of GLE by 16 %, 61 % and 30 % in Han Chinese, Japanese, and Caucasian subjects. Considering that the doses of GLE and PIB evaluated in this trial are higher than the clinically recommended dose of GLE and PIB and both GLE and PIB exhibit non-linear increase in exposure, it is challenging to determine whether increase in GLE exposure across the various ethnic groups is clinically relevant.

The results of trial M15-432 (which evaluated clinically relevant dose combinations of GLE and PIB) showed that PIB increased the mean C_{max} and AUC of GLE by 16 % and 17 %, respectively. Although the applicant combined the pharmacokinetic data across the ethnic groups to assess the effect of PIB on GLE, the same magnitude of change in GLE exposures (when combined with PIB) at the clinically relevant doses can be expected in each ethnic group because the mean PK parameters of GLE and PIB at the clinically relevant dose are similar across ethnic groups.

Comparison of mean PK parameters of GLE observed on day 14 vs day 7 did not suggest a significant effect of PIB on the mean PK parameters of GLE across the various ethnic groups; however, comparison of the mean PK

parameters of PIB between day 14 vs day 7 indicated an impact of GLE on the systemic exposure of PIB. The applicant previously demonstrated the GLE increases the systemic exposure of PIB in a dose dependent manner and that at the clinically relevant dose of GLE (300 mg) and PIB (120 mg), GLE increased the mean C_{max} and AUC of PIB by approximately 2.86-fold and 3.1-fold, respectively. The magnitude of increase in PIB exposure when co-administered with GLE in this trial is higher than the magnitude of increase in PIB exposure when GLE and PIB are co-administered at the clinically relevant doses which is likely due to the non-linear increase in GLE exposure resulting in a dose dependent impact on transporters involved in the disposition of PIB.

Proposed Labeling Recommendation:

There is no labeling recommendation proposed based on the results of the trial. The trial was conducted at GLE and PIB doses (700 mg and 1760 mg, respectively) which will not be clinically recommended.

Study #	M15-432	Study Period	March 25, 2015- June 4, 2015	EDR Link
Title	Assessment of Multiple Dose Pharmacokinetics and Safety of the Co-administration of GLE and PIB in Healthy Han Chinese, Japanese, and Caucasian Adult Subjects			

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To assess the pharmacokinetics and safety of multiple oral doses of GLE and PIB given alone and in combination under non-fasting conditions in healthy Han Chinese, Japanese, and Caucasian adult subjects.

Rationale:

The trial was conducted to determine if there are differences in the systemic exposure of GLE and PIB in healthy Han Chinese, Japanese, and Caucasian adult subjects.

Dose Selection: GLE (300 mg) and PIB (120 mg) are the doses evaluated in Phase 3 and proposed for marketing.

Design and PK Assessments:

Cohort	N	Days 1 to 7	Day 8 to 14
Cohort 1	27	GLE 200 mg once daily	GLE 200 mg once daily + PIB 120 mg once daily
Cohort 2	27	GLE 300 mg once daily	GLE 300 mg once daily+ PIB 120 mg once daily
Cohort 3	27	PIB 120 mg once daily	GLE 300 mg once daily+ PIB 120 mg once daily
Cohort 4	27	PIB 80 mg once daily	GLE 200 mg once daily + PIB 80 mg once daily
Cohort 5	27	GLE 100 mg once daily	GLE 100 mg once daily + PIB 120 mg once daily

Source: Table prepared by reviewer based on information provided in the study report
Yellow highlighted rows represent the clinically relevant doses (column # 2) and dose combinations (row # 3) of GLE and PIB

Blood samples for determining the concentration of GLE and PIB were collected on day 1 (prior to dosing and up to 24 hours after dosing), days 5 and 6 (prior to dosing), day 7 (prior to dosing and up to 16 hours after dosing), day 8 (prior to dosing and up to 24 hours after dosing), day 12 and 13 (prior to dosing), day 14 (prior to dosing and up to 72 hours after dosing).

Population: ☑ Healthy Subjects ☐ Patients	Administration: ☐ Fasted ☑ Fed (30 minutes after starting a standardized race specific breakfast)

Formulations

Phase 2b tablet formulations of GLE (100 mg tablet), PIB (40 mg tablet)

RESULTS

Enrolled	135	Completed	129*	Discontinued Due to AE	0	PK Population	135	Safety Population	135

*: Four subjects withdrew consent and two subjects did not return to the site for study day 23 activities.

Bioanalytical Method: Link to Reports (GLE and PIB)

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	GLE, PIB		
Range	GLE: 0.2-100 ng/mL 80-10,300 ng/mL PIB: 0.2-102 ng/mL 81.4-1030 ng/mL		

Protocol Deviations

There were several protocol deviations noted such as enrollment in the trial despite meeting the exclusion criteria related to abnormal ECG (discovered after two subjects received all doses of study drugs), consumption of extra water following study doses, consumption of less than prescribed amounts of breakfast and conduct of

day 23 procedures prior to days stated in the protocol to accommodate subject availability. These protocol deviations are not expected to change the overall conclusions of the trial.

Pharmacokinetics

GLE: Geometric Mean (Mean, CV %) Pharmacokinetic Parameters of GLE, Cohort 2 (only mean PK data at the clinically relevant doses of GLE and PIB is included in the review)

	300 mg ABT-493 QD (Days 1 – 14) + 120 mg ABT-530 QD (Days 8 – 14)		
Parameter (units)	Caucasian (N = 9)	Han Chinese (N = 9)	Japanese (N = 9)
	Day 1		
C_{max} (ng/mL)	476 (553, 62)	1193 (1346, 54)	1097 (1303, 70)
T_{max}[a] (h)	3.0 (2.0 – 4.0)	4.0 (3.0 – 5.0)	4.0 (2.0 – 5.0)
C_{24} (ng/mL)	2.93 (3.19, 44)	4.67 (5.36, 55)	3.47 (4.12, 66)
AUC_{24} (ng•h/mL)	1674 (1909, 62)	3528 (3978, 55)	2991 (3475, 63)
	Day 7		
C_{max} (ng/mL)	583 (738, 78)	1193 (1347, 51)	1160 (1606, 91)
T_{max}[a] (h)	3.0 (2.0 – 4.0)	4.0 (3.0 – 5.0)	3.0 (2.0 – 4.0)
C_{24} (ng/mL)	3.07 (3.42, 54)	5.50 (6.08, 46)	3.72 (4.38, 71)
AUC_{24} (ng•h/mL)	2191 (2552, 61)	3767 (4212, 47)	3229 (4158, 81)
	Day 8		
C_{max} (ng/mL)	675 (804, 65)	1522 (1685, 55)	1308 (1778, 91)
T_{max}[a] (h)	3.0 (2.0 – 5.0)	4.0 (3.0 – 6.0)	4.0 (3.0 – 5.0)
C_{24} (ng/mL)	3.76 (4.50, 74)	6.20 (7.40, 61)	4.30 (5.53, 83)
AUC_{24} (ng•h/mL)	2715 (3168, 59)	5040 (5569, 52)	3838 (4783, 76)
	Day 14		
C_{max} (ng/mL)	787 (874, 43)	1180 (1364, 51)	1380 (2052, 97)
T_{max}[a] (h)	3.0 (2.0 – 4.0)	4.0 (3.0 – 5.0)	4.0 (3.0 – 5.0)
C_{24} (ng/mL)	3.22 (3.51, 42)	6.36 (7.65, 71)	4.32 (5.63, 87)
AUC_{24} (ng•h/mL)	2849 (3138, 44)	3936 (4386, 45)	3849 (5103, 76)
$t_{1/2}$[b] (h)	8.37 (7.82, 30)	6.01 (5.78, 21)	6.43 (6.42, 15)

a. Median (minimum to maximum).

b. Harmonic mean (median, pseudo CV %).

Source: M15-432 Clinical Study Report, Pages 75

Statistical comparison of **GLE** pharmacokinetic parameters **for day 14 vs day 7 in Cohorts 1, 2, and 5 (Day 14 vs Day 7) (Effect of PIB on GLE pharmacokinetics)**

		Central Value		Ratio of Central Values	
Cohort	Pharmacokinetic Parameter	Test[a]	Reference[b]	Point Estimate	90% Confidence Interval
1	C_{max}	370	316	1.171	0.978 – 1.403
	AUC_{24}	1314	1097	1.197	1.036 – 1.383
2	C_{max}	1086	931	1.167	1.004 – 1.356
	AUC_{24}	3507	2987	1.174	1.053 – 1.309
5	C_{max}	72.6	58.8	1.233	1.082 – 1.406
	AUC_{24}	311	198	1.567	1.404 – 1.748

Cohort 1: ABT-493 200 mg QD (Study Days 1 – 7). ABT-493 200 mg QD + ABT-530 120 mg QD (Study Days 8 – 14).

Cohort 2: ABT-493 300 mg QD (Study Days 1 – 7). ABT-493 300 mg QD + ABT-530 120 mg QD (Study Days 8 – 14).

Cohort 5: ABT-493 100 mg QD (Study Days 1 – 7). ABT-493 100 mg QD + ABT-530 120 mg QD (Study Days 8 – 14).

a. Study Day 14.

b. Study Day 7.

Source: M15-432 Clinical Study Report, Pages 81

At the clinically relevant dose of GLE 300 mg and PIB 120 mg (cohort 2), PIB increased the mean C_{max} and AUC of GLE by 16 % and 17 %, respectively.

PIB: Geometric Mean (Mean, CV %) Pharmacokinetic Parameters of PIB, Cohort 3 (only mean PK data at the clinically relevant doses of GLE and PIB is included in the review)

	120 mg ABT-530 QD (Days 1 – 14) + 300 mg ABT-493 QD (Days 8 – 14)		
Parameter (units)	Caucasian (N = 9)	Han Chinese (N = 9)	Japanese (N = 9)
	Day 1		
C_{max} (ng/mL)	105 (113, 41)	75.5 (82.8, 49)	83.9 (94.6, 49)
T_{max} [a] (h)	5.0 (3.0 – 5.0)	5.0 (3.0 – 5.0)	3.0 (2.0 – 5.0)
C_{24} (ng/mL)	5.29 (5.77, 42)	3.48 (4.01, 63)	3.69 (4.17, 50)
AUC_{24} (ng•h/mL)	596 (645, 41)	379 (415, 49)	423 (474, 49)
	Day 7		
C_{max} (ng/mL)	109 (124, 55)	84.4 (93.2, 47)	84.1 (89.0, 38)
T_{max} [a] (h)	4.0 (2.0 – 5.0)	5.0 (3.0 – 5.0)	4.0 (2.0 – 5.0)
C_{24} (ng/mL)	9.94 (12.5, 75)	5.33 (5.80, 48)	6.68 (7.55, 60)
AUC_{24} (ng•h/mL)	803 (936, 62)	463 (499, 44)	539 (592, 50)
	Day 8		
C_{max} (ng/mL)	289 (314, 41)	204 (214, 33)	273 (283, 28)
T_{max} [a] (h)	5.0 (3.0 – 5.0)	5.0 (3.0 – 5.0)	5.0 (5.0 – 6.0)
C_{24} (ng/mL)	23.2 (26.8, 60)	12.0 (13.1, 48)	18.2 (20.9, 57)
AUC_{24} (ng•h/mL)	1942 (2121, 45)	1134 (1199, 38)	1538 (1690, 44)
	Day 14		
C_{max} (ng/mL)	310 (344, 48)	212 (222, 36)	278 (291, 30)
T_{max} [a] (h)	5.0 (3.0 – 5.0)	5.0 (5.0 – 5.0)	5.0 (3.0 – 6.0)
C_{24} (ng/mL)	36.3 (57.2, 137)	16.7 (18.8, 58)	24.8 (28.0, 59)
AUC_{24} (ng•h/mL)	2472 (3005, 79)	1339 (1426, 42)	1875 (2005, 41)
$t_{1/2}$ [b] (h)	29.0 (28.6, 21)	23.1 (25.8, 37)	26.1 (26.3, 18)

a. Median (minimum to maximum).

b. Harmonic mean (median, pseudo CV %).

Source: M15-432 Clinical Study Report, Pages 86

Statistical comparison of **PIB** pharmacokinetic parameters **for day 14 vs day 7 in Cohorts 1, 2, and 5 (Day 14 vs Day 7) (Effect of GLE on PIB pharmacokinetics)**

				Ratio of Central Values	
Cohort	Pharmacokinetic Parameter	Central Value Test[a]	Central Value Reference[b]	Point Estimate	90% Confidence Interval
3	C_{max}	263	91.8	2.866	2.593 – 3.168
	AUC_{24}	1838	585	3.142	2.912 – 3.391
4	C_{max}	128	42.3	3.025	2.541 – 3.601
	AUC_{24}	830	285	2.910	2.539 – 3.335

Cohort 3: ABT-530 120 mg QD (Study Days 1 – 7). ABT-530 120 mg QD + ABT-493 300 mg QD (Study Days 8 – 14).

Cohort 4: ABT-530 80 mg QD (Study Days 1 – 7). ABT-530 80 mg QD + ABT-493 200 mg QD (Study Days 8 – 14).

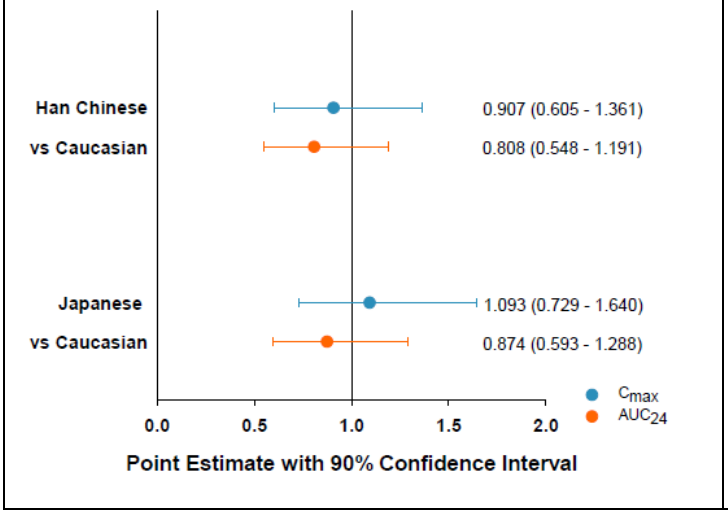
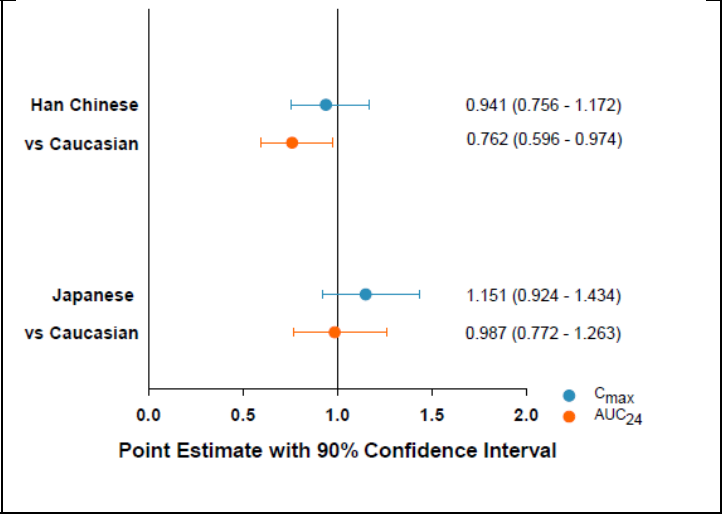
a. Study Day 14.

b. Study Day 7.

Source: M15-432 Clinical Study Report, Pages 90

At the clinically relevant dose of GLE 300 mg and PIB 120 mg (cohort 3), GLE increased the mean C_{max} and AUC of PIB by 186 % and 214 %, respectively. It is important to note that the applicant combined the pharmacokinetic data across the ethnic groups to assess the effect of GLE on PIB and *vice versa*. Considering that the pharmacokinetic parameters of GLE and PIB are similar across the ethnic groups (as shown in the

applicant's analysis below), the same magnitude of change in PIB exposure (when combined with GLE) and GLE exposures (when combined with PIB) at the clinically relevant doses can be expected in each ethnic group.
Ethnicity Effect: Statistical comparison of pharmacokinetic parameters in Han Chinese and Japanese subjects Vs Caucasian subjects on day 14 **at the clinically relevant doses** (combined data for cohort 2 and cohort 3)

GLE	PIB
	

Source: M15-432 Clinical Study Report, Pages 92 and 95

Safety
No deaths, serious adverse events or other significant adverse events were reported during the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct
- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No

Study Results
The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion:
Following administration of the clinically relevant dose of GLE and PIB (300 mg and 120 mg, respectively), the mean pharmacokinetic parameters of GLE and PIB were similar across the three ethnic groups evaluated in the trial.

The study also evaluated the drug interaction between PIB and GLE. At the clinically relevant dose of GLE 300 mg and PIB 120 mg:
- PIB increased the mean C_{max} and AUC of GLE by 16 % and 17 %, respectively.
- GLE increased the mean C_{max} and AUC of PIB by 186 % and 214 %, respectively. Because GLE/PIB 300/120 mg was used all Phase 3 trials, the safety data from the Phase 3 trials address any safety related implications associated with increase in PIB exposures when co-administered with GLE.

Proposed Labeling Recommendation:
There are no clinically relevant differences inthe pharmacokinetics of GLE and PIB across the ethnic groups (b) (4) **evaluated in the trial.**

SUMMARY OF PHARMACOGEMOICS OF GLECAPREVIR/PIBRENTASVIR
(Prepared by Dr. Jeffrey Kraft)

Background

The current submission is for glecaprevir (ABT-493), a HCV NS3/4A protease inhibitor, and pibrentasvir (ABT-530), a NS5A inhibitor, to be used in combination with each other for the treatment of chronic HCV infection. Glecaprevir is a substrate and inhibitor of multiple uptake and efflux transporters including OATP1B1, OATP1B3, P-gp, and BCRP while pibrentasvir is a substrate of P-gp and/or BCRP and an inhibitor of P-gp, BCRP and OATP1B1. In Study M14-723, coadministration of the OATP1B1/3 inhibitor rifampin (single dose) with the glecaprevir and pibrentasvir combination in healthy subjects increased glecaprevir exposures up to 8.6-fold, while pibrentasvir exposures were unaffected. The sponsor has submitted summary data of exposure (AUC) by transporter function. The purpose of this review is to determine if SLCO1B1 variation and its resulting effects on transporter function have a clinically relevant impact on glecaprevir exposure.

Contents

The sponsor submitted summary level data for SLCO1B1 genotyping performed in subjects from 12 clinical trials in an attempt to investigate the effect of SLCO1B1 variation on glecaprevir exposure. Subject-level genotype data were originally not included in the study report but were submitted by the sponsor after a FDA information request. No labeling claims related to SLCO1B1 genotype have been proposed.

Methods

The sponsor included 239 unique subjects who were genotyped for variants in SLCO1B1and were utilized for the statistical analyses. DNA samples were analyzed for two genetic variants in the SLCO1B1 gene (rs59502379 and rs4149056) via the Pyrosequencing® detection method on the Pyromark® Q96 MD (QIAGEN Inc., Valencia, CA). The sponsor was able to genotype for the *5 and *9 alleles of SLCO1B1and classify each subject's functional transporter status based on haplotypes. The sponsor clarified in their response to our IR (dated 4/14/2017) that the clinical relevance of the *9 allele has not been robustly established as it has been for the *5 allele and as a result, assignment of functional phenotype as extensive, intermediate, or poor transport function was based upon only the *5 allele.

The sponsor genotyped the most important allele to determine functional status for SLCO1B1 (*5/ rs4149056) but did not genotype the other common allele (*15/ rs2306283). This approach is acceptable since the *15 allele occurs on the same haplotype as the *5 allele and transport function will be captured by genotyping for rs4149056. The approach utilized by the sponsor for determining functional transport status based on genotypes is acceptable. Genotypes and classification into functional transporter categories were verified by the reviewer to be accurate.

Summary of Findings

The in vitro and clinical drug interaction studies indicated that glecaprevir is transported by SLCO1B1. To determine the impact of SLCO1B1 function on glecaprevir exposure, the exposure data (AUC) from the 12 clinical trials was summarized by SLCO1B1 transporter function and analyzed using ANCOVA. Analyses failed to show statistical significance between SLCO1B1 function and exposure (AUC) except in two-way interaction between SLCO1B1 function and sex (p=0.017) (Tables 1/2). There does not appear to be a

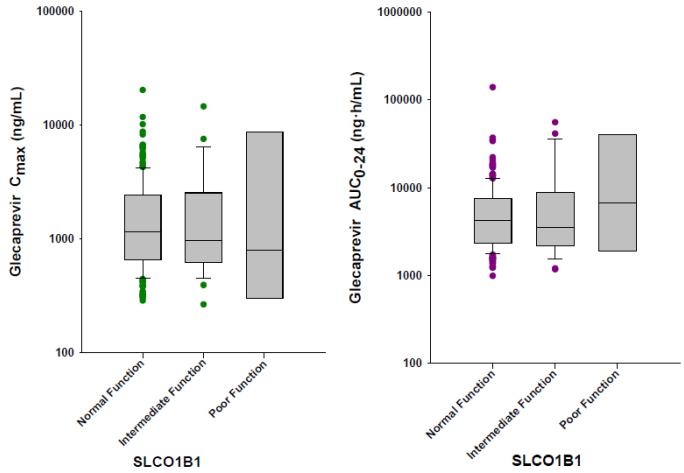
relationship between glecaprevir exposures (AUC) and SLCO1B1 transporter function, based on the sponsor's analyses of 239 subjects from 12 different trials. The sponsor did not investigate if SLCO1B1 genotype had any effect on safety or efficacy of glecaprevir.

Table 1: Glecaprevir Exposure by SLOC1B1 Function as Geometrical mean (Mean, %CV)

Pharmacokinetic Parameter (units)	***All Subjects (N=239)***	***SLCO1B1 Poor Function (N=3)***	***SLCO1B1 Intermediate Function (N=27)***	***SLCO1B1 Normal Function (N=209)***
Cmax (ng/mL)	1300 (2010, 117)	1280 (3260, 144)	1300 (2220, 135)	1310 (1960, 114)
AUC (ng*hr/mL)	4520 (6990, 161)	7880 (16000, 128)	4690 (8870, 150)	4460 (6620, 163)

Source: Study Report (R&D/16/0712), Page 11, Table 5

Figure 1: Glecaprevir Cmax and AUC by SLOC1B1 Function



Source: Study Report (R&D/16/0712), Page 11, Figure 1

Table 2: ANOVA Analyses of SLCO1B1 Function Using logAUC as Response

	Sum of Squares	***Mean Square***	***F Value***	***p-value (F statistic)***
SLCO1B1 Function	0.543	0.543	1.07	0.302
Sex	32.1	32.1	63.3	8.03×10^{-14}
Weight (kg)	5.63	5.63	11.1	0.001
Race	2.99	1.49	2.95	0.054
SLCO1B1 x Sex	2.91	2.91	5.74	0.017
Sex x Race	3.04	1.52	3.00	0.052

Source: Study Report (R&D/16/0712), Page 10, Table 4

In Vitro Studies

This section provides a review of selected in vitro studies. Design and conduct (experimental conditions) of these studies is acceptable. Table 1 lists the reviewed studies and their objectives. Note that in vitro metabolism studies were not reviewed because the applicant conducted in vivo probe substrate study to evaluate the effect of GLE/PIB on major enzymes and ADME studies demonstrated that GLE exhibited minimal metabolism and PIB is not metabolized. A summary of the major findings of the in vitro metabolism studies is provided.

Table 1. List of Reviewed In Vitro Studies.

Study Number	Objective
M15-1003 (GLE) M15-1005 (PIB)	-To assess the effect on P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2K-mediated transport. - To assess if GLE or PIB is a substrate for P-gp, BCRP, OATP1B1, OATP1B3 and OCT1.
R&D/16/0374 (GLE) R&D/16/0372 (PIB)	To determine the unbound fraction in human and animal plasma, human liver microsomes, and liver homogenate. To determine blood-to-plasma ratios (B/P) in animals and humans.

Results

Transporters

Substrate of Transporters

- GLE is a substrate of P-gp, BCRP, OATP1B1 and OATP1B3 (Table 2).
- GLE is not a substrate for OCT1 (Table 2).
- PIB is not a substrate OATP1B1, OATP1B3, or OCT1 (Table 3).

Note that PIB was determined to be a substrate of P-gp and/or BCRP based on in vivo studies with Mdr1a/1b$^{-/-}$ /Bcrp1$^{-/-}$ knockout mice and not based on in vitro studies.

Table 2. GLE Summary of Transporter Substrate Assessment

Transporter	A-1282576	Reference Compound
OATP1B1	K_m 0.098-0.11 µM	-
OATP1B3	K_m 0.19-0.25 µM	-
OCT1	Not a substrate	Fold difference (transfected/mock) >2-fold (ASP+)
P-gp	Net Efflux Ratio: 7.8	Net Efflux Ratio: 14 (Quinidine)
BCRP	Net Efflux Ratio: 9.3	Net Efflux Ratio: 9.0 (Prazosin)

-, not tested; ASP+, 4-[4-(dimethylamino)-styryl]-N-methylpyridinium

Table 3. PIB Summary of Transporter Substrate Assessment

Transporter	A-1325912	Reference Compound
OATP1B1	Not a substrate (± 1% BSA)	Fold difference (transfected/mock) >1.5 (f-MTX)
OATP1B3	Not a substrate (± 1% BSA)	Fold difference (transfected/mock) >2 (f-MTX)
OCT1	Not a substrate (± 1% BSA)	Fold difference (transfected/mock) >2 (ASP+)
Hepatic Uptake*	>2-fold (+1% BSA in the absence of inhibitors); however, not inhibited by rifampicin or verapamil	Pitavastatin uptake >2-fold and inhibited by rifampicin; MPP+ uptake >2-fold and inhibited by verapamil

f-MTX (fluorescein-methotrexate); ASP+ (4-[4-(dimethylamino)-styryl]-N-methylpyridinium); MPP+ (1-methyl-4-phenylpyridinium)

*Temperature dependent uptake (37°C/4°C) in human hepatocytes

Inhibition of Transporters

- GLE is an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, and BSEP (Table 4).
- GLE is not an inhibitor of OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2K (Table 4)
- PIB is an inhibitor of P-gp, BCRP, OATP1B1, and BSEP (Table 5).
- PIB is not an inhibitor of OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2K (Table 5)

Table 4. GLE Summary of Transporter Inhibition Assessment

	IC_{50} (µM) or % Inhibition	
Transporter	A-1282576	Reference Inhibitor
OATP1B1	0.017	0.30 (Rifampicin)
OATP1B3	0.064	0.13 (Rifampicin)
OCT1	>30	≥75% inhibition (100 µM Pyrimethamine)
OCT2	>100	91% inhibition (100 µM Pyrimethamine)
OAT1	>100	≥88% inhibition (300 µM Probenecid)
OAT3	>100	≥85% inhibition (300 µM Probenecid)
MATE1	>30	0.074 (Pyrimethamine)
MATE2K	>30	0.083 (Pyrimethamine)
P-gp (vesicles)	0.33	0.081 (LY335979)
P-gp (MDCK-MDR1 cells)	>100	15 (Cyclosporin A)
BCRP (vesicles)	2.3	0.053 (Ko143)
BCRP (MDCK-BCRP cells)	≥83	0.064 (Ko143)
BSEP (vesicles)	0.95	0.038 (Cyclosporin A)

Table 5. PIB Summary of Transporter Inhibition Assessment

	IC_{50} (μM) or % Inhibition			
	Initial Conditions		with 4% BSA	
Transporter	A-1325912	Reference Inhibitor	A-1325912	Reference Inhibitor
OATP1B1	>0.30	0.52 (Rifampicin)	1.3	4.1 (Rifampicin)
OATP1B3	>30	≥55% inhibition (30 μM Rifampicin)	>30	46% inhibition (30 μM Rifampicin)
OCT1	>30	≥76% inhibition (100 μM Verapamil)	>30	≥73% inhibition (100 μM Verapamil)
OCT2	>30	≥87% inhibition (100 μM Verapamil)	>30	≥84% inhibition (100 μM Verapamil)
OAT1	>30	87% inhibition (100 μM Probenecid)	>30	≥36% inhibition (100 μM Probenecid)
OAT3	>30	≥71% inhibition (100 μM Probenecid)	>30	56% inhibition (100 μM Probenecid)
MATE1	>30	≥93% inhibition (1 μM Pyrimethamine)	>30	≥68% inhibition (1 μM Pyrimethamine)
MATE2K	>30	83% inhibition (1 μM Pyrimethamine)	>30	≥68% inhibition (1 μM Pyrimethamine)
P-gp (vesicles)	0.036	0.043 (LY335979)		
P-gp (MDCK-MDR1 cells)	>150	3.0 (Cyclosporin A)		
BCRP (vesicles)	14	0.048 (Ko143)		
BCRP (MDCK-BCRP cells)	>150	0.12 (Ko143)		
BSEP (vesicles)	39	0.038 (Cyclosporin A)		

Distribution (data in human plasma and blood are reported)

Table 6. GLE and PIB Fraction Unbound and Blood/Plasma Ratio

	Unbound Fraction		**Blood/Plasma Ratio**
	Concentration	**Value**	
GLE	1 μM	0.025	0.57
PIB	1 μM – 30 μM	0.000057	0.62

Metabolism

Maximum concentrations following GLE 300 mg + PIB 120 mg QD in healthy subjects were equivalent to GLE 1.47 μM and PIB 0.265 μM. The inhibition potential of GLE or PIB on common drug metabolizing enzymes and transporters in vitro is summarized in Table 7.

Table 7. In Vitro Inhibitory Enzyme Inhibition Potential of GLE and PIB

Enzyme	**IC_{50} (μM)**	
	GLE	**PIB**
CYP2C8	31.7	>30
CYP2C9	175	>30
rCYP3A4	28.3	--
UGT1A1	17.2	2.54
UGT1A4	14.6	0.027

Clinical drug exposures are not expected to reach sufficient levels to inhibit CYP2C8, CYP2C9, or UGT1A1. GLE and PIB did not demonstrate any in vitro inhibitory potential towards CYP1A2, CYP2B6, CYP2C19, CYP2D6, UGT1A6, UGT1A9, or UGT2B7.
CYP3A was evaluated in vivo.

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