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RESEARCH**

APPLICATION NUMBER:

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**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	208,261
Submission type	505(b)(1) New Drug Application, priority review
Submission date	May 28, 2015
Applicant	Merck Sharp & Dohme Corp.
Brand name	ZEPATIER™
Generic name	Grazoprevir and elbasvir
Dosage form	Tablet for oral administration
Dosage strength	Fixed dose combination tablet containing 100 mg grazoprevir and 50 mg elbasvir
Proposed indication	Treatment of chronic hepatitis C virus genotypes 1, 4, or 6 infection in adults
Proposed dosing regimen	One tablet taken orally once daily with or without food <u>Treatment-naïve or prior relapsers</u> Genotype 1, 4: (b) (4) ZEPATIER 12 weeks Patients with history of (b) (4) Genotype 1b: ZEPATIER 12 weeks Genotype 1a, 4: (b) (4) ZEPATIER 16 weeks plus ribavirin
OCP division	Division of Clinical Pharmacology (DCP) 4
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1. EXECUTIVE SUMMARY

Merck Sharp & Dohme Corp is seeking approval for a fixed dose combination tablet containing two new molecular entities, 100 mg grazoprevir (GZR) and 50 mg elbasvir (EBR), for the treatment of chronic hepatitis C (CHC) virus genotypes 1, 4, or 6 infection in adults (proposed tradename: ZEPATIER). GZR is an inhibitor of hepatitis C virus NS3/4 protease and EBR is an inhibitor of hepatitis C virus NS5A protein. The recommended dosing regimen is to take one tablet orally once daily with or without food. The initial sponsor-proposed patient population and treatment duration is provided in Table 1.

Table 1. Proposed patient population and treatment duration for ZEPATIER

Patient Population	Treatment Regimen	Duration
Treatment-Naïve or Treatment-Experienced Relapsers		
Genotype 1, 4 (b) (4)	One tablet once daily	12 weeks (b) (4)
	(b) (4)	(b) (4)
Treatment-Experience		
Genotype 1b	One tablet once daily	12 weeks
Genotype 1a, 4 (b) (4)	One tablet once daily with ribavirin ¶, #	16 weeks

In clinical trials, the dose of ribavirin was weight-based administered in two divided doses with food. Refer to the ribavirin prescribing information

The consideration for approval is based on safety and efficacy data from 4 pivotal Phase 3 trials in a total of 1076 subjects: A ZEPATIER 12 week-regimen was evaluated in treatment-naïve genotype (GT) 1, 4, 6 patients with or without HIV-coinfection (PN061: C-EDGE COINFECTION and PN060: C-EDGE TN). ZEPATIER 12 or 16 week-regimens with or without ribavirin were evaluated in GT 1, 4, 6 patients with a history of pegylated-interferon (Peg-IFN) and ribavirin based treatment failure (PN068: C-EDGE TE). A ZEPATIER 12 week regimen was evaluated in GT-1 patients with severe chronic kidney disease (CKD; eGFR <30 mL/min/1.73 m²) or end-stage renal disease (ESRD) on dialysis (PN052: C-SURFER).

The following clinical pharmacology studies were conducted to support this NDA.

- Thirty-two *in vitro* studies determining the metabolic pathway, potential for drug interactions, and plasma protein binding of GZR and EBR
- Nine biopharmaceutics studies determining the pharmacokinetics of various formulations and food effects
- Five pharmacokinetic studies characterizing the pharmacokinetics of GZR and EBR in healthy volunteers and CHC patients, including mass balance trials

- Eight clinical pharmacology trials determining the effects of intrinsic factors on the pharmacokinetics of GZR and EBR including hepatic impairment, renal impairment, age and race
- Thirty-two drug interaction trials based on commonly used medications in the patient population and potential for drug interactions determined by *in vitro* studies
- Population pharmacokinetic studies and exposure-response relationship analyses for safety and efficacy and physiology-based pharmacokinetic studies
- Two TQT trials

1.1 Recommendations

The Office of Clinical Pharmacology finds that there is sufficient clinical pharmacology information for the approval of ZEPATIER pending labeling agreement with the applicant.

1.2 Phase 4 Commitments

The post-marketing commitments or requirements were under discussion at the time this review was completed.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Absorption, distribution, metabolism, and excretion

Following oral administration of ZEPATIER, GZR and EBR C_{max} were reached at 2 hours and 3 hours post-dose, respectively. Relative to the fasted state, the administration of a single dose of ZEPATIER with a high-calorie, high-fat (900 kcal, 500 kcal from fat) breakfast increased GZR AUC_{0-inf} and C_{max} by 1.5-fold and 2.8-fold, respectively, and decreased EBR AUC_{0-inf} and C_{max} by 11% and 15%, respectively, in healthy subjects. These changes are not considered clinically relevant and ZEPATIER can be taken with or without food. GZR and EBR are substrates of P-gp *in vitro*.

GZR and EBR are highly bound (98.8% and > 99.5%, respectively) to human plasma proteins. Both GZR and EBR bind to human serum albumin and α 1-acid glycoprotein. GZR is a substrate of OATP1B, thus significant distribution into liver is expected.

GZR and EBR are metabolized by CYP3A4 *in vitro*. For both drugs, approximately 20% of the dose administered was recovered in the form of oxidative metabolites in feces, but no circulating metabolites were detected in human plasma in mass balance trials. The primary route of excretion of both drugs is feces and less than 1% of the administered dose is excreted in urine. The mean elimination half-lives of GZR and EBR are approximately 31 hours and 24 hours, respectively, in HCV-infected patients.

In population pharmacokinetic analyses, the geometric mean of GZR AUC_{0-24} and C_{max} were 1860 nM•hr and 220 nM, respectively, and the geometric mean of EBR AUC_{0-24} and C_{max} were 2180 nM•hr and 137 nM, respectively, following GZR 100 mg and EBR 50 mg once daily administration in non-cirrhotic, HCV-infected subjects. GZR and EBR reached steady-state within 6 days following GZR 100 mg and EBR 50 mg once-daily administration.

Intrinsic factors

Hepatic impairment

GZR and EBR pharmacokinetics were evaluated in non-HCV-infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment. In addition, compensated cirrhotic (Child-Pugh A) CHC patients were included in Phase 2 and Phase 3 trials and population pharmacokinetic analyses were conducted.

GZR exposures (AUC_{24hr}) were increased by 1.7-fold, 4.8-fold and 11.7-fold, in non-HCV-infected subjects with mild, moderate, and severe hepatic impairment, respectively, as compared to matched healthy volunteers. In population pharmacokinetic analyses, GZR AUC_{0-24} was approximately 65% higher in patients with mild hepatic impairment compared to non-cirrhotic patients. The magnitude of the increased GZR exposure in patients with mild hepatic impairment is not considered clinically relevant. Significant increases in GZR exposure in subjects with moderate and severe hepatic impairment may increase the risk of ALT elevation, the exposure-dependent adverse event of interest for GZR.

EBR AUC_{0-inf} values were decreased by 40%, 28%, and 12% in non-HCV-infected subjects with mild, moderate, and severe hepatic impairment, respectively, as compared to matched healthy volunteers. However, no significant difference between subjects with mild hepatic impairment and with normal hepatic function was observed in population pharmacokinetic analyses.

In summary, ZEPATIER can be used in patients with mild hepatic impairment. ZEPATIER is not recommended in patients with moderate hepatic impairment and should be contraindicated in subjects with severe hepatic impairment due to significant increases in GZR exposure.

Renal impairment

GZR and EBR pharmacokinetics were evaluated in non-HCV-infected subjects with severe renal impairment ($eGFR < 30$ mL/min) and end-stage renal disease (ESRD; subjects on hemodialysis). In addition, CHC patients with severe renal impairment ($n=30$) and ESRD ($n=92$) were enrolled in a Phase 3 trial (PN052) and population pharmacokinetic analyses were conducted.

GZR and EBR AUCs were 65% and 86% higher in non-HCV-infected subjects with severe renal impairment as compared to matched healthy volunteers. No significant differences in EBR or GZR exposures were observed in non-HCV-infected subjects with ESRD receiving hemodialysis as compared to matched healthy volunteers. GZR and EBR were minimally eliminated by 4-hour hemodialysis. Similar results were observed in the population pharmacokinetic analyses and the changes are not considered clinically relevant. ZEPATIER can be used in patients with severe renal impairment or ESRD receiving hemodialysis.

Gender, age, and race

In population pharmacokinetic analyses, GZR AUCs were estimated to be 30% higher in females as compared to males, 50% higher in Asians as compared to White, and 20% higher in elderly (≥ 65 years old) as compared to young (< 65 years old) patients. Of note, the observed event rates of late AST/ALT

elevation were higher in Asians, elderly, or female patients as compared to White, young, or male patients, respectively. It is unclear to what extent the higher exposure is responsible for the higher adverse event rates.

Table 1.3.1 Observed rates of late AST/ALT elevation following 100 mg GZR administration in CHC patients

Population comparison	Observed AST/ALT elevation event rates
Female vs. Male	1.4% (11/791) vs. 0.23% (3/1296)
Asian vs. White	2.3% (4/175) vs. 0.8% (8/1579)
Elderly (65+) vs. Young	1.4% (3/224) vs. 0.6% (11/1863)

#The observed rates were calculated using data from any subject who received 100 mg GZR (\pm EBR, \pm Peg-IFN/ribavirin, \pm sofosbuvir) at least 8 weeks (PN003, PN035, PN038, PN039, PN047, PN048, PN052, PN058, PN059, PN060, PN061, PN068, and PN074).

In population pharmacokinetic analyses, EBR AUCs are estimated to be 50% higher in females as compared to males, 15% higher in Asians as compared to White, and 16% higher in elderly (\geq 65 years old) as compared to in young patients. These differences are not considered clinically relevant.

Patients

GZR exposure is approximately 2-fold higher in CHC patients as compared to healthy volunteers following 100 mg administration. EBR exposures at steady-state are comparable between healthy volunteers and patients following 50 mg administration.

Drug interactions

Potential for drug interactions based on *in vitro* study results

GZR is a substrate of P-gp, CYP3A4, OATP1B1, and OATP1B3. GZR inhibited CYP2C8 (IC_{50} :6 μ M), CYP3A4 (IC_{50} :73 μ M), OATP1B1 (IC_{50} :0.7 μ M), OATP1B3 (IC_{50} :1.1 μ M), BCRP (IC_{50} :12.5 μ M), BSEP (IC_{50} :0.15 μ M), MRP2 (IC_{50} :2.5 μ M), MRP3 (IC_{50} :3.8 μ M), and MRP4 (IC_{50} :1.0 μ M). EBR is a substrate of CYP3A4 and P-gp. EBR inhibited P-gp (IC_{50} :0.32 μ M), BCRP (IC_{50} :0.15 μ M) and OATP1B3 (IC_{50} :0.10 μ M). EBR or GZR did not induce CYP1A2, CYP2B6, or CYP3A4 in human hepatocytes.

In vivo drug interactions study results and clinical recommendations

The applicant conducted drug interaction studies based on *in vitro* study results or with commonly used drugs in the patient population. The study results and clinical recommendations are summarized as follows. Note that the clinical recommendations are the reviewer's recommendations, not the applicant's proposal. The recommendations were under discussion between the applicant and the review team when this review was written. The following list of interacting drugs and clinical recommendations does not include specific names of drugs that were not studied but anticipated to have drug interactions (e.g., Other OATP inhibitors or other strong CYP3A4 inducers).

1. Co-administration is contraindicated due to significant increases in GZR exposure, which may increase the risk of late AST/ALT elevation: atazanavir/ritonavir (ATV/r), lopinavir/ritonavir (LPV/r), cyclosporine (CsA), or other OATP1B inhibitors that may significantly increase GZR exposure.

Table 1.3.2 Effects of ATV/r, LPV/r, or CsA on the pharmacokinetics of GZR and EBR

Co-Administered Drug	Geometric Mean Ratio [90% CI] of GZR and EBR PK with/without Co-Administered Drug			
		AUC	C _{max}	C ₂₄
Atazanavir/ritonavir 300mg/100 mg QD	GZR	10.6 (7.78, 14.4)	6.24 (4.42, 8.81)	11.6 (7.96, 17.0)
	EBR	4.76 (4.07, 5.56)	4.15 (3.46, 4.97)	6.45 (5.51, 7.54)
Lopinavir/ritonavir 400 mg/100 mg BID	GZR	12.9 (10.3, 16.1)	7.31 (5.65, 9.45)	21.7 (13.00, 36.3)
	EBR	3.71 (3.05, 4.53)	2.87 (2.29, 3.58)	4.58 (3.72, 5.64)
Cyclosporine 400 mg single dose	GZR	15.2 (12.8, 18.0)	17.0 (12.9, 22.3)	3.39 (2.82, 4.09)
	EBR	1.98 (1.84, 2.13)	1.95 (1.84, 2.07)	2.21 (1.98, 2.47)

Note: the applicant proposed that the co-administration of these drugs with ZEPATIER is not recommended

2. Co-administration is not recommended due to significant increases in GZR exposure: ketoconazole or darunavir/ritonavir (DRV/r)

Table 1.3.3 Effects of ketoconazole or DRV/r on the pharmacokinetics of GZR and EBR

Co-Administered Drug	Geometric Mean Ratio [90% CI] of GZR and EBR PK with/without Co-Administered Drug			
		AUC	C _{max}	C ₂₄
Ketoconazole 400 mg QD	GZR	3.02 (2.42, 3.76)	1.13 (0.77, 1.66)	--
	EBR	1.80 (1.41, 2.29)	1.29 (1.00, 1.66)	1.89 (1.37, 2.60)
Darunavir/ritonavir 600 mg/100 mg QD	GZR	7.50 (5.92, 9.51)	5.27 (4.04, 6.86)	8.05 (6.33, 10.24)
	EBR	1.66 (1.35, 2.05)	1.67 (1.36, 2.05)	1.82 (1.39, 2.39)

Note: the applicant proposed that the drug interaction with ketoconazole is not clinically relevant.

3. Co-administration is contraindicated due to significant decreases in GZR or EBR exposures: efavirenz, rifampin and other strong CYP3A4 inducers

Table 1.3.4 Effects of rifampin or efavirenz on the pharmacokinetics of GZR and EBR

Co-Administered Drug	Geometric Mean Ratio [90% CI] of GZR and EBR PK with/without Co-Administered Drug (No Effect=1.00)			
		AUC	C _{max}	C ₂₄
Rifampin 600 mg QD	GZR	0.93 (0.75, 1.17)	1.16 (0.82, 1.65)	0.10 (0.07, 0.13)
Efavirenz 600 mg	GZR	0.17 (0.13, 0.24)	0.13 (0.09, 0.19)	0.31 (0.25, 0.38)

QD	EBR	0.46 (0.36, 0.59)	0.55 (0.41, 0.73)	0.41 (0.28, 0.59)
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Note: due to mixed effects of rifampin on OATP1B (inhibition) and CYP3A4 (induction) at steady-state of rifampin, a significant decrease was observed only in C₂₄, not in AUC and C_{max} of GZR. The applicant did not determine the effects of rifampin on the EBR exposure at the steady-state of rifampin but it is expected to be significantly decreased.

4. Dose adjustment of co-administrated drugs or close clinical monitoring is recommended:
atorvastatin, rosuvastatin and tacrolimus

Table 1.3.5 Effects of GZR and EBR on the pharmacokinetics of tacrolimus, atorvastatin, and rosuvastatin

Co-Administered Drug	GZR or/and EBR	Geometric Mean Ratio [90% CI] of Co-Administered Drug PK with/without GZR/EBR			Clinical recommendations
		AUC	C _{max}	C _{trough}	
Tacrolimus 2 mg single dose	GZR 200 mg + EBR 50 mg QD	1.43 (1.24, 1.64)	0.60 (0.52, 0.69)	1.70 (1.49, 1.94)	Frequent monitoring of tacrolimus whole blood concentrations, renal function and tacrolimus-related side effects are recommended upon initiating co-administration with ZEPATIER
Atorvastatin 10 mg single dose		1.94 (1.63, 2.33)	4.34 (3.10, 6.07)	0.21 (0.17, 0.26)	The dose of atorvastatin should not exceed a daily dose of 20 mg when co-administered with ZEPATIER
Rosuvastatin 10 mg single dose		2.26 (1.89, 2.69)	5.49 (4.29, 7.04)	0.98 (0.84, 1.13)	The dose of rosuvastatin should not exceed a daily dose of 10 mg when co-administered with ZEPATIER

Note: The applicant proposed that the increase in the tacrolimus exposure by ZEPATIER is not clinically relevant.

5. No clinically relevant drug interactions were observed

- Two-way drug interactions: dolutegravir, raltegravir, rilpivirine, mycophenolate mofetil, prednisone
- GZR or EBR as a victim: pantoprazole, phosphate binders (sevelamer, calcium carbonate)
- GZR or EBR as a perpetrator: oral contraceptives, pitavastatin, pravastatin, methadone, buprenorphine

Exposure-response relationship and dose selection

Grazoprevir

The Phase 1b GZR monotherapy dose ranging study (5172-P004) provided evidence that doses of 50 mg GZR and higher are on the plateau of the dose-response curve for HCV genotype 1 (GT1). The Phase 2 study (5172-P003) showed no dose-related differences in efficacy across doses ranging from 100 to 800 mg when GZR was co-administered with Peg-IFN and RBV (SVR12 was between 79.3% and 93.0%). ALT and/or AST elevation were observed after 4 or more weeks of treatment (referred to later in the

review as late ALT/AST elevations) disproportionately among subjects in 5172-P003 who received 200 mg, 400 mg, or 800 mg GZR, as compared to 100 mg. Due to the exposure-related increase in ALT/AST elevations on GZR treatment, further dosing of GZR in subsequent studies was capped at 100 mg QD (refer to clinical pharmacology review dated Sep 30, 2012). An evaluation of 25, 50 and 100 mg QD GZR in combination with Peg-IFN and RBV demonstrated similar SVR12 at 50 mg (21/25, 84%) and 100 mg (23/26, 89%), whereas a lower response was observed at the 25 mg dose (13/24, 54%). Based on all of these observations, 100 mg QD GZR was selected for further evaluation as the dose with the most appropriate balance of safety and efficacy for patients.

Elbasvir

The Phase 1b EBR monotherapy dose-ranging study (8742-P002) provided evidence that 50 mg EBR is associated with similar efficacy compared to 10 mg for GT1, but 50 mg EBR may provide more sustained suppression of GT1a compared to 10 mg. In the Phase 2 dose-ranging study (5172-P035), 50 mg QD EBR provided efficacy similar to that obtained with 20 mg QD EBR in a 12 week therapy with 100 mg QD GZR and RBV, with SVR12 rates of 100% (22/22) and >95% (23/24) observed at 20 and 50 mg, respectively. While the SVR12 response rates were similar between 20 mg QD and 50 mg QD EBR and there were also no dose-related toxicities identified for EBR, 50 mg of EBR was selected as the dose for further evaluation with 100 mg QD GZR so that there is a margin for potential decreases in EBR exposure without impacting efficacy.

Exposure-response Efficacy and Safety Analyses

An exposure-response analyses for efficacy was conducted using data from seven Phase 2/3 studies in which GZR and EBR were co-administered with and without RBV in patients infected with HCV GT1, 4, or 6. The analyses showed that GZR exposure was not a significant predictor of SVR12; however, EBR exposure was a significant predictor of SVR 12 with doses of 20 mg and 50 mg. Other significant predictors of treatment response were treatment duration, baseline log₁₀ HCV RNA, and presence of baseline resistance to NS5A inhibitors. Of these factors, the presence of baseline NS5A resistance was the most important predictor of treatment response.

The exposure-safety analysis used data from thirteen Phase 2/3 studies and included GZR doses from 25 to 800 mg QD and focused on incidents of late ALT/AST elevations. The exposure-response analyses show that occurrence of late ALT/AST elevation was correlated with GZR exposures. The predicted rate of late ALT/AST elevations in the reference population administered 100 mg GZR is approximately 0.5% which is in agreement with the observed rate of late ALT/AST elevations from patients in the reference population administered 100 mg GZR (0.5%; [7/1273]). The reference population consisted of non-Asian subjects without cirrhosis or severe chronic kidney disease (CKD). Increases in GZR exposure of 5-fold (dose of 200 mg) and ~13 to 14-fold (dose between 200 to 400 mg) relative to the exposures at a 100 mg GZR dose in the reference population correspond to predicted late ALT/AST elevation event rates of ~2% and ~5%, respectively.

Table 2.1.1. Composition of ZEPATIER

Components	Weight (mg)
Grazoprevir	100
Elbasvir	50
Copovidone	(b) (4)
Hydromellose (b) (4)	
Sodium lauryl sulfate	
Vitamin E polyethylene glycol succinate	
Cellulose, microcrystalline	
Mannitol	
Lactose, monohydrate	
Croscarmellose sodium	
Sodium chloride	
Magnesium stearate	
(b) (4) colloidal (b) (4)	
Film coat (b) (4)	
Final weight	(b) (4)

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

GZR inhibits the NS3/4A protease complex and EBR inhibits the NS5A protein of hepatitis C virus. The proposed indication is treatment of chronic hepatitis C infection.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The recommended dosing regimen is to take one ZEPATIER tablet (containing GZR 100 mg and EBR 50 mg) orally once daily with or without food. The original sponsor-proposed patient population and treatment duration is provided in Table 2.1.2.

Table 2.1.2. Proposed patient population and treatment duration for ZEPATIER

Patient Population	Treatment Regimen	Duration
Treatment-Naïve or Treatment-Experienced Relapsers		
Genotype 1, 4 (b) (4)	One tablet once daily	12 weeks (b) (4) (b) (4)
Treatment-Experienced*		
Genotype 1b	One tablet once daily	12 weeks
Genotype 1a, 4, (b) (4)	One tablet once daily with ribavirin †, #	16 weeks

In clinical trials, the dose of ribavirin was weight-based administered in two divided doses with food. Refer to the ribavirin prescribing information

The inter-disciplinary review team has identified the following issues with respect to the proposed dosing regimen.

(b) (4)

- The review team also has identified that

(b) (4)

A combination of longer duration (16 weeks) and the use of ribavirin lead to greater benefit in this patient population. Therefore, the review team is considering recommending the 16 week plus ribavirin regimen based on NS5A polymorphism screening results for all GT1a patients and treatment-experienced GT1b patients.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

CLINICAL PHARMACOLOGY STUDIES

An extensive range of clinical studies was conducted to characterize the pharmacokinetics of GZR and EBR. Please refer to the Executive Summary section for a full list of clinical pharmacology studies.

PIVOTAL CLINICAL TRIALS

Four pivotal trials were conducted to support the proposed indication. The study design, population, dosing regimens and key efficacy results are summarized in Table 2.2.1 (treatment-naïve patients) and 2.2.2 (patients who failed prior Peg-IFN/ribavirin-based treatment).

Table 2.2.1. Summary of pivotal trials in treatment-naïve patients

Trial	C-EDGE TN (PN060)	C-EDGE COINFECTION (PN061)	C-SURFER (CKD stage 4-5) (PN052)
Design	Randomized, parallel-group, double-blind, placebo-controlled trial in treatment-naïve mono-infected patients with or without cirrhosis	An open-label trial in treatment-naïve HIV co-infected patients with or without cirrhosis	A randomized placebo controlled trial in GT-1 subjects with advanced chronic kidney disease
Regimen	GZR/EBR 12 Weeks N=316	GZR/EBR 12 Weeks N=218	GZR/EBR 12 Weeks N=101
Overall SVR	95% (299/316)	95% (207/218)	95% (96/101)
Outcome for subjects without SVR			
On-treatment	<1% (1/316)	0% (0/218)	0% (0/101)

Virologic Failure			
Relapse	4% (12/316)	3% (7/218)	0% (0/101)
Other	1% (4/316)	2% (4/218)	5% (5/101)
SVR by Genotype			
GT 1a	92% (144/157)	94% (136/144)	98% (52/53)
GT 1b	98% (129/131)	96% (43/45)	92% (44/48)
GT 4	100% (18/18)	96% (27/28)	-----
(b) (4)			
SVR by Cirrhosis status			
No	94% (231/246)	94% (172/183)	95% (92/97)
Yes	97% (68/70)	100% (35/35)	100% (4/4)

Table 2.2.2 Summary of the pivotal trial in treatment-experienced patients [who failed prior peg-IFN with ribavirin (RBV)]

PN068 (C-EDGE TE): a randomized, parallel-group, open label trial of ZEPATIER administered once daily with or without ribavirin for 12 or 16 weeks to subjects with hepatitis C virus genotype (GT) 1, 4, or 6 infection, with and without compensated cirrhosis, who failed prior treatment with pegylated interferon (Peg-IFN) and ribavirin.				
Regimen	GZR/EBR 12 weeks N=105	GZR/EBR + RBV 12 weeks N=104	GZR/EBR 16 weeks N=105	GZR/EBR + RBV 16 weeks N=106
Overall SVR	92% (97/105)	94% (98/104)	92% (97/105)	97% (103/106)
Outcome for subjects without SVR				
On-treatment Virologic Failure	0% (0/105)	0% (0/104)	3% (3/105)	0% (0/106)
Relapse	6% (6/105)	6% (6/104)	4% (4/105)	0% (0/106)
Other	2% (2/105)	0% (0/104)	1% (1/105)	3% (3/106)
SVR by Genotype				
GT 1a	90% (55/61)	93% (56/60)	94% (45/48)	95% (55/58)
GT 1b	100% (35/35)	97% (28/29)	96% (46/48)	100% (38/38)
GT 4	78% (7/9)	93% (14/15)	60% (3/5)	100% (8/8)
(b) (4)				
SVR by Cirrhosis status				
No	94% (64/68)	97% (67/69)	93% (62/67)	96% (66/69)
Yes	89% (33/37)	89% (31/35)	92% (35/38)	100% (37/37)
Response to Prior HCV Therapy				
On-treatment Virologic Failure	89% (62/70)	91% (60/66)	93% (62/67)	95% (63/66)
Relapser	100% (35/35)	100% (38/38)	92% (35/38)	100% (40/40)

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD) and how are they measured in clinical pharmacology and clinical studies?

The sustained virologic response 12 weeks after stopping treatment (SVR12) was used as the primary endpoint of efficacy. SVR12 has been demonstrated to be a valid surrogate to establish the efficacy of drugs for the treatment of chronic hepatitis C infection. It is the recommended primary endpoint in the Draft Guidance for Industry Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment, published in Oct 2013.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The active moieties in the plasma are GZR and EBR. Both moieties were measured using validated analytical methods (LC/MS/MS).

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *efficacy*?

An exposure-response analyses for efficacy was conducted using data from seven Phase 2/3 studies in which GZR and EBR were co-administered with and without RBV in patients infected with HCV GT1, 4, or 6. The independent variable in these analyses was GZR or EBR exposure (AUC_{0-24h} or C_{trough}) and the dependent variable was SVR12. Patients in these studies were administered GZR 100 mg QD and EBR 20 or 50 mg QD. The analyses showed that exposure parameters for GZR (AUC_{0-24h} or C_{trough}) were not significant predictors of SVR12 ($P=0.574$ for AUC_{0-24h} , $P=0.306$ for C_{trough}). In contrast, EBR exposure was a significant predictor of SVR 12 ($P<0.001$ for both). In addition, three other significant covariates were identified for the exposure-response relationship analyses, including treatment duration, baseline log₁₀ HCV RNA, and presence or absence of baseline resistance to NS5A inhibitors. Figure 2.2.1 displays the predicted SVR12 rate versus GZR and EBR AUC_{0-24h} deciles. The data is further divided by those subjects with and without baseline NS5A resistance polymorphism, which was the most significant predictor of treatment outcomes.

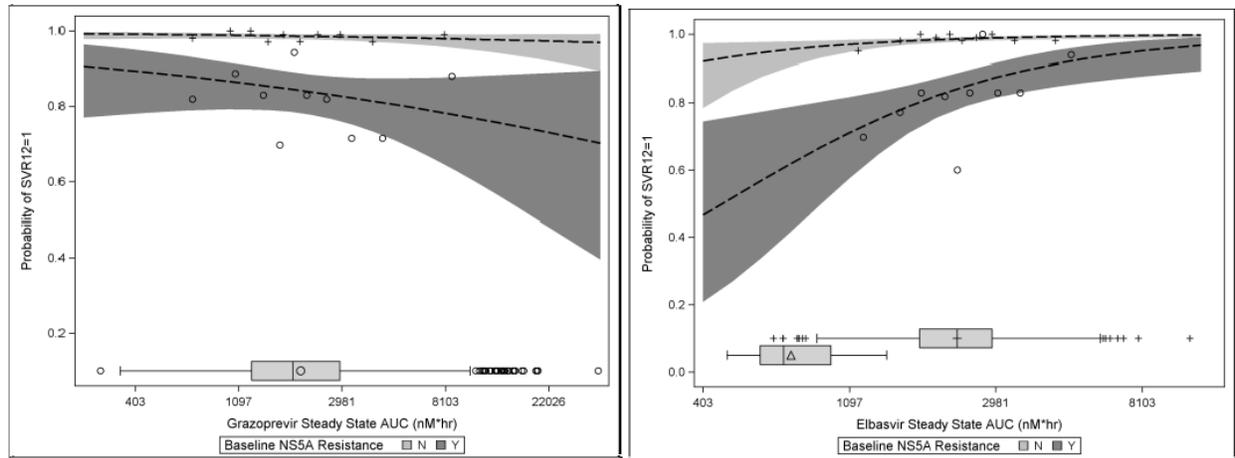


Figure 2.2.1 Predicted SVR12 versus GZR (left) and EBR (right) AUC_{0-24h} based on Observations from Phase 2 and Phase 3 Studies. Cross and circles denote subjects without and with baseline NS5A resistance, respectively. Boxplots at the bottom of each figure depict exposures for 100 mg GZR (left) and 20 mg (triangle, right) and 50 mg (cross, right) EBR.

Source: Applicant's exposure-response analysis for efficacy report, Page 36, Figure 6.

The exposure-response curves for GZR have an inverted slope, trending towards a lower SVR12 for higher GZR exposures. However, this is only evident in the subset of patients with baseline NS5A mutations and has a wide uncertainty around the prediction, suggesting that the relationship may actually be flat. The previous Phase 2 also demonstrated that 100 mg GZR or higher dose was saturating SVR12. Thus, the flat exposure-efficacy relationship for GZR would be expected. The exposure-response relationship for EBR suggests that SVR12 response rate is near 100% across the entire EBR exposure range for patients without baseline NS5A resistance, though there was a concentration-dependent SVR12 rate for the patients with baseline NS5A resistance. The predicted SVR12 rate for 20 mg was approximately 60%, while the predicted SVR12 rate was approximately 80% for 50 mg in patients with baseline NS5A resistance. These results support the proposed dose of 50 mg for EBR, (b) (4)

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

GZR/EBR has a generally favorable safety profile with common adverse events of fatigue, headache, and nausea. Late ALT/AST elevation events, a specific measure of GZR-related hepatic safety, occurred in a dose-related manner. The exposure-safety analysis used data from thirteen Phase 2/3 studies and included GZR doses from 25 to 800 mg QD and focused on incidents of late ALT/AST elevations. In this analysis, late ALT/AST elevations were defined as an ALT/AST elevation ≥ 5 -fold upper limit of normal (ULN) occurring 4 or more weeks into treatment in subjects who first achieved an on-treatment nadir ALT/AST \leq ULN after 2 to 4 weeks of treatment. Liver enzyme elevations is an expected adverse event associated with GZR treatment and observation of such events was the rationale behind halting higher dose arms with the compound in an earlier Phase 2 trial. As expected, the exposure-response analyses show that

occurrence of late ALT/AST elevation was correlated with GZR exposures. No other significant covariates besides GZR exposures were identified as predictors of late ALT/AST elevations in the analysis. A total of 25/2405 (1.0%) subjects in all Phase 2/3 studies had late ALT/AST elevations. Of the 25 subjects with late ALT/AST elevations, 2 (8.0%) had the initial detection at week 6 of treatment, 10 (40.0%) had the initial detection at week 8 of treatment, 7 (28.0%) had the initial detection at week 10 of treatment, 5 (20.0%) had the initial detection at week 12 of treatment, and 1 (4.0%) subject had the initial detection after 12 weeks of treatment (e.g., off treatment). Of the 25 subjects with a late ALT/AST elevation, 11 (44.0%) experienced resolution within 2 weeks, 11 (44.0%) experienced resolution between 2 to 4 weeks, and 1 (4.0%) experienced resolution after 4 to 6 weeks, and 2 (8.05%) experienced resolution after 6 weeks. The median (range) duration of the event was 14 (3 to 44) days. Of the 25 subjects, 20 did not discontinue study medication. Among the 5 subjects who discontinued study medication, 1 experienced resolution within 2 weeks, and 4 experienced resolution between 2 and 4 weeks.

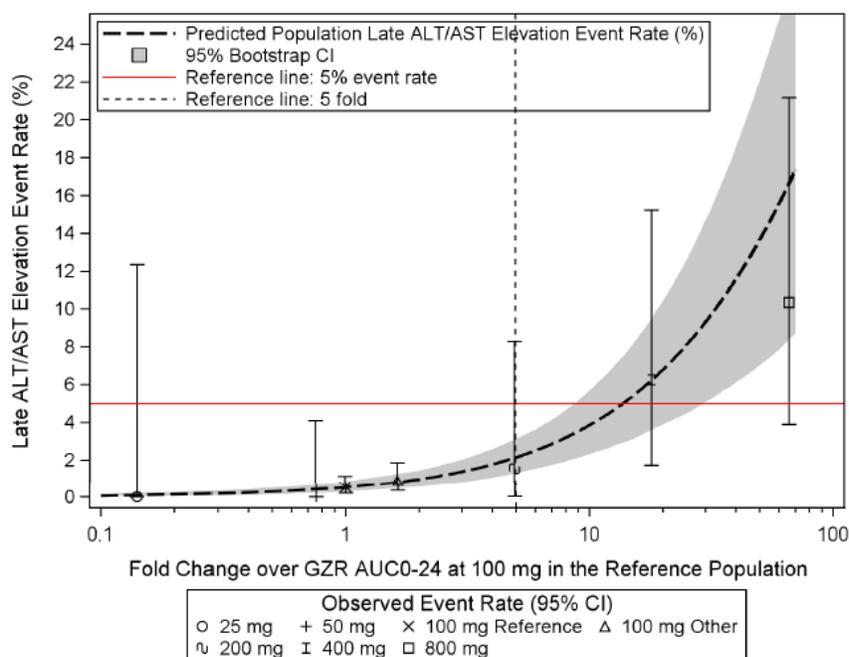


Figure 2.2.2 Predicted Late ALT/AST Elevation Event Rate versus Fold Change over GZR Steady State AUC₀₋₂₄. A Fold-Change of 1 Reflects Exposures for GZR 100 mg QD in the Reference Population. This reference population included non-cirrhotic, non-severe CKD, non-Asian HCV-infected patients in the 100 mg dosing arms of the Phase 2/3 studies/arms included in this analysis.
Source: Applicant’s exposure-response analysis for safety report, Page 47, Figure 8.

Figure 2.2.2 displays the relationship between predicted late ALT/AST elevations versus fold change in GZR exposure at the 100 mg QD dose in the reference population. Also shown are the observed event rates at various GZR doses and the corresponding fold-change in exposure (AUC₀₋₂₄) relative to the reference population. The predicted rate of late ALT/AST elevations in the reference population at a 100

mg GZR dose is approximately 0.5%, which is consistent with the observed rate from the Phase 3 studies. The exposure-response relationship shows 5-fold (dose of 200 mg) and ~13 to 14-fold (dose between 200 to 400 mg) increases in GZR exposure relative to the exposures at a 100 mg in the reference population correspond to a predicted event rate of Late ALT/AST Elevation Events of ~2% and ~5%, respectively.

2.2.4.3 Are the proposed comparability bounds for GZR and EBR acceptable based on exposure-response relationship for efficacy and safety?

Comparability bounds refers to a range of exposures that would be expected to have comparable safety and efficacy relative to either GZR exposure at a clinical dose of 100 mg QD or EBR exposure at a clinical dose of 50 mg QD in HCV-infected patients. A lower bound of (b) (4) for GZR is proposed based on the ratio of steady state GZR AUC values at 50 mg observed in 5172-P038 relative to 100 mg in a pooled non-cirrhotic, non-Japanese, non-CKD population. In the study of 5172-P038, similar SVR12 at 50 mg (21/25, 84%) and 100 mg (23/26, 89%) was demonstrated. An upper bound (b) (4) for GZR is proposed by the Applicant based on the relationship between GZR exposure and late ALT/AST elevations, as described in section 2.2.4.2. The clinical pharmacology review team conducted an independent assessment of these proposed bounds.

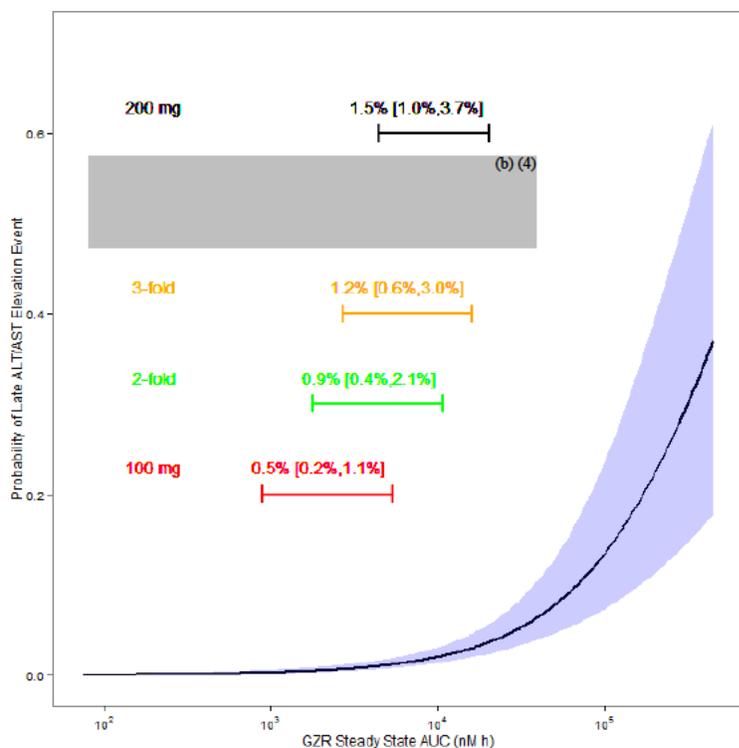


Figure 2.2.3 Predicted Late ALT/AST Elevation Event Rate versus GZR steady state AUC based on data from Applicant's exposure-safety analysis

Source: Reviewer's independent analysis

Figure 2.2.3 displays the exposure-response relationship between late ALT/AST elevations and GZR exposure. The red line represents the 90% prediction interval of GZR exposure covered by a dose of 100

mg and the number above the line shows the median (90%) predicted safety event rate for those exposures. The green and yellow bars represent a 2- and 3-fold increase in GZR exposure, respectively, compared to that of 100 mg. The results indicate that a 2-fold or 3-fold increase in exposure would result in safety event rate lower than 1.2% with upper bound less than 3%. These exposures may be attained by certain sub-populations (women, Asians, cirrhotic) of HCV-infected patients administered GZR 100 mg QD, for which higher event rates of late ALT/AST elevations were also observed. The clinical pharmacology review team considers a 3-fold upper bound as more appropriate for GZR and has proposed dose adjustments for certain intrinsic and extrinsic factors based on this boundary. For EBR, a lower bound of 0.5 is supported by the evidence that similar efficacy would be achieved when the EBR AUC associated with a 50 mg dose is reduced by 50% when dosed in combination with 100 mg GZR. An upper bound of 2.0 is proposed based on clinical experience with EBR, indicating there is no evidence of increased adverse events with EBR exposures up to ~2-fold higher than the average exposure at 50 mg QD.

2.2.4.4 Does this drug prolong the QT or QTc interval?

Neither of the drugs prolongs the QT or QTc interval. Following the administration of a single oral dose of 1600 mg GZR in 41 healthy volunteers, the upper limit of the 90% for placebo corrected QTcF change from baseline did not exceed 10 msec. The maximum mean difference from placebo in QTcF change from baseline was -0.48 msec (90% CI: -2.54 to 1.58). Following the administration of a single oral dose of 700 mg EBR in 42 healthy volunteers, the upper limit of the 90% for placebo corrected QTcF change from baseline did not exceed 10 msec. The maximum mean difference from placebo in QTcF change from baseline was -0.856 msec (90% CI: -1.06 to 2.78). Please refer to QT-IRT individual study review.

2.2.4.5 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes, the dose and dosing regimen proposed by the applicant are appropriate based on the known exposure-response relationship for safety and efficacy. Refer to 2.1.3 regarding the dosing regimen issues for certain genotypes that are currently under discussion.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

GZR and EBR pharmacokinetics (intensive PK sampling) were evaluated in non-cirrhotic patients in PN004 (GZR) and PN002 (EBR) (Tables 2.2.3-2.2.4). Please refer to subsequent sections for detailed discussions on PK differences in patients as compared to healthy volunteers, dose proportionality, time-dependency, and accumulation ratio. The steady-state pharmacokinetic parameters of GZR and EBR estimated from population pharmacokinetics using Phase 2 and Phase 3 trial data are summarized in Table 2.2.5.

Table 2.2.3 GZR pharmacokinetic parameters following once daily administration of GZR 10- 800 mg for 7 days in non-cirrhotic CHC patients (PN5172-004)

Pharmacokinetic Parameter	Dose (mg)	Day 1		Day 7		Day 7/Day 1 GMR (90% CI)	rMSE ¹
		N ²	GM (95% CI)	N ²	GM (95% CI)		
AUC ₀₋₂₄ (µM·hr) [†]	10	5	0.0159 (0.00804, 0.0313)	5	0.0628 (0.0318, 0.124)	3.96 (2.50, 6.25)	0.433
	30	5	0.0770 (0.0390, 0.152)	5	0.260 (0.132, 0.513)	3.37 (2.14, 5.33)	
	50	5	0.134 (0.0679, 0.265)	5	0.419 (0.212, 0.827)	3.12 (1.98, 4.93)	
	100	10	0.492 (0.304, 0.796)	10	1.16 (0.716, 1.87)	2.36 (1.70, 3.25)	
	200	10	0.965 (0.596, 1.56)	10	3.21 (1.98, 5.19)	3.33 (2.41, 4.60)	
	400	10	8.04 (4.97, 13.0)	10	18.2 (11.2, 29.4)	2.26 (1.64, 3.13)	
	600	10	17.2 (10.6, 27.8)	10	41.9 (25.9, 67.7)	2.44 (1.76, 3.37)	
	800	20	31.7 (22.6, 44.6)	18	72.5 (51.1, 103)	2.29 (1.80, 2.90)	
C _{max} (µM) [†]	10	5	0.00136 (0.000672, 0.00274)	5	0.00377 (0.00186, 0.00761)	2.77 (1.56, 4.93)	0.544
	30	5	0.0161 (0.00796, 0.0325)	5	0.0235 (0.0116, 0.0474)	1.46 (0.82, 2.59)	
	50	6	0.0134 (0.00704, 0.0254)	5	0.0430 (0.0216, 0.0855)	3.22 (1.83, 5.65)	
	100	10	0.0842 (0.0512, 0.138)	10	0.141 (0.0859, 0.232)	1.68 (1.12, 2.52)	
	200	10	0.161 (0.0978, 0.264)	10	0.684 (0.416, 1.12)	4.25 (2.83, 6.38)	
	400	10	1.68 (1.02, 2.76)	10	3.38 (2.06, 5.56)	2.02 (1.34, 3.03)	
	600	10	3.18 (1.93, 5.23)	10	7.69 (4.68, 12.6)	2.42 (1.61, 3.63)	
	800	20	5.85 (4.11, 8.31)	18	11.3 (7.81, 16.2)	1.92 (1.43, 2.60)	
C ₂₄ (nM) [†]	10	5	0.490 (0.248, 0.971)	5	2.41 (1.22, 4.78)	4.92 (3.44, 7.04)	0.339
	30	5	2.03 (1.03, 4.01)	5	7.20 (3.64, 14.2)	3.55 (2.48, 5.08)	
	50	5	4.14 (2.09, 8.19)	5	12.7 (6.40, 25.1)	3.06 (2.14, 4.37)	
	100	10	11.3 (6.99, 18.3)	10	20.1 (12.4, 32.6)	1.78 (1.38, 2.29)	
	200	10	13.5 (8.34, 21.9)	10	22.2 (13.7, 35.9)	1.64 (1.28, 2.11)	
	400	10	43.8 (27.0, 71.0)	10	70.2 (43.3, 114)	1.60 (1.25, 2.07)	
	600	10	70.9 (43.8, 115)	10	93.2 (57.6, 151)	1.31 (1.02, 1.69)	
	800	20	96.9 (68.9, 136)	18	174 (123, 247)	1.80 (1.49, 2.17)	
T _{max} (hr) [‡]	10	5	4.00 (2.02, 6.00)	5	2.00 (2.00, 12.00)		
	30	5	2.00 (1.00, 3.00)	5	2.00 (0.50, 3.00)		
	50	6	2.00 (1.00, 2.00)	5	2.00 (0.50, 3.00)		
	100	10	2.50 (1.00, 4.00)	10	2.50 (1.00, 4.03)		
	200	10	2.50 (1.00, 4.00)	10	2.50 (1.00, 4.00)		
	400	10	3.00 (2.00, 6.00)	10	3.00 (2.00, 8.00)		
	600	10	3.00 (1.00, 4.00)	10	3.00 (2.00, 4.00)		
	800	20	4.00 (3.00, 8.00)	18	4.00 (2.00, 6.00)		
Apparent t _{1/2} (hr) [§]	10			5	46.19 (36.50)		
	30			5	45.31 (26.35)		
	50			5	37.62 (38.09)		
	100			10	31.37 (33.71)		
	200			10	30.12 (30.91)		
	400			10	31.42 (24.60)		
	600			10	26.71 (36.34)		
	800			18	30.56 (25.01)		

[†]Geometric mean and geometric mean ratio back-transformed from the linear mixed effects model analyzed on natural log scale.
[‡]Median (minimum, maximum) reported for T_{max}.
[§]Geometric mean and percent geometric CV reported for apparent t_{1/2}.
¹rMSE: Square root of mean squared error (residual error) from the linear mixed effect model. rMSE*100% approximates the within-patient % CV on the raw scale.
Pharmacokinetic data from GT1 and GT3 HCV-infected patients were pooled for analysis.
One patient (GT1, 30 mg) had BLOQ value for Day 1 C₂₄, and this value was imputed with 0.5*LOQ for statistical model based analysis (LOQ = 1.30 nM).
²One patient (GT1, 50 mg) was discontinued from the study on Day 1, and only had Day 1 C_{max} and T_{max} reported. One (1) patient (GT1, 800 mg) did not take the Day 7 dose, and his Day 7 pharmacokinetic parameters values were not included in the analysis. One (1) patient (GT3, 800 mg) was discontinued from the study on Day 5 and therefore had no Day 7 pharmacokinetic parameter values.

Data Source: [16.4]

Formulation used in this study: MK05172-FFP (Fit-for-Purpose)

Table 2.2.4 EBR pharmacokinetic parameters following once daily administration of EBR 50 mg for 5 days in non-cirrhotic CHC patients (PN8742-002)

Pharmacokinetic Parameter	Dose (mg)	Day 1		Day 5		Day 5/Day 1		rMSE [‡]
		N	GM (95% CI)	N	GM (95% CI)	N	GMR (90% CI)	
AUC _{0-24hr} (hr*µM) [†]	5	5	0.101 (0.0596, 0.172)	5	0.155 (0.0909, 0.263)	5	1.53 (0.94, 2.47)	0.452
	10	15	0.0770 (0.0567, 0.105)	15	0.149 (0.110, 0.203)	15	1.94 (1.47, 2.56)	
	50	15	0.719 (0.529, 0.977)	15	1.36 (1.00, 1.85)	15	1.89 (1.43, 2.50)	
	100	5	1.41 (0.831, 2.40)	5	2.08 (1.22, 3.53)	5	1.47 (0.91, 2.38)	
C _{max} (µM) [†]	5	5	0.00962 (0.00542, 0.0171)	5	0.0126 (0.00711, 0.0224)	5	1.31 (0.75, 2.30)	0.525
	10	15	0.00608 (0.00436, 0.00847)	15	0.0109 (0.00779, 0.0151)	15	1.79 (1.29, 2.47)	
	50	15	0.0635 (0.0456, 0.0884)	15	0.106 (0.0758, 0.147)	15	1.66 (1.20, 2.30)	
	100	5	0.133 (0.0749, 0.236)	5	0.170 (0.0958, 0.302)	5	1.28 (0.73, 2.24)	
C _{24 hr} (nM) [†]	5	5	2.37 (1.44, 3.90)	5	3.89 (2.36, 6.41)	5	1.64 (1.07, 2.50)	0.396
	10	15	2.21 (1.66, 2.95)	15	4.08 (3.06, 5.44)	15	1.84 (1.44, 2.36)	
	50	15	18.1 (13.6, 24.1)	15	34.3 (25.7, 45.8)	15	1.90 (1.49, 2.42)	
	100	5	36.9 (22.4, 60.7)	5	56.2 (34.1, 92.5)	5	1.52 (1.00, 2.33)	
T _{max} (hr) [‡]	5	5	2.00 (2.00, 5.00)	5	3.00 (2.00, 5.00)			
	10	15	3.00 (2.00, 6.00)	15	2.13 (2.00, 6.00)			
	50	15	4.00 (2.00, 8.00)	15	3.00 (2.00, 5.00)			
	100	5	4.00 (2.00, 5.00)	5	3.00 (2.00, 4.00)			
Apparent t _{1/2} (hr) [§]	5			5	20.49 (11.47)			
	10			15	20.05 (12.81)			
	50			15	23.69 (24.71)			
	100			5	23.99 (12.60)			

[†]Geometric mean and geometric mean ratio back-transformed from the linear mixed effects model analyzed on natural log scale.
[‡]Median (minimum, maximum) reported for T_{max}.
[§]Geometric mean and percent geometric CV reported for apparent t_{1/2}.
[‡]rMSE: Square root of mean squared error (residual error) from the linear mixed effect model. rMSE*100% approximates the within-subject % CV on the raw scale.
Pharmacokinetic data from GT1, GT1a and GT3 HCV infected patients were pooled for analysis.

Formulation used in this study: MK-8742-FFP (Fit-for-Purpose)

Table 2.2.5 Steady-state GZR and EBR pharmacokinetic parameters in non-cirrhotic CHC patients following once daily administration of GZR 100 mg and EBR 50 mg

PK parameter	Grazoprevir	Elbasvir
AUC _{24hr} (µM·hr)	1.86 (1.83-1.99)	2.18 (2.13-2.23)
C _{max} (µM)	0.22 (0.21-0.23)	0.137 (0.133-0.140)
C ₂₄ (nM)	23.4 (23.2-25.9)	54.9 (53.6-56.2)

Data expressed as geometric mean (90% CI). Formulations used in 3 trials: FDC (fixed dose combination products) except PN052.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Grazoprevir

GZR exposure is approximately 2-fold higher in non-cirrhotic CHC patients as compared to healthy volunteers. This was observed following a single dose of GZR 100 mg administration under fasted conditions (Table 2.2.6). For this reason, GZR 200 mg was administered in healthy volunteers for most

drug interaction studies to match GZR exposures to those observed in CHC patients following administration of 100 mg.

Table 2.2.6 GZR pharmacokinetic parameters following once daily GZR 100 mg administration (FFP formulation) under fasted conditions

Study	Population	Day	AUC _{0-24hr} $\mu\text{M}\cdot\text{hr}$	C _{max} μM	C _{24hr} nM
PN001 (n=6)	Healthy male volunteers	Day 1	0.238 (0.136-0.417)	0.0244 (0.0126-0.0740)	6.71 (4.79-9.42)
		Day 10	0.713 (0.407-1.25)	0.0739 (0.0381-0.143)	13.8 (9.86-19.4)
PN004 (n=10)	CHC male patients	Day 1	0.492 (0.304-0.796)	0.0842 (0.0512-0.138)	11.3 (6.99-18.3)
		Day 7	1.16 (0.716-1.87)	0.141 (0.0859-0.232)	20.1 (12.4-32.6)

Data expressed as geometric mean (95% CI). A FFP (Fit-for-Purpose) formulation was used in this trial.

Elbasvir

EBR exposures at steady-state are comparable between healthy volunteers and patients following 50 mg QD administration. In patients, the geometric mean of AUC_{24hr} at steady-state was 2.18 $\mu\text{M}\cdot\text{hr}$ (90% CI: 2.13-2.23) based on population pharmacokinetic analyses. In healthy volunteers, geometric mean values of AUC_{24hr} at steady-state following 50 mg QD administration ranged from 2.14 to 2.86 $\mu\text{M}\cdot\text{hr}$ (study 5172-053, 054, 057, 073). Of note, more direct comparison (i.e., intensive PK sampling in healthy volunteers and CHC patients following EBR administration of the same dose and formulation) is not feasible due to significant inter- and intra-study variability in the EBR pharmacokinetics in the early phase of the development.

2.2.5.3 What are the characteristics of drug absorption?

Grazoprevir

Following oral administration, GZR reaches C_{max} approximately 2 hours post-dose. GZR is a substrate of P-gp *in vitro*. However, the role of P-gp for GZR intestinal transport appears to be minimal based on a drug interaction study comparing the effects of intravenous and oral rifampin on GZR exposure; a single oral dose of rifampin (an indicator of hepatic OATP1B, intestinal BCRP and P-gp involvement) increased GZR C_{max} and AUC_{inf} by 6.5-fold and 8.4-fold, respectively. A single intravenous dose of rifampin (an indicator of hepatic OATP1B involvement without inhibition of intestinal transporters) increased GZR C_{max} and AUC_{inf} by 10.9-fold and 10.2-fold, respectively.

Elbasvir

Following oral administration, EBR reaches C_{max} approximately 3 hours post-dose. EBR is a substrate of P-gp *in vitro* and a single oral dose of rifampin and cyclosporine increased EBR exposures (AUC) by 1.17-fold and 1.98-fold, respectively.

Effects of acid reducing agents on the absorption of GZR and EBR

Both GZR and EBR exhibit pH-dependent solubility thus the applicant conducted drug interaction trials with the acid-reducing agents, pantoprazole and famotidine. Acid reducing agents did not alter GZR absorption. The effects of acid reducing agents on the absorption of EBR are formulation-dependent; pantoprazole and famotidine did not alter the pharmacokinetics of EBR following single dose EBR administration as the FDC2 formulation (identical to the to-be-marketed formulation except the color

coat). However, famotidine decreased EBR AUC_{inf} by 53% following a single dose of the EBR-FFP formulation (formulation used in the early phase of the development).

2.2.5.4 What are the characteristics of drug distribution?

GZR

The plasma protein binding of GZR is approximately 98-99% over the concentration range of 0.1 to 10 μM *in vitro*. GZR binds to albumin and α 1-acid glycoproteins. Following the oral administration of 100 mg GZR, the apparent volume of distribution at steady state was approximately 1250 L in CHC patients as estimated from the population pharmacokinetic analysis.

Elbasvir

The protein binding of EBR is > 99.5% over the concentration range of 0.1 to 10 μM *in vitro*. EBR binds to albumin and α 1-acid glycoproteins. Following the oral administration of 50 mg EBR, the apparent volume of distribution at steady state was approximately 680 L in CHC patients as estimated from the population pharmacokinetic analysis.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Both GZR and EBR are primarily eliminated by the hepatic route. Following the oral administration of a single dose of radiolabeled GZR 200 mg or EBR 50 mg in healthy volunteers, more than 90% of the administered radioactivity was recovered in feces and less than 1% of the radioactivity was recovered in urine.

2.2.5.6 What are the characteristics of drug metabolism?

For both drugs, oxidative metabolites were mainly formed by CYP3A4 *in vitro*. The parent drugs (GZR and EBR) were the major contributor to total plasma radioactivity and no circulating metabolites in human plasma were detected in mass balance trials. For both drugs, approximately 20% of the dose administered was recovered in the form of oxidative metabolites in feces.

Fig 2.2.4 Proposed biotransformation pathway of GZR in humans

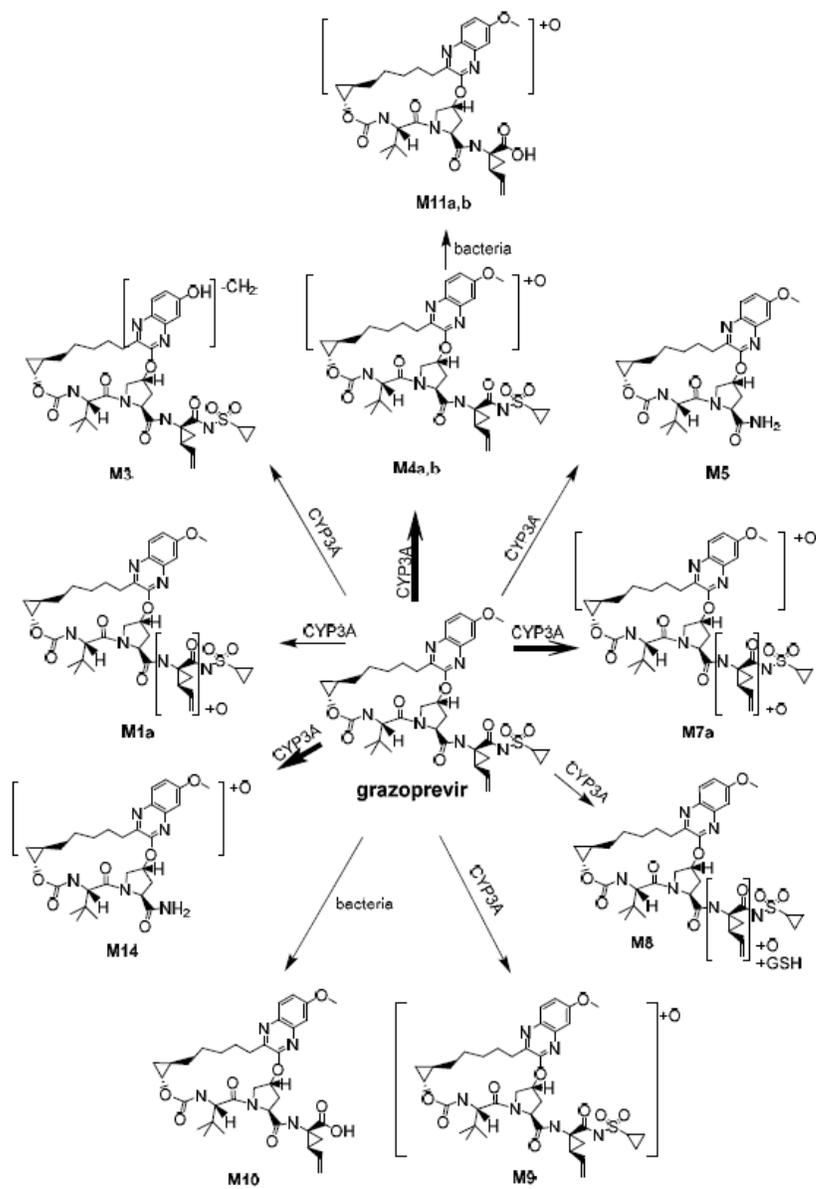
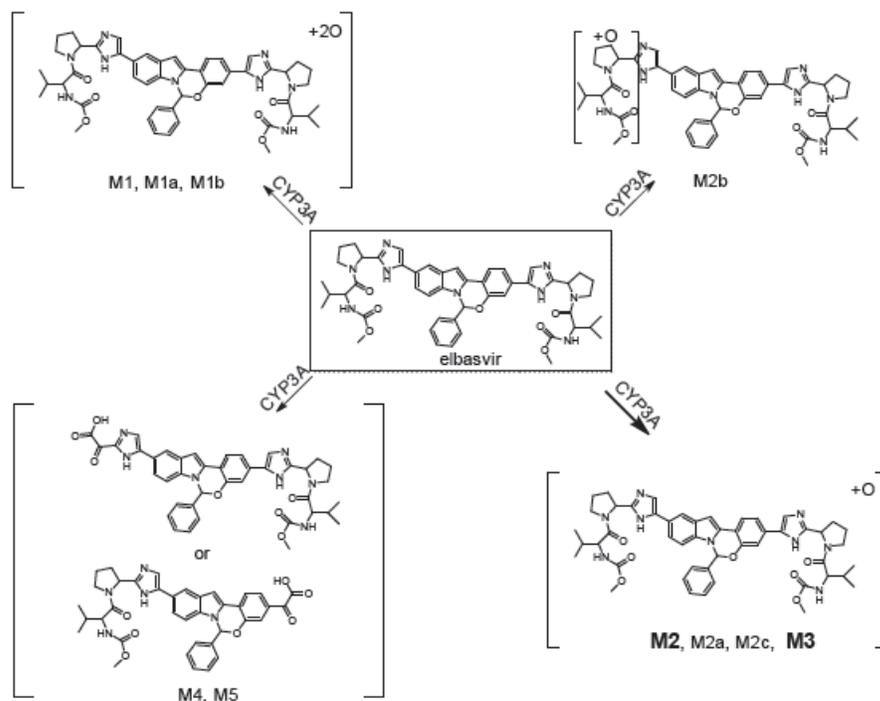


Fig 2.2.5 Proposed biotransformation pathway of EBR in humans



2.2.5.7 What are the characteristics of drug excretion?

Refer to 2.2.5.5

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Grazoprevir

GZR pharmacokinetic parameters were determined from 10 to 800 mg in patients (PN5172-004). The GZR exposure increased in a greater than dose-proportional manner above 100 mg. Following 200 mg, 400 mg, 600 mg, or 800 mg QD administration for 7 days, GZR AUCs were higher by 2.8-, 16-, 36-, and 63-fold, respectively as compared to GZR AUC following 100 mg QD administration for 7 days in non-cirrhotic CHC patients (Table 2.2.3). Similar trends were observed from population pharmacokinetic analyses using data from Phase 2 trials where GZR doses from 25 mg to 800 mg were evaluated. The sponsor claims that it is likely due to saturation of the OATP-mediated uptake processes rather than saturated metabolism or elimination. The applicant's claim is reasonable.

Of note, the dose-dependent hepatic adverse event (late AST/ALT elevation) was observed in a Phase 2 trial (PN003) and it resulted in a partial clinical hold and a dose cap of 100 mg in patients.

Elbasvir

EBR pharmacokinetic parameters were determined from 5 to 100 mg (PN8742-002) in non-cirrhotic CHC patients. Overall, the EBR exposure is approximately dose proportional up to 100 mg (Table 2.2.4). At supratherapeutic doses used in the TQT trial, the EBR exposure appears to increase in a less than dose-proportional manner in healthy volunteers.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Grazoprevir

The steady-state of grazoprevir was generally reached within 6 days following once daily administration in healthy volunteers (200 mg) and patients (100 mg). The accumulation ratio of GZR AUC, defined as AUC Day7/AUC Day1 ranged from 2-4 fold across the doses administered (10 mg – 800 mg), and the ratio tends to be higher at lower doses (Table 2.2.3).

Elbasvir

The steady-state of EBR is generally achieved within 6 days following once-daily dosing of 50 mg EBR in CHC patients and healthy volunteers. The accumulation ratio of AUC ranged from 1.47 to 1.89 across doses administered (Table 2.2.4) in CHC patients.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Grazoprevir

The inter-subject variability (%CV) of GZR ranged from 39% to >100% for AUC and 42% to >100% for C_{max} in healthy volunteers across Phase 1 studies. The inter-subject variability estimates for CL/F and V/F of GZR were 42.1 and 68.8%, respectively, based on population pharmacokinetic analyses. The intra-subject variability was ~26% for AUC and ~45% for C_{max} in a relative bioavailability study with partial replicate design (5172-P055). Age, race, sex, weight, and disease state (including cirrhosis and fibrosis status) are significant covariates for GZR pharmacokinetics thus these factors likely contribute to the moderate to high inter-individual variability observed in clinical trials. Also, GZR is a sensitive substrate of OATP1B thus heterogeneity in expression of this transporter may explain the variability.

Elbasvir

The inter-subject variability ranged from 25% to 62% for AUC and from 22% to 68% for C_{max} , respectively, across Phase 1 studies. The inter-subject variability estimates for CL/F and V/F of EBR were 13.4% and 26.3%, respectively based on population pharmacokinetics. The within-subject variability was estimated to be ~27% for AUC and ~35% for C_{max} in a relative bioavailability study with partial replicate design (5172-P055). The population pharmacokinetic analyses indicated that age, weight, and race have minimal or no influence on EBR exposures, but the EBR exposure was ~47% higher in females as compared to males. As EBR is a BCS class 4 drug, any intrinsic or extrinsic factors that alter the absorption of elbasvir may contribute to the variability.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

A. The influence of various intrinsic factors for GZR and EBR pharmacokinetics

2.3.2.1. Elderly

Grazoprevir

The GZR exposure is higher in elderly subjects (≥ 65 years old) as compared to young subjects < 65 years old). The cross-study comparison (5172-001 and 5172-015) showed that GZR AUC was 2.2-fold higher in elderly males ($n=6$, mean age: 69 years old) as compared to young males ($n=6$, mean age: 32 years old) following multiple dose administration of 400 mg GZR. In GZR population pharmacokinetic analyses, GZR AUC was 20% higher in elderly patients (≥ 65 years old) compared to the reference population (50 years-old non-cirrhotic White male). GZR AUC was estimated to be 72% higher for a 67 year-old patient (95th percentile of the age in the dataset) compared to a 31 year-old patient (5th percentile of the age in the dataset) when other covariates are held constant. Refer to Section B for discussions on GZR adverse events in elderly.

Elbasvir

Age has minimal effect on EBR pharmacokinetics. The cross-study comparison (8742-001 and 8742-004) showed comparable EBR pharmacokinetics following single dose administration of 100 mg EBR. Population pharmacokinetic analyses indicated that EBR AUC is slightly higher (14%) in elderly subjects as compared to young subjects but this magnitude of difference is not considered clinically relevant.

2.3.2.2 Pediatric

The pharmacokinetics of grazoprevir or elbasvir have not been evaluated in subjects under the age of 18 years old.

2.3.2.3. Gender

Population pharmacokinetic analyses indicated that GZR and EBR exposures are higher in female patients by 30% and 50%, respectively, as compared to male patients when all other covariates are held constant. For EBR, such an increase is not considered clinically relevant. Refer to Section B for discussions on GZR adverse events in female patients.

2.3.2.4. Race

Grazoprevir

GZR exposures are approximately 1.5- to 3-fold higher in Asian healthy volunteers as compared to White healthy volunteers across doses evaluated as summarized in Table 2.3.1

Table 2.3.1. Cross-study comparison of GZR pharmacokinetic parameters in Asians and White healthy volunteers following administration of a single oral dose of GZR (PN5172-009)

Dose	100 mg			200 mg		400 mg		800 mg		1200 mg	
Race	Japanese	Chinese	White	Chinese	White	Japanese	White	Japanese	White	Japanese	white
N	6	8	6	8	6	6	6	6	6	5	12
AUC ₂₄ μM·hr	0.347 (0.230- 0.522)	0.372 (0.268 - 0.514)	0.241 (0.129- 0.449)	0.917 (0.675- 1.25)	0.682 (0.384 -1.21)	8.75 (5.81- 13.2)	2.04 (1.10- 3.78)	47.8 (31.7- 71.9)	15.0 (8.03- 27.9)	43.9 (29.0- 66.5)	25.8 (16.7- 40.0)
C _{max} μM	32.3 (21.2- 49.1)	48.8 (31.8- 74.8)	27.0 (14.3- 50.7)	151 (101- 226)	71.2 (39.3- 129)	1980 (1290- 3020)	410 (219- 769)	11400 (7500- 17400)	4100 (5180- 7700)	8560 (5500- 13300)	5450 (3480- 85200)
C _{24hr} nM	9.51 (5.86- 15.4)	7.74 (5.88- 10.2)	6.29 (4.04- 9.81)	10.8 (8.34- 14.0)	11.7 (7.74- 17.3)	27.6 (17.0- 44.8)	13.6 (8.77- 21.1)	45.5 (28.1- 73.7)	26.0 (16.7- 40.5)	68.0 (40.8- 113)	42.9 (31.4- 58.5)

Data expressed as geometric mean (95% CI).

White: 5172-001, Japanese: 5172-009, Chinese: 5172-042

Asian race was also identified as a significant covariate in the population pharmacokinetic analyses. Approximately 8% of the patients enrolled in Phase 2 and 3 trials were Asians. GZR AUC is estimated to be 50% higher in Asian patients as compared to White patients when all other covariates are held constant in population pharmacokinetic analyses. GZR AUC was marginally lower (10%) in Black patients as compared to White patients in population pharmacokinetic analyses. Refer to Section B for discussions on GZR adverse events in Asian patients.

Elbasvir

EBR exposure is also higher in Asian patients but to a lesser extent compared to GZR. Following multiple doses of 50 mg EBR for 10 days, the EBR AUC was approximately 1.4-fold higher in Asian healthy volunteers as compared to White healthy volunteers (7009-P050). In population pharmacokinetic analyses, the EBR AUC is estimated to be 15% higher in Asian patients and 9% higher in Black patients as compared to White patients when all other covariates are held constant. The increased exposure of EBR is not considered clinically relevant.

2.3.2.5 Renal impairment

ZEPATIER can be administered in patients with varying degrees of renal impairment including patients with ESRD on dialysis based on available pharmacokinetic, safety, and efficacy data. The pharmacokinetics of GZR and EBR in subjects with renal impairment were determined in non-HCV-infected volunteers with advanced CKD (PN050) and population pharmacokinetic analyses from PN052 (a Phase 3 trial to determine the safety and efficacy of GZR/EBR in subjects with advanced CKD).

In PN050, GZR and EBR AUCs were 65% and 86% higher in non-HCV-infected volunteers with severe CKD (eGFR < 30, not on dialysis) as compared to matched healthy volunteers. No significant difference

in EBR or GZR PK was observed in non-HCV-infected volunteers with ESRD receiving hemodialysis compared to matched healthy volunteers (Table 2.3.2-3). GZR and EBR were minimally eliminated by 4-hour hemodialysis. This was expected as both drugs are highly protein bound.

Table 2.3.2 GZR and EBR pharmacokinetic parameters following multiple oral doses of 100 mg GZR and 50 mg EBR for 10 days in subjects with severe renal impairment (eGFR< 30 mL/min) and matched healthy volunteers

	PK parameters	Severe CKD N=8	Healthy N=8	Severe CKD/healthy Geometric mean ratio (90%CI)
GZR	AUC _{24hr} (μM·hr)	1.88 (1.23-2.86)	1.14 (0.843-1.54)	1.65 (1.09-2.49)
	C _{max} (μM)	0.255 (0.152-0.429)	0.154 (0.106-0.224)	1.66 (0.99-2.77)
	C _{24hr} (nM)	23.3 (15.4-35.2)	14.5 (10.7-19.6)	1.60 (1.06-2.42)
EBR	AUC _{24hr} (μM·hr)	4.07 (3.01-5.52)	2.19 (1.76-2.72)	1.86 (1.38-2.51)
	C _{max} (μM)	0.271 (0.196-0.373)	0.163 (0.129-0.206)	1.66 (1.21-2.28)
	C _{24hr} (nM)	60.9 (47.3-78.5)	60.9 (47.3-78.5)	2.07 (1.46-2.93)

Pharmacokinetic parameters are expressed as geometric mean (95% CI)

Table 2.3.3. GZR and EBR pharmacokinetic parameters following multiple oral doses of 100 mg GZR and 50 mg EBR for 10 days in subjects with ESRD and matched healthy volunteers

	PK parameter	ESRD on HD day N=8	ESRD On non-HD day N=8	Healthy N=8	ESRD on nonHD/healthy Geometric mean ratio (90%CI)	ESRD HD/nonHD day Geometric mean ratio (90%CI)
GZR	AUC _{24hr} (μM·hr)	0.944 (0.671-1.33)	0.969 (0.689-1.36)	1.14 (0.843-1.54)	0.85 (0.58-1.25)	0.97 (0.87-1.09)
	C _{max} (μM)	0.135 (0.088-0.206)	0.141 (0.092-0.215)	0.154 (0.106-0.224)	0.92 (0.57-1.48)	0.96 (0.75-1.22)
	C _{24hr} (nM)	11.3 (8.03-15.8)	11.4 (8.16-16.1)	14.5 (10.7-19.6)	0.79 (0.54-1.16)	0.98 (0.81-1.19)
EBR	AUC _{24hr} (μM·hr)	2.16 (1.69-2.77)	1.89 (1.48-2.42)	2.19 (1.76-2.72)	0.86 (0.65-1.14)	1.14 (1.08-1.21)
	C _{max} (μM)	0.154 (0.118-0.200)	0.137 (0.105-0.178)	0.163 (0.129-0.206)	0.84 (0.62-1.13)	1.12 (1.00-1.26)
	C _{24hr} (nM)	58.2 (43.7-77.5)	46.9 (23.4-38.3)	60.9 (47.3-78.5)	0.77 (0.56-1.06)	1.24 (1.17-1.32)

HD: hemodialysis

Data are expressed as geometric mean (95% CI)

PN052 was a Phase 3 trial to determine the safety and efficacy of ZEPATIER in subjects with advanced CKD. 30 CHC patients with severe CKD (not on dialysis) and 92 CHC patients with ESRD (on hemodialysis) received GZR100 mg and EBR 50 mg once daily for 12 weeks. The population pharmacokinetic analysis results were generally similar with those observed in PN050; approximately 50% increases in GZR and EBR AUCs were observed in subjects with severe CKD (not on dialysis). In subjects with ESRD on hemodialysis, GZR and EBR AUCs were higher by 11% and 25%, respectively as compared to matched healthy volunteers.

Increases in GZR and EBR exposures observed in subjects with severe renal impairment are thought to be due to be physiological changes accompanied with renal impairment (e.g., altered hepatic function or interactions with uremic toxins) rather than changes in renal elimination. Based on mass balance trial results, GZR and EBR are minimally (< 1%) eliminated in urine. Overall, the magnitude of changes observed in subjects with advanced CKD is not considered clinically significant and ZEPATIER can be administered to patients with varying degrees of renal impairment.

2.3.2.6. Hepatic impairment

ZEPATIER can be used in subjects with mild hepatic impairment (Child-Pugh A) based on the pharmacokinetic, safety, and efficacy data. The use of ZEPATIER is not recommended in subjects with moderate hepatic impairment (Child-Pugh B) and should be contraindicated in subjects with severe hepatic impairment (Child-Pugh C) due to significant increases in GZR exposure.

Grazoprevir

GZR pharmacokinetic parameters in non-HCV-infected subjects with mild, moderate, and severe hepatic impairment were compared to matched healthy volunteers (PN013; Table 2.3.4). GZR exposures were increased by 1.7-fold, 4.8-fold and 11.7-fold, in subjects with mild, moderate, and severe hepatic impairment, respectively, as compared to matched healthy volunteers. CHC patients with Child-Pugh A cirrhosis were enrolled in Phase 2 and 3 trials. The population pharmacokinetic analyses results are similar with PN013; the geometric mean of GZR AUC was approximately 65% higher in cirrhotic CHC patients as compared to non-cirrhotic CHC patients (Fig 2.3.1). Overall, the safety and efficacy were comparable between cirrhotic patients and non-cirrhotic patients across Phase 2 and 3 trials. Therefore, GZR can be administered in patients with mild hepatic impairment.

Table 2.3.4. GZR pharmacokinetic parameters at steady-state in non-HCV-infected subjects with varying degrees of hepatic impairment and matched healthy subjects (5172-013)

Population	GZR Dose	N	AUC _{24hr} (µM·hr)	C _{max} (µM)	C _{24hr} (nM)
Mild hepatic impairment	200 mg QD for 10 days	8	6.20 (4.19-9.18)	1.40 (0.903-2.17)	32.6 (24.8-42.8)
Matched healthy subjects		8	3.74 (2.53-5.54)	1.02 (0.658-1.58)	17.0 (12.9 - 22.3)
GMR: Mild HI /matched healthy (90%CI)			1.66 (1.05-2.61)	1.37 (0.83-2.27)	1.92 (1.40-2.63)
Moderate hepatic impairment	100 mg QD for 10 days	8	4.21 (2.48-7.14)	0.631 (0.334-1.19)	48.9 (27.2-87.9)
Matched healthy subjects		8	0.874 (0.515-1.48)	0.106 (0.0559-0.199)	13.6 (7.60-24.5)
GMR: moderate HI /matched healthy (90%CI)			4.82 (2.60-8.93)	5.98 (2.84-12.57)	3.59 (1.81-7.11)
Severe hepatic impairment	50 mg QD for 10 days	8	3.00 (1.71-5.26)	0.396 (0.203-0.774)	55.0 (31.9-94.8)
Matched healthy subjects		8	0.257	0.0304	5.89

		(0.146-0.451)	(0.0156-0.0595)	(3.42-10.2)
GMR: severe HI /matched healthy (90%CI)		11.68 (6.10-22.35)	13.01 (6.00-28.21)	9.34 (4.98-17.51)

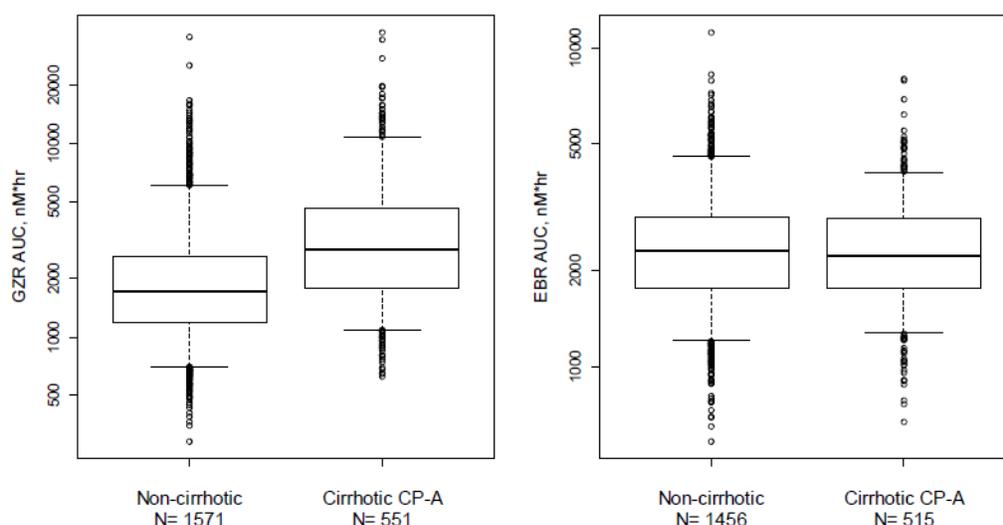
GMR: geometric mean ratio

Pharmacokinetic parameters are expressed as geometric mean (95% CI)

Elbasvir

Following a single oral dose administration of EBR 50mg, EBR AUCs were consistently lower (36-40% for AUC_{24hr}, 12-39% for AUC_{0-∞}) in subjects with varying degrees of hepatic impairment as compared to matched healthy volunteers. The underlying mechanism is unknown. However, in population pharmacokinetic analyses, EBR AUCs were comparable between non-cirrhotic CHC patients and CHC patients with Child-Pugh A cirrhosis (Fig 2.3.1).

Fig 2.3.1. Distribution of steady-state AUC_{24hr} of 100 mg GZR and 50 mg EBR in CHC patients



The boxes represent 25th and 75th percentiles; line in the box is median. Whiskers are 5th and 95th percentiles.

2.3.2.7 What pregnancy and lactate use information is there in the application?

Grazoprevir or elbasvir have not been evaluated in subjects in pregnant or lactating women.

B. Is the higher exposure of GZR in cirrhotic, female, elderly, and Asian populations clinically relevant? If so, are any dosage regimen adjustments recommended for each of these groups?

GZR exposures are higher in female, elderly, Asian, and cirrhotic patients. At the same time, rates of the observed hepatic adverse event (late AST/ALT elevation) were higher in these populations, except for cirrhotic patients. It is unclear whether higher GZR exposures are solely, or only in part, responsible for the higher rates of adverse events observed in specific populations; the observed event rates were 1.4%, 2.3%, and 1.4%, respectively, in females, Asians, and the elderly, while the overall event rate in all patients was 0.7%. These rates are comparable to the predicted and observed adverse event rates

associated with at least 3-fold or higher increases in the GZR exposure. However, in these populations, GZR exposures were increased less than 2-fold. Also, the hepatic adverse event rate was not higher in cirrhotic patients as compared to non-cirrhotic patients even though the GZR exposure was ~ 65% higher in cirrhotic patients. Therefore, although GZR exposures were higher and the adverse event rates were higher in females, the elderly, and Asians, it cannot be concluded that it is solely due to higher GZR exposures. These populations may be more susceptible to the adverse event due to physiological reasons (yet to be determined) rather than higher GZR exposures. Overall, based on the risk/benefit assessments, including the overall event rates and the nature of the hepatic adverse event (reversible AST/ALT elevation with no apparent clinical sequelae), the multidisciplinary review team is not considering restricting the use of ZEPATIER in these specific populations.

Table 2.3.6. Observed and predicted late AST/ALT event in various populations following 100 mg GZR administration

Population comparison	Observed AST/ALT elevation event rates following 100 mg	Exposure differences based on pop PK analyses
Female vs. Male	1.4% (11/791) vs. 0.23% (3/1296)	30% higher in female
Asian vs. White	2.3% (4/175) vs. 0.5% (8/1579)	50% higher in Asian
Elderly (65+) vs. Young	1.4% (3/224) vs. 0.6% (11/1863)	20% higher in Elderly
Cirrhotic vs. non cirrhotic	0.7% (4/533) vs. 0.6 % (10/1553)	65% higher in cirrhotic
Asian female vs. white male	3.7% (3/81) vs. 0.2% (2/977)	110% higher in Asian female
All patients at 100 mg [#]	0.7% (14/2087)	NA
All patients at 200 mg	1.5% (1/65)	*4.8-fold ↑ following 200 mg administration (vs.100 mg)
All patients at 400 mg	6.3% (4/64)	*18-fold ↑ following 200 mg administration (vs.100 mg)
All patients at 800 mg	10.3% (6/58)	*66-fold ↑ following 200 mg administration (vs.100 mg)

*Based on population pharmacokinetic analyses

[#]The observed rates were calculated using data from any subject who received 100 mg GZR (±EBR, ±Peg-IFN/ribavirin, ±sofosbuvir) at least 8 weeks (PN003, PN035, PN038, PN039, PN047, PN048, PN052, PN058, PN059, PN060, PN061, PN068, PN074).

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

The effects of concomitant use of various drugs were determined in drug interaction trials (refer to 2.4.2). The effects of herbal products, diet other than a high fat meal (refer to 2.5.3), smoking, and alcohol use were not determined.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

GZR is a substrate of P-gp, CYP3A4, OATP1B1, OATP1B3 *in vitro*. GZR inhibited CYP2C8, CYP3A4 and multiple hepatic transporters (OATP1B1, OATP1B3, BCRP, BSEP, MRP2, MRP3 and MRP4) *in vitro*. EBR is a substrate of CYP3A4 and P-gp *in vitro*. EBR inhibited P-gp, BCRP, and OATP1B3 *in vitro*.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

GZR and EBR are substrates of CYP3A4. Co-administration of ketoconazole, a strong CYP3A4 inhibitor, increased GZR and EBR AUC by 3.0-fold and 1.8-fold, respectively. GZR and EBR are not substrates of CYP1A2, CYP2C9, CYP2C19, or CYP2D6. Whether GZR and EBR are substrates of other CYPs (e.g., CYP2B6 or CYP2C8) have not been determined. The effects of CYP3A4 (or other enzymes) genetic polymorphisms on GZR or EBR exposures have not been determined.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

GZR and EBR did not induce CYP3A4, CYP2B6, or CYP1A1 at concentrations up to 20 μM in human hepatocytes from three different donors.

In vitro CYP inhibition study results are summarized in Table 2.4.1. GZR inhibited CYP2C8 ($\text{IC}_{50}=6 \mu\text{M}$) and CYP3A4 ($\text{IC}_{50}=73 \mu\text{M}$) *in vitro*. The IC_{50} values observed *in vitro* are significantly higher than the GZR C_{max} at steady-state ($\sim 0.2 \mu\text{M}$ as total plasma concentration, $\sim 0.002 \mu\text{M}$ as unbound plasma concentration). The applicant stated that GZR can potentially inhibit intestinal CYP3A4 as the maximum theoretical concentration of GZR in intestine is $\sim 520 \mu\text{M}$. EBR did not inhibit any major CYP enzymes *in vitro*.

The applicant conducted two drug interaction trials to evaluate the inhibitory effects of GZR on CYP2C8 (montelukast as a probe substrate) and CYP3A4 (midazolam as a probe substrate) *in vivo*. The co-administration of GZR increased monteleukast AUC and $C_{24\text{hr}}$ 11% and 39%, respectively, but did not change C_{max} . The co-administration of GZR increased midazolam C_{max} and AUC_{inf} by 15% and 34%, respectively.

Table 2.4.1. GZR and EBR CYP inhibition activity

	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP3A4	CYP2D6
GZR	> 100 μM	66 μM	6 μM	> 100 μM	> 100 μM	73 μM^{a} > 100 μM^{b}	> 100 μM
EBR	> 100 μM	> 100 μM					

a: measured by midazolam hydroxylation

b: measured by testosterone hydroxylation

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Both GZR and EBR are substrates of P-gp *in vitro*. Refer to 2.2.5.3 for further details. GZR did not, but EBR did, inhibit P-gp *in vitro*. The co-administration of digoxin 0.25 mg and EBR 50 mg increased digoxin C_{max} and AUC_{inf} by 47% and 11%, respectively.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

1. Grazoprevir and elbasvir as substrates of transporters

GZR is a substrate of OATP1B1 and OATP1B3 *in vitro* and *in vivo*. GZR exposure was significantly increased by OATP1B inhibitors; the co-administration of cyclosporine (a single oral dose), lopinavir/ritonavir (multiple oral doses), and rifampin (a single intravenous dose) increased GZR AUC by 15.2-fold, 12.8-fold, and 10.2-fold by, respectively. EBR is not a substrate of OATP1B.

2. Grazoprevir and elbasvir as inhibitors of hepatic or intestinal transporters

The potential of GZR and EBR for transporter inhibition is summarized in Table 2.4.2.

GZR inhibited all hepatic transporters evaluated. The applicant concluded that the inhibition of transporters observed *in vitro* is not clinically relevant based on the R values for OATP1B (< 1.25) and the comparison of the maximum theoretical unbound hepatic inlet concentrations ($C_{inlet, unbound}$; $\sim 0.1 \mu M$) and IC_{50} for other transporters. However, clinical relevance cannot be completely ruled out at this time; GZR concentrations are thought to be significantly higher in liver due to OATP1B-mediated uptake. Also, these transporters have overlapping substrates, thus additive effects are possible. GZR may inhibit intestinal BCRP. The theoretical maximum concentration of GZR in the intestine is approximately 520 μM , significantly higher than the IC_{50} (12.5 μM) for BCRP observed *in vitro*. The co-administration of GZR (without EBR) increased atorvastatin C_{max} and AUC by 5.7-fold and 3.0-fold, respectively, following single dose administration of atorvastatin 20 mg.

EBR is a potential clinically relevant inhibitor of OATP1B3 (R-value: 1.4) and BCRP ($C_{max, total}/IC_{50} = 1$). The IC_{50} values for other hepatic transporters (OATP1B1, BSEP, MRP2, MRP3, and MRP4) could not be determined in the *in vitro* system due to solubility limitations.

Table 2.4.2. The inhibitory effects of GZR or EBR on transporters *in vitro*

Transporter	GZR IC_{50}	EBR IC_{50}
OATP1B1	0.7 μM	$> 0.5 \mu M$
OATP1B3	1.1 μM	0.10 μM
BCRP	12.5 μM	0.15 μM
BSEP	0.15 μM	$> 0.3 \mu M$
MRP2	2.5 μM	$> 0.3 \mu M$
MRP3	3.8 μM	$> 0.3 \mu M$
MRP4	1.0 μM	$> 0.3 \mu M$

3. Inhibition potential for other enzymes

GZR and EBR did not inhibit CES1, CES2, CatA, or UGT1A1 *in vitro* ($IC_{50} > 50 \mu M$).

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

In CHC patients with a history of on-treatment failure, the proposed dosing regimen is to take ZEPATIER once daily in combination with ribavirin for 16 weeks. As ribavirin does not undergo CYP-mediated metabolism and is mainly eliminated by the renal route, the potential for drug interactions between ribavirin and ZEPATIER was deemed minimal. Therefore, ribavirin was co-administered with GZR and EBR in Phase 2 and Phase 3 trials without conducting a drug interaction trial. The population pharmacokinetic analyses indicated that the co-administration of RBV has no significant effect on GZR or EBR exposures.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Medications that are likely to be coadministered to CHC patients include antiretroviral medications (for HIV/HCV co-infected patients) and drugs for opiate replacement therapy (methadone and buprenorphine/naloxone). Drugs commonly used in patients with CKD, such as phosphate binders or drugs for the treatment of anemia, will likely be used with ZEPATIER, too. In addition, all drugs commonly used in the general adult population in the US will likely be co-administered (e.g., cholesterol lowering agents, anti-hypertensive, antidiabetics, antidepressants, proton pump inhibitors, over-the-counter drugs, herbal and vitamin supplements). Female patients may also receive combined oral contraceptives.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

The applicant conducted a panel of drug interaction studies based on in vitro assay results or drugs commonly used in the patient population. *In vivo* drug-drug interaction study results are summarized as follows. Note that the clinical recommendations are the reviewer's recommendations, not the applicant's proposal. The recommendations were under discussion between the applicant and the review team when this review was written.

1. Co-administration is not recommend or should be contraindicated due to significant increases in GZR (and EBR) exposures

Drugs that increase GZR or EBR exposures are summarized in Table 2.4.3. For GZR, the interactions are mainly driven by OATP1B and/or CYP3A4 inhibition. For EBR, interactions are likely due to the inhibition of CYP3A4 and P-gp. Based on the exposure-response relationship for GZR safety (refer to 2.2.4.2), the review team has determined that a 3-fold increase or above in GZR exposure is considered clinically relevant and co-administration is not recommended. A 10-fold increase and above in the GZR exposure should be contraindicated as the magnitude is unacceptably high and the use of these drugs in combination with GZR cannot be justified under any circumstances. For EBR, although no exposure-dependent adverse events were observed, clinical experience with doses above 100 mg QD is limited.

Therefore, there are no safety data to support the use of EBR when the EBR exposure is increased by a 2-fold or greater. Based on criteria described above, the co-administration of ketoconazole or DRV/rtv is not recommended. The co-administration of ATV/r, LPV/r or cyclosporine should be contraindicated. Other OATP1B inhibitors which were not evaluated in drug interaction trials (e.g., tipranavir/ritonavir, saquinavir/ritonavir, eltrombopag, and gemfibrozil) should be contraindicated.

Table 2.4.3. Drug interactions resulting in the increased exposures of GZR or EBR and clinical recommendations

Co-Administered Drug	Regimen of GZR or/and EBR	Geometric Mean Ratio [90% CI] of GZR and EBR PK with/without Co-Administered Drug				Clinical recommendations	
			AUC	C _{max}	C ₂₄		
Ketoconazole 400 mg QD	GZR 100 mg single-dose	GZR	3.02 (2.42, 3.76)	1.13 (0.77, 1.66)	--	<u>Co-administration is not recommended</u>	
	EBR 50 mg single-dose	EBR	1.80 (1.41, 2.29)	1.29 (1.00, 1.66)	1.89 (1.37, 2.60)		
Darunavir/ ritonavir 600 mg/100 mg QD	GZR 200 mg once daily	GZR	7.50 (5.92, 9.51)	5.27 (4.04, 6.86)	8.05 (6.33, 10.24)		
	EBR 50 mg once daily	EBR	1.66 (1.35, 2.05)	1.67 (1.36, 2.05)	1.82 (1.39, 2.39)		
Atazanavir/ ritonavir 300mg/100 mg QD	GZR 200 mg once daily	GZR	10.58 (7.78, 14.39)	6.24 (4.42, 8.81)	11.64 (7.96, 17.02)		<u>Co-administration is contraindicated</u>
	EBR 50 mg once daily	EBR	4.76 (4.07, 5.56)	4.15 (3.46, 4.97)	6.45 (5.51, 7.54)		
Lopinavir/ ritonavir 400 mg/100 mg BID	GZR 200 mg once daily	GZR	12.86 (10.25, 16.13)	7.31 (5.65, 9.45)	21.70 (12.99, 36.25)		
	EBR 50 mg once daily	EBR	3.71 (3.05, 4.53)	2.87 (2.29, 3.58)	4.58 (3.72, 5.64)		
Cyclosporine 400 mg single dose	GZR 200 mg+ EBR 50 mg once daily	GZR	15.21 (12.83, 18.04)	17.00 (12.94, 22.34)	3.39 (2.82, 4.09)		
	GZR 200 mg + EBR 50 mg once daily	EBR	1.98 (1.84, 2.13)	1.95 (1.84, 2.07)	2.21 (1.98, 2.47)		

2. Co-administration is contraindicated due to significant decreases in GZR or EBR exposures

The co-administration of efavirenz or rifampin should be contraindicated due to significant decreases in GZR and EBR exposures. Rifampin has mixed effects on GZR exposure. Following the co-administration

of a single dose of rifampin, significant increases in GZR AUC and C_{max} were observed, likely due to the inhibition of OATP1B. Following the co-administration of multiple doses of rifampin and GZR (at steady-state), a significant decrease was observed in C_{24hr} , but not in AUC and C_{max} . This is likely due to the mixed effects of rifampin on OATP1B (inhibition) and CYP3A4 (induction). It has not been determined whether GZR C_{24hr} is a more critical parameter in predicting antiviral activity than GZR AUC. However, generally speaking for antiviral drugs (not requiring an intracellular activation step), it is possible that the lower C_{24hr} may compromise the antiviral activity even though AUC remains the same. The sponsor did not conduct a drug interaction trial with rifampin and EBR at steady-state. EBR exposure is expected to be significantly decreased in the presence of rifampin at steady state. Other strong CYP3A4 inducers (e.g., carbamazepine, phenytoin) should be also contraindicated as those drugs are expected to significantly decrease GZR and EBR exposures, too.

Table 2.4.4. Drug interactions resulting in decreased exposures of GZR or EBR

Co-Administered Drug	Regimen of Co-Administered Drug	Regimen of GZR or/and EBR	Geometric Mean Ratio [90% CI] of GZR and EBR PK with/without Co-Administered Drug (No Effect=1.00)				Clinical recommendations
				AUC*	C_{max}	C24	
Rifampin	600 mg PO once daily	GZR 200 mg once daily	GZR	0.93 (0.75, 1.17)	1.16 (0.82, 1.65)	0.10 (0.07, 0.13)	Co-administration is contraindicated
	600 mg IV single-dose	GZR 200 mg single-dose	GZR	10.21 (8.68, 12.00)	10.94 (8.92, 13.43)	1.77 (1.40, 2.24)	
	600 mg PO single-dose	GZR 200 mg once daily	GZR	8.35 (7.38, 9.45) [†]	6.52 (5.16, 8.24)	1.62 (1.32, 1.98)	
	600 mg single-dose IV	EBR 50 mg single-dose	EBR	1.22 (1.06, 1.40)	1.41 (1.18, 1.68)	1.31 (1.12, 1.53)	
	600 mg single-dose PO	EBR 50 mg single-dose	EBR	1.17 (0.98, 1.39)	1.29 (1.06, 1.58)	1.21 (1.03, 1.43)	
Efavirenz	600 mg once daily	GZR 200 mg once daily	GZR	0.17 (0.13, 0.24)	0.13 (0.09, 0.19)	0.31 (0.25, 0.38)	Co-administration is contraindicated
	600 mg once daily	EBR 50 mg once daily	EBR	0.46 (0.36, 0.59)	0.55 (0.41, 0.73)	0.41 (0.28, 0.59)	

3. Dose adjustment of co-administered drug or close clinical monitoring is recommended due to the interactions

HMG-CoA reductase inhibitors (statins)

GZR and EBR increased the exposures of atorvastatin and rosuvastatin (Table 2.4.5). For atorvastatin, the magnitude of the increase by EBR and GZR co-administration is similar with the magnitude of the increase by fosamprenavir co-administration [a ~2-fold increase in AUC and a ~4-fold increase in C_{max} (Lipitor® USPI)]. As the atorvastatin dose is limited to 20 mg once daily when coadministered with fosamprenavir (Lipitor® USPI), the same recommendation can be made when atorvastatin is co-

administered with ZEPATIER. Similarly, the magnitude of the increase in the rosuvastatin exposure when coadministered with GZR and EBR (a 2.3-fold in AUC and a 5.5-fold in C_{max}) is comparable to the magnitude of the increase by lopinavir/ritonavir co-administration (a 2-fold increase in AUC and a 5-fold C_{max} increase). As the rosuvastatin dose is limited to 10 mg once daily when coadministered with lopinavir/ritonavir (CRESTOR® USPI), the same recommendation can be made when rosuvastatin is co-administered with ZEPATIER. No dose adjustment of pravastatin or pitavastatin is necessary when co-administered with ZEPATIER. Although the applicant did not conduct drug interaction trials with the following drugs, the applicant proposed (b) (4)

Tacrolimus

The co-administration of EBR and GZR increased tacrolimus AUC and C_{min} by 43% and 70%, respectively, but decreased C_{max} by 40%. The study results may not reflect the worst case scenario as a single low dose of tacrolimus was used in the drug interaction trial. As tacrolimus is drug with a narrow therapeutic index, the interaction may be clinically relevant. Therefore, frequent monitoring of tacrolimus whole blood concentrations, renal function and tacrolimus-related side effects are recommended upon initiating co-administration with Zepatier

Table 2.4.5. Potentially significant drug interactions that may require a dose adjustment of concomitant drugs or close monitoring

Co-Administered Drug	GZR or/and EBR Administration	Geometric Mean Ratio [90% CI] of Co-Administered Drug PK with/without GZR or/and EBR (No Effect=1.00)			Clinical recommendations
		AUC	C _{max}	C _{trough}	
Tacrolimus 2 mg single dose	GZR 200 mg + EBR 50 mg daily	1.43 (1.24, 1.64)	0.60 (0.52, 0.69)	1.70 (1.49, 1.94)	Frequent monitoring of tacrolimus whole blood concentrations, renal function and tacrolimus-related side effects are recommended upon initiating co-administration with Zepatier
Atorvastatin 10 mg single dose	GZR 200 mg + EBR 50 mg daily	1.94 (1.63, 2.33)	4.34 (3.10, 6.07)	0.21 (0.17, 0.26)	The dose of atorvastatin should not exceed a daily dose of 20 mg when co-administered with ZEPATIER
Pitavastatin 1 mg single dose	GZR 200 mg daily	1.11 (0.91, 1.34)	1.27 (1.07, 1.52)	--	No dose adjustment is necessary
Pravastatin 40 mg single dose	GZR 200 mg + EBR 50 mg daily	1.33 (1.09, 1.64)	1.28 (1.05, 1.55)	--	No dose adjustment is necessary
Rosuvastatin 10 mg single dose	GZR 200 mg + EBR 50 mg daily	2.26 (1.89, 2.69)	5.49 (4.29, 7.04)	0.98 (0.84, 1.13)	The dose of rosuvastatin should not exceed a daily dose of 10 mg when co-administered with ZEPATIER

4. No clinically relevant drug interactions were observed

- Two-way drug interactions: dolutegravir, raltegravir, rilpivirine, mycophenolate mofetil, prednisone
- GZR or EBR as a victim: pantoprazole, phosphate binders (sevelamer, calcium carbonate)
- GZR or EBR as a perpetrator: oral contraceptives, pitavastatin, pravastatin, methadone and buprenorphine

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no known mechanistic basis for pharmacodynamics drug-drug interactions for elbasvir or grazoprevir.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are no unresolved issues regarding metabolism, active metabolites, metabolic drug interactions, or protein binding.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

There are no issues related to dose, dosing regimens, or administration are unresolved or that represent significant omissions.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

According to the applicant, grazoprevir and elbasvir are BCS Class 2 and Class 4, respectively. Please refer to the ONDQA/biopharmaceutics review for further details.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

Fixed-dose tablets (FDC2 formulation) used in three pivotal Phase 3 trials (C-EDGE TN, C-EDGE COINFECTION, and C-EDGE TE) are identical to the to-be-marketed formulation except for color coating. Therefore, the sponsor did not conduct any *in vivo* BE studies to support the use of the final-to-be-marketed formulation. Please refer to the ONDQA/biopharmaceutics review for further details.

2.5.2.1. What data support or do not support a waiver of in vivo BE data?

The question is not applicable to this NDA

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Relative to the fasted state, the administration of a single dose of ZEPATIER with a high-calorie, high-fat (900 kcal, 500 kcal from fat) breakfast increased GZR AUC_{0-inf} and C_{max} by 1.5-fold and 2.8-fold, respectively, and decreased EBR AUC_{0-inf} and C_{max} by 11% and 15%, respectively, in healthy subjects. These changes are not considered clinically relevant and ZEPATIER can be taken with or without food.

2.5.4 When would a fed BE study be appropriate and was one conducted?

The question is not applicable to this NDA.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The active moieties were identified and measured in the plasma using validated LC/MS/MS analytical methods.

2.6.2 Which metabolites have been selected for analysis and why?

Metabolites were routinely not measured in clinical pharmacology studies because none of the metabolites represented > 10% of the total drug-related material in mass balance trials.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total concentrations of GZR and EBR were measured. This is appropriate because free fractions of both drugs in plasma are concentration independent in clinically relevant concentration ranges.

2.6.4 What bioanalytical methods are used to assess concentrations?

Validated LC/MS/MS analytical methods were used for the analysis of human plasma samples of GZR and EBR. The calibration ranges (lower limit of quantitation – upper limit of quantitation) of GZR and EBR in plasma are 1 -1000 ng/mL and 0.25-500 ng/mL, respectively. A linear, $1/x^2$ regression method was used to determine sample concentrations. The stability under various conditions (e.g., room-temperature, long-term storage, autosampler, processed sample, freeze-thaw cycle, stock solution) has been established. Refer to the individual study reviews for standard curve, accuracy, precision, selectivity, stability, QC plan and results.

3 DETAILED LABELING RECOMMENDATIONS

The following section highlights labeling recommendations by the Office of Clinical Pharmacology based on the interpretation of the review issues. Labeling negotiation was ongoing at the time this review was written.

Recommendations and comments from the Office of Clinical Pharmacology are highlighted in blue in response to the applicant's proposed labeling regimen. This section addresses clinical pharmacology related recommendations only.

4. Contraindications

Applicant's proposal

(b) (4)

- If ZEPATIER is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin.
- ZEPATIER is contraindicated in patients with severe hepatic impairment due to the expected significantly increased grazoprevir plasma concentration and the increased risk of alanine aminotransferase (ALT) elevations

OCP recommendation

We recommend adding the following contraindication

- ZEPATIER is contraindicated with OATP1B inhibitors
- ZEPATIER is contraindicated with strong CYP3A4 inducers and efavirenz

7. Drug interactions

7.1 Potential for Drug Interactions

Elbasvir and grazoprevir are substrates of CYP3A/P-gp. Co-administration of moderate or strong inducers of CYP3A/P-gp with ZEPATIER may decrease elbasvir and grazoprevir plasma concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration of ZEPATIER with moderate CYP3A/P-gp inducers is not recommended.

(b) (4)

(b) (4)

(b) (4)

(b) (4) As such, co-administration of ZEPATIER with OATP1B inhibitors is (b) (4)

OCP recommendation

As described in 4, we recommend contraindication for strong CYP3A inducers or OATP1B inhibitors.

(b) (4)

7.2 Established and other Potential Drug Interactions

If dose adjustments of concomitant medications are made due to treatment with ZEPATIER, doses should be readjusted after administration of ZEPATIER is completed.

Table (b) (4) provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either ZEPATIER, the components of ZEPATIER (elbasvir [EBR] and grazoprevir [GZR]) as individual agents, or are predicted drug interactions that may occur with ZEPATIER [see *Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*].

Table (b) (4) Potentially Significant Drug Interactions: Alteration in Dose May Be Recommended Based on Results from Drug Interaction Studies or Predicted Interactions*

Concomitant Drug Class: Drug Name	Effect on Concentration†	Clinical Comment
Antibiotic: Nafcillin	↓ EBR ↓ GZR	Co-administration of ZEPATIER with nafcillin, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended.
Endothelin Antagonist: Bosentan	↓ EBR ↓ GZR	Co-administration of ZEPATIER with bosentan, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended.
HIV Medications: efavirenz‡ etravirine	↓ EBR ↓ GZR	Co-administration of EBR and GZR with efavirenz or etravirine, moderate CYP3A inducers, decreased or may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of

(b) (4)

(b) (4)

		ZEPATIER. Co-administration is not recommended.
(b) (4)		
HMG-CoA Reductase Inhibitors#:		
atorvastatin [†]	↑ atorvastatin	Co-administration of EBR and GZR with atorvastatin increases the concentrations of atorvastatin. The dose of atorvastatin should not exceed a daily dose of 20 mg when co-administered with ZEPATIER.
rosuvastatin [†]	↑ rosuvastatin	Co-administration of EBR and GZR with rosuvastatin increases the concentrations of rosuvastatin. The dose of rosuvastatin should not exceed a daily dose of 10 mg when co-administered with ZEPATIER.
fluvastatin lovastatin simvastatin	↑ fluvastatin ↑ lovastatin ↑ simvastatin	Co-administration of ZEPATIER with these statins has not been studied but may increase the concentrations of these statins. (b) (4)
(b) (4)		
(b) (4)		
tacrolimus	↑ Tacrolimus	OCP recommendation: cyclosporine should be contraindicated Frequent monitoring of tacrolimus whole blood concentrations, renal function and tacrolimus-related side effects are recommended upon initiating co-administration with ZEPATIER.
Wakefulness-Promoting Agents: Modafinil	↓ EBR ↓ GZR	Co-administration of ZEPATIER with modafinil, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended.

*This table is not all inclusive. †↓ = decrease, † = increase.

†These interactions have been studied in healthy adults.

#See *Drug Interactions (7.3)* for a list of HMG Co-A reductase inhibitors without clinically relevant interactions with ZEPATIER.

7.3 Drugs without Clinically Significant Interactions with ZEPATIER

The interaction between the components of ZEPATIER (elbasvir or grazoprevir) or ZEPATIER and the following drugs were evaluated in clinical studies, and no dose adjustments are needed when ZEPATIER is used with the following drugs individually: acid reducing agents (proton pump inhibitors, H2 blockers, antacids), buprenorphine/naloxone, digoxin, dolutegravir, methadone, mycophenolate mofetil, oral contraceptive pills, phosphate binders, pitavastatin, pravastatin, prednisone, raltegravir, ribavirin, (b) (4) tenofovir disoproxil fumarate, and sofosbuvir [see *Clinical Pharmacology (12.3)*]. No clinically relevant drug-drug interaction is expected when ZEPATIER is co-administered with abacavir, emtricitabine, and lamivudine.

8. Use in specific populations

8.4 Pediatric Use

Safety and efficacy (b) (4) have not been established in pediatric patients less than 18 years of age.

8.5 Geriatric Use

Clinical trials of ZEPATIER with or without ribavirin included 187 subjects aged 65 and over. (b) (4)
~~e subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.~~

Higher elbasvir and grazoprevir plasma concentrations were observed in subjects aged 65 and over. (b) (4)
(b) (4) No dosage adjustment of ZEPATIER is recommended in geriatric patients.

Reviewer comments: Higher rates of ALT elevations (b) (4) in (b) (4) patients of age > 65 years. (b) (4)

8.6 Gender

Higher elbasvir and grazoprevir plasma concentrations were observed in females compared to males. (b) (4)

8.7 Race

Higher elbasvir and grazoprevir plasma concentrations were observed in Asians compared to White. (b) (4)

[see *Clinical Pharmacology (12.3)*].

8.8 Renal Impairment

No dosage adjustment of ZEPATIER is recommended in patients (b) (4) renal impairment. No dosage adjustment of ZEPATIER is recommended in patients who are on dialysis (including hemodialysis) (b) (4) [see *Clinical Pharmacology (12.3)*].

8.9 Hepatic Impairment

No dosage adjustment of ZEPATIER is recommended in patients with mild hepatic impairment (Child-Pugh A). ZEPATIER is (b) (4) in patients with moderate hepatic impairment (Child-Pugh B) (b) (4)

ZEPATIER is contraindicated in patients with severe hepatic impairment (Child-Pugh C) based on the expected significant increase in grazoprevir exposure (b) (4) [see *Dosage and Administration* (2.3), *Contraindications* (4), and *Clinical Pharmacology* (12.3)].

12.3 Pharmacokinetics

The pharmacokinetic properties of elbasvir and grazoprevir have been evaluated in non-HCV-infected adult subjects and in HCV-infected adult subjects. Elbasvir pharmacokinetics were similar in healthy subjects and HCV-infected subjects and were approximately dose-proportional over the range of 5-100 mg once daily. Grazoprevir oral exposures are approximately 2-fold greater in HCV-infected subjects as compared to healthy subjects. Grazoprevir pharmacokinetics increased in a greater than dose-proportional manner over the range of 10-800 mg once daily in HCV-infected subjects. Ribavirin co-administration with ZEPATIER had no clinically relevant impact on plasma AUC and C_{max} of elbasvir and grazoprevir compared to administration of ZEPATIER alone. (b) (4)

Following once daily administration of ZEPATIER to HCV-infected subjects, elbasvir and grazoprevir reached steady state within approximately 6 days.

Absorption

Following administration of ZEPATIER to HCV-infected subjects, elbasvir peak concentrations occur at a median T_{max} of 3 hours (range of 3 to 6 hours); grazoprevir peak concentrations occur at a median T_{max} of 2 hours (range of 30 minutes to 3 hours).

Effect of Food

Relative to fasting conditions, the administration of a single dose of ZEPATIER with a high-fat (900 kcal, 500 kcal from fat) meal to healthy subjects resulted in decreases in elbasvir AUC_{0-inf} and C_{max} of approximately 11% and 15%, respectively, and increases in grazoprevir AUC_{0-inf} and C_{max} of approximately 1.5-fold and 2.8-fold, respectively. These differences in elbasvir and grazoprevir exposure are not clinically relevant; therefore, ZEPATIER may be taken without regard to food.

Distribution

Elbasvir and grazoprevir are extensively bound (>99.9% and 98.8%, respectively) to human plasma proteins. Both elbasvir and grazoprevir bind to human serum albumin and α 1-acid glycoprotein. (b) (4)

In preclinical distribution studies, elbasvir distributes into most tissues including the liver; whereas grazoprevir distributes predominantly to the liver likely facilitated by the active transport through the OATP1B liver uptake transporter.

Elimination

The geometric mean apparent terminal half-life (b) (4) is approximately 24 (b) (4) hours at 50 mg elbasvir and approximately 31 (b) (4) hours at 100 mg grazoprevir in HCV-infected subjects.

Metabolism

Elbasvir and grazoprevir are partially eliminated by oxidative metabolism, primarily by CYP3A. No circulating metabolites of either elbasvir or grazoprevir were detected in human plasma.

Excretion

The primary route of elimination of elbasvir and grazoprevir is through feces with almost all (>90%) of radiolabeled dose recovered in feces compared to <1% in urine.

Specific Populations

Hepatic Impairment

The pharmacokinetics of elbasvir and grazoprevir were evaluated in non-HCV-infected subjects with mild hepatic impairment (Child-Pugh Category A [CP-A], score of 5-6), moderate hepatic impairment (Child-Pugh Category B [CP-B], score of 7-9) and severe hepatic impairment (Child-Pugh Category C [CP-C], score of 10-15). In addition, the pharmacokinetics of elbasvir and grazoprevir were also evaluated in HCV-infected subjects (b) (4)

(b) (4)

(b) (4)

Renal Impairment

(b) (4)

(b) (4)

In population pharmacokinetic analysis, elbasvir AUC was 25% higher in dialysis-dependent subjects and 46% higher in non-dialysis-dependent subjects with severe renal impairment compared to elbasvir AUC in subjects without severe renal impairment. In population pharmacokinetic analysis in HCV-infected subjects, grazoprevir AUC was 10% higher in dialysis-dependent subjects and 40% higher in non-dialysis-dependent subjects with severe renal impairment compared to grazoprevir AUC in subjects without severe renal impairment.

Overall, changes in exposure of elbasvir and grazoprevir in HCV-infected subjects with renal impairment with or without dialysis are not clinically relevant. (b) (4)

[see Use in

Specific Populations (8.8)].

Pediatric Population

The pharmacokinetics of ZEPATIER in pediatric patients less than 18 years of age have not been established.

Geriatric Population

In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be (b) (4) higher, respectively, in (b) (4) 65-year-old subjects compared to young subjects. (b) (4)

Gender

In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 50% and 30% higher, respectively, in females compared to males. (b) (4)

Weight/BMI

In population pharmacokinetic analyses, there was no effect of weight on elbasvir pharmacokinetics. Grazoprevir AUC is estimated to be 15% higher in subjects who are ^{(b) (4)}53 kg. This change is not clinically relevant for grazoprevir. ^{(b) (4)}

Race/Ethnicity

In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 15% and 50% higher, respectively, for Asians compared to White. Population pharmacokinetics estimates of exposure of elbasvir and grazoprevir were comparable between White and Black/African Americans. ^{(b) (4)}

Drug Interaction Studies

Drug interaction studies were performed in healthy adults with elbasvir, grazoprevir, or co-administered elbasvir and grazoprevir and drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interactions. Table ^{(b) (4)} summarizes the effects of co-administered drugs on the exposures of the individual components of ZEPATIER (elbasvir and grazoprevir). Table ^{(b) (4)} summarizes the effects of the individual components of ZEPATIER on the exposures of the co-administered drugs. For information regarding clinical recommendations, see *Warnings and Precautions (5.3) and Drug Interactions (7)*. Elbasvir and grazoprevir are substrates of CYP3A/P-gp, but the role of intestinal P-gp in the absorption of elbasvir and grazoprevir is minimal. ^{(b) (4)}

Grazoprevir is a substrate of OATP1B. Co-administration of ZEPATIER with drugs that inhibit OATP1B transporters may result in a clinically relevant increase in grazoprevir plasma concentrations.

Elbasvir is not a CYP3A inhibitor *in vitro* and grazoprevir is a weak CYP3A inhibitor in humans. Co-administration with grazoprevir ^{(b) (4)}

^{(b) (4)} a 34% increase in plasma exposure of midazolam and a 43% increase in plasma exposure of tacrolimus (see Table ^{(b) (4)}). ^{(b) (4)}

Clinically significant drug interactions with ZEPATIER as an inhibitor of other CYP enzymes, UGT1A1, and esterases (CES1, CES2, and CatA), are not expected, and multiple-dose administration of elbasvir or grazoprevir is unlikely to induce the metabolism of drugs metabolized by CYP isoforms based on *in vitro* data. A clinical interaction study with montelukast confirmed that grazoprevir is not a CYP2C8 inhibitor (CYP isoform with lowest *in vitro* IC₅₀). ^{(b) (4)}

Grazoprevir is not a P-gp inhibitor *in vitro*. ^{(b) (4)}

Elbasvir and grazoprevir are inhibitors of the drug transporter breast cancer resistance protein (BCRP) at the intestinal level in humans and may increase plasma concentrations of co-administered BCRP substrates. (b) (4)

Table 6: Drug Interactions: Changes in Pharmacokinetics of Elbasvir or Grazoprevir in the Presence of Co-Administered Drug

Co-Administered Drug	Regimen of Co-Administered Drug	Regimen of EBR or/and GZR	N	Geometric Mean Ratio [90% CI] of EBR and GZR PK with/without Co-Administered Drug (No Effect=1.00)			
					AUC*	C _{max}	C ₂₄
Antifungal							
Ketoconazole	400 mg once daily	EBR 50 mg single-dose	7	EBR	1.80 (1.41, 2.29)	1.29 (1.00, 1.66)	1.89 (1.37, 2.60)
	400 mg once daily	GZR 100 mg single-dose	8	GZR	3.02 (2.42, 3.76)	1.13 (0.77, 1.67)	(b) (4)
Antimycobacterial							
Rifampin	600 mg single-dose IV	EBR 50 mg single-dose	14	EBR	1.22 (1.06, 1.40)	1.41 (1.18, 1.68)	1.31 (1.12, 1.53)
	600 mg single-dose PO	EBR 50 mg single-dose	14	EBR	1.17 (0.98, 1.39)	1.29 (1.06, 1.58)	1.21 (1.03, 1.43)
	600 mg PO once daily	GZR 200 mg once daily	12	GZR	0.93 (0.75, 1.17)	1.16 (0.82, 1.65)	0.10 (0.07, 0.13)
	600 mg IV single-dose	GZR 200 mg single-dose	12	GZR	10.21 (8.68, 12.00)	10.94 (8.92, 13.43)	1.77 (1.40, 2.24)
	600 mg PO single-dose	GZR 200 mg once daily	12	GZR	8.35 (7.38, 9.45) [†]	6.52 (5.16, 8.24)	1.62 (1.32, 1.98)
HCV Antiretroviral							
EBR	20 mg once daily	GZR 200 mg once daily	10	GZR	0.90 (0.63, 1.28)	0.87 (0.50, 1.52)	0.94 (0.77, 1.15)
GZR	200 mg once daily	EBR 20 mg once daily	10	EBR	1.01 (0.83, 1.24)	0.93 (0.76, 1.13)	1.02 (0.83, 1.24)
HIV Protease Inhibitor							
Atazanavir/ritonavir	300 mg/ 100 mg once daily	EBR 50 mg once daily	10	EBR	4.76 (4.07, 5.56)	4.15 (3.46, 4.97)	6.45 (5.51, 7.54)
	300 mg/ 100 mg once daily	GZR 200 mg once daily	12	GZR	10.58 (7.78, 14.39)	6.24 (4.42, 8.81)	11.64 (7.96, 17.02)
Darunavir/ritonavir	600 mg/ 100 mg twice daily	EBR 50 mg once daily	10	EBR	1.66 (1.35, 2.05)	1.67 (1.36, 2.05)	1.82 (1.39, 2.39)
	600 mg/ 100 mg twice daily	GZR 200 mg once daily	13	GZR	7.50 (5.92, 9.51)	5.27 (4.04, 6.86)	8.05 (6.33, 10.24)
Lopinavir/ritonavir	400 mg/ 100 mg twice daily	EBR 50 mg once daily	10	EBR	3.71 (3.05, 4.53)	2.87 (2.29, 3.58)	4.58 (3.72, 5.64)
	400 mg/ 100 mg twice daily	GZR 200 mg once daily	13	GZR	12.86 (10.25, 16.13)	7.31 (5.65, 9.45)	21.70 (12.99, 36.25)
Ritonavir [‡]	100 mg twice daily	GZR 200 mg single-dose	10	GZR	2.03 (1.60, 2.56)	1.15 (0.60, 2.18)	1.88 (1.65, 2.14)
HIV Integrase Strand Transfer Inhibitor							
Dolutegravir	50 mg single-dose	EBR 50 mg + GZR 200 mg once daily	12	EBR	0.98 (0.93, 1.04)	0.97 (0.89, 1.05)	0.98 (0.93, 1.03)
	50 mg single-	EBR 50 mg +	12	GZR	0.81 (0.67, 0.97)	0.64 (0.44, 0.93)	0.86 (0.79, 0.93)

	dose	GZR 200 mg once daily					
Raltegravir	400 mg single-dose	EBR 50 mg single-dose	10	EBR	0.81 (0.57, 1.17)	0.89 (0.61, 1.29)	0.80 (0.55, 1.16)
	400 mg twice daily	GZR 200 mg once daily	11	GZR	0.89 (0.72, 1.09)	0.85 (0.62, 1.16)	0.90 (0.82, 0.99)
HIV Non-Nucleoside Reverse Transcriptase Inhibitor							
Efavirenz	600 mg once daily	EBR 50 mg once daily	10	EBR	0.46 (0.36, 0.59)	0.55 (0.41, 0.73)	0.41 (0.28, 0.59)
	600 mg once daily	GZR 200 mg once daily	12	GZR	0.17 (0.13, 0.24)	0.13 (0.09, 0.19)	0.31 (0.25, 0.38)
Rilpivirine	200 mg once daily	EBR 50 mg + GZR 200 mg once daily	19	EBR	1.07 (1.00, 1.15)	1.07 (0.99, 1.16)	1.04 (0.98, 1.11)
	200 mg once daily	EBR 50 mg + GZR 200 mg once daily	19	GZR	0.98 (0.89, 1.07)	0.97 (0.83, 1.14)	1.00 (0.93, 1.07)
HIV Nucleotide Reverse Transcriptase Inhibitor							
Tenofovir disoproxil fumarate	300 mg once daily	EBR 50 mg once daily	10	EBR	0.93 (0.82, 1.05)	0.88 (0.77, 1.00)	0.92 (0.81, 1.05)
	300 mg once daily	GZR 200 mg once daily	12	GZR	0.86 (0.65, 1.12)	0.78 (0.51, 1.18)	0.89 (0.78, 1.01)
Immunosuppressant							
Cyclosporine	400 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	EBR	1.98 (1.84, 2.13)	1.95 (1.84, 2.07)	2.21 (1.98, 2.47)
	400 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	GZR	15.21 (12.83, 18.04)	17.00 (12.94, 22.34)	3.39 (2.82, 4.09)
Mycophenolate mofetil	1000 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	EBR	1.07 (1.00, 1.14)	1.07 (0.98, 1.16)	1.05 (0.97, 1.14)
	1000 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	GZR	0.74 (0.60, 0.92)	0.58 (0.42, 0.82)	0.97 (0.89, 1.06)
Prednisone	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	EBR	1.17 (1.11, 1.24)	1.25 (1.16, 1.35)	1.04 (0.97, 1.12)
	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	GZR	1.09 (0.95, 1.25)	1.34 (1.10, 1.62)	0.93 (0.87, 1.00)
Tacrolimus	2 mg single-dose	EBR 50 mg + GZR 200 mg once daily	16	EBR	0.97 (0.90, 1.06)	0.99 (0.88, 1.10)	0.92 (0.83, 1.02)
	2 mg single-dose	EBR 50 mg + GZR 200 mg once daily	16	GZR	1.12 (0.97, 1.30)	1.07 (0.83, 1.37)	0.94 (0.87, 1.02)
Opioid-Substitution Therapy							
Buprenorphine/naloxone	8 mg/2 mg single-dose	EBR 50 mg single-dose	15	EBR	1.22 (0.98, 1.52)	1.13 (0.87, 1.46)	1.22 (0.99, 1.51)

(b) (4)

Acid-Reducing Agent							
Famotidine	20 mg single-dose	EBR 50 mg/ GZR 100 mg single-dose	16	EBR	1.05 (0.92, 1.18)	1.11 (0.98, 1.26)	1.03 (0.91, 1.17)
	20 mg single-dose	EBR 50 mg/ GZR 100 mg single-dose	16	GZR	1.10 (0.95, 1.28)	0.89 (0.71, 1.11)	1.12 (0.97, 1.30)
Pantoprazole	40 mg once daily	EBR 50 mg/ GZR 100 mg single-dose	16	EBR	1.05 (0.93, 1.18)	1.02 (0.92, 1.14)	1.03 (0.92, 1.17)
	40 mg once daily	EBR 50 mg/ GZR 100 mg single-dose	16	GZR	1.12 (0.96, 1.30)	1.10 (0.89, 1.37)	1.17 (1.02, 1.34)
Phosphate Binder							
Calcium acetate	2668 mg single-dose	EBR 50 mg + GZR 100 mg single-dose	12	EBR	0.92 (0.75, 1.14)	0.86 (0.71, 1.04)	0.87 (0.70, 1.09)
	2668 mg single-dose	EBR 50 mg + GZR 100 mg single-dose	12	GZR	0.79 (0.68, 0.91)	0.57 (0.40, 0.83)	0.77 (0.61, 0.99)
Sevelamer carbonate	2400 mg single-dose	EBR 50 mg + GZR 100 mg single-dose	12	EBR	1.13 (0.94, 1.37)	1.07 (0.88, 1.29)	1.22 (1.02, 1.45)
	2400 mg single-dose	EBR 50 mg + GZR 100 mg single-dose	12	GZR	0.82 (0.68, 0.99)	0.53 (0.37, 0.76)	0.84 (0.71, 0.99)
Statin							
Atorvastatin	20 mg single-dose	GZR 200 mg once daily	9	GZR	1.26 (0.97, 1.64)	1.26 (0.83, 1.90)	1.11 (1.00, 1.23)
Pitavastatin	1 mg single-dose	GZR 200 mg once daily	9	GZR	0.81 (0.70, 0.95)	0.72 (0.57, 0.92)	0.91 (0.82, 1.01)
Pravastatin	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	12	EBR	0.98 (0.93, 1.02)	0.97 (0.89, 1.05)	0.97 (0.92, 1.02)
	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	12	GZR	1.24 (1.00, 1.53)	1.42 (1.00, 2.03)	1.07 (0.99, 1.16)
Rosuvastatin	10 mg single-dose	EBR 50 mg + GZR 200 mg single-dose	11	EBR	1.09 (0.98, 1.21)	1.11 (0.99, 1.26)	0.96 (0.86, 1.08)
	10 mg single-dose	GZR 200 mg once daily	11	GZR	1.16 (0.94, 1.44)	1.13 (0.77, 1.65)	0.93 (0.84, 1.03)
	10 mg single-dose	EBR 50 mg + GZR 200 mg once daily	11	GZR	1.01 (0.79, 1.28)	0.97 (0.63, 1.50)	0.95 (0.87, 1.04)

EBR + GZR, administration of EBR and GZR as separate pills; EBR/GZR, administration of EBR and GZR as a single fixed-dose combination tablet *AUC_{0-inf} for single-dose, AUC₀₋₂₄ for once daily †AUC₀₋₂₄ ‡Higher doses of ritonavir have not been tested in a drug interaction study with GZR

Table 7: Drug Interactions: Changes in Pharmacokinetics for Co-Administered Drug in the Presence of Elbasvir, Grazoprevir, or Co-Administered Elbasvir and Grazoprevir

Co-Administered Drug	Regimen of Co-Administered Drug	EBR or/and GZR Administration	EBR or/and GZR Regimen	N	Geometric Mean Ratio [90% CI] of Co-Administered Drug PK with/without EBR or/and GZR (No Effect=1.00)		
					AUC*	C _{max}	C _{trough} [†]
P-gp Substrate							
Digoxin	Digoxin 0.25 mg single-dose	EBR	50 mg once daily	18	1.11 (1.02, 1.22)	1.47 (1.25, 1.73)	--
CYP3A Substrate							
Midazolam	Midazolam 2 mg single-dose	GZR	200 mg once daily	11	1.34 (1.29, 1.39)	1.15 (1.01, 1.31)	--
CYP2C8 Substrate							
Montelukast	Montelukast 10 mg single-dose	GZR	200 mg once daily	23	1.11 (1.01, 1.20)	0.92 (0.81, 1.06)	1.39 (1.25, 1.56)
HCV Antiretroviral							
GS-331007	Sofosbuvir 400 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	16	1.13 (1.05, 1.21)	0.87 (0.78, 0.96)	1.53 (1.43, 1.63)
Sofosbuvir	Sofosbuvir 400 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	16	2.43 (2.12, 2.79) [‡]	2.27 (1.72, 2.99)	--
HIV Protease Inhibitor							
Atazanavir/ritonavir	Atazanavir 300 mg/ritonavir 100 mg once daily	EBR	50 mg once daily	8	1.07 (0.98, 1.17)	1.02 (0.96, 1.08)	1.15 (1.02, 1.29)
	Atazanavir 300 mg/ritonavir 100 mg once daily	GZR	200 mg once daily	11	1.43 (1.30, 1.57)	1.12 (1.01, 1.24)	1.23 (1.13, 1.34)
Darunavir/ritonavir	Darunavir 600 mg/ritonavir 100 mg twice daily	EBR	50 mg once daily	8	0.95 (0.86, 1.06)	0.95 (0.85, 1.05)	0.94 (0.85, 1.05)
	Darunavir 600 mg/ritonavir 100 mg twice daily	GZR	200 mg once daily	13	1.11 (0.99, 1.24)	1.10 (0.96, 1.25)	1.00 (0.85, 1.18)
Lopinavir/ritonavir	Lopinavir 400 mg/ritonavir 100 mg twice daily	EBR	50 mg once daily	9	1.02 (0.93, 1.13)	1.02 (0.92, 1.13)	1.07 (0.97, 1.18)
	Lopinavir 400 mg/ritonavir 100 mg twice daily	GZR	200 mg once daily	13	1.03 (0.96, 1.16)	0.97 (0.88, 1.08)	0.97 (0.81, 1.15)

HIV Integrase Strand Transfer Inhibitor							
Dolutegravir	Dolutegravir 50 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	12	1.16 (1.00, 1.34)	1.22 (1.05, 1.40)	1.14 (0.95, 1.36)
Raltegravir	Raltegravir 400 mg single-dose	EBR	50 mg single-dose	10	1.02 (0.81, 1.27)	1.09 (0.83, 1.44)	0.99 (0.80, 1.22) [§]
	Raltegravir 400 mg twice daily	GZR	200 mg once daily	11	1.43 (0.89, 2.30)	1.46 (0.78, 2.73)	1.47 (1.09, 2.00)
HIV Non-Nucleoside Reverse Transcriptase Inhibitor							
Efavirenz	Efavirenz 600 mg once daily	EBR	50 mg once daily	7	0.82 (0.78, 0.86)	0.74 (0.67, 0.82)	0.91 (0.87, 0.96)
	Efavirenz 600 mg once daily	GZR	200 mg once daily	11	1.00 (0.96, 1.05)	1.03 (0.99, 1.08)	0.93 (0.88, 0.98)
Rilpivirine	Rilpivirine 200 mg once daily	EBR + GZR	50 mg + 200 mg once daily	19	1.13 (1.07, 1.20)	1.07 (0.97, 1.17)	1.16 (1.09, 1.23)
HIV Nucleotide Reverse Transcriptase Inhibitor							
Tenofovir disoproxil fumarate	Tenofovir DF 300 mg once daily	EBR	50 mg once daily	10	1.34 (1.23, 1.47)	1.47 (1.32, 1.63)	1.29 (1.18, 1.41)
	Tenofovir DF 300 mg once daily	GZR	200 mg once daily	12	1.18 (1.09, 1.28)	1.14 (1.04, 1.25)	1.24 (1.10, 1.39)
Immunosuppressant							
Cyclosporine	Cyclosporine 400 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	14	0.96 (0.90, 1.02)	0.90 (0.85, 0.97)	1.00 (0.92, 1.08) [§]
Mycophenolic acid	Mycophenolate mofetil 1000 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	14	0.95 (0.87, 1.03)	0.95 (0.67, 1.07)	--
Prednisolone	Prednisone 40 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	14	1.08 (1.01, 1.16)	1.04 (0.99, 1.09)	--
Prednisone	Prednisone 40 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	14	1.08 (1.00, 1.17)	1.05 (1.00, 1.10)	--
Tacrolimus	Tacrolimus 2 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	16	1.43 (1.24, 1.64)	0.60 (0.52, 0.69)	1.70 (1.49, 1.94) [§]
Oral Contraceptive							
Ethinyl estradiol (EE)	0.03 mg EE/ 0.15 mg LNG single-dose	EBR	50 mg once daily	20	1.01 (0.97, 1.05)	1.10 (1.05, 1.16)	--
		GZR	200 mg once daily	20	1.10 (1.05, 1.14)	1.05 (0.98, 1.12)	--
Levonorgestrel (LNG)		EBR	50 mg once daily	20	1.14 (1.04, 1.24)	1.02 (0.95, 1.08)	--
		GZR	200 mg once daily	20	1.23 (1.15, 1.32)	0.93 (0.84, 1.03)	--

Opioid Substitution Therapy							
Buprenorphine	Buprenorphine 8 mg/Naloxone 2 mg single-dose	EBR	50 mg once daily	15	0.98 (0.89, 1.08)	0.94 (0.82, 1.08)	0.98 (0.88, 1.09)
	Buprenorphine 8-24 mg/Naloxone 2-6 mg once daily	GZR	200 mg once daily	12	0.98 (0.81, 1.19)	0.90 (0.76, 1.07)	--
R-Methadone	Methadone 20-150 mg once daily	EBR	50 mg once daily	10	1.03 (0.92, 1.15)	1.07 (0.95, 1.20)	1.10 (0.96, 1.26)
		GZR	200 mg once daily	12	1.09 (1.02, 1.17)	1.03 (0.96, 1.11)	--
S-Methadone		EBR	50 mg once daily	10	1.09 (0.94, 1.26)	1.09 (0.95, 1.25)	1.20 (0.98, 1.47)
		GZR	200 mg once daily	12	1.23 (1.12, 1.35)	1.15 (1.07, 1.25)	--
Statin							
Atorvastatin	Atorvastatin 10 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	16	1.94 (1.63, 2.33)	4.34 (3.10, 6.07)	0.21 (0.17, 0.26)
		(b) (4)					
Pitavastatin	Pitavastatin 1 mg single-dose	GZR	200 mg once daily	9	1.11 (0.91, 1.34)	1.27 (1.07, 1.52)	--
Pravastatin	Pravastatin 40 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	12	1.33 (1.09, 1.64) [†]	1.28 (1.05, 1.55)	--
Rosuvastatin	Rosuvastatin 10 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	12	2.26 (1.89, 2.69) [#]	5.49 (4.29, 7.04)	0.98 (0.84, 1.13)
		GZR	200 mg once daily	12	1.59 (1.33, 1.89) [#]	4.25 (3.25, 5.56)	0.80 (0.70, 0.91)

Abbreviations: EBR, elbasvir; GZR, grazoprevir; EBR + GZR, administration of EBR and GZR as separate tablets

*AUC_{0-inf} for single-dose administration; AUC₀₋₂₄ for once daily administration; AUC₀₋₁₂ for twice daily administration

[†]C24 for once daily administration; C12 for twice daily administration

[#]N=14 [§]C12 [†]N=10 [#]N=8

4. INDIVIDUAL STUDY REVIEWS

4.1. Hepatic impairment

Title: A Three-Part, Open-Label, Single-Dose Study to Investigate the Influence of Hepatic Impairment on the Pharmacokinetics of Elbasvir (MK-8742)

Trial initiation date: 08-Mar-2013

Trial completion date: 27-Aug-2014

Trial centers: Orlando Clinical Research Center, Orlando, FL; Clinical Pharmacology of Miami, Inc, Miami, FL; University of Miami, Miami, FL

Study design

This was a 3-part, open-label, sequential-panel, single-dose study to compare the pharmacokinetics of a single oral dose of elbasvir in subjects with mild, moderate, or severe hepatic impairment (as assessed by the criteria of the Child-Pugh classification) to healthy matched control subjects. Twenty-three (23) male and female hepatic impairment subjects and 8 healthy male and female subjects were enrolled in 4 sequential panels. Panel I consisted of 8 subjects with mild hepatic impairment; Panel II consisted of 11 subjects with moderate hepatic impairment; Panel III consisted of 7 subjects with severe hepatic impairment; Panel IV consisted of 8 healthy control subjects matched by gender and to the mean of all the hepatic impairment subjects for age and weight. Each patient/subject received a single oral dose of 50 mg elbasvir in the fasted state.

Subjects fasted for at least 8 hours prior to study drug administration. Elbasvir doses were administered with approximately 240 mL of water, with additional water and other fluid restricted 1 hour prior to and 1 hour after study drug administration. For each panel, blood sampling for pharmacokinetic evaluation of elbasvir was performed at predose and at specific time points up to 168 hours postdose.

Key inclusion criteria

Inclusion Criteria – Hepatic Impairment Subjects

- A male or female between 18 to 75 years of age, BMI 18-40 kg/m² (inclusive)
- Female subjects may be of non-childbearing potential. For females of childbearing potential should be either sexually inactive (abstinent) for 14 days or be using acceptable birth control methods. Non-vasectomized male subjects must agree to use a condom with spermicide or abstain from sexual intercourse during the trial and for 3 months after study drug administration.
- Apart from hepatic impairment with features of cirrhosis, subject is otherwise judged to be in good health and no clinically significant abnormality on electrocardiogram (ECG)
- Diagnosis of chronic (> 6 months), stable hepatic insufficiency with features of cirrhosis due to any etiology.
- Subject's score on the Child-Pugh scale must range from 5 to 6 (mild hepatic impairment) to from 7 to 9 (moderate hepatic impairment) to from 10 to 15 (severe hepatic impairment). In Part II (CP-B), 50% of the subjects must have a score of 2 or higher on at least 1 of the laboratory parameters (i.e., albumin, prothrombin time, bilirubin). For subjects who have compensated

hepatic impairment while on medical therapy, they should be classified by their pre-treatment parameter values.

Healthy Matched Control Subjects

- Healthy adult male or female, 18 - 75 years of age, inclusive, and within ± 15 years of the mean age of the same-gender subjects with hepatic impairment.
- BMI 19 - 40 kg/m², inclusive and weight within $\pm 20\%$ of the mean weight of the same gender subjects with hepatic impairment.
- Subject is judged to be in good health based on medical history, physical examination, vital signs, and laboratory safety tests. Subject has no clinically significant abnormality on ECG.
- Female subjects may be of non-childbearing or of reproductive potential. For females of childbearing potential should be either sexually inactive (abstinent) for 14 days or be using acceptable birth control methods. Non-vasectomized male subjects must agree to use a condom with spermicide or abstain.

Key exclusion criteria

- CrCL of ≤ 30 mL/min based on the Cockcroft-Gault equation
- Significant past and present medical history (except liver disease for subjects with hepatic impairment)
- HIV or untreated HCV (cured subjects are eligible to enroll)
- Subject consumes excessive amounts of alcohol (> 3 glasses of alcoholic beverages /day), excessive caffeinated beverage (> 6 servings/day), uses drugs, or have a history of drug and alcohol abuse
- Significant blood loss or blood donation within 56 days prior to study drug administration
- Lactating or pregnant subjects
- Positive screening results for HBsAg (matched healthy subjects only)

Identity of investigational product

Elbasvir 10 mg (b) (4) (Lot number DL00018432, DL00018002) were supplied for this trial.

Concomitant medications

All prescription or non-prescription medications (including herbal preparations) that are strong CYP3A4 or P-gp inhibitors, inhibitors of OATP1B transporters, or strong inducers of CYP3A4 or P-gp transporters were prohibited (at least 28 days and 14 days, respectively or 5 half-lives of the drug whichever was longer), prior to study drug administration and throughout the study. Certain prescription medications used to treat manifestations of hepatic disease or medications needed to treat stable diseases (e.g., diuretics, lactulose, etc.) were allowed during the study, but the patient must have been on a steady dose, drug, and regimen for 14 days prior to study drug administration on Day 1.

Any acid-suppressing agents (i.e., H₂ antagonists and proton pump inhibitors) were restricted for the 3 days prior to the first dose of the study since it could potentially affect absorption of elbasvir. If medically necessary, antacids (e.g., Maalox, Tums, Rolaids, Gaviscon, Gelusil, etc.) for acid reflux or heartburn may have been administered 4 hours predose or 4 hours post dose on Day 1. Lactulose was restricted for the 6 hours prior to and after dosing on Day 1 since it could potentially affect absorption of elbasvir.

Pharmacokinetic assessments

Blood samples for elbasvir analysis in plasma were collected at predose and at selected time points over 168 hours following a single dose of 50 mg elbasvir. All pharmacokinetic parameter values, with the exception of C_{24} , were calculated using WinNonlin Professional (Version 6.3). C_{max} and T_{max} were generated from the observed elbasvir plasma concentration-time data. AUCs were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down). Blood samples were also collected at pre-dose and 4 hours post-dose for *in vitro* protein binding analysis of elbasvir.

Bioanalysis

Plasma concentrations of elbasvir were determined by (b) (4) (using validated high performance liquid chromatographic tandem mass spectrometric (LC/MS/MS) methods. The lower limit of quantification (LLOQ) was 0.28 nM.

Table 1. Summary of bioanalysis

Analyte	Elbasvir (MK-8742)
Internal standard	[² H ₆]MK-8742
Matrix/anticoagulant/aliquot	Plasma
Method of detection	K ₂ EDTA
Range of linearity	0.25 – 500 ng/mL
QC concentration	0.75 ng/mL, 75 ng/mL, 375 ng/mL
Highest diluted QC concentration	10000 ng/mL (5X and 25X dilution)
Demonstrated storage stability	At least 651 days at -20 °C
Extraction methods	Liquid-liquid extraction
Inter-run precision	3.8 to 5.1%
Inter-run accuracy	-0.7 to 3.9%

Results

Subject baseline demographics

The demographic information and baseline characteristics are summarized in Table 2.

Table 2. Baseline characteristics of subjects

	Mild hepatic impairment	Moderate hepatic impairment	Severe hepatic impairment	Matched healthy volunteers
Number of subjects	8	8	7	8
Age (mean, range)	54 (39-66)	54 (42-68)	56 (48-62)	54 (46-69)
BMI (mean, range)	31.1 (19.4-39.8)	31.8 (23.0-35.9)	27.2 (22.1-34.4)	29.1 (25.9-35.1)
Race	White: 8	White 6 Black/African American: 2	White: 7	White: 7 Black/African American: 1

Gender (female/male)	0/8	1/7	4/3	2/6
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Reviewer comments: Race and gender are not matched between hepatic impairment groups and the healthy volunteer group. Refer to reviewer comments under pharmacokinetic study results.

Pharmacokinetic results

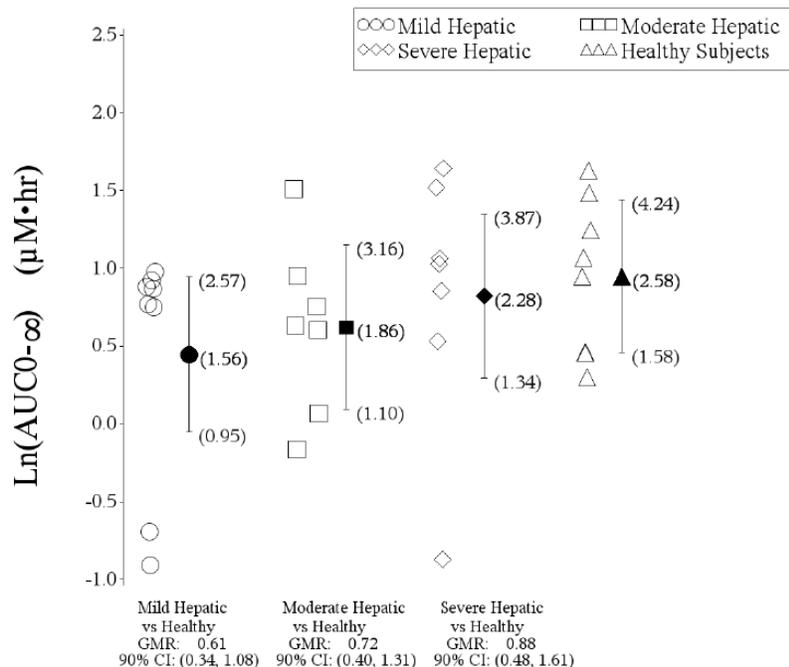
Following a single oral dose administration of EBR 50 mg, EBR AUCs were consistently lower (36-40% for AUC_{24hr}, 12-39% for AUC_{0-∞}) in subjects with varying degrees of hepatic impairment as compared to matched healthy volunteers. C_{max} and C_{min} were also 22-40% lower in subjects with varying degrees of hepatic impairment as compared to matched healthy volunteers. The observed median T_{max} were similar in subjects with varying degrees of hepatic impairment compared to matched healthy volunteers.

Table 3. Pharmacokinetics of elbasvir following a single oral dose of 50 mg elbasvir administered to subjects with mild, moderate, and severe hepatic impairment and matched healthy volunteers

Elbasvir Pharmacokinetic Parameter	Mild Hepatic Insufficiency Patients			Moderate Hepatic Insufficiency Patients			Severe Hepatic Insufficiency Patients			Healthy Control Subjects		
	N	GM	95% CI	N [‡]	GM	95% CI	N	GM	95% CI	N	GM	95% CI
AUC _{0-∞} [†] (μM·hr)	8	1.56	(0.95, 2.57)	7	1.86	(1.10, 3.16)	7	2.28	(1.34, 3.87)	8	2.58	(1.58, 4.24)
AUC ₀₋₂₄ [†] (μM·hr)	8	0.87	(0.54, 1.41)	7	0.92	(0.55, 1.55)	7	0.92	(0.55, 1.54)	8	1.45	(0.90, 2.35)
C _{max} [†] (nM)	8	70.1	(42.3, 116)	8	83.0	(50.1, 137)	7	70.7	(41.3, 121)	8	121	(73.1, 200)
C ₂₄ [†] (nM)	8	22.9	(14.0, 37.5)	7	25.9	(15.3, 43.9)	7	29.6	(17.4, 50.1)	8	37.7	(23.0, 61.7)
T _{max} [§] (hr)	8	3.50	(2.00, 6.00)	8	3.50	(2.00, 4.00)	7	4.00	(3.00, 4.00)	8	3.50	(2.00, 4.00)
Apparent terminal t _{1/2} (hr)	8	24.80	21.65	7	25.39	34.24	7	33.72	20.82	8	20.74	12.64
Elbasvir Pharmacokinetic Parameter	Mild Hepatic Insufficiency/Healthy Control		Moderate Hepatic Insufficiency/Healthy Control		Severe Hepatic Insufficiency/Healthy Control		rMSE ^{††}					
	GMR	90% CI	GMR	90% CI	GMR	90% CI						
AUC _{0-∞} [†] (μM·hr)	0.61	(0.34, 1.08)	0.72	(0.40, 1.31)	0.88	(0.48, 1.61)	0.681					
AUC ₀₋₂₄ [†] (μM·hr)	0.60	(0.34, 1.05)	0.64	(0.35, 1.14)	0.63	(0.35, 1.13)	0.661					
C _{max} [†] (nM)	0.58	(0.32, 1.05)	0.69	(0.38, 1.24)	0.58	(0.32, 1.08)	0.695					
C ₂₄ [†] (nM)	0.61	(0.34, 1.08)	0.69	(0.38, 1.25)	0.78	(0.43, 1.43)	0.678					

Treatment: Single oral dose of 50 mg elbasvir (5 x 10 mg capsules) administered orally with approximately 240 mL of water on the morning of Day 1 following an overnight fast of at least 8 hours.
Mild Hepatic Insufficiency: Patients with a score of 5 to 6 on the Child Pugh scale enrolled in Panel I of the study.
Moderate Hepatic Insufficiency: Patients with a score of 7 to 9 on the Child Pugh scale enrolled in Panel II of the study.
Severe Hepatic Insufficiency: Patients with a score of 10 to 15 on the Child Pugh scale enrolled in Panel III of the study.
Healthy Matched Control: Healthy subjects enrolled in Panel IV of the study, matched for age, gender, and weight to the mean of all patients with hepatic insufficiency (Panels I, II, and III).
[†]Back-transformed least-squares mean and confidence interval from linear fixed effect model performed on natural log-transformed values.
[‡]Three (3) patients reenrolled in Panel II were not included in the analysis. One (1) patient was discontinued prior to the 12-hour blood draw (due to serious adverse event of acute alcohol withdrawal seizure). Consequently, only C_{max} and T_{max} data from this patient were included in the analysis.
[§]Median (min, max) reported for T_{max}.
^{||}Geometric mean and percent geometric coefficient of variation reported for apparent terminal t_{1/2}.
^{††}rMSE root mean square error from the linear model; when multiplied by 100, approximates the between-subject coefficient of variation.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatment populations

Fig. 1. Individual EBR AUC_∞ values (log-transformed) in subjects with varying degrees of hepatic impairment and matched healthy volunteers



Reviewer comments

EBR exposures were approximately 20-40% lower in subjects with varying degrees of hepatic impairment as compared to matched healthy volunteers. As shown in Fig 1, the ~ 40% decrease in EBR AUC in subjects with mild hepatic impairment appears to be driven by two outliers. The underlying mechanism is unknown. It is unlikely the results of changes in albumin binding as these two subjects' albumin levels were normal (4.4-4.7 g/dL). Phase 2-3 data indicated that the safety, efficacy, and pharmacokinetics (population pharmacokinetic analysis) of EBR are comparable between chronic hepatitis C (CHC) patients without cirrhosis and those with compensated cirrhosis and are classified as CP-A. Therefore, EBR can be used in subjects with mild hepatic impairment without a dose adjustment. The magnitude of changes in EBR exposures observed in moderate and severe hepatic impairment appears not to be clinically relevant. However, EBR is one component of the fixed dose combination product (proposed name: ZEPATIER) that also contains grazoprevir (GZR). Since the use of GZR is not recommended in patients with moderate and severe hepatic impairment, EBR won't be used in these populations either.

Gender and race were not matched between hepatic impairment groups and the healthy volunteer group (Table 1). Population pharmacokinetic analysis indicated that EBR exposures are approximately 50% higher in female patients as compared to male patients. Therefore, the imbalance in the number of female subjects between the hepatically impaired study groups and the healthy controls group in this trial may result in results that either under- or overestimated the true effect for each group.

4. The sponsor conducted a protein binding assay using samples from this study. Pre-dose samples were collected, elbasvir was added, and equilibrium dialysis was conducted. Therefore, the results do not directly represent in vivo changes in plasma protein binding following oral administration of elbasvir and the protein binding study is not considered a part of the hepatic impairment PK study. According to the

protocol, the sponsor collected 4 hours post-dose samples for a protein binding assay but no study reports have been submitted.

Conclusion

- Following a single oral dose administration of EBR 50mg, EBR AUCs were consistently lower (36-40% for AUC_{24hr} , 12-39% for $AUC_{0-\infty}$) in subjects with varying degrees of hepatic impairment as compared to matched healthy volunteers.
- ZEPATIER (fixed dose combination tablet containing GZR and EBR) can be used without a dose adjustment in patients with mild hepatic impairment.
- The use of ZEPATIER in moderate or severe hepatic impairment is not recommended due to increased GZR exposures. Refer to PN013 study review.

Title: An Open-label, 3-Part, Multiple Dose Study to Investigate the Influence of Hepatic Insufficiency on the Pharmacokinetics of Grazoprevir (5172-PN013)

Trial Initiation Date: 25-Jul-2011

Trial Completion Date: 12-Sep-2014

Trial centers: multi-center (1 in New Zealand, 1 in Australia, 2 in the United States)

Study Design

This was a 3-part, open-label, sequential-panel, multiple-dose study comparing the pharmacokinetics of grazoprevir (MK-5172; GZR) in subjects (non-HCV-infected) with mild, moderate or severe hepatic impairment (assessed by the Child-Pugh scale) with healthy matched control subjects.

Part I: 8 subjects with mild hepatic impairment (a score of 5 to 6, on the Child-Pugh's scale) and 8 healthy matched control subjects [race, age (\pm 5 years), gender, BMI (\pm 15%)] were enrolled. All subjects received oral doses of 200 mg GZR (2X 100 mg tablets) once daily for 10 days.

In Part II, 8 subjects with moderate hepatic impairment (a score of 7 to 9, on the Child-Pugh's scale) and 8 healthy matched control subjects [race, age (\pm 5 years), gender, BMI (\pm 20%)] were enrolled. All subjects received oral doses of 100 mg (1X 100 mg tablet) grazoprevir once daily for 10 days.

In Part III, 8 subjects with severe hepatic impairment (a score of 10 to 15 on the Child-Pugh's scale) and 8 healthy matched control subjects [race, age (\pm 5 years), gender, BMI (\pm 15%)] were enrolled. All subjects received oral doses of 50 mg (2X 25 mg tablets) GZR once daily for 10 days.

For all parts, GZR was administered with 240 mL of water after an overnight fast.

Key Inclusion Criteria

Hepatic Impairment Subjects

- A male or female between 18 to 65 years of age, BMI 18-40 kg/m² (inclusive)
- Female subjects may be of non-childbearing potential.
- Apart from hepatic impairment with features of cirrhosis, subject is otherwise judged to be in good health and no clinically significant abnormality on ECG.
- Diagnosis of chronic (> 6 months), stable hepatic impairment with features of cirrhosis due to any etiology.
- Subject's score on the Child-Pugh scale must range from 5 to 6 (mild hepatic impairment) to from 7 to 9 (moderate hepatic impairment) to from 10 to 15 (severe hepatic impairment). In Part II (CP-B), 50% of the subjects must have a score of 2 or higher on at least 1 of the laboratory parameters (i.e., albumin, prothrombin time, bilirubin). In Part III (CP-C), 50% of the severe subjects must have a score of 2 or higher on at least 1 of the laboratory parameters.

Healthy Matched Control Subjects

- A male or female between 18 to 65 years of age
- Female subjects may be of non-childbearing potential.
- Subject has a matched BMI, race, gender age as described in Study Design

- Judged to be in good health, no clinically significant abnormality on ECG

Key Exclusion Criteria

- Subject has a history of hepatitis C infection by serology, regardless of most recent viral load status.
- CrCL of ≤ 60 mL/min based on the Cockcroft-Gault equation
- Significant past and present medical history (except liver disease for subjects with hepatic impairment)
- Subject consumes excessive amounts of alcohol (> 3 glasses of alcoholic beverages /day), excessive caffeinated beverage (> 6 servings/day), uses drugs, or have a history of drug and alcohol abuse
- (Healthy volunteer only): Subject has a history of any chronic and/or active hepatic disease

Concomitant medications

All prescription or non-prescription medications (including herbal preparations) that are strong CYP3A4 or P-gp inhibitors, inhibitors of OATP1B transporters, or strong inducers of CYP3A4 or P-gp transporters were prohibited. These metabolizing enzyme inducers and inhibitors were not allowed for 14 days prior to study drug administration and throughout the study. For hepatic impairment subjects, certain prescription medications used to treat manifestations of hepatic disease or medications needed to treat diseases (e.g., diuretics, lactulose, rifaximin, etc.) were allowed during the study, but the subject must have been on a steady dose, drug, and regimen for ~ 14 days prior to study drug administration on Day 1. Lactulose and rifaximin were restricted for the 4 hours prior to and after dosing since they may potentially affect absorption of grazoprevir.

Pharmacokinetic endpoints

Blood samples for the determination of single-dose (Day 1) plasma GZR pharmacokinetics were collected at predose and selected time points over 24 hours post-dose. Blood samples were collected from each subject at predose on Days 2 - 9 and at predose and selected time points over 168 hours postdose on Day 10. Plasma samples for protein binding analysis were collected at pre-dose on Day 1 and 4 hours post-dose on Day 10.

All the pharmacokinetic parameter values were calculated using the software Phoenix® WinNonlin® (Version 6.3). C_{max} and T_{max} were generated by Phoenix® WinNonlin® from the plasma GZR concentration-time data. AUC₀₋₂₄ was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations.

Bioanalysis

Bioanalysis was conducted by [REDACTED]^{(b) (4)} Plasma GZR concentrations were determined using a validated LC-MS/MS method (method ID: LCMSC 556 V 1.00). Validated methods and assay results are summarized in Table 1. Overall, all methods were adequately validated. The standard curve, QC data, and ISR (incurred sample analyses) results met the predefined criteria and indicated assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data except one sample.

Table 1. Summary of bioanalysis

Analyte	Grazoprevir (MK-5172)
Internal standard	MK-5172-d6
Matrix	Plasma
Matrix/anticoagulant/aliquot	Human plasma/ K2DETA/ 200 µL
Method of detection	LC/MS/MS (1/X ² weighed regression)
Range of linearity	1-1000 ng/mL
QC concentration	3, 75 and 750 ng/mL
Highest diluted QC concentration	5000 ng/mL
Demonstrated storage stability*	734 days at -20° C
Analytical procedure	Liquid-liquid extraction
Inter-run precision	3.7%-5.7%
Inter-run accuracy	- 3.01 to -0.94%

*Study sample XWX 216 was stored at -20° C for 1111 days. All other samples were analyzed within established stability.

Reviewer comments: A sensitivity analysis was conducted by the reviewer to determine the impact of including the results of sample XWX 216 (subject 006, Part A, 4 hour post-dose sample on Day 10). The overall conclusion of the study was not changed by excluding the results of XWX216.

Results

Subject disposition and demographic information

Subject disposition and demographic information are summarized in Table 2.

Table 2. Baseline characteristics of study subjects

	Mild hepatic impairment	Moderate hepatic impairment	Severe hepatic impairment	Matched (pooled)
Total	8	9*	8	25
Female/male (number)	3/5	0/9	3/5	6/19
Median age (range)	53 (50-61)	55 (42-60)	53 (38-62)	55 (38-65)
Race (number)	Asian:1 Multiracial: 1 White: 6	Black: 1 Polynesian: 1 White: 7	White: 8	Asian:1 Balck:1 Polynesian: 1 White: 22

*One subject withdrew consent

Prior and concomitant therapy

A listing of prior and concomitant medication taken during the study has been provided. None of the subjects received prohibited medications per protocol such as strong CYP3A4 inducers or OATP1B inhibitors.

Pharmacokinetic results

GZR plasma pharmacokinetics in subjects with mild, moderate, and severe hepatic impairment and matched healthy subjects are summarized in Table 3, 4, 5, respectively. Following multiple oral doses of GZR (once daily for 10 days), the steady-state GZR AUCs were increased by 1.66-, 4.82-, and 11.68-fold in subjects with mild, moderate, and severe hepatic impairment, respectively as compared to matched healthy volunteers. A similar magnitude of increase was observed for C_{max} and C_{min} . T_{max} values were largely comparable (from 1 to 3 hours) in subjects with varying degrees of hepatic impairment and healthy volunteers. The apparent terminal half-lives tended to be longer in subjects with hepatic impairment (39-54 hours) than those observed in matched healthy volunteers (31-36 hours).

Table 3. GZR pharmacokinetics in subjects with mild hepatic impairment and matched healthy volunteers

Grazoprevir Pharmacokinetic Parameter	Mild Hepatic			Healthy Subjects Matched to Mild Hepatic			Mild Hepatic / Healthy Subjects Matched to Mild Hepatic		rMSE [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
Day 1									
AUC ₀₋₂₄ [‡] (μM•hr)	8	1.71	(1.10, 2.65)	8	1.42	(0.912, 2.20)	1.21	(0.73, 2.01)	0.565
C _{max} [‡] (μM)	8	0.257	(0.121, 0.545)	8	0.305	(0.144, 0.646)	0.84	(0.35, 2.01)	0.966
C ₂₄ [‡] (nM)	8	21.4	(18.2, 25.2)	8	11.5	(9.80, 13.5)	1.86	(1.54, 2.24)	0.207
T _{max} [§] (hr)	8	3.50	(1.00, 12.00)	8	2.50	(1.00, 4.00)			
Day 10									
AUC ₀₋₂₄ [‡] (μM•hr)	8	6.20	(4.19, 9.18)	8	3.74	(2.53, 5.54)	1.66	(1.05, 2.61)	0.504
C _{max} [‡] (μM)	8	1.40	(0.903, 2.17)	8	1.02	(0.658, 1.58)	1.37	(0.83, 2.27)	0.562
C ₂₄ [‡] (nM)	8	32.6	(24.8, 42.8)	8	17.0	(12.9, 22.3)	1.92	(1.40, 2.63)	0.350
T _{max} [§] (hr)	8	3.00	(2.00, 4.00)	8	3.01	(1.50, 4.00)			
Apparent terminal t _{1/2} (hr)	8	54.24	22.32	8	35.85	47.15			
Mild Hepatic: Subjects with a score of 5-6 on the Child-Pugh scale.									
Healthy Subjects Matched to Mild Hepatic: Healthy subjects matched (race, age [± 5 years], gender, BMI [± 15%]) to mild hepatic insufficiency.									
[†] rMSE: Square root of conditional mean squared error (residual error) from the ANCOVA model containing population, categorical covariate gender, and continuous covariates age and BMI.									
rMSE*100% approximates the between-subject %CV on the raw scale.									
[‡] Back-transformed least-squares means and confidence intervals from the ANCOVA model performed on natural log-transformed values.									
[§] Median (min, max) reported for T _{max} .									
Geometric mean and geometric coefficient of variation reported for apparent terminal t _{1/2} .									
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.									

Table 4. GZR pharmacokinetics in subjects with moderate hepatic impairment and matched healthy volunteers

Grazoprevir Pharmacokinetic Parameter	Moderate Hepatic			Healthy Subjects Matched to Moderate Hepatic			Moderate Hepatic / Healthy Subjects Matched to Moderate Hepatic		rMSE [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
Day 1									
AUC ₀₋₂₄ [‡] (µM•hr)	8	1.61	(0.791, 3.29)	8	0.321	(0.157, 0.655)	5.03	(2.19, 11.56)	0.916
C _{max} [‡] (µM)	8	0.443	(0.184, 1.07)	8	0.0580	(0.0242, 0.139)	7.64	(2.74, 21.27)	1.126
C ₂₄ [§] (nM)	8	17.7	(8.73, 35.8)	8	5.90	(2.92, 11.9)	2.99	(1.31, 6.82)	0.906
T _{max} [§] (hr)	8	2.00	(1.50, 4.00)	8	1.75	(1.00, 4.00)			
Day 10									
AUC ₀₋₂₄ [‡] (µM•hr)	8	4.21	(2.48, 7.14)	8	0.874	(0.515, 1.48)	4.82	(2.60, 8.93)	0.679
C _{max} [‡] (µM)	8	0.631	(0.334, 1.19)	8	0.106	(0.0559, 0.199)	5.98	(2.84, 12.57)	0.817
C ₂₄ [§] (nM)	8	48.9	(27.2, 87.9)	8	13.6	(7.60, 24.5)	3.59	(1.81, 7.11)	0.753
T _{max} [§] (hr)	8	3.00	(1.50, 8.00)	8	2.00	(1.00, 6.00)			
Apparent terminal t _{1/2} [¶] (hr)	8	39.59	23.76	8	39.80	17.34			

Moderate Hepatic: Subjects with a score of 7-9 on the Child-Pugh scale.
Healthy Subjects Matched to Moderate Hepatic: Healthy subjects matched (race, age [± 10 years], gender, BMI [± 20%]) to moderate hepatic insufficiency.
[†]rMSE: Square root of conditional mean squared error (residual error) from the ANCOVA model containing population, categorical covariate gender, and continuous covariates age and BMI.
[‡]rMSE*100% approximates the between-subject %CV on the raw scale.
[‡]Back-transformed least-squares means and confidence intervals from the ANCOVA model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max}.
[¶]Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

Data Source: [16.4]

Table 5. GZR pharmacokinetics in subjects with severe hepatic impairment and matched healthy volunteers

Grazoprevir Pharmacokinetic Parameter	Severe Hepatic			Healthy Subjects Matched to Severe Hepatic			Severe Hepatic / Healthy Subjects Matched to Severe Hepatic		rMSE [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
Day 1									
AUC ₀₋₂₄ [‡] (µM•hr)	8	1.17	(0.541, 2.55)	8	0.0592	(0.0273, 0.129)	19.83	(8.11, 48.51)	0.996
C _{max} [‡] (µM)	8	0.238	(0.107, 0.531)	8	0.0157	(0.00705, 0.0350)	15.18	(6.02, 38.25)	1.029
C ₂₄ [§] (nM)	8	15.6	(2.89, 60.2)	8	1.86	(0.00, 3.32)			
T _{max} [§] (hr)	8	1.75	(1.00, 3.00)	8	1.50	(1.00, 4.00)			
Day 10									
AUC ₀₋₂₄ [‡] (µM•hr)	8	3.00	(1.71, 5.26)	8	0.257	(0.146, 0.451)	11.68	(6.10, 22.35)	0.723
C _{max} [‡] (µM)	8	0.396	(0.203, 0.774)	8	0.0304	(0.0156, 0.0595)	13.01	(6.00, 28.21)	0.862
C ₂₄ [§] (nM)	8	55.0	(31.9, 94.8)	8	5.89	(3.42, 10.2)	9.34	(4.98, 17.51)	0.700
T _{max} [§] (hr)	8	1.75	(0.50, 4.00)	8	1.00	(0.50, 3.00)			
Apparent terminal t _{1/2} [¶] (hr)	8	42.00	26.55	8	31.02	41.99			

Severe Hepatic: Subjects with a score of 10-15 on the Child-Pugh scale.
Healthy Subjects Matched to Severe Hepatic: Healthy subjects matched (race, age [± 10 years], gender, BMI [± 20%]) to severe hepatic insufficiency.
[†]rMSE: Square root of conditional mean squared error (residual error) from the ANCOVA model containing population, categorical covariate gender, and continuous covariates age and BMI.
[‡]rMSE*100% approximates the between-subject %CV on the raw scale.
[‡]Back-transformed least-squares means and confidence intervals from the ANCOVA model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max} and C₂₄ (Day 1) for both populations.
[¶]3 healthy subjects out of 8 have BLOQ C₂₄ values on Day 1; therefore, the median (min, max) were reported for C₂₄, Day 1.
[¶]Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

Reviewer comments

1. A 66% increase of GZR AUC_{steady-state} was observed in subjects with mild hepatic impairment as compared to healthy volunteers. This is not considered clinically relevant based on the exposure-response relationship for safety. Also, a significant number of CHC patients with mild hepatic impairment were

enrolled in various phase 3 trials and the safety and efficacy of GZR in this population appears to be acceptable.

2. A 4.8-fold increase in GZR $AUC_{steady-state}$ was observed in subjects with moderate hepatic impairment.

3. An 11.7-fold increase in GZR $AUC_{steady-state}$ was observed in subjects with severe renal impairment as compared to matched healthy volunteers. As such, the sponsor proposed (b) (4) in this population.

4. The sponsor conducted a protein binding assay using samples from this study. Pre-dose samples were collected, GZR was added, and equilibrium dialysis was conducted. Therefore, the results do not directly represent in vivo changes in plasma protein binding after the oral administration of GZR. According to the protocol, the sponsor collected 4 hours post-dose samples for a protein binding assay but no study results have been submitted.

Conclusions

- Following 10 days of multiple dosing with 200 mg GZR, AUC_{ss0-24} is ~1.66-fold higher in non-HCV subjects with mild hepatic impairment compared with healthy matched control subjects. This magnitude of change is not considered clinically relevant.
- Following 10 days of multiple dosing with 100 mg GZR, AUC_{ss0-24} is ~5-fold higher in non-HCV subjects with moderate hepatic impairment compared with healthy matched control subjects. The use of GZR is (b) (4) in patients with moderate hepatic impairment.
- Following 10 days of dosing with 50 mg GZR, AUC_{ss0-24} is ~12-fold higher in non-HCV subjects with severe hepatic impairment compared with healthy matched control subjects. The use of GZR should be contraindicated in patients with severe hepatic impairment.

4.2. Renal impairment

Title: An Open-Label Study to Investigate the Pharmacokinetics of MK-5172 and MK-8742 in Subjects with Renal Insufficiency (PN050)

Trial Initiation Date: 13-Sep-2013 **Trial Completion Date:** 17-Dec-2013

Trial Sites: Clinical Pharmacology of Miami (Miami, FL) and Orlando Clinical Research Center (Orlando, FL)

Primary Objectives

- To compare the plasma pharmacokinetics of MK-5172 and MK-8742 co-administered to subjects with ESRD on non-HD days and HD days
- To compare the plasma pharmacokinetics of MK-5172 and MK-8742 co-administered to subjects with ESRD on HD days to healthy matched control subjects.
- To compare the plasma pharmacokinetics of MK-5172 and MK-8742 co-administered to subjects with severely impaired renal function to that of healthy matched control subjects.

Study Design

This was an open-label, 2-part, multiple-dose study to investigate the pharmacokinetics of MK-5172 and MK-8742 in subjects with renal impairment. In Part 1, 8 subjects with End-Stage Renal Disease (ESRD) on hemodialysis (HD) were enrolled. In Part 2, 8 subjects with severe renal impairment were enrolled. Once all subjects with renal impairment (Part 1 and Part 2) were enrolled, 8 healthy control subjects matched (for age, body mass index [BMI], and gender) to the mean of subjects with impaired renal function in Parts 1 and 2 were enrolled. All subjects received a once daily oral dose of 100 mg MK-5172 and 50 mg MK-8742 for 10 days. When HD was performed, it was timed to occur after the median T_{\max} of MK-5172 and MK-8742 (i.e., 5 hours postdose). For HD, Fresenius 2008 K2 hemodialysis machine using a high flux dialysis membrane was used.

Table 1. Definition of severe renal impairment and ESRD in this trial

Group	N	eGFR (mL/min/1.73 m ²) [†]
ESRD on HD	8	Requiring dialysis
Severe Renal Impairment	8	< 30, not on dialysis
Healthy Matched Controls	8	≥ 80 ^{‡, §}

[†]eGFR based on the MDRD equation at screening. Baseline eGFRs were obtained twice during screening period and the mean of the 2 values used for group assignment.

[‡]For the control group, actual creatinine clearance, as determined by a 24-hour urine collection, may have been used in place of or in conjunction with the MDRD equation, at the Investigator's discretion.

[§]Due to the age population selected in this study, and hence, the impact on recruiting, an eGFR ≥ 80 was selected instead of an eGFR ≥ 90 as proposed in the Draft Guidance for Industry – Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling – March 2010 [16.1.1.17].

Key inclusion criteria

All subjects

- Healthy adult male and female volunteers, 18-80 years of age, BMI: 18 to 40 kg/m², inclusive

- Non-smokers (have not used nicotine-containing products for at least 3 months prior to the first dose)
- A female of childbearing potential must either sexually inactive or use acceptable birth control methods. Male subjects must use a condom (or abstain from sexual intercourse) and agree not to donate sperm from the first dose until 90 days after the last dose
- Liver function test must be at or lower than ULN

Matched healthy subjects

- Medically healthy with no clinically significant history, physical exam, lab profiles
- Within \pm 10 years of the mean age of ESRD subjects and subjects with severe renal impairment.
- Within \pm 10% of the mean BMI of ESRD subjects and subjects with severe renal impairment.
- Subject's eGFR based on the MDRD equation at screening is \geq 80 mL/min/1.73 m².

ESRD subjects

- Baseline health is judged to be stable based on medical history, lab profiles, vital signs or ECG.
- (Subjects with ESRD only): subject is maintained on a stable regimen of HD within 3 months prior to first dosing
- (Subjects with severe renal impairment only): eGFR less than 30 mL/min/1.73 m² based on MDRD equation. Subject has had no clinically significant change in renal status at least 1 month prior to first study medication administration, and is not currently or has not previously been on HD.

Key exclusion criteria

- History of any illness that might confound the results of the study or pose an additional risk to the subjects by their participation in the study
- History of alcoholism or drug abuse (within 6 months)
- Female subjects who are pregnant or lactating
- Positive results at screening for HIV, hepatitis B, hepatitis C, urine drug or cotinine screening
- Donation of blood or had significant blood loss within 56 days prior to the first dose of study drug or plasma donation within 7 days prior to the first dose of study drug.
- Participation in another clinical trial within 28 days prior to the first dose of study drug.
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients
- Have been on a diet incompatible with the on-study diet within the 28 days prior to the first dose of study medications and throughout the study.
- Unable to refrain from or anticipates the use of statins, HIV protease inhibitors, strong inhibitors of CYP3A/P-gp or OATP, or strong and moderate inducers of CYP3A/P-gp, beginning approximately 14 days prior to first dosing and throughout the study. Hormonal contraceptives and hormone replacement therapy are not prohibited. Acetaminophen (up to 2 g per 24 hour period) may be permitted during the study.
- Subjects has had a renal transplant or has had nephrectomy (severe renal impairment subjects and healthy control subjects)

Identity of Investigational Products

Table 2. Identity of Investigational Products

Drug	Potency	Dosage Form	Lot No.	Control No.	Assay Potency (N = 2)	Site of Manufacture
MK-5172	100 mg	Tablet	WL00047516	WL00053913	98.6%	Merck & Co., Inc., West Point, PA
MK-8742	50 mg	Tablet	WL00052481	WL00053914	98.3%	Merck & Co., Inc., West Point, PA

Pharmacokinetic Assessments

For ESRD subjects, samples were collected predose and at selected time points over 24 hours on Day 9 (non-HD day). On Day 10 (HD day), samples were collected predose and at selected time points over 120 hours. Dialysate samples were collected for 1 minute every half hour during HD for analysis of MK-5172 and MK-8742 drug concentrations. Urine samples of MK-5172 and MK-8742 were collected on Days 9-12. For subjects with severe renal impairment and matched healthy volunteers, plasma samples for assessment of MK-5172 and MK-8742 were collected predose and at selected time points over 120 hours on Day 10. Urine samples through 72 hours post the Day 10 dose were collected for assessment of MK-5172 and MK-8742. Samples for plasma protein binding were also collected at 3 and 8 hours post dose on Day 10.

With the exception of parameters C_{24} , C_2 which were obtained using SAS® (Version 9.3), all the pharmacokinetic parameters were calculated using the software WinNonlin Professional® (Version 6.3). The AUC was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down). For urine samples, the cumulative amounts of MK-5172 and MK-8742 excreted unchanged in urine over the entire 24-hour collection interval (Ae_{0-24hr}) and 72-hour collection interval (Ae_{0-72hr}) were determined. Dialysis pharmacokinetic parameters such as CL_D (dialysis clearance based on plasma), Ae_D (the amount of drug recovered from the dialysate), AUC_D (plasma AUC values determined from samples collected from the pre-dialyzer line), and fe_D (fraction of the dose recovered in the dialysate) were also determined.

Bioanalysis

Plasma and dialysate samples for MK-5172 and MK-8742 quantitation were analyzed by Merck Research Laboratories (The Netherlands). The concentrations of these drugs were determined using validated LC/MS/MS methods. Method validation and sample analyses were acceptable. Of note, urine bioanalysis is considered explorative as the method was not fully validated. Urine sample quantitation was conducted using the validated bioanalytical method for dialysate.

Table 3. Summary of Bioanalysis

Analyte	MK-5172	MK-8742	MK-5172	MK-8742
Internal standard	MK-5172-d ₆	MK-8742-d ₆	MK-5172-d ₆	MK-8742-d ₆
Matrix	Plasma	Plasma	Dialysate	Dialysate
Extraction method	Liquid-liquid extraction	Liquid-liquid extraction	Liquid-liquid extraction	Liquid-liquid extraction

Calibration range	1 to 1000 ng/mL	0.25 to 500 ng/mL	0.1 to 100 ng/mL	0.2 to 200 ng/mL
QC concentration	3, 75, and 750 ng/mL	0.75, 75, and 375 ng/mL	0.3, 5, and 75 ng/mL	0.6, 10, 150 ng/mL
Interday precision and accuracy	P: 2.2 to 3.8% A: -8.0 to -7.6%	P: 6.2 to 10.5%* A: -2.4 to 2.5%	P: 0.15 to 2.18%# A: -6.2 to 0.5%#	P: 0.11 to 3.31%# A: -5.2 to 0%#
Storage stability	825 days at – 20 °C	651 days at – 20 °C	34 days at – 20 °C	34 days at – 20 °C

*after excluding 2 outliers which failed to meet the acceptance criteria ($\pm 15\%$ of nominal concentrations)

Intraday precision and accuracy are reported as sample analyses were completed in a day.

RESULTS

Demographics and Subject Characteristics

Twenty-four male and female subjects (8 subjects with ESRD on HD, 8 subjects with severe renal insufficiency, and 8 healthy matched control subjects) were enrolled into the study and all subjects completed the study per protocol. All 24 subjects were included in the evaluation of safety and pharmacokinetics.

Table 4. Subject baseline characteristics

	ESRD	Severe renal impairment	Matched healthy volunteers
Age in Years, Mean (range)	48 (38 to 61)	65.8 (54 to 75)	55.1 (47 to 63)
Sex, n (%)			
Female:	3	4	4
Male:	5	4	4
BMI (kg/m²), range	30.79 (26.96 to 35.8)	28.63 (24.20 to 34.10)	29.35 (26.8 to 31.6)
Height (cm), range	172.9 (158 to 184)	164.6 (146 to 179)	166.9 (151 to 189)
Weight (kg), range	92.3 (73.4 to 121.2)	78.75 (57.3 to 97.0)	82.05 (68.3 to 107.5)
Ethnicity, n (%)			
Hispanic or Latino:	1	5	6
Not Hispanic or Latino:	7	3	2
Others			
Race, n (%)			
White	1	5	8
African American/Black	7	3	
Asian			
eGFR (mL/min/1.73 m ²)	N/A*	18.0 (11.5 to 23.5)	93.4 (80.0 to 124)#

*Most subjects were anuric thus eGFR could not be determined.

#: Two subjects did not have eGFR measurements. CrCL values were calculated for these subjects.

Pharmacokinetic Results

MK-5172

MK-5172 exposures were approximately 65% higher in subjects with severe renal impairment as compared to matched healthy volunteers (Table 5). MK-5172 exposures were similar between subjects with ESRD and matched healthy volunteers (Table 6). MK-5172 pharmacokinetic parameters were similar on HD days and non-HD days in ESRD subjects, indicating that MK-5172 is not significantly dialyzed by a 4-hour hemodialysis session (Table 7). This was also confirmed by the dialysate pharmacokinetics; the geometric mean amount recovered from the dialysate was 0.0172 mg (less than 0.2% of the dose) and the dialysis clearance based on plasma was 1.45 mL/min (Table 8). No significant

difference in the fraction unbound of MK-5172 was observed between subjects with renal impairment and matched healthy volunteers (Table 9). MK-5172 is minimally eliminated in urine (less than 0.5% of the administered dose, Table 10).

Table 5. MK-5172 plasma pharmacokinetics in subjects with severe renal impairment and matched healthy volunteers

Pharmacokinetic Parameter	Severe Renal Insufficiency			Healthy Matched Control			Severe Renal Insufficiency/ Healthy Matched Control		rMSE [†]	Total SD [‡]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI		
AUC ₀₋₂₄ [†] (µM·hr)	8	1.88	(1.23, 2.86)	8	1.14	(0.843, 1.54)	1.65	(1.09, 2.49)	0.119	0.405
C _{max} [‡] (µM)	8	0.255	(0.152, 0.429)	8	0.154	(0.106, 0.224)	1.66	(0.99, 2.77)	0.253	0.505
C ₂₄ [‡] (nM)	8	23.3	(15.4, 35.2)	8	14.5	(10.7, 19.6)	1.60	(1.06, 2.42)	0.204	0.405
C ₂ [‡] (µM)	8	0.152	(0.0816, 0.281)	8	0.0961	(0.0610, 0.151)	1.58	(0.85, 2.92)	0.448	0.613
CL/F [†] (L/hr)	8	69.4	(45.6, 106)	8	114	(84.5, 155)	0.61	(0.40, 0.92)	0.119	0.405
Vz/F [†] (L)	8	3490	(2320, 5260)	8	5760	(4180, 7930)	0.61	(0.39, 0.94)	0.428	
T _{max} [§] (hr)	8	3.00	(0.50, 6.00)	8	2.50	(1.00, 6.00)				
Apparent terminal t _½ (hr)	8	36.30	30.53	8	35.18	19.64				

Single daily oral dose of 100 mg MK-5172 (1 x 100 mg tablet) and 50 mg MK-8742 (1 x 50 mg tablet pre-market formulation 2 [PMF2]) on Days 1 to 10.

[†]rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model rMSE×100% approximates the within-subject %CV (except for Vz/F, for which rMSE approximates the total %CV) on the raw scale. Total SD is the square root of the sum of the residual variance component and the subject variance component from the mixed model.

[‡]Back-transformed least-squares geometric means, ratios, and CI from linear mixed-effect model performed on natural log-transformed values.

[§]Median (min, max) reported for T_{max}.

^{||}The geometric mean and geometric CV reported for apparent terminal t_½.

^{††}CL/F values are based on AUC₀₋₂₄.

GM = Geometric least-square mean; GMR = Geometric least-square mean ratio; CI = Confidence interval.

Since Vz/F is not available for ESRD Subjects on Day 9, only the rMSE is presented from the ANCOVA fixed effects model.

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Table 6. MK-5172 plasma pharmacokinetics in subjects with ESRD and matched healthy volunteers

Pharmacokinetic Parameter	ESRD on Non-HD Day 9			Healthy Matched Control			ESRD on Non-HD Day 9/ Healthy Matched Control		rMSE [†]	Total SD [‡]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI		
AUC ₀₋₂₄ [†] (µM·hr)	8	0.969	(0.689, 1.36)	8	1.14	(0.843, 1.54)	0.85	(0.58, 1.25)	0.119	0.405
C _{max} [‡] (µM)	8	0.141	(0.0920, 0.215)	8	0.154	(0.106, 0.224)	0.92	(0.57, 1.48)	0.253	0.505
C ₂₄ [‡] (nM)	8	11.4	(8.16, 16.1)	8	14.5	(10.7, 19.6)	0.79	(0.54, 1.16)	0.204	0.405
C ₂ [‡] (µM)	8	0.111	(0.0666, 0.184)	8	0.0961	(0.0610, 0.151)	1.15	(0.65, 2.05)	0.448	0.613
CL/F [†] (L/hr)	8	135	(95.6, 189)	8	114	(84.5, 155)	1.18	(0.80, 1.73)	0.119	0.405
Vz/F [†] (L)	8			8	5760	(4180, 7930)				
T _{max} [§] (hr)	8	2.00	(1.00, 6.00)	8	2.50	(1.00, 6.00)				
Apparent terminal t _½ (hr)	8			8	35.18	19.64				

Single daily oral dose of 100 mg MK-5172 (1 x 100 mg tablet) and 50 mg MK-8742 (1 x 50 mg tablet pre-market formulation 2 [PMF2]) on Days 1 to 10.

[†]rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model. rMSE×100% approximates the within-subject %CV on the raw scale. Total SD is the square root of the sum of the residual variance component and the subject variance component from the mixed model.

[‡]Back-transformed least-squares geometric means, ratios, and CI from linear mixed-effect model performed on natural log-transformed values.

[§]Median (min, max) reported for T_{max}.

^{||}The geometric mean and geometric CV reported for apparent terminal t_½.

^{††}CL/F values are based on AUC₀₋₂₄.

GM = Geometric least-square mean; GMR = Geometric least-square mean ratio; CI = Confidence interval.

Volume and apparent terminal t_½ values are not reported for ESRD on non-HD Day 9 since only 24-hour collections were made.

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Table 7. MK-5172 plasma pharmacokinetics on non-HD day and on HD day in subjects with ESRD

Pharmacokinetic Parameter	ESRD on HD Day 10			ESRD on Non-HD Day 9			ESRD on HD Day 10/ ESRD on Non-HD Day 9		rMSE [†]	Total SD [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI		
AUC ₀₋₂₄ [‡] (µM·hr)	8	0.944	(0.671, 1.33)	8	0.969	(0.689, 1.36)	0.97	(0.87, 1.09)	0.119	0.405
C _{max} [‡] (µM)	8	0.135	(0.0882, 0.206)	8	0.141	(0.0920, 0.215)	0.96	(0.75, 1.22)	0.253	0.505
C ₂₄ [‡] (nM)	8	11.3	(8.03, 15.8)	8	11.4	(8.16, 16.1)	0.98	(0.81, 1.19)	0.204	0.405
C ₂ [‡] (µM)	8	0.0896	(0.0539, 0.149)	8	0.111	(0.0666, 0.184)	0.81	(0.53, 1.25)	0.448	0.613
CL/F ^{‡,§} (L/hr)	8	138	(98.1, 194)	8	135	(95.6, 189)	1.03	(0.92, 1.15)	0.119	0.405
V _Z /F [‡] (L)	8	5430	(3660, 8050)							
T _{max} [‡] (hr)	8	2.50	(0.50, 7.00)	8	2.00	(1.00, 6.00)				
Apparent terminal t _{1/2} (hr)	8	28.38	20.88							

Single daily oral dose of 100 mg MK-5172 (1 x 100 mg tablet) and 50 mg MK-8742 (1 x 50 mg tablet pre-market formulation 2 [PMF2]) on Days 1 to 10.

[†]rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model. rMSE×100% approximates the within-subject %CV on the raw scale. Total SD is the square root of the sum of the residual variance component and the subject variance component from the mixed model.

[‡]Back-transformed least-squares geometric means, ratios, and CI from linear mixed-effect model performed on natural log-transformed values.

[§]Median (min, max) reported for T_{max}.

^{||}The geometric mean and geometric CV reported for apparent terminal t_{1/2}.

^{††}CL/F values are based on AUC₀₋₂₄.

GM = Geometric least-square mean; GMR = Geometric least-square mean ratio; CI = Confidence interval.
Volume and apparent terminal t_{1/2} values are not reported for ESRD on non-HD Day 9 since only 24-hour collections were made.
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Table 8. MK-5172 dialysis pharmacokinetic parameters

Parameter	ESRD	
	N	GM (95% CI)
CL _D [†] (mL/min)	6 [‡]	1.45 (0.852, 2.47)
Ae _D (mg)	6 [‡]	0.0172 (0.00796, 0.0372)
AUC _D (nM.hr)	8	192 (112, 329)
fe _D	6 [‡]	0.000172 (0.0000796, 0.000372)
Ae _D (% Dose)	6 [‡]	0.0172 (0.00796, 0.0372)

Single daily oral dose of 100 mg MK-5172 (1 x 100 mg tablet) and 50 mg MK-8742 (1 x 50 mg tablet pre-market formulation 2 [PMF2]) on Days 1 to 10

CL_D = Dialysis Clearance based on plasma.

Ae_D = The amount of drug recovered from the dialysate.

AUC_D = Plasma AUC values determined from samples collected from the pre-dialyzer line during the HD period.

fe_D = Fraction of the dose recovered in the dialysate.

Ae_D (% Dose) = fe_D x 100%.

CI = Confidence interval.

[†]CL_D values are based on Ae_D/AUC_D.

[‡]Subjects AN 0007 and AN 0008 did not have any reportable MK-5172 dialysate concentrations.

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Table 9. MK-5172 plasma protein binding (unbound fraction) in subjects with ESRD, severe renal impairment and matched healthy volunteers

MK-5172 Fraction Unbound			
	3 Hours	8 Hours	Mean of 3 and 8 Hours
ESRD (Subjects 1 - 8)	0.019 ± 0.005	0.016 ± 0.005	0.018 ± 0.005
Severe Renal Impairment (Subjects 9 – 16)	0.021 ± 0.005	0.022 ± 0.004	0.022 ± 0.004
Healthy (Subjects 17 – 24)	0.017 ± 0.002	0.017 ± 0.003	0.017 ± 0.003

Data represent the arithmetic mean ± standard deviation.

Table 10. MK-5172 Urine pharmacokinetic parameters

Parameters	ESRD Renal Impairment (Day 9)		ESRD Renal Impairment (Day 10)		Severe Renal Impairment		Healthy Matched Control	
	N [†]	(min, max)	N [†]	(min, max)	N	GM (95% CI)	N	GM (95% CI)
fe _{0-24hr}	3	(0.00000164, 0.00865)	3	(0.000000463, 0.0199)	8	0.000156 (0.0000691, 0.000353)	8	0.000492 (0.000379, 0.000639)
fe _{0-72hr}	0		3	(0.00000117, 0.0185)	8	0.000211 (0.0000906, 0.000493)	8	0.000631 (0.000500, 0.000797)
CL _R [‡] (L/hr)	3	(0.000854, 0.834)	3	(0.000288, 1.91)	8	0.00961 (0.00473, 0.0195)	8	0.0561 (0.0386, 0.0813)
C _{ur} _{24hr} (nM)	3	(8.42, 506)	3	(0.630, 1770)	8	37.0 (15.1, 90.4)	8	51.0 (38.6, 67.2)
C _{ur} _{72hr} (nM)	3	(8.42, 506)	3	(0.978, 1670)	8	41.7 (17.4, 100)	8	57.0 (43.7, 74.5)
V _{ur} _{24hr} (mL)	3	(65.5, 6170)	3	(26.7, 15200)	8	1570 (1250, 1980)	8	2990 (2430, 3680)
V _{ur} _{72hr} (mL)	0		3	(294, 16400)	8	4130 (3150, 5410)	8	7220 (5820, 8940)
Ae _{0-24hr} (mg)	3	(0.000164, 0.865)	3	(0.0000463, 1.99)	8	0.0156 (0.00691, 0.0353)	8	0.0492 (0.0379, 0.0639)
Ae _{0-72hr} (mg)	0		3	(0.000117, 1.85)	8	0.0211 (0.00906, 0.0493)	8	0.0631 (0.0500, 0.0797)

Single daily oral dose of 100 mg MK-5172 (1 x 100 mg tablet) and 50 mg MK-8742 (1 x 50 mg tablet pre-market formulation 2 [PMF2]) on Days 1 to 10.
fe = fraction of dose excreted in urine over the collection interval; CL_R = renal clearance; C_u = concentration in urine; V_u = urine volume excreted during each interval;
Ae_{0-interval} = amount of unchanged drug excreted in urine.
CI = Confidence interval.
[†]Subjects AN 0001, AN 0002, AN 0004, AN 0005, and AN 0006 did not have urine data due to anuria. Only minimum and maximum were reported when N = 3.
[‡]CL_R values are based on Ae_{0-24h}/AUC₀₋₂₄.
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MK-8742

MK-8742 exposure (AUC_{24hr}) was approximately 86% higher in subjects with severe renal impairment as compared to matched healthy volunteers (Table 11). MK-8742 exposures were similar between subjects with ESRD and matched healthy volunteers (Table 12). MK-8742 exposures were similar on HD days and non-HD days in ESRD subjects, indicating that MK-8742 is not significantly dialyzed by a 4-hour hemodialysis session (Table 13). Concentrations of MK-8742 in dialysate samples and unbound MK-8742 in plasma were below quantitation limit. MK-8742 is minimally eliminated in urine (less than 0.1% of the administered dose, Table 14).

Table 11. MK-8742 pharmacokinetics in subjects with severe renal impairment and matched healthy volunteers

Pharmacokinetic Parameter	Severe Renal Insufficiency			Healthy Matched Control			Severe Renal Insufficiency/ Healthy Matched Control		rMSE [†]	Total SD [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI		
AUC ₀₋₂₄ [‡] (µM•hr)	8	4.07	(3.01, 5.52)	8	2.19	(1.76, 2.72)	1.86	(1.38, 2.51)	0.057	0.291
C _{max} [‡] (µM)	8	0.271	(0.196, 0.373)	8	0.163	(0.129, 0.206)	1.66	(1.21, 2.28)	0.120	0.311
C ₂₄ [‡] (nM)	8	126	(88.6, 179)	8	60.9	(47.3, 78.5)	2.07	(1.46, 2.93)	0.064	0.338
C ₂ [‡] (µM)	8	0.196	(0.140, 0.274)	8	0.117	(0.0915, 0.149)	1.68	(1.20, 2.34)	0.215	0.328
CL/F [‡] (L/hr)	8	13.9	(10.3, 18.9)	8	25.9	(20.8, 32.2)	0.54	(0.40, 0.72)	0.057	0.291
Vz/F [‡] (L)	8	569	(420, 772)	7 ^{††}	901	(699, 1160)	0.63	(0.45, 0.89)	0.315	
T _{max} [§] (hr)	8	4.00	(4.00, 6.00)	8	4.00	(2.00, 4.00)				
Apparent terminal t _½ (hr)	8	28.97	18.26	7 ^{††}	25.02	19.08				

Single daily oral dose of 100 mg MK-5172 (1 x 100 mg tablet) and 50 mg MK-8742 (1 x 50 mg tablet pre-market formulation 2 [PMF2]) on Days 1 to 10.

[†]rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model. rMSE×100% approximates the within-subject %CV (except for Vz/F, for which rMSE approximates the total %CV) on the raw scale. Total SD is the square root of the sum of the residual variance component and the subject variance component from the mixed model.

[‡]Back-transformed least-squares geometric means, ratios, and CI from linear mixed-effect model performed on natural log-transformed values.

[§]Median (min, max) reported for T_{max}.

^{||}The geometric mean and geometric CV reported for apparent terminal t_½.

[†]CL/F values are based on AUC₀₋₂₄.

^{††}For Subject AN 0018, the apparent terminal t_½ and Vz/F values were not calculated due to ill-defined terminal phase.

GM = Geometric least-square mean; GMR = Geometric least-square mean ratio; CI = Confidence interval.

Since Vz/F is not available for ESRD subjects on Day 9, only the rMSE is presented from the ANCOVA fixed effects model.

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Table 12. MK-8742 pharmacokinetics in subjects with ESRD and matched healthy volunteers

Pharmacokinetic Parameter	ESRD on HD Day 10			Healthy Matched Control			ESRD on HD Day 10/ Healthy Matched Control		rMSE [†]	Total SD [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI		
AUC ₀₋₂₄ [‡] (µM•hr)	8	2.16	(1.69, 2.77)	8	2.19	(1.76, 2.72)	0.99	(0.75, 1.30)	0.057	0.291
C _{max} [‡] (µM)	8	0.154	(0.118, 0.200)	8	0.163	(0.129, 0.206)	0.94	(0.70, 1.27)	0.120	0.311
C ₂₄ [‡] (nM)	8	58.2	(43.7, 77.5)	8	60.9	(47.3, 78.5)	0.95	(0.69, 1.32)	0.064	0.338
C ₂ [‡] (µM)	8	0.0987	(0.0750, 0.130)	8	0.117	(0.0915, 0.149)	0.84	(0.62, 1.15)	0.215	0.328
CL/F [‡] (L/hr)	8	26.2	(20.5, 33.5)	8	25.9	(20.8, 32.2)	1.01	(0.77, 1.34)	0.057	0.291
Vz/F [‡] (L)	8	857	(641, 1150)	7 ^{††}	901	(699, 1160)	0.95	(0.70, 1.30)	0.315	
T _{max} [§] (hr)	8	5.00	(3.00, 5.00)	8	4.00	(2.00, 4.00)				
Apparent terminal t _½ (hr)	8	23.04	6.34	7 ^{††}	25.02	19.08				

Single daily oral dose of 100 mg MK-5172 (1 x 100 mg tablet) and 50 mg MK-8742 (1 x 50 mg tablet pre-market formulation 2 [PMF2]) on Days 1 to 10.

[†]rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model. rMSE×100% approximates the within-subject %CV (except for Vz/F, for which rMSE approximates the total %CV) on the raw scale. Total SD is the square root of the sum of the residual variance component and the subject variance component from the mixed model.

[‡]Back-transformed least-squares geometric means, ratios, and CI from linear mixed-effect model performed on natural log-transformed values.

[§]Median (min, max) reported for T_{max}.

^{||}The geometric mean and geometric CV reported for apparent terminal t_½.

[†]CL/F values are based on AUC₀₋₂₄.

^{††}For Subject AN 0018, the apparent terminal t_½ and Vz/F values were not calculated due to ill-defined terminal phase.

GM = Geometric least-square mean; GMR = Geometric least-square mean ratio; CI = Confidence interval.

Since Vz/F is not available for ESRD subjects on Day 9, only the rMSE is presented from the ANCOVA fixed effects model.

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Table 13. MK-8742 pharmacokinetics on HD day and non-HD day in ESRD subjects

Pharmacokinetic Parameter	ESRD on HD Day 10			ESRD on Non-HD Day 9			ESRD on HD Day 10/ ESRD on Non-HD Day 9		rMSE [†]	Total SD [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI		
AUC ₀₋₂₄ [‡] (µM•hr)	8	2.16	(1.69, 2.77)	8	1.89	(1.48, 2.42)	1.14	(1.08, 1.21)	0.057	0.291
C _{max} [‡] (µM)	8	0.154	(0.118, 0.200)	8	0.137	(0.105, 0.178)	1.12	(1.00, 1.26)	0.120	0.311
C ₂₄ [‡] (nM)	8	58.2	(43.7, 77.5)	8	46.9	(35.2, 62.4)	1.24	(1.17, 1.32)	0.064	0.338
C ₂ [‡] (µM)	8	0.0987	(0.0750, 0.130)	8	0.113	(0.0862, 0.149)	0.87	(0.71, 1.07)	0.215	0.328
CL/F [‡] (L/hr)	8	26.2	(20.5, 33.5)	8	29.9	(23.4, 38.3)	0.88	(0.83, 0.92)	0.057	0.291
Vz/F [‡] (L)	8	857	(641, 1150)							
T _{max} [§] (hr)	8	5.00	(3.00, 5.00)	8	4.00	(3.00, 4.00)				
Apparent terminal t _½ (hr)	8	23.04	6.34							

Single daily oral dose of 100 mg MK-5172 (1 x 100 mg tablet) and 50 mg MK-8742 (1 x 50 mg tablet pre-market formulation 2 [PMF2]) on Days 1 to 10.

[†]rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model. rMSE×100% approximates the within-subject %CV on the raw scale. Total SD is the square root of the sum of the residual variance component and the subject variance component from the mixed model.

[‡]Back-transformed least-squares geometric means, ratios, and CI from linear mixed-effect model performed on natural log-transformed values.

[§]Median (min, max) reported for T_{max}.

^{||}The geometric mean and geometric CV reported for apparent terminal t_½.

^{††}CL/F values are based on AUC₀₋₂₄.

GM = Geometric least-square mean; GMR = Geometric least-square mean ratio; CI = Confidence interval.

Volume and apparent terminal t_½ values are not reported for ESRD on non-HD Day 9 since only 24-hour collections were made.

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Table 14. MK-8742 urine pharmacokinetics

Parameters	ESRD Renal Impairment (Day 9)		ESRD Renal Impairment (Day 10)		Severe Renal Impairment		Healthy Matched Control	
	N [†]	GM (95% CI)	N [†]	GM (95% CI)	N	GM (95% CI)	N	GM (95% CI)
fe _{0-24hr}	3	(0.0000106, 0.000813)	3	(0.0000118, 0.00540)	8	0.000916 (0.000663, 0.00127)	8	0.000701 (0.000416, 0.00118)
fe _{0-72hr}	0		3	(0.0000596, 0.00348)	8	0.00150 (0.00108, 0.00208)	8	0.000979 (0.000574, 0.00167)
CL _R [‡] (L/hr)	3	(0.000341, 0.0290)	3	(0.0000417, 0.134)	8	0.0114 (0.00883, 0.0147)	8	0.0180 (0.0125, 0.0260)
Cur _{24hr} (nM)	3	(12.3, 52.5)	3	(0.854, 251)	8	101 (76.9, 133)	8	38.0 (21.7, 66.6)
Cur _{72hr} (nM)	3	(12.3, 52.5)	3	(1.96, 203)	8	124 (93.6, 165)	8	44.7 (25.6, 77.8)
Vur _{24hr} (mL)	3	(65.5, 6170)	3	(26.7, 15200)	8	1570 (1250, 1980)	8	2990 (2430, 3680)
Vur _{72hr} (mL)	0		3	(294, 16400)	8	4130 (3150, 5410)	8	7220 (5820, 8940)
Ae _{0-24hr} (mg)	3	(0.000528, 0.0406)	3	(0.0000592, 0.270)	8	0.0458 (0.0332, 0.0633)	8	0.0351 (0.0208, 0.0591)
Ae _{0-72hr} (mg)	0		3	(0.000298, 0.174)	8	0.0750 (0.0542, 0.104)	8	0.0490 (0.0287, 0.0835)

Single daily oral dose of 100 mg MK-5172 (1 x 100 mg tablet) and 50 mg MK-8742 (1 x 50 mg tablet pre-market formulation 2 [PMF2]) on Days 1 to 10.

fe = fraction of dose excreted in urine over the collection interval; CL_R = renal clearance; C_{ur} = concentration in urine; V_{ur} = urine volume excreted during each interval; Ae_{0-interval} = amount of unchanged drug excreted in urine.

CI = Confidence interval.

[†]Subjects AN 0001, AN 0002, AN 0004, AN 0005, and AN 0006 did not have urine data due to anuria. Only minimum and maximum were reported when N = 3.

[‡]CL_R values are based on Ae_{0-24hr}/AUC₀₋₂₄.

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Discussions and conclusions

- In this study, MK-5172 and MK-8742 AUCs were 65% and 86% higher, respectively, in non-HCV-infected volunteers with severe renal impairment as compared to matched healthy volunteers. No significant difference in the pharmacokinetics of MK-5172 or MK-8742 was observed in non-HCV-infected volunteers with ESRD receiving hemodialysis compared to

matched healthy volunteers. MK-5172 and MK-8742 were minimally eliminated by 4-hour hemodialysis.

- In a Phase 3 trial (PN052), the safety, efficacy, and pharmacokinetics (population pharmacokinetics) of MK-5172 and MK-8742 were evaluated. The population pharmacokinetic analysis results were generally similar with those observed in this study.
- Based on study results from PN050 and PN052, MK-5172/MK-8742 can be administered in patients with varying degrees of renal impairment without a dose adjustment.

4.3. Mass balance trials

Study Title: A study to investigate the absorption, distribution, metabolism, and mass balance of MK-8742

Study Initiation Date: 13-Sep-2013 **Study Completion Date:** 18-Oct-2013

Study Site: (b) (4)

Study Design

This was a single-dose, open-label study to investigate the absorption, distribution, metabolism, and elimination of [¹⁴C]MK-8742. 6 healthy adult male subjects received a single oral dose of 50 mg (~200 µCi, 2 mL of a 25 mg/mL solution in PEG 400 vehicle) [¹⁴C]MK-8742 with 240 mL of water, following an overnight fast, at least 10 hours. Plasma, urine, and fecal samples were collected to measure total radioactivity (all samples), MK-8742 concentrations (plasma samples only), and for metabolic profiling (all samples, as feasible) for at least 96 hours postdose (Day 5). Subjects remained confined to the clinic site for a minimum of 96 hours postdose (Day 5). Following the minimum 96-hour confinement, subjects were discharged when they met the following discharge criteria:

- ≥ 90% of the administered radioactivity had been recovered in the urine and feces; or
- There was ≤ 1% of the administered radioactivity in each of 2 samples from combined 24-hour urine and fecal collections.

However, if discharge criteria were not met on Day 5, collection of blood (for determination of total radioactivity and metabolic profiling only), urine, and fecal samples was to continue until the discharge criteria were met or up to a maximum stay of 28 days (Day 29).

Key Inclusion Criteria

- Healthy adult male subjects, 19-55 years of age, inclusive
- BMI: 18.5-32 kg/m², inclusive. Weigh at least 52 kg.
- Non-smokers (have not used nicotine-containing products for at least 3 months prior to the dose)
- Medically healthy with no clinically significant history, physical exam, or lab profiles

Key Exclusion Criteria

- History of any illness that might confound the results of the study or pose an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 90 mL/min
- History of alcoholism or drug abuse within the past 2 years.
- Have less than 1 bowel movement every 2 days. Recent history of abnormal bowel habits.
- Being unable to refrain from or anticipates the use of any medication, including prescription and non-prescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study drug, throughout the study.
- Positive urine cotinine at screening.
- Positive results at screening for HIV hepatitis B surface antigen (HBsAg) or HCV.
- Unable to refrain from or anticipates the use of any medication beginning 2 weeks prior to dosing and throughout the study. Milk of Magnesia (≤ 60 mL per day) may be permitted during the study

for cases of symptomatic constipation, except that Milk of Magnesia may not be administered from 24 hours before to 24 hours after the administration of MK-8742. Acetaminophen (up to 2 g per 24 hour period) may also be permitted during the study

- Use of any drugs or substances known to be inducers of cytochrome P450 (CYP) enzymes and/or P-glycoprotein (P-gp), including St. John’s Wort, within 28 days or 5 times the half-life of the product (whichever is longer) prior to dosing.
- Have been on a special diet (for whatever reason) within the 28 days
- Have received radiolabeled substances or have been exposed to radiation sources over the past 12 months or is likely to receive radiation exposure or radioisotopes within the next 12 months such that participation in this study would increase their total exposure beyond the recommended levels considered safe (i.e., weighted annual limit recommended by the ICRP of 3000 mrem).

Identity of Investigational Products

Table 1. Identity of investigational products

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency	Site of Manufacture
[¹⁴ C]MK-8742	NA	005T006	(b) (4)	NA	97.8%	Merck & Co., Inc., Rahway, NJ
Carbowax™ (b) (4)	NA	NA	(b) (4)	NA	NA	NA
†Carbowax™ (b) (4)						(b) (4)

Pharmacokinetic Assessments

Blood samples for determination of plasma total radioactivity, MK-8742 plasma concentrations, and for metabolic profiling (pooled across subjects and time points) were collected predose and at specified time points up to 96 hours postdose. Urine was collected in discrete intervals from predose until 240 hours postdose, or before when discharge criteria was met, for determination of total radioactivity and for metabolic profiling. Fecal samples were collected in daily intervals from within 48 hours prior to drug administration to up to 240 hours postdose, or before when discharge criteria was met, for determination of total radioactivity and for metabolic profiling as feasible.

Metabolic profiling was performed on plasma and fecal samples collected throughout the study. Trace amount of radioactivity recovered in urine precluded metabolite profiling in urine. The results were used to identify the metabolites in plasma and feces, if any, and to quantify their percentage relative to the administered dose.

Bioanalysis

Plasma assay for MK-8742

Plasma MK-8742 concentrations were determined by Merck Research Laboratories (West Point, PA) using a validated LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.25 ng/mL and the analytical range was 0.25 to 500 ng/mL.

Plasma, urine, and feces for total radioactivity

MK-8742 concentration equivalents (total radioactivity) in plasma, urine, and feces were determined using liquid scintillation counting (LSC) by (b) (4) Urine and plasma (K₂EDTA) were analyzed by (b) (4)

Study Results

The pharmacokinetic time-concentration profiles were similar between plasma MK-8742 and total radioactivity (Fig 1). Feces and urine were collected up to 10 days and the mean overall recovery of the radioactive dose was 94.3% (94.1% in feces and 0.175% in urine; Table 2)

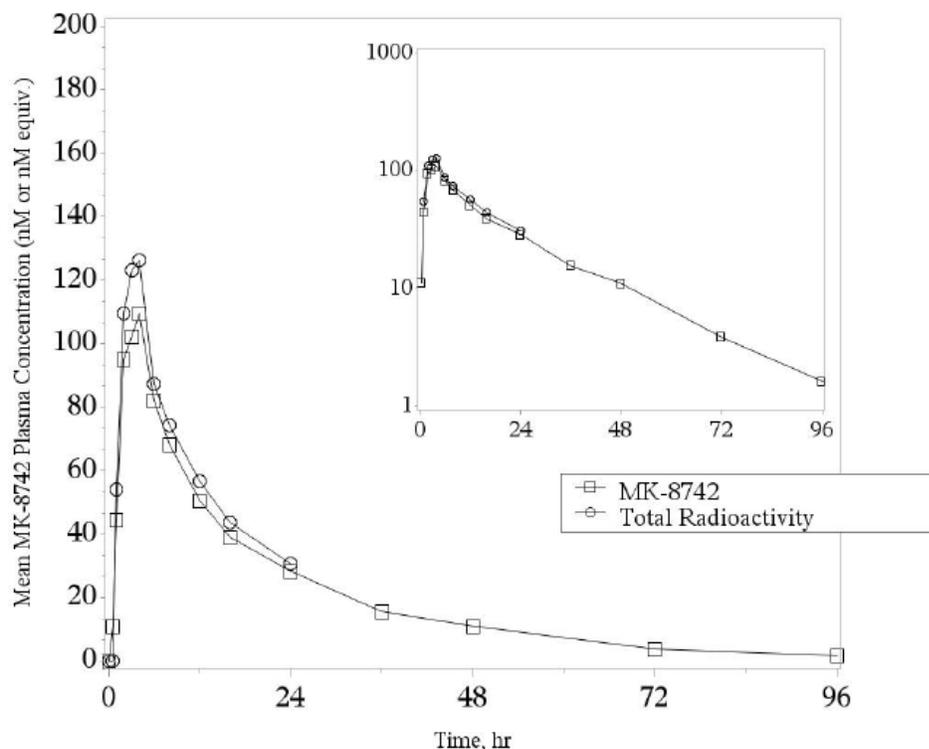
Table 2. Pharmacokinetic parameters of MK-8742 compared to total radioactivity and the recovery of the radioactive dose following administration of 50 mg [¹⁴C]MK8742 in healthy male subjects

Parameter/Analyte	N	GM [†]	95% CI	GMR [‡]	95% CI [†]	rMSE [§]
AUC₀₋₁₆ (µM•hr or µM equivalents•hr)						
MK-8742	6	1.01	(0.75, 1.36)	0.89	(0.88, 0.91)	0.015
Total Radioactivity	6	1.13	(0.84, 1.52)			
AUC_{0-∞} (µM•hr or µM equivalents•hr)						
MK-8742	6	1.95	(1.57, 2.43)			
C_{max} (nM or nM equivalents)						
MK-8742	6	107	(73.4, 156)	0.86	(0.79, 0.94)	0.060
Total Radioactivity	6	124	(85.4, 181)			
C₂₄[¶] (nM or nM equivalents)						
MK-8742	6	27.8	[21.0, 34.3]			
Total Radioactivity	6	35.7	[0, 40.8]			
T_{max}[¶] (hr)						
MK-8742	6	3.07	[2.01, 4.01]			
Total Radioactivity	6	3.06	[2.00, 4.01]			
Apparent terminal t_{1/2}^{††} (hr)						
MK-8742	6	17.30	17.72			
Proportion of The Radioactivity Dose Recovered^{‡‡}						
Fraction of Radioactivity Recovery (%)				Urine	Feces	Total
95% Confidence Interval				0.175 (0.118, 0.232)	94.1 (88.1, 100)	94.3 (88.3, 100)

[†]Back-transformed least squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values.
[‡]GMR = Ratio of geometric least-squares means with respect to total radioactivity (i.e., MK-8742 / Total Radioactivity).
[§]rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effects model.
rMSE*100% approximates the within-subject %CV on the raw scale.
[¶]Geometric mean and 95% confidence interval from the summary statistics were reported for AUC_{0-∞}.
[¶]Median (min, max) reported for T_{max} and C₂₄.
^{††}Geometric mean and percent of geometric coefficient of variation reported for apparent terminal t_{1/2}.
^{‡‡}Arithmetic mean and 95% confidence interval from the summary statistics were reported for the proportion of the radioactive dose recovered in urine, feces, and overall.
GMR = Geometric Least-Squares Mean Ratio; GM = Geometric Least-Squares Mean; CI = Confidence Interval.

Note: Subject AN 0002 had a BLQ value for C₂₄ and therefore the BLQ value was set to zero for descriptive statistics and the median (min, max) was reported in the summary statistics.

Fig 1. Arithmetic mean plasma concentration-time profiles of MK-8742 and total radioactivity following administration of a single oral dose of 50 mg [¹⁴C]MK8742 in healthy male subjects



Plasma metabolite profiles

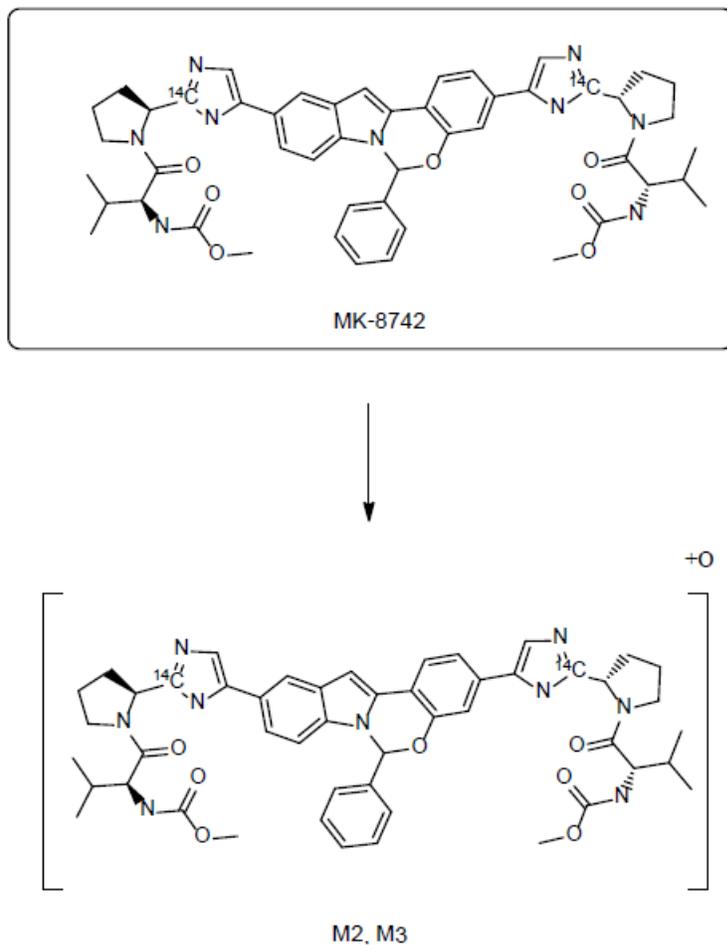
Due to the low amount of total radioactivity in the plasma samples, plasma from the 3- or 8-hour time points were pooled across subjects and analyzed. In the 3- or 8-hour plasma pools, only [¹⁴C]MK-8742 was detected by radio-detection and LC-MS/MS. No circulating human metabolites were detected by radiochemical detection

Fecal metabolite profiles

The majority ($94.0 \pm 6.3\%$) of the radioactivity was recovered in 0 – 168 hours. The feces samples were pooled from 0 to 168 hours across subjects and profiled. Two mono-oxidative metabolites, M2 and M3, were identified in human feces (Fig 2). These metabolites accounted for about 19% of the administered dose. Unchanged MK-8742 accounted for about 75% of the administered dose.

Fig 2. Proposed metabolic scheme for MK-8742

Proposed Metabolic Scheme for [¹⁴C]MK-8742



Urine metabolites

Metabolic profiling was not performed in urine due to the trace amount of radioactivity recovered.

Conclusion

Following the administration of a single dose of 50 mg [¹⁴C]MK-8742 to healthy adult male subjects, mass balance was achieved. The majority of the radioactivity was recovered in feces in the first 7 days (168 hours). Approximately 94% of the administered dose was recovered in the feces in the first 168 hours. The radioactivity in feces was comprised of MK-8742 (~75% of the administered dose) and M2 and M3 oxidative metabolites (~19% of the administered dose). Only a trace amount of total radioactivity was recovered in urine (~0.2%). No circulating metabolites were detected in plasma.

Study Title: A study to investigate the absorption, distribution, metabolism, and mass balance of MK-5172 (grazoprevir): PN007

Study Initiation Date: 16-Nov-2011

Study Completion Date: 23-Dec-2011

Study Site: (b) (4)

Study Design

This was a single-dose, open-label study to investigate the absorption, distribution, metabolism, and elimination of [¹⁴C]MK-5172. 6 healthy adult male subjects received a single oral dose of 200 mg (~200 μCi) [¹⁴C]MK-5172 (b) (4) with 240 mL of water, following an overnight fast, at least 10 hours. Blood, urine and feces were collected until the majority of radioactivity was recovered to evaluate [¹⁴C]MK-5172 excretion and possible metabolites up to a maximum of 24 days post-dose (576 hours).

Identity of Investigational Products

The [¹⁴C]MK-5172 LFC were prepared 24 hours prior to dosing. An aliquot of the [¹⁴C]MK-5172 LFC solution was assayed by liquid scintillation counting (LSC) to confirm the radioactive concentration.

Table 1. Identity of investigational products

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency	Site of Manufacture
[¹⁴ C]-MK-5172	NA	020F001	(b) (4)	NA	97.8%	Merck & Co., Inc., Rahway, NJ
Carbowax™ (b) (4)	NA	ZF2201AAJC	(b) (4)	NA	NA	(b) (4)
(b) (4)	NA	70649291	(b) (4)	NA	NA	(b) (4)
† Carbowax	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Key Inclusion Criteria

- Healthy adult male subjects, 19-45 years of age, inclusive
- BMI: 20-32 kg/m², inclusive
- Non-smokers (have not used nicotine-containing products for at least 3 months prior to the dose)
- Medically healthy with no clinically significant history, physical exam, or lab profiles

Key Exclusion Criteria

- History of any illness that might confound the results of the study or pose an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 80 mL/min
- History of liver disease, biliary tract disease, or has a positive screening test for hepatitis C.

- being unable to refrain from or anticipates the use of any medication, including prescription and non-prescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study drug, throughout the study.
- Consuming excessive amounts of alcohol defined as > 3 glasses of alcoholic beverages per day.
- Consuming excessive amounts of caffeine defined as > 6 servings of caffeinated beverages per day.
- Recent major surgery, blood donation, or blood loss within 8 weeks prior to the screening visit.
- History of significant multiple and/or severe allergies, or has had an anaphylactic reaction or significant intolerance to prescription or non-prescription drugs or food.
- Currently a regular user (including “recreational use”) of any illicit drugs or has a history of drug (including alcohol) abuse within approximately 12 months.
- Recent history (within 2 weeks) of abnormal bowel habits
- Not using an acceptable form of birth control during the conduct of the study and for 90 days postdose and subjects who are unable to refrain from donating sperm during the study and for 90 days postdose.
- A subject has received radio-labeled substances or has been exposed to radiation sources over the past 12 months or is likely to receive radiation exposure or radioisotopes within the next 12 months such that participation in this study would increase their total exposure beyond the recommended levels considered safe (i.e., weighted annual limit recommended of 500 mrem)

Pharmacokinetic Assessments

Blood samples for plasma total radioactivity, plasma MK-5172 assay, and metabolic profiling were collected at predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, and 192 hours postdose, and then every 48 hours until discharge criteria were met, up to a maximum of 576 hours postdose. Subjects were discharged if the radioactive counts were less than 1000 dpm/mL in urine and less than 1000 dpm/g feces.

Urine samples were collected predose and from 0 - 4, 4 - 8, 8 - 12, 12 - 24, 24 - 36, and 36 - 48 hours on Day 1 and then every 24 hours thereafter until discharge. Due to low levels of total radioactivity in the urine, the urine was not profiled for potential metabolites.

Fecal samples were pooled across subjects from 0 - 168 hours.

Bioanalysis

Plasma assay for MK-5172

Plasma MK-5172 concentrations were determined by Merck Research Laboratories (West Point, PA) using a LC-MS/MS method. The lower limit of quantification (LLOQ) was 1.00 ng/mL and the analytical range was 1.00 to 1000 ng/mL. Inter-day accuracy and precision of QC samples (3, 75, 750 ng/mL) ranged from 5.7% to 7.8% and from 1.3% to 3.1%, respectively. Overall, method validation and sample analyses are acceptable.

Plasma, urine, and feces for total radioactivity

MK-5172 concentration equivalents (total radioactivity) in plasma, urine, and feces were determined using liquid scintillation counting (LSC) by (b) (4) All samples were analyzed (b) (4)

(b) (4) The LLOQ values were 40.9 ng equivalents/g (53.330 nM equivalents) for plasma, 9.90 ng equivalents/g (12.909 nM equivalents) for urine, and 178 ng equivalents/g (232.097 nM equivalents) for feces.

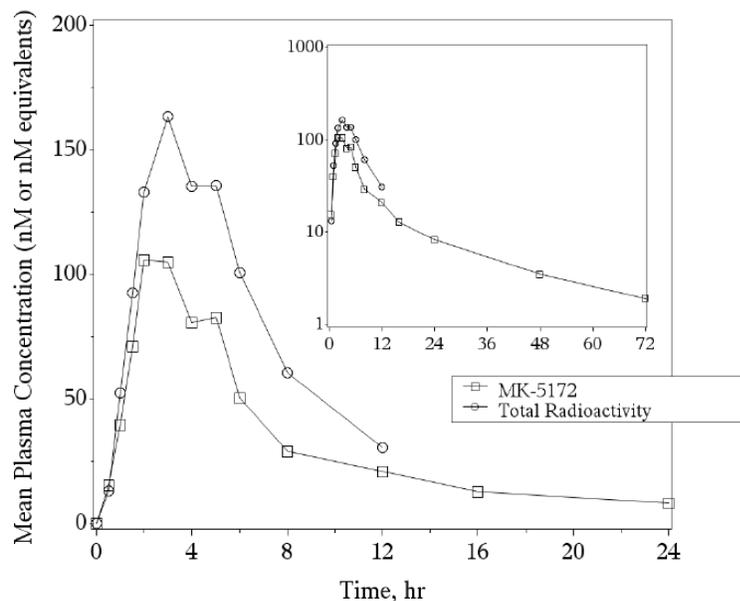
Study Results

Pharmacokinetic parameters of MK-5172 and the recovery of the radioactive dose following single dose administration of 200 mg [¹⁴C]MK5172 in healthy male subjects are summarized in Table 2. Plasma concentrations of MK-5172 were determined by LC/MS/MS and total radioactivity was measured by LSC. AUC₀₋₈ and C_{max} were chosen to be the primary endpoint because more than 50% subjects had both quantifiable MK-5172 and total radioactivity data at and before 8 hours post-dose. The pharmacokinetic time-concentration profiles were similar between plasma MK-5172 and total radioactivity. The majority of the radioactive dose appeared to have been excreted in feces, with less than 0.3% being excreted in urine.

Table 2. Pharmacokinetic parameters of MK-5172 compared to total radioactivity and of the recovery of the radioactive dose following administration of 200 mg [¹⁴C]MK5172 in healthy male subjects

Pharmacokinetic Parameter/ Analyte	N ^{‡‡}	GM [†]	95% CI	GMR [‡]	95% CI	rMSE [§]
AUC_{0-8hr} (nM•hr or nM equivalents•hr)						
MK-5172	6	467	(270, 808)	0.71	(0.59, 0.87)	0.111
Total Radioactivity ^{§§}	5	655	(379, 1130)			
C_{max} (nM or nM equivalents)						
MK-5172	6	135	(65.2, 278)	0.81	(0.69, 0.96)	0.094
Total Radioactivity	5	166	(80.6, 344)			
T_{max} (hr)						
MK-5172	6	2.59	(2.01, 5.01)			
Total Radioactivity	5	3.01	(2.01, 5.01)			
AUC_{0-∞} (nM•hr or nM equivalents•hr)[¶]						
MK-5172	6	1010	(711, 1440)			
Apparent terminal t_{1/2} (hr)^{††}						
MK-5172	6	23.75	(74.14)			
Proportion of the Radioactivity Dose Recovered						
		Urine	Feces	Total		
Fraction of Radioactivity Recovery (%)		0.29	109.77	110.30		
95% Confidence Interval		(0.22, 0.36)	(93.26, 126.27)	(93.61, 126.99)		
[†] Back-transformed least squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values. [‡] GMR = Ratio of geometric least squares means (MK-5172/Total Radioactivity) [§] rMSE: Square root of conditional mean squared error (residual error) from the linear mixed-effect model. rMSE*100% approximates the within-subject %CV on the raw scale. Median (min, max) reported for T _{max} . [¶] Geometric mean and 95% confidence interval from the summary statistics were reported for AUC _{0-∞} . ^{††} Geometric mean (GM) and geometric coefficient of variation (GCV) presented for apparent terminal t _{1/2} . CI = Confidence Interval. ^{‡‡} Subject AN 0002 had all BLQ values for total radioactivity. Therefore, all pharmacokinetic parameters for total radioactivity from Subject AN 0002 could not be quantified and were excluded from total radioactivity statistics. ^{§§} AUC _{0-8hr} for total radioactivity was extrapolated for Subject AN 0004 due to a BLQ value at the 8-hour time point.						

Fig 1. Arithmetic mean plasma concentration-time profiles of MK-5172 and total radioactivity following administration of a single oral dose of 200 mg [¹⁴C]MK5172 in healthy male subjects



Plasma metabolite profiles

Due to the low amount of total radioactivity in the plasma samples, plasma from the 3- or 8-hour time points were pooled across subjects for each of these time points and analyzed. In the 3- or 8-hour plasma pools, only [¹⁴C]MK-5172 was detected by radio-detection and LC-MS/MS. No metabolites were detected in plasma.

Fecal metabolite profiles

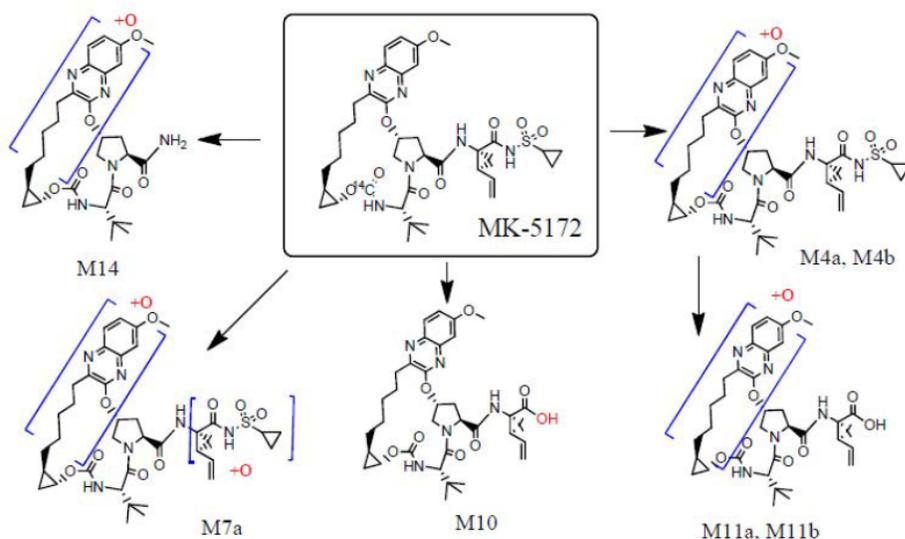
Metabolic profiling results in feces from the pooled fecal homogenate aliquots (up to 168 hours post-dose) are summarized in Table 3. The most prominent components were unchanged MK-5172 and M10, at approximately 44.75% and 33.93% of the total radioactivity in feces, respectively. Oxidative metabolites (M4a, M4b, M7a, M11a, M11b, and M14) accounted for 21% of the total radioactivity in feces.

Table 3. Percent distribution of each metabolite and MK-5172 quantified in human feces (0-168 hours)

Peak	% Total*
M4a, M4b	4.76
M7a	4.19
M11a, M11b	7.99
M14	4.37
M10	33.93
MK-5172	44.75
Total	100

Reviewer comment

According to the applicant, M10 is a gut bacterial reductive metabolite. Other metabolites are thought to be formed by CYP3A4 based on in vitro study results. See below for proposed biotransformation pathways



Urine metabolites

Metabolic profiling was not performed in urine due to the trace amount of radioactivity recovered.

Conclusion

Following the administration of a single dose of 200 mg [¹⁴C]MK-5172 to healthy adult male subjects, mass balance was achieved. The majority of the radioactivity was recovered in feces in the first 7 days (168 hours). The radioactivity recovered in feces was comprised of MK-5172 (~45%), a gut bacterial reductive product of MK-5172 (M10, ~34%) and oxidative metabolites (~21%). Only a trace amount of total radioactivity was recovered in urine (~0.3%). No circulating metabolites were detected in plasma.

4.4 Food effects

Study Title: A Relative Bioavailability Study to Assess the Effect of Food on the Pharmacokinetics of Both MK-5172 and MK-8742 Following the Administration of the Fixed Dose Combination FDC2 of MK-5172A to Healthy Subjects

Study Initiation Date: 12-April-2014 **Study Completion Date:** 19-May-2014

Study Site: (b) (4)

Study Design

This was an open-label, single-dose, randomized, two-treatment, two-period, two-sequence, crossover study in 26 healthy subjects under fasting and fed conditions. In one of the study periods, subjects received a single dose of MK-5172A (50 mg MK-8742 and 100 mg MK-5172) fixed-dose tablet formulation (FDC2) at 30 minutes following the start of consumption of a standardized high-fat, high-calorie breakfast completed, preceded by an overnight fast of at least 10 hours (Treatment A). In the other study period, subjects received a single dose of MK-5172A (50 mg MK-8742 and 100 mg MK-5172) fixed-dose tablet formulation (FDC2) following an overnight fast of at least 10.5 hours (Treatment B). Blood samples were collected at pre-dose and at intervals over 96 hours after dosing each period.

The breakfast consisted of 2 eggs fried in butter, 2 strips of bacon, 4 oz of hash brown potatoes, 2 slices of toast with butter, and 8 oz of whole milk. This contains about 150 protein calories, 250 carbohydrate calories and 500 fat calories.

Key Inclusion Criteria

- Non-tobacco using adult male and female volunteers, 18-55 years of age, inclusive
- BMI: 18 to 30 kg/m², inclusive.
- Good health as determined by lack of clinically significant abnormalities in health assessments
- AST, ALT, and bilirubin are within the clinically acceptable normal range at screening and prior to initial dosing
- Female subjects of childbearing potential must either abstain from sexual intercourse or use a reliable double-barrier method of contraception for at least 30 days prior to initial dosing and during the duration of the study until 14 days after their last dose in the study.

Key Exclusion Criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 80 mL/min
- Presence of a medical condition requiring regular treatment with prescription drugs
- History of drug or alcohol abuse (within 12 months)
- Female subjects who are pregnant or lactating
- Positive results at screening for HIV, hepatitis B, or hepatitis C
- Positive results for urine drug or alcohol screening or check in

- Participation in another clinical trial within 30 days prior to the first dose of study drug.
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients
- Use of pharmacologic agents known to significantly induce or inhibit drug-metabolizing enzymes (e.g. CYP3A, Pgp, and/or OATP) within 30 days before initial dosing

Concomitant medications

Before check-in for each period of the study, the subjects were not permitted to take prescription medications within 14 days before initial study dosing and throughout the duration of the study, or over-the-counter medications or diet supplement products within 3 days before dosing in each period and throughout the times of sample collection each period.

Identity of Investigational Product

Table 1. Identity of Investigational Products

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency	Site of Manufacture (b) (4)
MK-5172/MK-8742	100 mg/50 mg	WL00056471	Tablet	WL00056813	98.2/98.3%	

Reviewer comments

The fixed-dose tablet formulation used in this trial is identical to the to-be-marketed formulation except for color coating. This is also the formulation used in Phase 3 trials.

Pharmacokinetic assessments

Following the administration of MK-517A, blood samples were collected at pre-dose and at intervals over 96 hours after dosing each period. SAS (Version 9.3) was used for all pharmacokinetic and statistical calculations. Areas under the curve from time zero to the time of last measurable concentration (AUC_{0-t}) were calculated by the “lin-up/log-down” variation of the linear trapezoidal method. Area under the curve from time zero to time infinity (AUC_{0-inf}) was calculated as follows: $AUC_{0-inf} = AUC_{0-t} + C_{est,last}/K_{el}$, where $C_{est,last}$ is, and K_{el} is the elimination rate constant. K_{el} , $t_{1/2}$, and AUC_{0-inf} estimates were not reported unless both the associated adjusted R^2 value and AUC_{0-t}/AUC_{0-inf} were greater than 0.7.

Bioanalysis

Plasma samples collected for MK-5172 and MK-8742 assays were analyzed by Merck (Oss, The Netherlands). The concentrations of these drugs were determined using validated LC/MS/MS methods. The standard curve and QC data indicated that the assays were acceptable. All samples were stored and processed in the time frame supported by the stability data.

Table 2. Summary of Bioanalysis

Analyte	MK-5172	MK-8742
Internal standard	MK-5172-d ₆	MK-8742-d ₆
Matrix/Anticoagulant	Plasma/ K ₂ EDTA	Plasma/ K ₂ EDTA
Extraction method	Liquid-liquid extraction	Liquid-liquid extraction

Calibration range	1 to 1000 ng/mL	0.25 to 500 ng/mL
QC concentration	3, 20, 75, and 750 ng/mL	0.75, 75, and 375 ng/mL
Interday precision and accuracy	P: 3.3 to 4.3% A: -2.5 to 2.5%	P: 0.05 to 11.9% A: 2.3 to 7.3%
Storage stability	825 days at -20 °C	651 days at -20 °C

RESULTS

Subject disposition and baseline characteristics

A total of 26 subjects were entered into this study and dosed in Period I, and 25 subjects completed the study per protocol. Subject 21 voluntarily withdrew from the study for personal reasons after the 24 hour blood sample in Period I.

Table 3. Subject baseline demographics

All Combined (N=26)	
Sex (n,%)	
Female	3 (12)
Male	23 (88)
Race (n,%)	
White	3 (12)
Non-White	23 (88)
American Indian or Alaskan Native	0 (0)
Asian	0 (0)
Black or African American	13 (50)
Hispanic or Latino	4 (15)
Multiracial	4 (15)
Native Hawaiian or other Pacific Islander	1 (4)
Other	1 (4)
Age (yrs)	
Mean (SD)	30.2 (6.9)
Median	30.0
Range	20 - 45
Weight (kg)	
Mean (SD)	78.5 (10.6)
Median	79.9
Range	59.0 - 94.5
Height (cm)	
Mean (SD)	172.9 (7.7)
Median	172.7
Range	157.5 - 185.4
BMI (kg/m²)	
Mean (SD)	26.2 (2.5)
Median	26.7
Range	19.8 - 29.4

Pharmacokinetic Results

Relative to the fasted state, the administration of a single dose of 5172A (FDC2) with a high-calorie, high-fat (900 kcal, 500 kcal from fat) breakfast increased GZR $AUC_{0-\infty}$ and C_{max} by 1.5-fold and 2.8-fold, respectively, and decreased EBR $AUC_{0-\infty}$ and C_{max} by 11% and 15%, respectively, in healthy subjects (Table 4-5).

Table 4. MK-5172 plasma pharmacokinetics under fasted or fed conditions

Pharmacokinetic Parameter	MK-5172 Fasted ¹			MK-5172 Fed ²			MK-5172 Fed /MK-5172 Fasted		Pseudo Within-Subject %CV ⁹
	N ⁴	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$ (nM·hr)	17 ^{3,4}	548	(392,623)	22 ^{3,4}	742	(653,882)	1.54	(1.34,1.76)	21.4
AUC_{0-t} (nM·hr)	25	342	(268,438)	25 ⁴	657	(570,754)	1.91	(1.67,2.18)	27.3
C_{max} (nM)	25	30.8	(23.7,39.8)	26	87.1	(68.2,111)	2.83	(2.16,3.72)	56.7
C_{24hr} (nM)	25	4.20	(3.50,5.09)	26	6.95	(6.05,7.99)	1.65	(1.47,1.85)	23.3
C_{2hr} ⁵ (nM)	25	18.8	(2.88, 188)	26	46.9	(0.00,134)	-	-	-
T_{max} ⁶ (h)	25	3.00	(1.00,6.00)	26	2.00	(1.00,6.00)	-	-	-
$t_{1/2}$ ⁷ (h)	17 ³	35.80	35.6	22 ^{3,4}	30.98	23.3	-	-	-

¹ MK-5172 Fasted: MK-5172 pharmacokinetic parameters of FDC tablet prototype FDC2 of MK-5172A (50 mg MK-8742 and 100 mg MK-5172) administered under fasted conditions

² MK-5172 Fed: MK-5172 pharmacokinetic parameters of FDC tablet prototype FDC2 of MK-5172A (50 mg MK-8742 and 100 mg MK-5172) administered under fed conditions

³ Elimination data not available for some subjects. $AUC_{0-t}/AUC_{0-\infty}$ ratios were less than 70% for Subjects 08, 14, 18, 20. Adjusted R^2 values were less than 0.7 for data sets from Subjects 15 (fasted), 16 (fasted), and 21. Some values for Subjects 03, 4, 15 (fed), 16 (fed), and 23 were deemed not reportable by the PK analyst in consultation with Sponsor; please refer to Table 14.2.5 for details.

⁴ Subject 21 withdrew consent after day 2 of fed study. Subject was not dosed under fasting conditions and fed data extend to $t=24hr$. $t_{1/2}$ and $AUC_{0-\infty}$ are not estimable because of low adjusted R^2 and AUC_{0-t} would be underestimated because of lack of available data.

⁵ Median (Min-Max) reported for C_{2hr} , because the C_{2hr} for Subject 13 was below LLOQ.

⁶ Median (Min-Max) reported for T_{max} .

⁷ For $t_{1/2}$, Geometric CV(%) is reported: $100 \cdot \sqrt{\exp(s^2-1)}$, where s^2 is the observed variance on the log scale

⁹ Pseudo Within-Subject %CV = $100 \cdot \sqrt{\frac{s_1^2 + s_2^2 - 2s_{12}}{2}}$, where s_1^2 and s_2^2 are the estimated variances on the log scale for the two treatment groups, and s_{12} is the corresponding estimated covariance, each obtained from the linear mixed effects model.

Data Source: Statistical (SAS[®]) Geometric Means, 90% Confidence Interval Calculations at Alpha=0.05 and Intra-Subject CV% Data provided in Appendix 16.1.9.1

Table 5. MK-8742 plasma pharmacokinetics under fasted or fed conditions

Pharmacokinetic Parameter	MK-8742 Fasted ¹			MK-8742 Fed ²			MK-8742 Fed /MK-8742 Fasted		Pseudo Within-Subject %CV ⁶
	N ³	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC _{0-∞} (nM·hr)	25	2300	(2020,2630)	25 ³	2060	(1800,2350)	0.891	(0.817,0.971)	17.8
AUC _{0-t} (nM·hr)	25	2250	(1980,2570)	25 ³	2000	(1750,2270)	0.885	(0.812,0.964)	17.7
C _{max} (nM)	25	128	(111,145)	26	108	(96.4,121)	0.852	(0.772,0.941)	20.4
C _{24hr} (nM)	25	35.2	(31.0,39.9)	26	32.6	(28.5,37.3)	0.926	(0.850,1.01)	17.7
C _{2hr} (nM)	25	92.2	(78.1,111)	26	48.2	(32.9,70.6)	0.518	(0.353,0.762)	81.0
T _{max} ⁴ (h)	25	3.50	(2.00, 4.00)	26	3.00	(1.50, 6.00)	-	-	-
t _{1/2} ⁵ (h)	25	17.72	12.2	25 ³	17.79	13.5	-	-	-

¹ MK-8742 Fasted: MK-8742 pharmacokinetic parameters of FDC tablet prototype FDC2 of MK-5172A (50 mg MK-8742 and 100 mg MK-5172) administered under fasted conditions

² MK-8742 Fed: MK-8742 pharmacokinetic parameters of FDC tablet prototype FDC2 of MK-5172A (50 mg MK-8742 and 100 mg MK-5172) administered under fed conditions

³ Subject 21 withdrew consent after day 2 of fed study. Subject was not dosed under fasting conditions and fed data extend to t=24hr. t_{1/2} and AUC_{0-inf} are not estimable because of low adjusted R² and AUC_{0-t} would be underestimated because of lack of available data.

⁴Median (Min-Max) reported for T_{max}.

⁵ For t_{1/2}, Geometric CV(%) is reported: 100*sqrt(exp(s²-1)), where s² is the observed variance on the log scale

⁶Pseudo Within-Subject %CV = 100*sqrt((s₁²+s₂²-2s₁₂)/2), where s₁² and s₂² are the estimated variances on the log scale for the two treatment groups, and s₁₂ is the corresponding estimated covariance, each obtained from the linear mixed effects model.

Data Source: Statistical (SAS[®]) Geometric Means, 90% Confidence Interval Calculations at Alpha=0.05 and Intra-Subject CV% Data provided in Appendix 16.1.9.1

Discussion and conclusion

Relative to the fasted state, the administration of a single dose of 5172A (FDC2) with a high-calorie, high-fat (900 kcal, 500 kcal from fat) breakfast increased GZR AUC_{0-inf} and C_{max} by 1.5-fold and 2.8-fold, respectively, and decreased EBR AUC_{0-inf} and C_{max} by 11% and 15%, respectively, in healthy subjects. These changes are not considered clinically relevant based on the exposure-response relationship of MK-5172 and MK-8742 for safety and efficacy. The fixed-dose tablet formulation used in this trial (MK-5172A FDC2) is identical to the to-be-marketed formulation except for color coating. This is also the formulation used in Phase 3 trials and patients received MK-5172A FDC2 without regard to food in Phase 3 trials. Therefore, ZEPATIER™ can be administered without regard to food.

4.5 Drug interactions

Study Title: A Study to Evaluate the Effect of Ritonavir on the Pharmacokinetics of MK-5172 (grazoprevir)

Study Initiation Date: 12-May-2011

Study Completion Date: 09-Aug-2011

Study Site: [REDACTED]

(b) (4)

Study Design

This was an open-label, fixed-sequence study to evaluate the safety, tolerability, and pharmacokinetics of grazoprevir when co-administered with ritonavir. Ten healthy subjects were enrolled. In Period 1, subjects received a single oral dose of 200 mg grazoprevir on Day 1. In Period 2, the same subjects received multiple oral doses of 100 mg ritonavir BID for 21 days. On Day 15, subjects received the morning ritonavir dose with a single oral dose of 200 mg grazoprevir. There was a washout period of at least 8 days between the last grazoprevir dose in Period 1 and the first ritonavir dose in Period 2. Grazoprevir was administered orally with approximately 240 mL of water in the fasted state, with additional water restricted 1 hour prior to and 1 hour after grazoprevir administration. Ritonavir was administered with food within 30 minutes prior to or after drug administration except in the morning on Day 15 when it was administered in the fasted state.

In Period 1, blood samples for the determination of grazoprevir plasma concentrations were obtained at predose and at specified time points over 96 hours postdose. In Period 2, blood samples for the determination of grazoprevir plasma concentrations were obtained at predose and over 168 hours postdose

Key Inclusion Criteria

- Subject is a male or female of non-childbearing potential between 18 to 45 years of age
- BMI \leq 32kg/m²
- Have not used nicotine-containing products for at least 3 months prior to the first dose)
- Medically healthy with no clinically significant history, physical exam, lab profiles

Key Exclusion Criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 80 mL/min
- Positive results at screening for HIV, hepatitis B, or hepatitis C
- Subject consumes excessive amounts of alcohol or caffeine
- History of drug abuse within 12 months
- Subject has had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit

- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients
- Unable to refrain from the use of any medication prior to the first dose of study drug (28 days prior to the first dose for CYP/P-gp inducers and inhibitors) and throughout the study

Concomitant medications

If a subject did not discontinue all prior medications within 14 days or 5 half-lives of study start, he/she may have been included in the study if the Investigator could rationalize that the specific use of a prior medication was not clinically relevant within the context of this study. Paracetamol/acetaminophen may have been used for minor ailments.

Identity of Investigational Product

Table 1. Identity of Investigational Products

Bulk Product Description	Manufacturing Lot Number
(b) (4) MK-5172 (grazoprevir) (b) (4) 100 mg Tablet Norvir [®] (ritonavir) 100 mg [†]	WL00040653 Not Applicable
[†] Norvir [®] (ritonavir) 100 mg tablet (lot number 964648D; September 2012; Abbott Laboratories) was supplied by the Investigator.	

Pharmacokinetic assessments

Blood samples for the determination of grazoprevir plasma concentration were collected from each subject at predose and at selected time points over 96 hours following administration of a single oral dose of 200 mg grazoprevir on Day 1 of Period 1 and over 168 hours following multiple oral doses of 100 mg ritonavir BID co-administered with a single oral dose of 200 mg grazoprevir on Day 15 of Period 2.

All the pharmacokinetic parameter values were calculated using the software Phoenix[®] WinNonlin[®] Professional[®] (Version 6.3). C_2 and C_{24} were obtained directly from the plasma concentrations determined at the actual sampling time of 2 and 24 hours postdose, respectively. C_{max} and T_{max} values were obtained directly from the plasma concentration-time data. AUC_{0-24} and AUC_{0-last} were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/logdown).

Bioanalysis

Plasma samples collected for MK-5172 assay were analyzed by (b) (4) using a validated LC/MS/MS method. The assay was precise and accurate. All samples were stored and processed in the time frame supported by the stability data.

Table 2. Summary of Bioanalysis

Analyte	MK-5172
Internal standard	MK-5172-d ₆

Matrix/Anticoagulant	Plasma/K2EDTA
Extraction method	Liquid-liquid extraction
Calibration range	1 to 1000 ng/mL
QC concentration	3, 75, 750 ng/mL
Interday precision and accuracy	P: 2.12 to 2.51% A: -0.26 to 2.31%
Storage stability	397 at – 20° C

RESULTS

Subject disposition and baseline characteristics

Ten healthy male subjects were enrolled into the study and all 10 subjects completed the study per protocol

Table 3. Subject characteristics

	All Subjects	
	n	(%)
Subjects in population	10	
Gender		
Male	10	(100.0)
Age (Years)		
1 to 17	0	(0.0)
18 to 45	10	(100.0)
> 45	0	(0.0)
Mean	30.7	
SD	6.4	
Median	28.5	
Range	24 to 44	
Race		
White	10	(100.0)
Ethnicity		
Not Hispanic Or Latino	10	(100.0)

Pharmacokinetic Results

Table 4. MK-5172 plasma pharmacokinetics with or without the co-administration of ritonavir

Pharmacokinetic Parameters	MK-5172 Alone			MK-5172 + Ritonavir			MK-5172 + Ritonavir/ MK-5172 Alone		rMSE [†]
	N	GM	95 % CI	N	GM	95 % CI	GMR	90 % CI	
AUC _{0-∞} [‡] (μM•hr)	10	1.50	(1.03, 2.19)	10	3.05	(2.09, 4.44)	2.03	(1.60, 2.56)	0.286
AUC ₀₋₂₄ [‡] (μM•hr)	10	1.02	(0.656, 1.57)	10	1.94	(1.25, 3.00)	1.91	(1.31, 2.79)	0.461
C _{max} [‡] (μM)	10	0.202	(0.115, 0.355)	10	0.232	(0.132, 0.407)	1.15	(0.60, 2.18)	0.782
C ₂₄ [‡] (nM)	10	10.7	(7.15, 15.8)	10	20.0	(13.4, 29.8)	1.88	(1.65, 2.14)	0.157
T _{max} [§] (hr)	10	4.00	(1.00, 6.00)	10	4.00	(1.50, 6.00)			
Apparent terminal t _{1/2} (hr)	10	29.78	(24.53)	10	42.02	(21.24)			

MK-5172 Alone: A single oral dose of 200 mg MK-5172 administered on Day 1.
MK 5172 + Ritonavir: 100 mg ritonavir BID on Days 1-21 co-administered with a single oral dose of 200 mg MK-5172 on Day 15.
[†]rMSE: Square root of mean squared error (residual error) from the linear mixed-effects model. rMSE*100% approximates the within-subject % CV on the raw scale.
[‡]Back transformed least square mean (ratio) and confidence interval from linear mixed-effects model performed on natural log transformed values.
[§]Median (min, max) reported for T_{max}.
^{||}Geometric mean and percent geometric CV reported for apparent terminal t_{1/2}.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

Discussion and Conclusion

The co-administration of ritonavir (100 mg BID for 21 days) increased MK-5172 AUC_{inf}, C_{max}, and C_{24hr} by 2.03-, 1.15-, 1.88-fold. This is likely due to the inhibition of CYP3A4 by ritonavir. The sponsor also conducted drug interaction trials with ritonavir-boosted HIV protease inhibitors (atazanavir/ritonavir, lopinavir/ritonavir, and darunavir/ritonavir). Refer to PN029 study review for study results and clinical recommendations.

8742-010

1. Title

A Multiple Dose Study to Evaluate the Safety and Pharmacokinetics of MK-8742 (Elbasvir) and Opiates in Subjects Receiving Opiate Maintenance Therapy

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted from March 18, 2013 (trial initiation) to April 29, 2013 (trial completion).

3. Objectives

The objectives of the trial included evaluating the effect of elbasvir on the exposure of methadone.

4. Trial Design

010 was a clinical trial that enrolled subjects 18 to 55 years old that were receiving a stable regimen of methadone. As designed, methadone dosage regimens ranging from 20 mg to 150 mg once daily were administered on day 1 and on days 2 to 11, elbasvir 50 mg once daily was administered with 20 mg to 150 mg once daily of methadone.

5. Excluded Medications, Restrictions or Exceptions

Specific medications were not permitted during the trial, including CYP3A inhibitors and certain CYP3A inducers.

6. Dosage and Administration

The trial medications were administered under fasted conditions. This is consistent with the proposed U.S. prescribing information (USPI) recommendation for grazoprevir in combination with elbasvir (with or without food). The methadone USPI does not include specific dosing recommendations with regards to food or meals.

7. Rationale for Doses Used in the Trial

The elbasvir dosing regimen of 50 mg once daily is consistent with the recommended dosage regimen in the proposed U.S. prescribing information for elbasvir and grazoprevir (50 mg of elbasvir with 100 mg of grazoprevir once daily). For opioid dependence detoxification, the methadone USPI states that typical stable doses occur between 80 mg to 120 mg/day.

8. Drugs Used in the Trial

The medications administered in trial 010 are displayed in Table 1.

Table 1-Medications administered in trial 010

Bulk Product Description	Manufacturing Lot Number
(b) (4) elbasvir (b) (4) 10 mg	DL00018002
† Oral Concentrate Methadone 10 mg/mL	NA
† Methadone 10 mg/mL (Lot numbers 0527U84263, 0527U84264; expiration date (b) (4) Mallinckrodt) was supplied by the Investigator.	

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included methadone predose and postdose blood samples up to 24 hours on day 1 and day 11 and elbasvir blood samples at predose and up to 72 hours postdose on day 11.

Bioanalysis

The method and bioanalysis of methadone are acceptable.

Methadone plasma samples were analyzed using a validated LC/MS/MS method in K₃EDTA anticoagulated plasma by (b) (4). The method was validated to measure the R and S enantiomers of methadone, not total methadone. The blood samples for analysis of methadone appear to have been collected in tubes containing K₃EDTA as an anticoagulant.

For the plasma samples from the P10 trial that were analyzed for methadone, the lower limit of quantification for R-methadone and S-methadone was 5 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for methadone based on the bioanalytical report. For the P10 trial, precision and accuracy for R methadone and S methadone were evaluated using plasma methadone quality control (QC) samples at 10 ng/mL, 25 ng/mL, 70 ng/mL, 200 ng/mL and 750 ng/mL. For R-methadone, the corresponding methadone inter-run accuracy values were 0.768% for 10 ng/mL, 1.27% for 25 ng/mL, 2.71% for 70 ng/mL, 4.55% for 200 ng/mL and 0.659% for 750 ng/mL. The corresponding methadone inter-run precision values were 10.1% for 10 ng/mL, 5.85% for 25 ng/mL, 4.67% for 70 ng/mL, 5.85% for 200 ng/mL and 3.13% for 750 ng/mL. For S-methadone, the corresponding methadone inter-run accuracy values were 5.49% for 10 ng/mL, 1.88% for 25 ng/mL, 2.32% for 70 ng/mL, 5.63% for 200 ng/mL and -1.69% for 750 ng/mL. The corresponding methadone inter-run precision values were 9.24% for 10 ng/mL, 3.88% for 25 ng/mL, 5.72% for 70 ng/mL, 3.77% for 200 ng/mL and 4.07% for 750 ng/mL.

Incurred sample reanalysis for methadone was not conducted for the P10 trial.

For the P10 trial, the bioanalytical report states that the maximum length of storage for the methadone samples was 22 days at -20°C. Specific information regarding whether current reference standards were used as part of the stability evaluations was not provided by (b) (4). For the P10 trial, the long term R-methadone and S-methadone stability data of 280 days at -70°C and 365 days at -20°C in K₃EDTA anticoagulated plasma generated by (b) (4) appears sufficient based on the information provided in the submission (the bioanalytical report states that the date of last analysis was April 28, 2013).

The bioanalysis of elbasvir was acceptable.

Elbasvir plasma samples were analyzed using a LC/MS/MS method in EDTA (the counterion was not specified) anticoagulated plasma by Merck Research Laboratories (DM-1001). The method validation information, including the long term stability data, for elbasvir was not reviewed because the method is being used for multiple trials. The blood samples for analysis of elbasvir appear to have been collected in tubes containing K₂EDTA as an anticoagulant.

For the plasma samples from the P10 trial that were analyzed for elbasvir, the lower limit of quantification for elbasvir was 0.25 ng/mL and the upper limit of quantification was 500 ng/mL. There were no precision or accuracy issues identified for elbasvir based on the bioanalytical report. For the P10 trial, precision and accuracy were evaluated using plasma elbasvir quality control (QC) samples at 0.75 ng/mL, 75 ng/mL and 375 ng/mL. The corresponding elbasvir inter-run accuracy values were 2.9% for 0.75 ng/mL, 5.1% for 75 ng/mL and 3.7% for 375 ng/mL. The elbasvir inter-run precision values were 2.9% for 0.75 ng/mL, 5.1% for 75 ng/mL and 3.7% for 750 ng/mL.

Incurred sample reanalysis for elbasvir was not conducted for the P10 trial.

For the P10 trial, no information was provided regarding either the duration or the storage temperature for the elbasvir plasma samples. Based on information provided by the applicant, elbasvir long term stability data for 218 days at -20°C and at -70°C are available. The long term stability data appears sufficient if the elbasvir long term stability data used to support the analysis of the P10 trial samples is acceptable ((based on the information in the bioanalytical report, the date of last analysis appeared to be April 27, 2013) and elbasvir plasma samples were stored at -20°C or at -70°C.

Pharmacokinetic Assessments

Based on the information included in the trial report, noncompartmental analysis was performed using actual sampling times to derive R-methadone, S-methadone, and elbasvir plasma pharmacokinetic parameters. The trial report states that for methadone, the AUC_{0-last} was substituted for the dose normalized AUC_(0-24 hours). It appears total methadone concentrations were derived based on adding together the R and S methadone plasma concentrations. Dose normalized pharmacokinetic parameters were derived by dividing by the subject's dose for R-methadone, S-methadone and total methadone (for R and S methadone the doses were half of the total methadone dose).

Statistical Analysis

The statistical analyses included deriving 90% confidence intervals for relevant pharmacokinetic parameters comparing R, S, and total methadone with concomitant use of methadone and elbasvir (test arm) to the reference arm (methadone alone).

Additionally, with concomitant use of methadone, statistical analyses were conducted for elbasvir by comparing to historical data (MK-8742 PN001: Part 2- 50 mg multiple dosing).

10. Results

10.1 Subject Demographics

Table 2-P10 subject demographics

	TOTAL	
	n	(%)
Subjects in population	10	
Gender		
Male	6	(60.0)
Female	4	(40.0)
Age (Years)		
0 to 17	0	(0.0)
18 to 55	10	(100.0)
>55	0	(0.0)
Mean	31.9	
SD	11.0	
Median	28.5	
Range	21 to 53	
Race		
White	10	(100.0)
Ethnicity		
Hispanic Or Latino	1	(10.0)
Not Hispanic Or Latino	9	(90.0)
TOTAL: Daily dose of methadone 20 - 150 mg QD on Days 1 through 11 and daily dose of MK-8742 50 mg on Days 2 through 11.		

10.2 Concomitant Medications

The concomitant medications that were administered in the trial included acetaminophen. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

10.3 Dosage regimens of methadone administered in the trial

In the P10 trial, the actual administered methadone dosage regimens ranged from 20 mg to 120 mg once daily.

10.4 Pharmacokinetic and Statistical Analysis

Note: in the tables below the trial report states that C_{24h} was the plasma drug concentration 24 hours postdose.

A) Methadone

Table 3A R-methadone pharmacokinetic parameters

	R-Methadone Pharmacokinetic Parameters										
	AUC0-24/D (hr*ng/mL/mg)			C24/D (ng/mL/mg)			Cmax/D (ng/mL/mg)			Tmax (hr)	
	Methadone Alone	Methadone + Elbasvir	Methadone + Elbasvir /Methadone Alone	Methadone Alone	Methadone + Elbasvir	Methadone + Elbasvir /Methadone Alone	Methadone Alone	Methadone + Elbasvir	Methadone + Elbasvir /Methadone Alone	Methadone Alone	Methadone + Elbasvir
N	10	10	10	10	10	10	10	10	10	10	10
AM	117	117	1.05	3.93	4.17	1.13	6.99	7.29	1.09	3.15	3.10
SD	32.1	17.9	0.21	1.29	0.71	0.27	1.96	1.26	0.23	1.37	1.29
ACV	27.5	15.3	19.7	32.9	17.0	24.1	28.0	17.3	21.6	43.6	41.5
Med	114	122	1.02	3.74	4.17	1.05	7.38	7.26	1.03	3.00	3.00
Min	68.8	93.6	0.71	2.11	3.13	0.72	3.80	5.53	0.86	1.50	2.00
Max	182	152	1.41	6.32	5.33	1.64	10.7	9.52	1.61	6.00	6.00
GM	113	116	1.03	3.75	4.12	1.10	6.73	7.19	1.07	2.90	2.89
GCV	28.2	15.2	19.8	33.9	17.1	24.3	30.4	17.4	20.2	45.4	39.2

Methadone Alone: Oral maintenance dose of 20 - 120 mg methadone administered on Day 1.
Methadone + Elbasvir: Co-administration of oral doses of 50 mg elbasvir QD with oral maintenance doses of 20 mg - 120 mg methadone QD on Days 2 to 11.
AM = Arithmetic mean; SD = Standard deviation; GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (SD/AM)$; GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: $100 \times \sqrt{(\exp(s^2) - 1)}$, where s^2 is the observed variance on the natural log-scale.
D = Dose normalized

Table 3B S-methadone pharmacokinetic parameters

	S-Methadone Pharmacokinetic Parameters										
	AUC0-24/D (hr*ng/mL/mg)			C24/D (ng/mL/mg)			Cmax/D (ng/mL/mg)			Tmax (hr)	
	Methadone Alone	Methadone + Elbasvir	Methadone + Elbasvir /Methadone Alone	Methadone Alone	Methadone + Elbasvir	Methadone + Elbasvir /Methadone Alone	Methadone Alone	Methadone + Elbasvir	Methadone + Elbasvir /Methadone Alone	Methadone Alone	Methadone + Elbasvir
N	10	10	10	10	10	10	10	10	10	10	10
AM	132	139	1.12	3.98	4.49	1.26	9.24	9.78	1.12	2.55	2.40
SD	51.0	43.6	0.29	2.02	1.75	0.43	3.28	2.67	0.28	0.98	0.93
ACV	38.5	31.3	25.8	50.8	39.0	34.3	35.4	27.3	25.1	38.5	38.8
Med	138	140	1.06	3.76	4.10	1.06	10.4	10.5	1.02	2.51	2.00
Min	53.9	76.0	0.69	1.11	2.00	0.65	3.98	5.58	0.78	1.50	1.50
Max	203	220	1.59	7.85	7.52	1.95	13.3	12.9	1.71	4.00	4.00
GM	122	133	1.09	3.48	4.17	1.20	8.61	9.42	1.09	2.38	2.26
GCV	45.9	34.0	26.4	62.9	43.0	35.8	43.7	30.9	23.9	41.0	36.6

Methadone Alone: Oral maintenance dose of 20 - 120 mg methadone administered on Day 1.
Methadone + Elbasvir: Co-administration of oral doses of 50 mg elbasvir QD with oral maintenance doses of 20 mg - 120 mg methadone QD on Days 2 to 11.
AM = Arithmetic mean; SD = Standard deviation; GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (SD/AM)$; GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: $100 \times \sqrt{(\exp(s^2) - 1)}$, where s^2 is the observed variance on the natural log-scale.
D = Dose normalized

Table 3C Total methadone pharmacokinetic parameters

	Total Methadone Pharmacokinetic Parameters										
	AUC0-24/D (hr*ng/mL/mg)			C24/D (ng/mL/mg)			Cmax/D (ng/mL/mg)			Tmax (hr)	
	Methadone Alone	Methadone + Elbasvir	Methadone + Elbasvir /Methadone Alone	Methadone Alone	Methadone + Elbasvir	Methadone + Elbasvir /Methadone Alone	Methadone Alone	Methadone + Elbasvir	Methadone + Elbasvir /Methadone Alone	Methadone Alone	Methadone + Elbasvir
N	10	10	10	10	10	10	10	10	10	10	10
AM	125	128	1.08	3.96	4.33	1.18	8.08	8.49	1.10	2.60	2.55
SD	40.0	29.9	0.24	1.60	1.19	0.33	2.57	1.91	0.26	0.94	0.89
ACV	32.1	23.3	22.5	40.4	27.4	28.3	31.8	22.5	23.4	36.0	34.9
Med	132	131	1.04	4.01	4.19	1.04	9.09	8.77	1.02	2.51	2.00
Min	70.9	84.8	0.70	1.88	2.57	0.68	4.32	5.38	0.82	1.50	1.52
Max	192	186	1.50	6.78	6.43	1.79	12.0	10.7	1.67	4.00	4.00
GM	119	125	1.06	3.67	4.19	1.14	7.67	8.28	1.08	2.45	2.42
GCV	34.9	24.0	22.8	43.8	28.3	29.0	36.8	24.5	22.0	37.9	34.2

Methadone Alone: Oral maintenance dose of 20 - 120 mg methadone administered on Day 1.
Methadone + Elbasvir: Co-administration of oral doses of 50 mg elbasvir QD with oral maintenance doses of 20 mg - 120 mg methadone QD on Days 2 to 11.
AM = Arithmetic mean; SD = Standard deviation; GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (SD/AM)$; GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: $100 \times \sqrt{(\exp(s^2) - 1)}$, where s^2 is the observed variance on the natural log-scale.
D = Dose normalized

Table 4A R-methadone statistical analyses

R-Methadone Pharmacokinetic Parameter	Methadone Alone			Methadone + Elbasvir			Methadone + Elbasvir/Methadone Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ /D [‡] (hr•ng/mL/mg)	10	113	(92.7, 138)	10	116	(104, 130)	1.03	(0.92, 1.15)	13.882
C ₂₄ /D [‡] (ng/mL/mg)	10	3.75	(2.96, 4.74)	10	4.12	(3.65, 4.65)	1.10	(0.96, 1.26)	16.957
C _{max} /D [‡] (ng/mL/mg)	10	6.73	(5.44, 8.33)	10	7.19	(6.35, 8.14)	1.07	(0.95, 1.20)	14.112
T _{max} [§] (hr)	10	3.00	(1.50, 6.00)	10	3.00	(2.00, 6.00)			

Methadone Alone: Oral maintenance dose of 20 - 120 mg methadone administered on Day 1.
Methadone + Elbasvir: Co-administration of oral doses of 50 mg elbasvir QD with oral maintenance doses of 20 mg – 120 mg methadone QD on Days 2 to 11.
[†]Pseudo within-subject %CV = 100 x sqrt[($\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB}$)/2], where σ_A^2 and σ_B^2 are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
D = Dose normalized; GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric mean ratio.

Table 4B S-methadone statistical analyses

S-Methadone Pharmacokinetic Parameter	Methadone Alone			Methadone + Elbasvir			Methadone + Elbasvir/Methadone Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ /D [‡] (hr•ng/mL/mg)	10	122	(89.4, 167)	10	133	(105, 168)	1.09	(0.94, 1.26)	18.346
C ₂₄ /D [‡] (ng/mL/mg)	10	3.48	(2.30, 5.26)	10	4.17	(3.11, 5.60)	1.20	(0.98, 1.47)	24.552
C _{max} /D [‡] (ng/mL/mg)	10	8.61	(6.39, 11.6)	10	9.42	(7.59, 11.7)	1.09	(0.95, 1.25)	16.686
T _{max} [§] (hr)	10	2.51	(1.50, 4.00)	10	2.00	(1.50, 4.00)			

Methadone Alone: Oral maintenance dose of 20 - 120 mg methadone administered on Day 1.
Methadone + Elbasvir: Co-administration of oral doses of 50 mg elbasvir QD with oral maintenance doses of 20 mg – 120 mg methadone QD on Days 2 to 11.
[†]Pseudo within-subject %CV = 100 x sqrt[($\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB}$)/2], where σ_A^2 and σ_B^2 are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
D = Dose normalized; GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric mean ratio.

Table 4C Total methadone statistical analyses

Total Methadone Pharmacokinetic Parameter	Methadone Alone			Methadone + Elbasvir			Methadone + Elbasvir/Methadone Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ /D [‡] (hr•ng/mL/mg)	10	119	(93.0, 151)	10	125	(106, 148)	1.06	(0.93, 1.20)	15.931
C ₂₄ /D [‡] (ng/mL/mg)	10	3.67	(2.72, 4.95)	10	4.19	(3.43, 5.10)	1.14	(0.97, 1.35)	20.111
C _{max} /D [‡] (ng/mL/mg)	10	7.67	(5.94, 9.89)	10	8.28	(6.97, 9.84)	1.08	(0.95, 1.22)	15.369
T _{max} [§] (hr)	10	2.51	(1.50, 4.00)	10	2.00	(1.52, 4.00)			

Methadone Alone: Oral maintenance dose of 20 - 120 mg methadone administered on Day 1.
Methadone + Elbasvir: Co-administration of oral doses of 50 mg elbasvir QD with oral maintenance doses of 20 mg – 120 mg methadone QD on Days 2 to 11.

[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A² + σ_B² - 2 σ_{AB})/2], where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

D = Dose normalized; GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric mean ratio.

B) Elbasvir

Table 5-Elbasvir pharmacokinetic parameters with concomitant use of methadone

		Elbasvir Pharmacokinetic Parameters				
Methadone + Elbasvir	0001	2.25	59.6	0.174	6.00	16.94
	0002	2.84	73.7	0.233	3.00	20.41
	0003	3.40	77.7	0.268	3.98	21.01
	0004	1.88	48.6	0.142	3.98	19.03
	0005	3.54	119	0.232	6.00	24.94
	0006	1.76	49.9	0.155	2.00	24.15
	0007	1.96	50.1	0.174	4.00	18.20
	0008	6.29	200	0.489	3.00	23.45
	0009	2.75	72.9	0.236	4.00	17.26
	0010	1.51	43.3	0.134	4.00	16.51
	N	10	10	10	10	10
	AM	2.82	79.4	0.224	4.00	20.19
	SD	1.40	47.7	0.104	1.25	3.12
	ACV	49.8	60.0	46.4	31.2	15.4
Med	2.50	66.2	0.203	3.99	19.72	
Min	1.51	43.3	0.134	2.00	16.51	
Max	6.29	200	0.489	6.00	24.94	
GM	2.58	70.7	0.208	3.82	19.98	
GCV	44.3	50.0	39.8	33.4	15.4	

Methadone + Elbasvir: Co-administration of oral doses of 50 mg elbasvir QD with oral maintenance doses of 20 mg – 120 mg methadone QD on Days 2 to 11.
AM = Arithmetic mean; SD = Standard deviation; GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (SD/AM)$; GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: $100 \times \sqrt{\exp(s^2) - 1}$, where s^2 is the observed variance on the natural log-scale.
D = Dose normalized

Table 6-Elbasvir statistical analysis with concomitant use of methadone

Elbasvir Pharmacokinetic Parameter	Elbasvir Alone			Methadone + Elbasvir			Methadone + Elbasvir/Elbasvir Alone		rMSE [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (μM•hr)	6	1.51	(1.04, 2.19)	10	2.58	(1.93, 3.44)	1.71	(1.16, 2.51)	0.424
C ₂₄ [‡] (nM)	6	38.0	(25.4, 57.0)	10	70.7	(51.7, 96.6)	1.86	(1.22, 2.83)	0.461
C _{max} [‡] (μM)	6	0.108	(0.0737, 0.157)	10	0.208	(0.155, 0.279)	1.93	(1.30, 2.86)	0.433
T _{max} [§] (hr)	6	4.00	(3.00, 4.00)	10	3.99	(2.00, 6.00)			
Apparent terminal t _{1/2} (hr)	6	20.65	17.65	10	19.98	15.35			

Elbasvir Alone: Oral doses of 50 mg Elbasvir QD administered on Days 1 to 10 (historical data from MK-8742 PN001).
Methadone + Elbasvir: Co-administration of oral doses of 50 mg elbasvir QD with oral maintenance doses of 20 mg – 120 mg methadone QD on Days 2 to 11.
[†]rMSE: Square root of conditional mean squared error (residual error) from the linear fixed-effects model. rMSE*100% approximates the between-subject %CV on the raw scale.
[‡]Back-transformed least-squares mean and confidence interval from the linear fixed-effects model performed on natural log-transformed values, with treatment as the fixed effect.
[§]Median (Minimum, Maximum) reported for T_{max}.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
D = Dose normalized; GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric mean ratio.

10.4 Safety Analysis

According to the trial report, no deaths or serious adverse events were reported for the trial and the most common adverse event were gastrointestinal related (e.g. upper abdominal pain, nausea and vomiting).

11. Discussion and Conclusions

Based on the results from the P10 trial, the following conclusions can be made:

- When methadone dosage regimens ranging from 20 mg to 120 mg once daily were administered with elbasvir 50 mg once daily:
 - the dose normalized R-methadone C_{24h} , $AUC_{(0-24hr)}$ and C_{max} were increased by 10%, 3% and 7%, respectively, and only the 90% confidence intervals for $AUC_{(0-24hr)}$ and C_{max} were within the standard limits of 80% to 125%.
 - the dose normalized S-methadone C_{24h} , $AUC_{(0-24hr)}$ and C_{max} were increased by 20%, 9% and 9%, respectively, and only the 90% confidence interval for C_{max} was within the standard limits of 80% to 125%.
 - the dose normalized total methadone C_{24h} , $AUC_{(0-24hr)}$ and C_{max} were increased by 14%, 6% and 8%, respectively, and only the 90% confidence interval for $AUC_{(0-24hr)}$ and C_{max} were within the standard limits of 80% to 125%.

The results support the absence of a clinically significant effect of elbasvir on R-methadone, S-methadone or total methadone exposure.

Additionally, the analyses that were conducted for elbasvir exposure compared to historical data indicate that while elbasvir concentrations may be increased with concomitant use of methadone, the use of historical control data precludes a definitive assessment of safety risk from being made.

Title: A Study to Evaluate the Interaction with Elbasvir with Rifampin in Healthy Subjects (PN011)

Trial Initiation Date: 16-May-2014 **Trial Completion Date:** 06-Aug-2014

Trial Site: (b) (4)

Primary Objective: To assess the effect of a single IV or oral dose of rifampin on the pharmacokinetics of a single oral dose of elbasvir.

Study Design

This trial was a single center, 3-period fixed-sequence single dose trial in healthy subjects. Fourteen male and female subjects were enrolled and received the following treatment regimen in a 3-treatment period fixed-sequence. All drugs were administered as a single dose. A washout of at least 10 days occurred between Period 1 and Period 2, with a washout of at least 14 days between Period 2 and Period 3.

- Period 1: 50 mg oral elbasvir
- Period 2: 50 mg oral elbasvir immediately after 30 minute IV 600 mg rifampin
- Period 3: 50 mg oral elbasvir co-administered with 600 mg oral rifampin

Rationale for Trial Design

Elbasvir is a substrate of CYP 3A4/P-gp. *In vitro*, the role of BCRP in the disposition of elbasvir could not be conclusively determined due to high background in the host cell line. Rifampin, when administered as a single dose, is an inhibitor of BCRP, P-gp and OATP1B. In this trial, a single IV and a single oral dose of rifampin were administered to test the ability of rifampin to inhibit transport mechanisms (liver OATP1B1/1B3 and BCRP versus gut P-gp and BCRP) for their potential to mediate drug-drug interactions with elbasvir.

Key Inclusion Criteria

- Healthy adult male and female volunteers, 18-55 years of age, BMI: 19-32 kg/m², inclusive
- Have not used nicotine-containing products for at least 3 months prior to the first dose
- Medically healthy with no clinically significant history, physical exam, lab profiles.
- A female of childbearing potential must either sexually inactive or use acceptable birth control methods. Male subjects must use a condom (or abstain from sexual intercourse) and agree not to donate sperm from the first dose until 90 days after the last dose

Key Exclusion Criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 90 mL/min
- Female subjects who are pregnant or lactating
- Positive results at screening for HIV, hepatitis B, hepatitis C, or urine drug
- Subject has a history of repeated or frequent syncope or vasovagal episodes
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients
- Consuming excessive alcohols or caffeinated beverages
- Unable to refrain from the use of any medication for the 14 days (28 days prior to, if CYP or P-gp inducers) prior to the first dose of study medications and throughout the study.

Identity of Investigational Product

Table 1. Identify of investigational products

Trial Drugs	Dose	Dosage Form ^{(b) (4)}	Route of Administration	Lot Number	Site of Manufacture
Elbasvir [*]	50 mg (5 x 10 mg)		Oral	DL00018432	Merck Sharpe & Dohme Corp.
Rifampin	600 mg	Capsule ^{**}	Oral	2013141287	Lannett CO, Inc
Rifampin	600 mg	Infusion ^{***}	IV (30-minute infusion)	1A3008	Sanofi-Aventis
Rifampin	600 mg	Infusion ^{****}	IV (30-minute infusion)	A3009	Sanofi-Aventis

Concomitant Medications and Dietary Restrictions

Acetaminophen (2 g maximum daily) may have been used for minor ailments. Subjects using hormonal contraception were requested to use a double barrier contraceptive method for the duration of the trial due to possible interaction of rifampin and hormonal contraceptives. Subjects were to refrain from consumption of grapefruit juice, grapefruits and grapefruit-containing products beginning approximately 2 weeks prior to administration of the initial dose of trial drug, throughout the trial. Subjects also were to refrain from all other fruits, fruit juices, alcohol, and caffeine at least 24 hours prior to and after administration of each dose of trial drug on PK sampling days.

Pharmacokinetic Assessments

Blood samples for determination of elbasvir plasma concentrations were collected at pre-dose and at specified time points over 96 hours following the elbasvir dose in each treatment period. Pharmacokinetic parameter values were calculated by non-compartmental analysis methods from the concentration-time data using Phoenix® WinNonlin® Professional (Version 6.3 or higher).

Bioanalysis

Plasma PK samples were analyzed by (b) (4) according to a validated LC/MS/MS method. The standard curve and QC data indicated that assays were precise and accurate. All samples were stored and processed (48 days) in the time frame supported by the stability data.

Table 2. Summary of bioanalysis

Analyte/ Internal standard	Elbasvir / Elbasvir-d ₆
Matrix/Anticoagulant	Plasma/K ₂ DTA
Calibration range	0.25-500 ng/mL, 1/x ² regression
QC concentration	0.75, 12.5, 75, 250, and 375 ng/mL
Inter-day precision and accuracy	P: 0.5 to 3.5%, A: -0.24 to 2.00 %
Long term stability	83 days at - 20°C

Study Results

Subject Baseline Demographics

Baseline demographic information is summarized in Table 3. Subject AN0011 was discontinued from the study after a single administration of 50 mg elbasvir on Day 1, Period 1 due to low hemoglobin and hematocrit levels. This was not considered treatment-emergent adverse events by the sponsor.

Table 3. Subject baseline demographics

Subject	Gender	Ethnicity	Race	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m ²)
AN0001	Male	Not Hispanic or Latino	Black or African American	45	181	97.8	29.9
AN0002	Female	Hispanic or Latino	White	32	152	70.8	30.6
AN0003	Female	Not Hispanic or Latino	Black or African American	37	170	78.5	27.2
AN0004	Male	Not Hispanic or Latino	Black or African American	45	170	78.1	27.0
AN0005	Male	Not Hispanic or Latino	Black or African American	49	185	76.6	22.4
AN0006	Female	Not Hispanic or Latino	Black or African American	33	172	78.8	26.6
AN0007	Female	Not Hispanic or Latino	Black or African American	33	167	59.7	21.4
AN0008	Female	Not Hispanic or Latino	Black or African American	37	167	69.5	24.9
AN0009	Female	Not Hispanic or Latino	American Indian or Alaska Native	50	156	70.7	29.1
AN0010	Male	Hispanic or Latino	White	26	175	65.2	21.3
AN0011	Female	Not Hispanic or Latino	Black or African American	39	169	74.0	25.9
AN0012	Female	Not Hispanic or Latino	Black or African American	20	159	59.4	23.5
AN0013	Male	Not Hispanic or Latino	Black or African American	31	171	90.1	30.8
AN0014	Male	Not Hispanic or Latino	Black or African American	39	190	100.2	27.8
Statistical Summary							
N				14	14	14	14
Range				20 - 50	152 - 190	59.4 - 100.2	21.3 - 30.8
Arithmetic Mean (SD)				36.9 (8.56)	170.3 (10.51)	76.39 (12.514)	26.31 (3.251)

Pharmacokinetic Results

The co-administration of a single IV dose of rifampin increased elbasvir exposures (C_{max} , AUC_{inf} , and C_{24} by 41%, 22%, and 31%, respectively). The co-administration of a single oral dose of rifampin increased elbasvir exposures to a similar extent (Table 4 and Table 5).

Table 4. Elbasvir plasma pharmacokinetics with or without the co-administration of a single IV dose of rifampin

Parameter	Elbasvir alone			IV Rifampin + Elbasvir			IV Rifampin + Elbasvir/ Elbasvir alone		Pseudo Within Subject CV% [1]
	N	GM	95% CI	N [4]	GM	95% CI	GMR	90% CI	
AUC_{0-inf} (uM.h)	14	2.19	(1.66, 2.90)	13	2.67	(1.98, 3.61)	1.22	(1.06, 1.40)	19.931
AUC_{0-last} (uM.h)	14	2.10	(1.60, 2.76)	13	2.62	(1.94, 3.53)	1.24	(1.08, 1.44)	20.285
AUC_{0-12hr} (uM.h)	14	0.807	(0.636, 1.02)	13	1.12	(0.855, 1.47)	1.39	(1.20, 1.61)	20.695
AUC_{0-24hr} (uM.h)	14	1.25	(0.982, 1.60)	13	1.73	(1.31, 2.29)	1.38	(1.19, 1.60)	20.855
C_{max} (uM)	14	0.107	(0.0852, 0.133)	13	0.150	(0.115, 0.196)	1.41	(1.18, 1.68)	25.581
C_{24hr} (nM)	14	32.3	(24.6, 42.4)	13	42.2	(30.7, 58.0)	1.31	(1.12, 1.53)	22.731
CL/F (L/h)	14	25.8	(19.5, 34.2)	13	21.2	(15.7, 28.6)	0.82	(0.71, 0.94)	19.906
Vd/F (L)	14	755	(606, 940)	13	517	(388, 690)	0.69	(0.58, 0.81)	23.948
T_{max} (h)[2]	14	3.00	(2.00, 4.00)	13	4.00	(3.00, 4.12)	-	-	-
$t_{1/2}$ (h)[3]	14	20.2	20.9	13	16.5	11.2	-	-	-

Treatment: Elbasvir (Period 1 Day 1), IV Rifampin + Elbasvir (Period 2 Day 1), Oral Rifampin + Elbasvir (Period 3 Day 1).
 [1] For each model, the associated variance-covariance matrix was used to estimate the within-subject coefficient of variation as $pseudo\ CV\% = 100 * \sqrt{(\text{Var}(x1) + \text{Var}(x2) - 2 * \text{Cov}(x1, x2)) / 2}$, where $\text{Var}(x1)$ is the estimated variance of Treatment 'Elbasvir (Period 1 Day 1)' and $\text{var}(x2)$ is the estimated variance of 'IV Rifampin + Elbasvir (Period 2 Day 1)', and $\text{Cov}(x1, x2)$ is the estimated covariance of the 2 treatments.
 [2] Median, minimum and maximum reported.
 [3] GM and GCV% reported.
 [4] No PK data were obtained from 1 subject in Period 2 and Period 3 as this subject was permanently withdrawn from the trial on admission to Period 2. See Section 10.4 for more details.

Table 5. Elbasvir plasma pharmacokinetics with or without the co-administration of a single oral dose of rifampin

Parameter	Elbasvir alone			Oral Rifampin + Elbasvir			Oral Rifampin + Elbasvir/ Elbasvir alone		Pseudo Within Subject CV% [1]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC _{0-inf} (uM.h)	14	2.19	(1.66, 2.90)	13	2.56	(1.86, 3.53)	1.17	(0.98, 1.39)	24.482
AUC _{0-last} (uM.h)	14	2.10	(1.60, 2.76)	13	2.51	(1.82, 3.45)	1.19	(1.01, 1.42)	24.427
AUC _{0-12hr} (uM.h)	14	0.807	(0.636, 1.02)	13	1.08	(0.779, 1.49)	1.34	(1.11, 1.61)	26.699
AUC _{0-24hr} (uM.h)	14	1.25	(0.982, 1.60)	13	1.67	(1.22, 2.30)	1.34	(1.12, 1.59)	25.232
C _{max} (uM)	14	0.107	(0.0852, 0.133)	13	0.138	(0.0961, 0.198)	1.29	(1.06, 1.58)	28.897
C _{24hr} (nM)	14	32.3	(24.6, 42.4)	13	39.1	(27.9, 54.8)	1.21	(1.03, 1.43)	23.797
CL/F (L/h)	14	25.8	(19.5, 34.2)	13	22.1	(16.0, 30.5)	0.86	(0.72, 1.02)	24.485
Vd/F (L)	14	755	(606, 940)	13	549	(403, 749)	0.73	(0.61, 0.86)	24.160
T _{max} (h)[2]	14	3.00	(2.00, 4.00)	13	3.50	(1.50, 6.02)	-	-	-
t _{1/2} (h)[3]	14	20.2	20.9	13	16.8	11.0	-	-	-

Treatment: Elbasvir (Period 1 Day 1), IV Rifampin + Elbasvir (Period 2 Day 1), Oral Rifampin + Elbasvir (Period 3 Day 1).

[1] For each model, the associated variance-covariance matrix was used to estimate the within-subject coefficient of variation as pseudo CV% = 100*sqrt[(Var(x1) + Var(x2) - 2*Cov(x1,x2))/2].

where Var(x1) is the estimated variance of Treatment 'Elbasvir (Period 1 Day 1)' and var(x2) is the estimated variance of 'Oral Rifampin + Elbasvir (Period 3 Day 1)', and Cov(x1,x2) is the estimated covariance of the 2 treatments.

[2] Median, minimum and maximum reported.

[3] GM and GCV% reported.

[4] No PK data were obtained from 1 subject in Period 2 and Period 3 as this subject was permanently withdrawn from the trial on admission to Period 2. See Section 10.4 for more details.

Data Source: [Table 14.2.3.2]

Reviewer comments and conclusion

The co-administration of a single dose of IV or oral rifampin slightly increased elbasvir exposures, but the magnitude is relatively small (20~40%). In study 074, the co-administration of a single oral dose of cyclosporine (an inhibitor of various hepatic and intestinal transporters including P-gp, BCRP, and OATP1B) increased elbasvir AUC by 1.98-fold. The study results from this trial and 074 indicate that elbasvir is a substrate of one or more of these transporters (P-gp, BCRP, and OATP1B) in vivo. However, the magnitude of interactions with these strong inhibitors is small, particularly as compared to study results with grazoprevir (more than a 10-fold increase in AUC following a single dose administration of rifampin or cyclosporine). Therefore, no significant drug interaction (elbasvir being a victim drug) is expected with other transporter inhibitors.

The sponsor did not determine the effects of multiple doses of rifampin on elbasvir pharmacokinetics. Due to the induction of CYP3A4 by rifampin, the co-administration of multiple doses of rifampin will likely significantly decrease elbasvir exposures. Therefore, the co-administration of rifampin and elbasvir is not recommended.

8742-013

1. Title

A Study to Assess the Effects of Multiple Oral Doses of MK-8742 on the Single-Dose Pharmacokinetics of an Oral Contraceptive (Ethinyl Estradiol and Levonorgestrel) in Healthy Adult Female Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted from March 27, 2013 (trial initiation) to May 24, 2013 (trial completion).

3. Objectives

The objectives of the trial included evaluating the effect of multiple dosing of MK-8742 (elbasvir) on the exposure of a single dose of ethinyl estradiol and levonorgestrel (Nordette 28).

4. Trial Design

013 was a clinical trial that enrolled healthy female postmenopausal or oophorectomized subjects 18 to 65 years old. In period 1, a single dose of 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel (Nordette 28) was administered. Between period 1 and period 2, there was a washout period consisting of at least 7 days. In period 2, 50 mg once daily of elbasvir was administered for 13 days and a single dose of 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel (Nordette 28) was administered on day 10.

5. Excluded Medications, Restrictions or Exceptions

Medications, including nonprescription and herbal products, were not permitted within either 14 days (or 28 days for CYP or P-gp inducers) or 5 half lives, depending on which was longer, before the first dose.

6. Dosage and Administration

The trial medications were administered under fasted conditions. This is consistent with the proposed U.S. prescribing information (USPI) recommendation for grazoprevir in combination with elbasvir (with or without food). The Nordette 28 USPI recommends dose administration after the evening meal or at bedtime and at the same time each day.

7. Rationale for Doses Used in the Trial

The elbasvir dosing regimen of 50 mg once daily is consistent with the recommended dosage regimen in the proposed U.S. prescribing information for elbasvir and grazoprevir (50 mg of elbasvir with 100 mg of grazoprevir once daily). The doses of ethinyl estradiol and levonorgestrel are consistent with Nordette 28.

8. Drugs Used in the Trial

The medications administered in trial 013 are displayed in Table 1

Table 1-Medications administered in trial 013

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency (N = X)	Site of Manufacture
MK-8742	10 mg	DL00018002	Capsule	WL00051617	102.6%	Merck & Co., Inc., West Point, PA
Nordette [®] -28 [†]	0.03 mg EE/ 0.15 mg LNG	NA	Tablet	NA	NA	NA
[†] Nordette [®] -28 (a product of TEVA Women's Health, Inc., subsidiary of TEVA Pharmaceuticals USA, Inc.) was purchased by the Investigator. The lot number was 33803617A; expiration date Jan-2014.						

(Note: the trial report states that either use of Nordette 28 or a generic equivalent was permitted)

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included ethinyl estradiol and levonorgestrel predose and postdose blood samples up to 96 hours in period 1 and period 2.

Bioanalysis

The method and bioanalysis of ethinyl estradiol are acceptable.

Ethinyl estradiol plasma samples were analyzed using a validated LC/MS/MS method in K₂EDTA anticoagulated plasma by (b) (4). The blood samples for analysis of ethinyl estradiol appear to have been collected in tubes containing K₂EDTA as an anticoagulant.

For the plasma samples from the P13 trial that were analyzed for ethinyl estradiol, the lower limit of quantification for ethinyl estradiol was 1 pg/mL and the upper limit of quantification was 200 pg/mL. There were no precision or accuracy issues identified for ethinyl estradiol based on the bioanalytical report. However, not all of the plasma quality control samples that were evaluated as part of the P13 bioanalysis were included in the QC concentrations that were validated. In the method validation, QC concentrations of 3.01 g/mL, 70.14 pg/mL and 150.30 pg/mL were validated. For the P13 trial, precision and accuracy were evaluated using plasma ethinyl estradiol quality control (QC) samples at 3 pg/mL, 10 pg/mL, 100 pg/mL, and 150 pg/mL. The corresponding ethinyl estradiol inter-run accuracy values were -2.37% for 3 pg/mL, -1.97% for 10 pg/mL, -1.4% for 100 pg/mL and -5.96% for 150 pg/mL. The ethinyl estradiol inter-run precision values were 2.06% for 3 pg/mL, 1.62% for 10 pg/mL, 1.55% for 100 pg/mL and 1.24% for 150 pg/mL.

Of the samples selected for incurred sample reanalysis for ethinyl estradiol, all samples were within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of ethinyl estradiol samples that were reanalyzed represents 7% of the total number of samples that were initially analyzed.

For the P13 trial, no information was provided regarding either the duration or the storage temperature for the ethinyl estradiol plasma samples. Specific information regarding whether fresh calibration standards were used as part of the stability evaluations was not provided by (b) (4). For the P13 trial, the long

term ethinyl estradiol stability data (fortified with 4960 pg/mL of levonorgestrel) of 273 days at -20°C and -80°C in K₂EDTA anticoagulated plasma generated by (b) (4) appears sufficient if the information in section 2 is correct (the bioanalytical report states that the date of last analysis was May 23, 2013) and samples were stored at either -20°C or -80°C.

The method and bioanalysis of levonorgestrel are acceptable.

Levonorgestrel plasma samples were analyzed using a validated LC/MS/MS method in K₂EDTA anticoagulated plasma by (b) (4). The blood samples for analysis of levonorgestrel appear to have been collected in tubes containing K₂EDTA as an anticoagulant.

For the plasma samples from the P13 trial that were analyzed for levonorgestrel, the lower limit of quantification for levonorgestrel was 25 pg/mL and the upper limit of quantification was 5000 pg/mL. There were no precision or accuracy issues identified for levonorgestrel based on the bioanalytical report. However, not all of the plasma quality control samples that were evaluated as part of the P13 bioanalysis were included in the QC concentrations that were validated. In the method validation, QC concentrations of 75.45 pg/mL, 1760.50 pg/mL and 3772.5 pg/mL were validated. For the P13 trial, precision and accuracy were evaluated using plasma levonorgestrel quality control (QC) samples at 75 pg/mL, 375 pg/mL, 2500 pg/mL, and 3750 pg/mL with a 7000 pg/mL dilution QC. The corresponding levonorgestrel inter-run accuracy values were -4.33% for 75 pg/mL, 0.83% for 375 pg/mL, 0.13% for 2500 pg/mL, and -0.48% for 3750 pg/mL and 5.4% for the 7000 pg/mL dilution QC. The levonorgestrel inter-run precision values were 5.03% for 75 pg/mL, 2.66% for 375 pg/mL, 1.23% for 2500 pg/mL, and 2.32% for 3750 pg/mL and 1.05% for the 7000 pg/mL dilution QC.

Of the samples selected for incurred sample reanalysis for levonorgestrel, all samples were within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of levonorgestrel samples that were reanalyzed represents 7% of the total number of samples that were initially analyzed.

For the P13 trial, no information was provided regarding either the duration or the storage temperature for the levonorgestrel plasma samples. Specific information regarding whether current reference standards were used as part of the stability evaluations was not provided by (b) (4). For the P13 trial, the long term levonorgestrel stability data (fortified with 201 pg/mL of ethinyl estradiol) of 101 days at -20°C and -80°C in K₂EDTA anticoagulated plasma generated by (b) (4) appears sufficient if the information in section 2 is correct (the bioanalytical report states that the date of last analysis was May 23, 2013) and samples were stored at either -20°C or -80°C.

Pharmacokinetic Assessments

Based on the information included in the trial report, noncompartmental analysis was performed using actual sampling times to derive ethinyl estradiol and levonorgestrel plasma pharmacokinetic parameters, including C_{max} and AUC_(0-inf).

Statistical Analysis

The statistical analyses included deriving 90% confidence intervals for ethinyl estradiol and levonorgestrel pharmacokinetic parameters comparing the test arm (concomitant use of ethinyl estradiol and levonorgestrel [Nordette 28] with elbasvir to the reference arm (concomitant use of ethinyl estradiol and levonorgestrel [Nordette 28] alone).

10. Results

10.1 Subject Demographics

Table 2-P13 subject demographics

AN	Gender	Race	Ethnicity	Age (yr)	Height (cm)	Weight (kg)	Body Mass Index (kg/m ²)
0001	Female	White	Not Hispanic or Latino	57	165.0	61.5	22.56
0002	Female	Black or African American	Not Hispanic or Latino	58	159.0	71.8	28.42
0003	Female	White	Hispanic or Latino	51	165.0	83.5	30.71
0004	Female	White	Not Hispanic or Latino	64	162.0	77.4	29.37
0005	Female	White	Hispanic or Latino	49	157.0	74.7	30.30
0006	Female	White	Not Hispanic or Latino	59	171.0	76.4	26.06
0007	Female	White	Hispanic or Latino	48	156.0	72.0	29.52
0008	Female	White	Not Hispanic or Latino	57	164.0	65.5	24.33
0009	Female	White	Not Hispanic or Latino	65	167.0	75.7	27.28
0010	Female	White, Asian and Native Hawaiian/ Pacific Islander	Not Hispanic or Latino	54	170.0	87.3	30.22
0011	Female	White	Hispanic or Latino	48	154.0	69.9	29.29
0012	Female	White	Hispanic or Latino	54	160.0	72.3	28.42
0013	Female	White	Hispanic or Latino	48	171.0	80.9	27.69
0014	Female	White	Not Hispanic or Latino	61	174.0	70.6	23.38
0015	Female	White	Not Hispanic or Latino	61	152.0	67.2	29.04
0016	Female	White	Hispanic or Latino	49	156.0	61.5	25.37
0017	Female	White	Hispanic or Latino	48	163.0	80.6	30.48
0018	Female	White	Hispanic or Latino	47	165.0	74.6	27.53
0019	Female	White	Hispanic or Latino	54	162.0	78.7	29.95
0020	Female	Black or African American	Not Hispanic or Latino	59	165.0	60.8	22.30
N:				20	20	20	20
Range:				47 to 65	152.0 to 174.0	60.8 to 87.3	22.30 to 30.71
Arithmetic Mean:				55	162.9	73.1	27.61
AN = Allocation Number.							

10.2 Concomitant Medications

The concomitant medications that were administered in the trial included ibuprofen and methylprednisolone. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Table 3-Ethinyl estradiol pharmacokinetic parameters

Ethinyl Estradiol Pharmacokinetic Parameters										
	AUC _{0-∞} (nM•hr)			C _{max} (nM)			T _{max} (hr)		Apparent terminal t _{1/2} (hr)	
AN	Nordette® -28 Alone	Nordette® -28 + MK-8742	Nordette® -28 + MK- 8742 / Nordette® -28 Alone	Nordette® -28 Alone	Nordette® -28 + MK-8742	Nordette® -28 + MK- 8742 / Nordette® -28 Alone	Nordette® -28 Alone	Nordette® -28 + MK-8742	Nordette® -28 Alone	Nordette® -28 + MK-8742
N	20	19	19	20	20	20	20	20	20	19
AM	3.26	3.33	1.02	0.242	0.266	1.11	1.28	1.38	20.45	20.29
SD	1.23	1.28	0.11	0.0772	0.0789	0.15	0.34	0.32	3.95	4.05
ACV	37.9	38.5	10.8	31.9	29.6	13.7	26.3	23.1	19.3	20.0
GM	3.07	3.13	1.01	0.231	0.255	1.10	1.25	1.34	20.12	19.94
G CV	35.2	37.0	11.0	32.2	30.9	14.0	25.1	23.8	18.4	19.4
Med	2.86	3.08	1.00	0.228	0.237	1.14	1.06	1.50	20.09	19.70
Min	1.77	1.66	0.80	0.141	0.125	0.87	1.00	1.00	15.85	13.98
Max	7.21	7.22	1.23	0.407	0.416	1.36	2.01	2.00	29.34	29.52
<p>Nordette®-28 Alone: Single oral dose of Nordette®-28 (1 x 0.03 mg/0.15 mg tablet) on Day 1 of Period 1. Nordette®-28+MK-8742: Multiple oral doses of 50 mg (5 x 10 mg capsules) MK-8742 qd for 13 consecutive days, starting on Day 1 of Period 2 and a single oral dose of Nordette®-28 (1 x 0.03 mg/0.15 mg tablet) on Day 10 of Period 2. AN = Allocation number; AM = Arithmetic mean; SD = Standard deviation; GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (SD/AM)$ GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: $100 \times \sqrt{\exp(s^2) - 1}$, where s^2 is the observed variance on the natural log-scale †Subject AN 0009 did not receive the last dose of MK-8742 on Day 13 of Period 2 at 72 hours postdose Nordette®-28; therefore, the elimination phase of EE and LNG may not have been accurately estimated in the presence of MK-8742. Thus, AUC_{0-∞} and apparent terminal t_{1/2} for this subject and period were excluded from the descriptive statistics.</p>										

Table 4-Levonorgestrel pharmacokinetic parameters

Levonorgestrel Pharmacokinetic Parameters										
	AUC _{0-∞} (nM•hr)			C _{max} (nM)			T _{max} (hr)		Apparent terminal t _{1/2} (hr)	
AN	Nordette® -28 Alone	Nordette® -28 + MK-8742	Nordette® -28 + MK- 8742 / Nordette®- 28 Alone	Nordette® -28 Alone	Nordette® -28 + MK-8742	Nordette®- 28 + MK- 8742 / Nordette®- 28 Alone	Nordette® -28 Alone	Nordette® -28 + MK-8742	Nordette® -28 Alone	Nordette® -28 + MK-8742
N	20	19	19	20	20	20	20	20	20	19
AM	159	180	1.16	9.30	9.37	1.03	1.26	1.33	48.80	51.04
SD	81.9	85.9	0.23	4.38	3.96	0.16	0.34	0.49	20.09	23.68
ACV	51.3	47.7	19.8	47.2	42.3	15.4	27.1	36.9	41.2	46.4
GM	141	160	1.14	8.46	8.59	1.02	1.22	1.27	45.26	46.73
G CV	54.0	54.7	22.0	46.5	45.4	16.0	25.3	30.9	41.5	44.6
Med	149	158	1.23	8.41	9.09	1.01	1.03	1.03	44.30	48.27
Min	54.5	67.2	0.68	3.48	3.56	0.68	1.01	1.00	21.90	21.20
Max	378	324	1.58	23.1	19.6	1.32	2.01	3.00	102.85	125.53

Nordette®-28 Alone: Single oral dose of Nordette®-28 (1 x 0.03 mg/0.15 mg tablet) on Day 1 of Period 1.
 Nordette®-28+MK-8742: Multiple oral doses of 50 mg (5 × 10 mg capsules) MK-8742 qd for 13 consecutive days, starting on Day 1 of Period 2 and a single oral dose of Nordette®-28 (1 × 0.03 mg/0.15 mg tablet) on Day 10 of Period 2.
 AN = Allocation number; AM = Arithmetic mean; SD = Standard deviation; GM = Geometric mean; Med = Median;
 Min = Minimum; Max = Maximum
 ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: 100 x (SD/AM)
 GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation:
 100 x sqrt(exp(s²) - 1), where s² is the observed variance on the natural log-scale
[†]The percent extrapolated part of AUC_{0-∞} was ≥ 25% of AUC_{0-last} for the following subjects and periods
 (with Period 1= Nordette®-28 Alone and Period 2 = Nordette®-28+MK-8742): AN 0003 – Period 1 and 2,
 AN 0008 – Period 1 and 2, AN 0012 – Period 1 and 2, AN 0013 – Period 1 and 2, AN 0017 – Period 2, AN 0018 – Period 1 and 2, and
 AN 0019 – Period 1.
[‡]The apparent terminal t_{1/2} for subject AN 0003 (Periods 1 and 2, where Period 1= Nordette®-28 Alone and Period 2 =
 Nordette®-28+MK-8742) was greater than the sampling duration (96 hours postdose – nominal time)
[§]Subject AN 0009 did not receive the last dose of MK-8742 on Day 13 of Period 2 at 72 hours postdose Nordette®-28; therefore, the
 elimination phase of EE and LNG may not have been accurately estimated in the presence of MK-8742. Thus, AUC_{0-∞} and apparent
 terminal t_{1/2} for this subject and period were excluded from the descriptive statistics.

Table 5-Ethinyl estradiol and levonorgestrel statistical analyses

Nordette®-28 Component	Pharmacokinetic Parameter	Nordette®-28 Alone			Nordette®-28+MK-8742			Nordette®-28+MK-8742/ Nordette®-28 Alone		Pseudo Within Subject %CV
		N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
Ethinyl Estradiol (EE)	AUC _{0-∞} ^{††} (nM•hr)	20	3.07	(2.62, 3.61)	19	3.10	(2.63, 3.66)	1.01	(0.97, 1.05)	7.727
	C _{max} [‡] (nM)	20	0.231	(0.200, 0.268)	20	0.255	(0.222, 0.294)	1.10	(1.05, 1.16)	9.860
	T _{max} [‡] (hr)	20	1.06	(1.00, 2.01)	20	1.50	(1.00, 2.00)			
	Apparent terminal t _{1/2} ^{§†} (hr)	20	20.12	18.4	19	19.94	19.4			
Levonorgestrel (LNG)	AUC _{0-∞} ^{††} (nM•hr)	20	141	(112, 179)	19	161	(127, 203)	1.14	(1.04, 1.24)	15.338
	C _{max} [‡] (nM)	20	8.46	(6.88, 10.4)	20	8.59	(7.01, 10.5)	1.02	(0.95, 1.08)	11.261
	T _{max} [‡] (hr)	20	1.03	(1.01, 2.01)	20	1.03	(1.00, 3.00)			
	Apparent terminal t _{1/2} ^{§†} (hr)	20	45.26	41.5	19	46.73	44.6			

Nordette®-28 Alone: Single oral dose of Nordette®-28 (1 x 0.03 mg/0.15 mg tablet) on Day 1 of Period 1.
 Nordette®-28+MK-8742: Multiple oral doses of 50 mg (5 x 10 mg capsules) MK-8742 qd for 13 consecutive days, starting on Day 1 of Period 2 and a single oral dose of Nordette®-28 (1 x 0.03 mg/0.15 mg tablet) on Day 10 of Period 2.
[†]Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on ln-transformed values.
[‡]Median and (Minimum, Maximum) reported for T_{max}.
[§]Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
^{||}Pseudo within-subject %CV = 100* $\sqrt{(\sigma^2_A + \sigma^2_B - 2*\sigma_{AB})/2}$, where σ^2_A and σ^2_B are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.
^{*}Subject AN 0009 did not receive the last dose of MK-8742 on Day 13 of Period 2 at 72 hours postdose Nordette®-28; therefore, the elimination phase of EE and LNG may not have been accurately estimated in the presence of MK-8742. Thus, AUC_{0-∞} and apparent terminal t_{1/2} for this subject and period were excluded from the statistical comparison.

10.4 Safety Analysis

According to the trial report, no deaths or serious laboratory abnormalities were reported along with one serious adverse event (severe laceration) for the trial and the most common adverse events were nausea and cough.

11. Discussion and Conclusions

Based on the results from the P13 trial, the following conclusions can be made:

- When a single dose of 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel (Nordette 28) was administered with elbasvir 50 mg once daily:
 - the ethinyl estradiol AUC_(0-∞) and C_{max} were increased by 1% and 10%, respectively, and the 90% confidence intervals were within the standard limits of 80% to 125% for both parameters
 - the levonorgestrel AUC_(0-∞) and C_{max} were increased by 14% and 2%, respectively, and the 90% confidence intervals were within the standard limits of 80% to 125% for both parameters

The results support the absence of a clinically significant effect of elbasvir on ethinyl estradiol or levonorgestrel exposure.

Title: A Three-Part Study to Evaluate the Two-Way Pharmacokinetic Interaction of MK-8742 With Tenofovir, Efavirenz, and Raltegravir in Healthy Subjects (P016)

Study Initiation Date: 15-Mar-2013

Study Completion Date: 12-May-2013

Study Site: (b) (4)

Study Design

This was a 3-part study, each part being a fixed-sequence, 3-treatment, 3-period, open-label study to evaluate the 2-way pharmacokinetic interaction of MK-8742 with tenofovir, efavirenz, and raltegravir. In each study part, 10 healthy adult male and female subjects, with at least 4 female subjects, were enrolled in the study. Each subject participated in only one study part. In part 1, a washout period of at least 5 days separated the last dose in Period 1 and the first dose in Period 2. In part, 2 a washout period of at least 3 days separated doses in Periods 1 and 2, and a washout period of at least 7 days separated Periods 2 and 3. In part 3, a washout period of at least 7 days separated the last dose in Period 1 and the first dose in Period 2. All study drugs were administered under fasted conditions.

Table 1. Study Design

Study Part	Treatment
Part 1 (MK-8742 + tenofovir)	<u>Period 1:</u> 300 mg tenofovir (1 x 300 mg tablet) qd for 7 days (Days 1 to 7)
	<u>Period 2:</u> 50 mg MK-8742 (5 x 10 mg capsules) qd for 8 days (Days 1 to 8)
	<u>Period 3:</u> 300 mg tenofovir (1 x 300 mg tablet) qd + 50 mg MK-8742 (5 x 10 mg capsules) qd, for 7 days (Days 1 to 7)
Part 2 (MK-8742 + raltegravir)	<u>Period 1:</u> Single oral dose of 400 mg raltegravir (1 x 400 mg tablet) (Day 1)
	<u>Period 2:</u> Single oral dose of 50 mg MK-8742 (5 x 10 mg capsules) (Day 1)
	<u>Period 3:</u> Single oral dose of 400 mg raltegravir (1 x 400 mg tablet) + single oral dose of 50 mg MK-8742 (5 x 10 mg capsules) (Day 1)
Part 3 (MK-8742 + efavirenz)	<u>Period 1:</u> 50 mg MK-8742 (5 x 10 mg capsules) qd for 8 days (Days 1 to 8)
	<u>Period 2:</u> 600 mg efavirenz (1 x 600 mg tablet) qd for 14 days (Days 1 to 14)
	<u>Period 3:</u> 50 mg MK-8742 (5 x 10 mg capsules) qd + 600 mg efavirenz (1 x 600 mg tablet) qd, for 8 days (Days 1 to 8)

Key Inclusion Criteria

- Healthy adult male and female volunteers, 19-55 years of age, inclusive
- BMI: 19- 32 kg/m², inclusive. Weigh at least 52 kg for males and 45 kg for females.
- Non-smokers (have not used nicotine-containing products for at least 3 months prior to the first dose)
- Medically healthy with no clinically significant history, physical exam, lab profiles

- For females of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using acceptable birth control methods. Male subjects must use a condom (or abstain from sexual intercourse) and agree not to donate sperm from the first dose until 90 days after the last dose

Key Exclusion Criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study
- Part 1 only: any abnormality in the urinalysis test
- Estimated creatinine clearance less than 90 mL/min
- History of drug or alcohol abuse (within 2 years)
- History or presence of diabetes mellitus or hyperglycemia
- Female subjects who are pregnant or lactating
- Positive results at screening for HIV, hepatitis B, or hepatitis C, urine drug or cotinine screening
- Donation of blood or had significant blood loss within 4 weeks prior to the first dose of study drug or plasma donation within 7 days prior to the first dose of study drug.
- Participation in another clinical trial within 28 days prior to the first dose of study drug.
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients
- Subject is unable to refrain from or anticipates the use of any medication beginning 2 weeks (or 5 half-lives of the compound, whichever is longer) prior to first dosing and throughout the study.
- Use of strong inducers or inhibitors of CYP enzymes and/or strong inhibitors or substrates of P-gp and/or OATP within 14 days (28 days for inducers) or 5 times the half-life of the product (whichever is longer) prior to the first dose of study drug

Identity of Clinical Supplies

Table 2. Identity of Clinical Supplies

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency	Site of Manufacture
MK-8742	10 mg	DL00018002	(b) (4)	WL00051487	102.6%	Merck & Co., Inc., West Point, PA
Viread® (tenofovir disoproxil fumarate) [†]	300 mg	NA	Tablet	NA	NA	NA
Isentress® (raltegravir) [‡]	400 mg	NA	Tablet	NA	NA	NA
Sustiva® (efavirenz) [§]	600 mg	NA	Tablet	NA	NA	NA

[†]Viread (tenofovir disoproxil fumarate) (a product of Gilead Sciences, Inc.) was purchased by the Investigator. The lot number was 001264; expiration date Jul-2017.
[‡]Isentress® (raltegravir) (a product of MSD International GmbH (Singapore Branch)) was purchased by the Investigator. The lot number was J000053; expiration date Feb-2015.
[§]Sustiva® (efavirenz) (a product of Bristol-Myers Squibb Pharma Company) was purchased by the Investigator. The lot number was 2H61717B; expiration date Aug-2015.

Concomitant medications

No drugs, including over-the-counter and herbal products or vitamin supplements were to be taken within 14 days (or 28 days for CYP or P-gp inducers) or 5 half-lives of the product, whichever was longer, prior

to the first dose of the study. Acetaminophen (up to 2 g per 24 hour period) may be permitted during the study.

Pharmacokinetic assessments

Blood samples for determination of MK-8742 concentrations were collected at predose and at specified time points after dosing in Periods 2 and 3 of Parts 1 and 2 and after dosing in Periods 1 and 3 of Part 3. Blood samples for determination of tenofovir concentrations were collected at predose and specified time points after dosing in Periods 1 and 3 of Part 1. Blood samples for determination of raltegravir were collected at predose and at specified time points after dosing in Periods 1 and 3 of Part 2. Blood samples for determination of efavirenz concentrations were collected at predose and specified time points after dosing in Periods 2 and 3 in Part 3.

All parameters were calculated using the software WinNonlin Phoenix 6.3 except C_{24} and C_{trough} values which were obtained using SAS (Version 9.1). C_{max} and T_{max} were generated by WinNonlin from each analytes plasma concentration-time data. All AUC parameters were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down).

Bioanalysis

Plasma samples collected for MK-8742 and raltegravir assays were analyzed Merck (Westpoint, PA). Plasma samples collected for tenofovir and efavirenz assays were analyzed by (b) (4)

The concentrations of these drugs were determined using validated LC/MS/MS methods. All methods were adequately validated. The standard curve and QC data indicated assays were acceptable. All samples were stored and processed in the time frame supported by the stability data.

Table 3. Summary of Bioanalysis

Analyte	MK-8742	Tenofovir	Efavirenz	Raltegravir
Internal standard	MK-8742-d ₆	Tenofovir -d ₆	Efavirenz -d ₅	Raltegravir- ¹³ C ₆
Matrix/Anticoagulant	Plasma/K ₂ EDTA	Plasma/K ₂ EDTA	Plasma/K ₂ EDTA	Plasma/K ₂ EDTA
Extraction method	Liquid-liquid extraction	Protein precipitation	Liquid-liquid extraction	Liquid-liquid extraction
Calibration range	0.25 to 500 ng/mL	5 to 500 ng/mL	20 to 4000 ng/mL	2 to 1000 ng/mL
QC concentration	0.75, 75 and 375 ng/mL	1.5, 25, 250, and 375 ng/mL	60, 400, 2000, 2800 ng/mL	6, 75, and 750 ng/mL
Interday precision and accuracy	P: 3.7 to 8.1*% A: 3.8 to 6.5%	P: 1.72% to 1.99% A: -7.68 to -5.80%	P: 0.92 to 3.39% A: 0.44 to 9.15%	P: 3.7 to 12.8% A: 3.8 to 6.5%
Long term stability	651 Days at -20 °C	66 Days at -20 °C	113 Days at -20 °C	77 days at -20 °C

*:After excluding 3 QC samples which failed to meet the criteria ($\pm 15\%$ of the nominal concentrations)

RESULTS

Population analyzed and baseline demographics

All 30 subjects (10 per each part) enrolled in the study were included in the evaluation of safety. Three subjects were discontinued from the study in Part 3 due to adverse experiences (drug eruption) following administration of efavirenz alone (AN 0043, AN0045, and AN0047).

Table 4. Subject baseline demographics

	Part 1 N=10	Part 2 N=10	Part 3 N=10
Age in Years , Mean (range)	33 (21 to 53)	29 (20 to 47)	37 (23 to 53)
Sex , n (%)			
Female	4 (40%)	4 (40%)	5 (50%)
Male;	6 (60%)	6 (60%)	5 (50%)
BMI (kg/m²) , range	25.18 (19.61 to 31.45)	26.28 (20.01 to 31.84)	26.45 (21.95 to 31.39)
Height (cm) , range	173.2 (162.0 to 184.0)	170.7 (155.0 to 188.0)	173.8 (158.0 to 189.0)
Weight (kg) , range	75.6 (51.3 to 88.5)	77.3 (56.9 to 105.0)	80.1 (58.7 to 94.8)
Ethnicity , n (%)			
Hispanic or Latino:	1 (10%)	2 (20%)	1 (10%)
Not Hispanic or Latino:	9 (90%)	8 (80%)	9 (90%)
Race , n (%)			
White	9 (10%)	6 (50%)	8 (80%)
African American/Black	0 (0%)	1 (10%)	2 (20%)
Others	1 (10%; Non-White)	2 (20%; one Asian, one American Indian/Alaska native)	0 (0%)

Concomitant Therapy

Nine subjects received concomitant therapy (acetaminophen, loperamide, cetirizine, diphenhydramine) due to pain, cold, and adverse events of the study drugs. One subject (AN044) experienced renal colic and received multiple medications 4 days after the last dose of the study drug. None of these medications were judged to have an effect on the assessment of the study objectives.

Pharmacokinetic Results

Part 1. Drug interactions between MK-8742 and TDF

The co-administration of MK-8742 increased AUC_{24hr}, C_{max}, C_{min} of tenofovir by 34%, 47%, and 29%, respectively (Table 5). The exposure of MK-8742 was not significantly altered by the co-administration of TDF (Table 6).

Reviewer comments

TDF is a substrate of BCRP. Therefore, the increase in tenofovir exposure caused by the co-administration of EBR is possibly due to the inhibition of BCRP by MK-8742. Based on the magnitude of the interaction, safety data from clinical trials (PN061) where 75% of the subjects received TDF

containing regimens, and the limited duration of co-administration (no more than 16 weeks), the review team concluded that TDF can be co-administered with MK-8742.

Table 5. Tenofovir plasma pharmacokinetics with or without the co-administration of MK-8742

Tenofovir Pharmacokinetic Parameter	Tenofovir Alone			Tenofovir + MK-8742			Tenofovir + MK-8742/ Tenofovir Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µg/mL•hr)	10	2.36	(2.01, 2.77)	10	3.17	(2.71, 3.71)	1.34	(1.23, 1.47)	10.643
C _{max} [‡] (ng/mL)	10	302	(247, 368)	10	442	(359, 545)	1.47	(1.32, 1.63)	12.879
C ₂₄ [‡] (ng/mL)	10	51.7	(43.0, 62.1)	10	66.5	(55.3, 79.9)	1.29	(1.18, 1.41)	10.939
T _{max} [§] (hr)	10	1.00	(0.50, 1.00)	10	1.01	(0.51, 1.51)			

Tenofovir Alone: Multiple oral doses of 300 mg tenofovir (1 x 300 mg tablet) qd for 7 days (Days 1 to 7)
Tenofovir + MK-8742: Multiple oral doses of 300 mg tenofovir (1 x 300 mg tablet) qd + multiple oral doses of 50 mg MK-8742 (5 x 10 mg capsules) qd, for 7 days (Days 1 to 7)
[†]Pseudo within-subject %CV = 100* $\sqrt{[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model
[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max}.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments

Table 6. MK-8742 plasma pharmacokinetics with or without the co-administration of TDF

MK-8742 Pharmacokinetic Parameter	MK-8742 Alone			Tenofovir +MK-8742			Tenofovir +MK-8742/ MK-8742 Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µM•hr)	10	2.45	(2.05, 2.94)	10	2.28	(1.84, 2.81)	0.93	(0.82, 1.05)	14.657
C _{max} [‡] (nM)	10	199	(169, 234)	10	174	(143, 212)	0.88	(0.77, 1.00)	15.293
C ₂₄ [‡] (nM)	10	62.3	(51.2, 76.0)	10	57.5	(45.7, 72.5)	0.92	(0.81, 1.05)	15.637
T _{max} [§] (hr)	10	4.00	(2.00, 5.00)	10	4.00	(3.00, 4.00)			

MK-8742 Alone: Multiple oral doses of 50 mg MK-8742 (5 x 10 mg capsules) qd for 8 days (Days 1 to 8)
Tenofovir + MK-8742: Multiple oral doses of 300 mg tenofovir (1 x 300 mg tablet) qd + multiple oral doses of 50 mg MK-8742 (5 x 10 mg capsules) qd, for 7 days (Days 1 to 7)
[†]Pseudo within-subject %CV = 100* $\sqrt{[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model
[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max}.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments

Part 2. Drug interactions between MK-8742 and raltegravir

The co-administration of a single dose raltegravir slightly decreased MK-8742 exposure (AUC_{inf}, C_{max}, and C₂₄ by 19%, 11% and 20%, respectively, Table 7) following the administration of a single dose of

MK-8742. This is not considered clinically relevant. Raltegravir exposures were not altered by the co-administration of MK-8742 (Table 8).

Table 7. MK-8742 plasma pharmacokinetics with or without the co-administration of raltegravir

MK-8742 Pharmacokinetic Parameter	MK-8742 Alone			Raltegravir + MK-8742			Raltegravir + MK-8742/ MK-8742 Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (μM•hr)	10	2.19	(1.69, 2.83)	10	1.78	(1.14, 2.77)	0.81	(0.57, 1.17)	43.837
C _{max} [‡] (nM)	10	123	(92.0, 164)	10	109	(68.1, 173)	0.89	(0.61, 1.29)	46.001
C ₂₄ [‡] (nM)	10	33.9	(26.4, 43.4)	10	27.1	(17.5, 41.8)	0.80	(0.55, 1.16)	45.222
T _{max} (hr)	10	4.00	(3.00, 4.00)	10	4.01	(1.51, 4.02)			.
Apparent terminal t _{1/2} [§] (hr)	10	16.05	8.96	10	15.74	9.70			.

MK-8742 Alone: Single oral dose of 50 mg MK-8742 (5 × 10 mg capsules) (Day 1)
Raltegravir + MK-8742: Single oral dose of 400 mg raltegravir (1 x 400 mg tablet) + single oral dose of 50 mg MK-8742 (5 × 10 mg capsules) (Day 1)

[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model

[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.

^{||}Median (min, max) reported for T_{max}.

[§]Geometric mean, geometric coefficient of variation reported for the apparent terminal t_{1/2}.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments

*Both drugs were administered as single doses.

Table 8. Raltegravir plasma pharmacokinetics with or without the co-administration of MK-8742

Raltegravir Pharmacokinetic Parameter	Raltegravir Alone			Raltegravir + MK-8742			Raltegravir + MK-8742/ Raltegravir Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (μg•hr/mL)	10	5.35	(3.05, 9.40)	10	5.45	(3.18, 9.35)	1.02	(0.81, 1.27)	27.207
C _{max} [‡] (μg/mL)	10	1.53	(0.806, 2.90)	10	1.67	(0.839, 3.34)	1.09	(0.83, 1.44)	33.755
C ₁₂ [‡] (ng/mL)	10	42.7	(30.4, 60.1)	10	42.4	(31.2, 57.5)	0.99	(0.80, 1.22)	25.475
T _{max} (hr)	10	2.50	(0.50, 5.00)	10	1.76	(0.51, 5.00)			.
Apparent terminal t _{1/2} [§] (hr)	10	8.56	101.36	10	9.23	53.66			.

Raltegravir Alone: Single oral dose of 400 mg raltegravir (1 x 400 mg tablet) (Day 1)
Raltegravir + MK-8742: Single oral dose of 400 mg raltegravir (1 x 400 mg tablet) + single oral dose of 50 mg MK-8742 (5 × 10 mg capsules) (Day 1)

[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model

[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.

^{||}Median (min, max) reported for T_{max}.

[§]Geometric mean, geometric coefficient of variation reported for the apparent terminal t_{1/2}.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments

*Both drugs were administered as single doses.

Part 3. Drug interactions between MK-8742 and efavirenz

The co-administration of efavirenz decreased AUC_{24hr} , C_{max} , C_{24hr} of MK-8742 by 54%, 45%, and 59%, respectively, likely due to CYP3A4 induction (Table 9). The exposure of efavirenz was slightly decreased by the co-administration of MK-8742 (Table 10).

Table 9. MK-8742 plasma pharmacokinetics with or without the co-administration of efavirenz.

MK-8742 Pharmacokinetic Parameter	MK-8742 Alone			Efavirenz +MK-8742			Efavirenz +MK-8742/ MK-8742 Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC_{0-24}^{\ddagger} ($\mu M \cdot hr$)	10	2.21	(1.76, 2.77)	7	1.01	(0.665, 1.54)	0.46	(0.36, 0.59)	20.528
C_{max}^{\ddagger} (nM)	10	173	(139, 215)	7	94.5	(59.7, 150)	0.55	(0.41, 0.73)	23.525
C_{24}^{\ddagger} (nM)	10	54.1	(42.2, 69.5)	7	22.0	(15.2, 31.7)	0.41	(0.28, 0.59)	29.774
T_{max}^{\S} (hr)	10	3.50	(2.00, 5.02)	7	4.00	(3.00, 5.00)			

MK-8742 Alone: Multiple oral doses of 50 mg MK-8742 (5 x 10 mg capsules) qd for 8 days (Days 1 to 8)
Efavirenz + MK-8742: Multiple oral doses of 600 mg efavirenz (1 x 600 mg tablet) qd + multiple oral doses of 50 mg MK-8742 (5 x 10 mg capsules) qd for 8 days (Days 1 to 8)
[†]Pseudo within-subject %CV = $100 \cdot \text{Sqrt}[(\sigma_A^2 + \sigma_B^2 - 2 \cdot \sigma_{AB})/2]$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model
[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max} .
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments
Subjects AN 0043 and AN 0045 were discontinued from the study on Day 9 of Period 2 due to the adverse event of drug eruption following administration of efavirenz alone.
Subject AN 0047 was discontinued from the study on Day 10 of Period 2 due to the adverse events of drug eruption and generalized maculopapular rash following administration of efavirenz alone.

Table 10. Efavirenz plasma pharmacokinetics with or without the co-administration of MK-8742

Efavirenz Pharmacokinetic Parameter	Efavirenz Alone			Efavirenz + MK-8742			Efavirenz + MK-8742/Efavirenz Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC_{0-24}^{\ddagger} ($\mu g \cdot hr/mL$)	7	64.9	(56.1, 75.0)	7	53.0	(46.7, 60.2)	0.82	(0.78, 0.86)	4.465
C_{max}^{\ddagger} ($\mu g/mL$)	7	4.46	(3.85, 5.15)	7	3.30	(3.04, 3.58)	0.74	(0.67, 0.82)	9.720
C_{24}^{\ddagger} (ng/mL)	7	1910	(1620, 2250)	7	1740	(1520, 1990)	0.91	(0.87, 0.96)	4.734
T_{max}^{\S} (hr)	7	3.10	(2.00, 5.00)	7	4.00	(2.00, 5.00)			

Efavirenz Alone: Multiple oral doses of 600 mg efavirenz (1 x 600 mg tablet) qd for 14 days (Days 1 to 14)
Efavirenz + MK-8742: Multiple oral doses of 600 mg efavirenz (1 x 600 mg tablet) qd + multiple oral doses of 50 mg MK-8742 (5 x 10 mg capsules) qd for 8 days (Days 1 to 8)
[†]Pseudo within-subject %CV = $100 \cdot \text{Sqrt}[(\sigma_A^2 + \sigma_B^2 - 2 \cdot \sigma_{AB})/2]$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model
[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max} .
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments
Subjects AN 0043 and AN 0045 were discontinued from the study on Day 9 of Period 2 due to the adverse event of drug eruption following administration of efavirenz alone.
Subject AN 0047 was discontinued from the study on Day 10 of Period 2 due to the adverse events of drug eruption and generalized maculopapular rash following administration of efavirenz alone.

Reviewer comments

The magnitude of the decrease in MK-8742 exposures may be clinically relevant, especially for patients with baseline NS5A polymorphism. Due to the risk of developing resistance with subtherapeutic exposure to MK-8742 and the lack of availability of re-treatment options, co-administration should be contraindicated.

Conclusion

- No clinically relevant interaction was observed between MK-8742 and TDF
- No clinically relevant interaction was observed between MK-8742 and raltegravir.
- MK-8742 exposure was significantly (> 50%) decreased by the co-administration of efavirenz. The co-administration should be contraindicated.

Title: A Study to determine the two-way pharmacokinetic interaction of MK-8742 (Elbasvir) with atazanavir/ritonavir, lopinavir/ritonavir, and darunavir/ritonavir (PN017)

Study Initiation Date: 05-Mar-2015

Study Completion Date: 14-May-2013

Study Site: (b) (4)

Study design

This was a 3-part study, each part being a fixed-sequence, 3-treatment, 3-period, open-label study to determine the pharmacokinetic interaction of MK-8742 with atazanavir/ritonavir (ATV/r), lopinavir/ritonavir (LPV/r) and darunavir/ritonavir (DRV/r). In each study part, a total of 10 healthy adult male and female subjects, with at least 4 female subjects, were enrolled in the study. Each subject participated in only one study part. There was a washout period of at least 7 days separated the last dose of Period 1 and the first dose of Period 2. There was no washout period between Period 2 and Period 3.

Table 1. Study Design

	Part 1	Part 2	Part 3
Period 1	50 mg MK-8742 QD for 7 days		
Period 2	300 mg/100 mg ATV/r QD for 14 days	400 mg/100 mg LPV/r BID for 14 days	600 mg/100 mg DRV/r BID for 14 days
Period 3	50 mg MK-8742 QD + 300 mg/100 mg ATV/r QD for 7 days	50 mg MK-8742 QD + 400 mg/100 mg LPV/r BID for 7 days	50 mg MK-8742 QD + 600 mg/100 mg DRV/r BID for 7 days

Plasma samples for a full pharmacokinetic assessments of MK-8742 and (Periods 1 and 3) and protease inhibitors (Periods 2 and 3) were collected at specified time points pre-dose and post-dose on Days 7 (Periods 1 and 3) and on Day 14 (Period 2). All treatments were administered following a moderate calorie/low-fat meal.

Key inclusion criteria

- Healthy adult male and female volunteers, 19-55 years of age, inclusive
- BMI: 18.5-32 kg/m², inclusive. Weigh at least 52 kg for males and 45 kg for females.
- Non-smokers (have not used nicotine-containing products for at least 3 months prior to the first dose)
- Medically healthy with no clinically significant history, physical exam, lab profiles. Liver function tests must be below the upper limit of normal for inclusion
- A female of childbearing potential must either sexually inactive or use acceptable birth control methods.
- Male subjects must use a condom (or abstain from sexual intercourse) and agree not to donate sperm from the first dose until 90 days after the last dose

Key exclusion criteria

- History of any illness that might confound the results of the study or pose an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 80 mL/min
- History of alcoholism or drug abuse (within 2 years)
- History of diabetes mellitus or hyperglycemia
- Female subjects who are pregnant or lactating
- Positive results at screening for HIV, hepatitis B, hepatitis C, urine drug or cotinine screening
- Donation of blood or had significant blood loss within 56 days prior to the first dose of study drug or plasma donation within 7 days prior to the first dose of study drug.
- Participation in another clinical trial within 28 days prior to the first dose of study drug.
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients
- Have been on a special diet (for whatever reason) within 28 days prior to the first dose of the study drug and throughout the study

Identity of investigational products

Table 2. Identity of investigational products

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency (N = X)	Site of Manufacture
MK-8742	10 mg	DL00018002	(b) (4)	WL0051292	102.6	(b) (4)
Reyataz® (atazanavir sulfate) [†]	300 mg	NA	Capsule	NA	NA	NA
Novir® Ritonavir [‡]	100 mg	NA	Tablets	NA	NA	NA
Kaletra® (lopinavir/ritonavir) [§]	200 mg/50 mg	NA	Tablets	NA	NA	NA
Prezista® (darunavir)	600 mg	NA	Tablet	NA	NA	NA

[†]Reyataz® (atazanavir sulfate) (a product of Bristol-Myers Squibb Company) was purchased by the Investigator. The lot number was 2K5073A; expiration date Oct-2014.

[‡]Novir® Ritonavir (a product of Abbott) was purchased by the Investigator. The lot number was 240142E; expiration date 10-Sep-2014.

[§]Kaletra® (lopinavir/ritonavir) (a product of Abbott) was purchased by the Investigator. The lot number was 21303AA; expiration date 20-Oct-2015.

^{||}Prezista® (darunavir) (a product of Janssen) was purchased by the Investigator. The lot number was 2LG413; expiration date Sep-2015.

Concomitant medications and diet restrictions

No subject was to take medication (including over-the-counter products, especially proton-pump inhibitor and antacids), herbal products or vitamin supplements for the 14 days (or 28 days for CYP or P-gp inducers) or 5 half-lives of the medication(s), whichever was longer, prior to the first dose of the study and until the end of the study. During the study, acetaminophen (up to 2 g per 24 hours) could have been administered at the discretion of the Investigator.

Consumption of foods and beverages containing the following substances were prohibited.

- Xanthines/Caffeine: 24 hours before the first study drug administration in Periods 1 and 2 and throughout the period of sample collection

- Alcohol: 48 hours before the first study drug administration in Periods 1 and 2 and throughout the period of sample collection.
- Vegetables from the mustard green family and charbroiled meats: 14 days before the first study drug administration in Period 1 and throughout the study.
- Fruit Juice: 24 hours before the first study drug administration in each period and following the last study drug administration in Periods 1 and 3.
- Grapefruit/Seville orange: 14 days before the first study drug administration in Period 1 and throughout the study.

Pharmacokinetic assessments

Plasma samples for MK-8742 concentrations were collected at predose and specified time points over 96 hours on Day 7 of Period 1 and Period 3. Plasma samples for protease inhibitors' concentrations were collected over 24 hours and 96 hours on Day 14 of Period 2 (protease inhibitors alone) and on Day 7 of Period 3, respectively.

C_{12} , C_{24} , and C_{trough} values were obtained using SAS (Version 9.1). All other pharmacokinetic parameters were calculated using the software WinNonlin Phoenix 6.3 C_{max} and T_{max} were generated by WinNonlin from each analytes plasma concentration-time data. All AUC parameters were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down).

Reviewer comments: Plasma samples for ritonavir were also collected but the data will not be reviewed as changes in ritonavir concentrations have minimal clinical implications.

Bioanalysis

Blood samples (~ 4mL for MK-8742 in K_2 EDTA-coated containers and ~2mL for HIV protease inhibitors in K_3 EDTA-coated containers) were collected for bioanalysis. Bioanalyses for plasma concentrations of MK-8742 and protease inhibitors were conducted by (b) (4). The concentrations of these drugs were determined using validated LC/MS/MS methods. All methods were adequately validated and the standard curve and QC data indicated assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data.

Table 3. Summary of Bioanalysis

Analyte	Darunavir	Lopinavir	Atazanavir	Elbasvir (MK-8742)
Internal standard	Darunavir-d ₉	Lopinavir-d ₈	Atazanavir-d ₅	Elbasvir-d ₆
Matrix/Anticoagulant	Plasma/ K_3 EDTA	Plasma/ K_3 EDTA	Plasma/ K_3 EDTA	Plasma/ K_2 DTA
Extraction method	Protein precipitation followed by filtration	Protein precipitation followed by filtration	Liquid-liquid extraction	Liquid-liquid extraction
Calibration range and regression method	10- 10000 ng/mL 1/x ² regression	10- 10000 ng/mL 1/x ² regression	10- 10000 ng/mL 1/x ² regression	0.25-500 ng/mL 1/x ² regression
QC concentration	30, 75, 300, 1200	30, 75, 300, 1200	30, 75, 300, 1200	0.75, 75, and 375

	and 7500 ng/mL	and 7500 ng/mL	and 7500 ng/mL	ng/mL
Interday precision and accuracy	P: 1.7-4.5% A: -3.2-5.2%	P: 5.4-6.4% A: 1.4-6.5%	P: 3.1-5.0 % A: -3.0 – 3.3%	P: 2.7-7.9% A: -3.7 – 2.3
Storage stability	309 days at – 20°C	1060 days at – 20°C	699 days at – 20°C	651 days at – 20°C

Results

Demographic information and baseline characteristics

The demographic information and baseline characteristics are summarized in Table 4. Five subjects were discontinued from the study due to adverse events likely related to protease inhibitors. Refer to Safety Evaluation.

Table 4. Subject baseline demographics

Part	Part 1 (N=10)	2 (N=10)	3 (N=10)
Number of subjects completed the study	8	9	8
Age in Years, Mean (range)	31 (20-48)	25 (21-52)	34 (23-49)
Sex, n (%)			
Female:	4 (40%)	4 (40%)	4 (40%)
Male:	6 (60%)	6 (60%)	6 (60%)
BMI (kg/m²), range	24.5 (19.0-30.5)	26.0 (21.6-30.4)	26.2 (20.0-31.9)
Height (cm), range	175.3 (165.0-195.0)	173.2 (158.0-190.0)	173.0 (154.0-189.0)
Weight (kg), range	75.4 (58.6-90.9)	78.5 (58.8-109.7)	78.8 (53.9-101.9)
Ethnicity, n (%)			
Hispanic or Latino:	2 (20%)	1 (10%)	1 (10%)
Not Hispanic or Latino:	8 (80%)	8 (80%)	8 (80%)
Others	0 (0%)	1 (10%; unknown)	1 (10%; unknown)
Race, n (%)			
White	8 (80%)	9 (90%)	9 (90%)
African American/Black	2 (20%)	1 (10%)	0 (0%)
Asian	0 (0%)	0 (0%)	1 (10%)

Concomitant medications

Two subjects received acetaminophen to treat headache or muscle ache. One subject received cetirizine to treat itchiness. One subject received ibuprofen for neck pain. One subject (Subject 0050) received 1% diphenhydramine (topical) to treat rash. Rash of Subject 0050 was considered an adverse event of study drug (DRV/r). These medications were judged not to have an effect on the assessment of the pharmacokinetics of study drugs.

Pharmacokinetic Results

Part 1 (drug interactions between MK-8742 and ATV/r)

MK-8742 exposures were increased by the co-administration of ATV/r (Table 5). The steady-state AUC, C_{max}, and C_{min} of MK-8742 were increased by 4.76-fold, 4.15-fold, and 6.45-fold, respectively when MK-8742 was co-administered with ATV/r. The co-administration of MK-8742 did not alter the steady-state pharmacokinetics of ATV (Table 6)

Table 5. Plasma pharmacokinetics of MK-8742 with or without co-administration of ATV/r

MK-8742 Pharmacokinetic Parameter	MK-8742 Alone			MK-8742 + Atazanavir/r			MK-8742 + Atazanavir/r / MK-8742 Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	[‡] N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (uM•hr)	10	1.42	(1.04, 1.96)	8	6.77	(5.18, 8.85)	4.76	(4.07, 5.56)	16.943
C _{max} [‡] (nM)	10	97.5	(68.9, 138)	8	405	(317, 516)	4.15	(3.46, 4.97)	20.498
C ₂₄ [‡] (nM)	10	37.9	(27.3, 52.6)	8	245	(181, 330)	6.45	(5.51, 7.54)	16.555
T _{max} [‡] (hr)	10	4.09	(3.00, 6.04)	8	4.01	(3.01, 8.01)			
Apparent terminal t _{1/2} [§] (hr)	10	18.48	14.08	8	16.56	11.50			

MK-8742 Alone: Multiple oral doses of 50 mg MK-8742 (5 × 10 mg capsules) qd for 7 days (Days 1 to 7) (Treatment A).
 MK-8742 + Atazanavir/r: Multiple oral doses of 50 mg MK-8742 (5 × 10 mg capsules) qd + 300/100 mg atazanavir/r (1 × 300 mg atazanavir capsule + 1 × 100 mg ritonavir tablet) qd for 7 days (Days 1 to 7) (Treatment C).
[†]Pseudo within-subject %CV = 100 × Sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the ANOVA linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
[¶]Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
 GM = Geometric least-squares means; CI = Confidence interval; GMR = Geometric least-squares mean ratio.
^{**}Note: Subject AN 0005 was dropped by the Investigator on Day 13, Period 2 due to the adverse experience of maculo-papular rash and Subject AN 0008 was discontinued from the study on Day 7 of Period 2 due to elevated total bilirubin values meeting protocol specified discontinuation criteria.

Table 6. Plasma pharmacokinetics of atazanavir with or without co-administration of MK-8742

Atazanavir Pharmacokinetic Parameter	Atazanavir/r Alone			MK-8742 + Atazanavir/r			MK-8742 + Atazanavir/r / Atazanavir/r Alone		Pseudo Within Subject %CV [†]
	[‡] N	GM	95% CI	[‡] N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (ng•hr/mL)	8	57800	(46000, 72500)	8	61700	(47500, 80000)	1.07	(0.98, 1.17)	9.381
C _{max} [‡] (ng/mL)	8	5740	(4720, 6970)	8	5840	(4790, 7110)	1.02	(0.96, 1.08)	6.264
C ₂₄ [‡] (ng/mL)	8	1230	(803, 1880)	8	1410	(899, 2220)	1.15	(1.02, 1.29)	12.455
T _{max} [‡] (hr)	8	3.00	(2.00, 5.00)	8	3.50	(2.00, 5.00)			
Apparent terminal t _{1/2} [§] (hr)				8	8.45	14.25			

Atazanavir/r Alone: Multiple oral doses of 300/100 mg atazanavir/r (1 × 300 mg atazanavir capsule + 1 × 100 mg ritonavir tablet) qd for 14 days (Days 1 to 14) (Treatment B).
 MK-8742 + Atazanavir/r: Multiple oral doses of 50 mg MK-8742 (5 × 10 mg capsules) qd + 300/100 mg atazanavir/r (1 × 300 mg atazanavir capsule + 1 × 100 mg ritonavir tablet) qd for 7 days (Days 1 to 7) (Treatment C).
[†]Pseudo within-subject %CV = 100 × Sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the ANOVA linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
[¶]Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.
^{**}Note: Subject AN 0005 was dropped by the Investigator on Day 13, Period 2 due to the adverse experience of maculo-papular rash and Subject AN 0008 was discontinued from the study on Day 7 of Period 2 due to elevated total bilirubin values meeting protocol specified discontinuation criteria.

Part 2: Drug interactions between MK-8742 and LPV/r

MK-8742 exposures were increased by the co-administration of LPV/r (Table 7). The steady-state AUC, C_{max}, and C_{min} of MK-8742 were increased by 3.71-fold, 2.87-fold, and 4.58-fold, respectively when MK-8742 was co-administered with LPV/r. The co-administration of MK-8742 did not alter the steady-state pharmacokinetics of LPV (Table 8).

Table 7. Plasma pharmacokinetics of MK-8742 with or without co-administration of LPV/r

MK-8742 Pharmacokinetic Parameter	MK-8742 Alone			MK-8742 + Lopinavir/r			MK-8742 + Lopinavir/r / MK-8742 Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	[‡] N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (uM•hr)	10	1.43	(1.11, 1.83)	9	5.29	(3.86, 7.26)	3.71	(3.05, 4.53)	22.384
C _{max} [‡] (nM)	10	109	(86.7, 137)	9	313	(225, 434)	2.87	(2.29, 3.58)	25.275
C ₂₄ [‡] (nM)	10	40.6	(30.1, 54.7)	9	186	(136, 254)	4.58	(3.72, 5.64)	23.718
T _{max} [§] (hr)	10	5.00	(4.00, 8.00)	9	5.00	(4.00, 6.00)			
Apparent terminal t _{1/2} (hr)	10	18.73	10.63	9	16.51	15.24			

MK-8742 Alone: Multiple oral doses of 50 mg MK-8742 (5 × 10 mg capsules) qd for 7 days (Days 1 to 7) (Treatment A).
 MK-8742 + Lopinavir/r : Multiple oral doses of 50 mg MK-8742 (5 × 10 mg capsules) qd + 400/100 mg lopinavir/r (2 × 200 mg lopinavir/50 mg ritonavir tablets) bid for 7 days (Days 1 to 7) (Treatment E).
[†]Pseudo within-subject %CV = 100 × Sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the ANOVA linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.
[¶]Note: Subject AN 0025 withdrew from the study in Part 2 on Day 4 of Period 2 due to multiple mild gastrointestinal adverse experiences.

Table 8. Plasma pharmacokinetics of LPV with or without co-administration of MK-8742.

Lopinavir Pharmacokinetic Parameter	Lopinavir/r Alone			MK-8742 + Lopinavir/r			MK-8742 + Lopinavir/r /Lopinavir/r Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₁₂ [‡] (ng•hr/mL)	9	101000	(83300, 121000)	9	103000	(84000, 126000)	1.02	(0.93, 1.13)	11.398
C _{max} [‡] (ng/mL)	9	11600	(9880, 13600)	9	11800	(10200, 13800)	1.02	(0.92, 1.13)	11.436
C ₁₂ [‡] (ng/mL)	9	5780	(4210, 7930)	9	6170	(4490, 8480)	1.07	(0.97, 1.18)	10.891
T _{max} [§] (hr)	9	4.00	(3.00, 6.00)	9	4.01	(3.00, 8.00)			

Lopinavir/r Alone: Multiple oral doses of 400/100 mg lopinavir/r (2 × 200 mg lopinavir/50 mg ritonavir tablets) bid for 14 days (Days 1 to 14) (Treatment D).
 MK-8742 + Lopinavir/r : Multiple oral doses of 50 mg MK-8742 (5 × 10 mg capsules) qd + 400/100 mg lopinavir/r (2 × 200 mg lopinavir/50 mg ritonavir tablets) bid for 7 days (Days 1 to 7) (Treatment E).
[†]Pseudo within-subject %CV = 100 × Sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the ANOVA linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.
[¶]Note: Subject AN 0025 withdrew from the study in Part 2 on Day 4 of Period 2 due to multiple mild gastrointestinal adverse experiences.

Part 3. Drug interactions with MK-8742 and DRV/r.

MK-8742 exposures were increased by the co-administration of DRV/r (Table 9). The steady-state AUC, C_{max}, and C_{min} of MK-8742 were increased by 1.66-fold, 1.67-fold, and 1.82-fold, respectively when MK-8742 was co-administered with DRV/r. The co-administration of MK-8742 did not alter the steady-state pharmacokinetics of DRV (Table 10)

Table 9. Plasma pharmacokinetics of MK-8742 with or without co-administration of DRV/r.

MK-8742 Pharmacokinetic Parameter	MK-8742 Alone			MK-8742 + Darunavir/r			MK-8742 + Darunavir/r / MK-8742 Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	[‡] N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (uM•hr)	10	1.40	(0.972, 2.00)	8	2.32	(1.71, 3.15)	1.66	(1.35, 2.05)	22.403
C _{max} [‡] (nM)	10	96.4	(65.5, 142)	8	161	(114, 228)	1.67	(1.36, 2.05)	22.098
C ₂₄ [‡] (nM)	10	38.4	(24.9, 59.2)	8	70.0	(47.8, 102)	1.82	(1.39, 2.39)	28.866
T _{max} [§] (hr)	10	4.50	(2.00, 6.00)	8	4.00	(2.01, 5.00)			
Apparent terminal t _{1/2} (hr)	10	18.61	18.90	8	18.47	16.41			

MK-8742 Alone: Multiple oral doses of 50 mg MK-8742 (5 × 10 mg capsules) qd for 7 days (Days 1 to 7) (Treatment A).
 MK-8742 + Darunavir/r: Multiple oral doses of 50 mg MK-8742 (5 × 10 mg capsules) qd + 600/100 mg darunavir/r (1 × 600 mg darunavir tablet + 1 × 100 mg ritonavir tablet) bid for 7 days (Days 1 to 7) (Treatment G).
[†]Pseudo within-subject %CV = 100 × Sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the ANOVA linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.
[¶]Note: Subject AN 0046 was discontinued from the study on Day 11 of Period 2 due to the adverse experience of papular rash and Subject AN 0050 was discontinued from the study on Day 13 of Period 2 due to the adverse experience of maculo-papular rash.

Table 10. Plasma pharmacokinetics of DRV with or without co-administration of MK-8742.

Darunavir Pharmacokinetic Parameter	Darunavir/r Alone			MK-8742 + Darunavir/r			MK-8742 + Darunavir/r / Darunavir/r Alone		Pseudo Within Subject %CV [†]
	[‡] N	GM	95% CI	[‡] N	GM	95% CI	GMR	90% CI	
AUC ₀₋₁₂ [‡] (ng•hr/mL)	8	54000	(48700, 60000)	8	51400	(42800, 61900)	0.95	(0.86, 1.06)	10.878
C _{max} [‡] (ng/mL)	8	7190	(6550, 7900)	8	6800	(5720, 8090)	0.95	(0.85, 1.05)	10.789
C ₁₂ [‡] (ng/mL)	8	2870	(2230, 3700)	8	2700	(2030, 3600)	0.94	(0.85, 1.05)	11.411
T _{max} [§] (hr)	8	3.00	(2.00, 5.00)	8	3.50	(2.00, 5.00)			

Darunavir/r Alone: Multiple oral doses of 600/100 mg darunavir/r (1 × 600 mg darunavir tablet + 1 × 100 mg ritonavir tablet) bid for 14 days (Days 1 to 14) (Treatment F).
 MK-8742 + Darunavir/r: Multiple oral doses of 50 mg MK-8742 (5 × 10 mg capsules) qd + 600/100 mg darunavir/r (1 × 600 mg darunavir tablet + 1 × 100 mg ritonavir tablet) bid for 7 days (Days 1 to 7) (Treatment G).
[†]Pseudo within-subject %CV = 100 × Sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the ANOVA linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.
[¶]Note: Subject AN 0046 was discontinued from the study on Day 11 of Period 2 due to the adverse experience of papular rash and Subject AN 0050 was discontinued from the study on Day 13 of Period 2 due to the adverse experience of maculo-papular rash.

Reviewer comments:

MK-8742 exposures were increased by the co-administration of protease inhibitors. It is likely due to the inhibition of CYP3A4 and transporters such as P-gp. The magnitude of interaction with ATV/r or LPV/r is considered clinically significant. Although no exposure-dependent adverse events were observed, clinical experience is limited for doses above 100 mg QD. Therefore, there are no safety data to support the use of MK-8742 when the MK-8742 exposure is increased by 2-fold or more.

Safety evaluation**Part 1**

One subject (AN 0005) was discontinued from the study by the Investigator on Day 13 of Period 2 due to a drug-related adverse experience of maculo-papular rash following administration of ATV/r alone. and Subject AN 0008 was discontinued from the study on Day 7 of Period 2 due to elevated total bilirubin values meeting protocol specified discontinuation criteria. All subjects presented with elevation in total bilirubin values in Periods 2 and 3 of the study. These are known adverse events associated with ATV/ritonavir administration.

Part 2

One subject, Subject AN 0025, withdrew himself from the study on Day 4 of Period 2 due to multiple gastrointestinal adverse experiences following administration of LPV/r alone. The adverse event is likely due to LPV/r administration.

Part 3

Two subjects were discontinued from the study by the Investigator due to adverse experiences. Subject AN 0046 was discontinued from the study on Day 11 of Period 2 due to the drug-related adverse experience of papular rash following administration of DRV/r alone. Subject AN 0050 was discontinued from the study on Day 13 of Period 2 due to the drug-related adverse experience of maculo-papular rash following administration of DRV/r alone. The adverse event is likely due to DRV/r administration.

Conclusion

- The steady-state AUC, C_{max}, and C_{min} of MK-8742 were increased by 4.76-fold, 4.15-fold, and 6.45-fold, respectively when MK-8742 was co-administered with ATV/r. The steady-state AUC, C_{max}, and C_{min} of MK-8742 were increased by 3.71-fold, 2.87-fold, and 4.58-fold, respectively when MK-8742 was co-administered with LPV/r. There are no safety data to support the use of MK-8742 when MK-8742 exposure is increased by a 2-fold or above. Therefore, the co-administration of MK-8742 and ATV/r or LPV/r is not recommended.
- MK-8742 exposures were increased by the co-administration of DRV/r. The steady-state AUC, C_{max}, and C_{min} of MK-8742 were increased by 1.66-fold, 1.67-fold, and 1.82-fold, respectively when MK-8742 was co-administered with DRV/r. This is not considered clinically significant.
- The pharmacokinetic parameters of ATV, LPV, or DRV were not altered by the co-administration of MK-8742.

8742-021

1. Title

A Study to Evaluate the Drug-Drug Interaction Between Buprenorphine/Naloxone and MK-8742 (Elbasvir) in Healthy Volunteers

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted from July 22, 2014 (trial initiation) to September 23, 2014 (trial completion).

3. Objectives

The objectives of the trial included evaluating the effect of elbasvir on the exposure of buprenorphine.

4. Trial Design

021 was a clinical trial that enrolled healthy subjects 19 to 55 years old.

In period 1, a naltrexone challenge (a single 50 mg dose) was administered 14 hours before buprenorphine/naloxone dosing to test for opioid dependence. Two additional naltrexone doses were subsequently administered at approximately twelve hour intervals. This was also performed during period 3. In period 1, subjects received a single dose of 8 mg buprenorphine/2 mg naloxone on day 1. Subsequent to a 15 day washout period, in period 2, subjects received a single dose of 50 mg elbasvir on day 1. In period 3, after a 13 day washout period, a single dose of 50 mg elbasvir and a single dose of 8 mg buprenorphine/2 mg naloxone were administered within five minutes of each other on day 1.

5. Excluded Medications, Restrictions or Exceptions

Medications, including nonprescription and herbal products, were not permitted within either 14 days (or 28 days for CYP or P-gp inducers) before the first dose on day 1, period 1 and during the trial.

6. Dosage and Administration

The trial medications were administered under fasted conditions. This is consistent with the proposed U.S. prescribing information (USPI) recommendation for grazoprevir in combination with elbasvir (with or without food). The buprenorphine/naloxone USPI does not include specific dosing recommendations with regards to food or meals.

7. Rationale for Doses Used in the Trial

The elbasvir 50 mg dose is consistent with the recommended dosage regimen in the proposed U.S. prescribing information for elbasvir and grazoprevir (50 mg of elbasvir with 100 mg of grazoprevir once daily). The dose of buprenorphine/naloxone is consistent with the recommendations in the buprenorphine/naloxone USPI.

8. Drugs Used in the Trial

The medications administered in trial 021 are displayed in Table 1.

Table 1-Medications administered in trial 021

Bulk Product Description	Manufacturing Lot Number
MK-8742 (Elbasvir) 50 mg Tablets	WL00058241
Suboxone [®] (buprenorphine and naloxone) sublingual film 8 mg/2 mg	NA
Naltrexone Hydrochloride Tablets USP 50 mg	NA
Suboxone [®] (buprenorphine and naloxone) sublingual film 8 mg/2 mg (lot number A14GW105; expiration date (b) (4) Reckitt Benckiser Pharmaceuticals Inc.) and naltrexone hydrochloride tablets USP 50 mg (lot number 1170X89847; expiration date (b) (4) Mallinckrodt Inc.) were supplied by the Investigator.	

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included buprenorphine, norbuprenorphine, and naloxone predose and postdose blood samples up to 144 hours in periods 1 and 3 and elbasvir blood samples at predose and up to 96 hours postdose in periods 2 and 3.

Bioanalysis

The method and bioanalysis of norbuprenorphine or naloxone was not reviewed because the applicant is not proposing to include data for either analyte from the 021 trial in the proposed U.S. prescribing information (USPI) for grazoprevir in combination with elbasvir.

The method and bioanalysis of buprenorphine are acceptable.

Buprenorphine plasma samples were analyzed using a validated LC/MS/MS method in K₂EDTA anticoagulated plasma by (b) (4). The blood samples for analysis of buprenorphine appear to have been collected in tubes containing K₂EDTA as an anticoagulant.

For the plasma samples from the P21 trial that were analyzed for buprenorphine, the lower limit of quantification for buprenorphine was 0.01 ng/mL and the upper limit of quantification was 10 ng/mL. There were no precision or accuracy issues identified for buprenorphine based on the bioanalytical report. For the P21 trial, precision and accuracy for buprenorphine were evaluated using plasma buprenorphine quality control (QC) samples at 0.03 ng/mL, 4 ng/mL, and 8 ng/mL with a 40 ng/mL dilution QC (dilution factor of 5). For buprenorphine, the corresponding inter-run accuracy values were 0.3% for 0.03 ng/mL, -0.2% for 4 ng/mL, -0.4% for 8 ng/mL, and -5.7% for the 40 ng/mL dilution QC. The corresponding buprenorphine inter-run precision values were 4.5% for 0.03 ng/mL, 2.7% for 4 ng/mL, 7.4% for 8 ng/mL, and 5.3% for the 40 ng/mL dilution QC.

Of the samples selected for incurred sample reanalysis for buprenorphine, two samples out of fifty samples were not within 20% using the percentage values of the repeat and original concentrations.

According to the bioanalytical report, the number of incurred samples represents approximately 10% of the total number of samples that were initially analyzed. The current FDA recommendation is 7%.

For the P21 trial, the bioanalytical report states that the maximum length of storage for the samples was 45 days at -80°C. Two different stability assessments were conducted. The first stability assessment was conducted for buprenorphine alone compared to nominal concentrations (consistent with current FDA recommendations). The second stability assessment was conducted for buprenorphine combined with various other analytes, including naloxone and norbuprenorphine, compared to time zero samples. For the P21 trial, the long term stability data from the first stability assessment (buprenorphine alone for 182 days at -80°C in K₂EDTA anticoagulated plasma) generated by (b) (4) appears sufficient based on the information provided in the submission (the bioanalytical report states that the date of last analysis was September 23, 2014) if samples were stored at -80°C. For the second stability assessment, an issue was noted that while buprenorphine long term stability was acceptable when compared to time zero samples, it was not acceptable when compared to nominal concentrations (a difference of 18% compared to the nominal concentration was observed). A further exploration of the issue was not conducted because the cause does not appear to be stability related.

The bioanalysis of elbasvir was acceptable.

Elbasvir plasma samples were analyzed using a LC/MS/MS method in K₂EDTA anticoagulated plasma by (b) (4) (ANI 10788.01). The method validation information, including the long term stability data, for elbasvir was not reviewed because the method is being used for multiple trials. The blood samples for analysis of elbasvir appear to have been collected in tubes containing K₂EDTA as an anticoagulant.

For the plasma samples from the P21 trial that were analyzed for elbasvir, the lower limit of quantification for elbasvir was 0.25 ng/mL and the upper limit of quantification was 500 ng/mL. There were no precision or accuracy issues identified for elbasvir based on the bioanalytical report. For the P21 trial, precision and accuracy were evaluated using plasma elbasvir quality control (QC) samples at 0.75 ng/mL, 12.5 ng/mL, 75 ng/mL, 250 ng/mL, and 375 ng/mL. The corresponding elbasvir inter-run accuracy values were 0.67% for 0.75 ng/mL, 1.25% for 12.5 ng/mL, -0.87% for 75 ng/mL, -1.78% for 250 ng/mL, and -2.01% for 375 ng/mL. The elbasvir inter-run precision values were 4.25% for 0.75 ng/mL, 2.7% for 12.5 ng/mL, 1.56% for 75 ng/mL, 1.8% for 250 ng/mL, and 2.12% for 375 ng/mL.

Of the samples selected for incurred sample reanalysis for elbasvir, all samples were within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of elbasvir samples that were reanalyzed represents 7% of the total number of samples that were initially analyzed.

For the P21 trial, the bioanalytical report states that the maximum length of storage for the samples was 29 days at -20°C. Based on information included in the bioanalytical report, elbasvir long term stability data for 83 days at -20°C is available. The long term stability data appears sufficient if the elbasvir long term stability data used to support the analysis of the P21 trial samples is acceptable (based on the information in the bioanalytical report, the date of last analysis was September 22, 2014) and elbasvir plasma samples were stored at -20°C.

Pharmacokinetic Assessments

Based on the information included in the trial report, noncompartmental analysis was performed using actual sampling times to derive plasma pharmacokinetic parameters.

Statistical Analysis

The statistical analyses included deriving 90% confidence intervals for relevant pharmacokinetic parameters comparing: a) buprenorphine, norbuprenorphine, and naloxone with concomitant use of buprenorphine/naloxone and elbasvir (test arm) to the reference arm (buprenorphine/naloxone alone), and b) elbasvir with concomitant use of buprenorphine/naloxone and elbasvir (test arm) to the reference arm (elbasvir alone).

10. Results

10.1 Subject Demographics

Table 2-P21 subject demographics

AN	Gender	Race	Ethnicity	Age (yr)	Height (cm)	Weight (kg)	Body Mass Index (kg/m ²)
0001	Female	White	Not Hispanic or Latino	35	170.0	85.1	29.40
0002	Male	White	Not Hispanic or Latino	23	173.0	93.2	31.25
0003	Female	White	Not Hispanic or Latino	44	163.0	84.2	31.56
0004	Male	White	Not Hispanic or Latino	24	182.0	96.4	29.22
0005	Female	White	Not Hispanic or Latino	44	174.0	88.9	29.45
0006	Male	White	Not Hispanic or Latino	26	179.0	89.3	27.76
0007	Male	White	Not Hispanic or Latino	34	186.0	102.2	29.49
0008	Female	Asian	Not Hispanic or Latino	29	163.0	66.8	25.03
0009	Female	Black or African American	Not Hispanic or Latino	28	174.0	81.3	26.87
0010	Female	Black or African American	Not Hispanic or Latino	29	160.0	73.6	28.93
0011	Female	White	Not Hispanic or Latino	23	164.0	68.1	25.38
0012	Male	White	Not Hispanic or Latino	30	180.0	88.9	27.32
0013	Male	White	Not Hispanic or Latino	29	184.0	77.8	23.08
0014	Male	White	Not Hispanic or Latino	23	173.0	83.8	28.02
0015	Male	White	Not Hispanic or Latino	23	168.0	70.7	24.99
0016	Male	White	Not Hispanic or Latino	27	169.0	76.8	26.77
Study Summary							
N:				16	16	16	16
Range:				23 to 44	160.0 to 186.0	66.8 to 102.2	23.08 to 31.56
Arithmetic Mean:				29	172.6	82.9	27.78
Female N:				7	7	7	7
Female Range:				23 to 44	160.0 to 174.0	66.8 to 88.9	25.03 to 31.56
Female Arithmetic Mean:				33	166.9	78.3	28.09
Male N:				9	9	9	9
Male Range:				23 to 34	168.0 to 186.0	70.7 to 102.2	23.08 to 31.25
Male Arithmetic Mean:				27	177.1	86.6	27.54
AN = Allocation number.							

10.2 Concomitant Medications

The concomitant medications that were administered in the trial appeared to include acetaminophen. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Note: in the tables below the trial report states that C_{24h} was the plasma drug concentration 24 hours postdose. The norbuprenorphine and naloxone pharmacokinetic data and statistical analyses are provided for informational purposes only

A) Buprenorphine

Table 3-Buprenorphine pharmacokinetic parameters

	Buprenorphine Pharmacokinetic Parameters								
	AUC _{0-∞} (ng•hr/mL)			AUC _{0-last} (ng•hr/mL)			C _{max} (ng/mL)		
	Buprenorphine + Naloxone Alone ^{1,†}	Elbasvir + Buprenorphine + Naloxone ²	Elbasvir + Buprenorphine + Naloxone/ Buprenorphine + Naloxone Alone	Buprenorphine + Naloxone Alone [†]	Elbasvir + Buprenorphine + Naloxone ²	Elbasvir + Buprenorphine + Naloxone/ Buprenorphine + Naloxone Alone	Buprenorphine + Naloxone Alone [†]	Elbasvir + Buprenorphine + Naloxone ²	Elbasvir + Buprenorphine + Naloxone/ Buprenorphine + Naloxone Alone
N	14	13	12	15	13	13	15	13	13
AM	43.2	40.5	0.98	39.8	38.5	0.96	4.11	3.94	0.97
SD	16.4	12.0	0.18	14.5	11.4	0.17	1.99	1.45	0.27
ACV	38.1	29.7	18.6	36.4	29.5	17.5	48.3	36.7	27.4
Med	40.4	42.4	0.91	38.3	41.2	0.90	3.23	3.78	0.91
Min	25.3	19.2	0.69	23.7	18.8	0.73	2.33	1.69	0.57
Max	76.4	59.8	1.24	67.8	57.0	1.24	10.1	5.85	1.47
GM	40.6	38.6	0.96	37.5	36.8	0.94	3.79	3.67	0.93
GCV	37.0	34.5	18.8	35.9	34.1	17.0	41.1	42.2	28.6

Buprenorphine + Naloxone Alone: A single sublingual dose of 8 mg buprenorphine/2 mg naloxone (with naltrexone blockade administered as 50 mg naltrexone HCl q12h starting 14 hours prior to the buprenorphine/naloxone dose for a total of 3 naltrexone doses).

Elbasvir + Buprenorphine + Naloxone: A single oral dose of 50 mg elbasvir co-administered with a single sublingual dose of 8 mg buprenorphine/2 mg naloxone (with naltrexone blockade administered as 50 mg naltrexone HCl q12h starting 14 hours prior to the buprenorphine/naloxone dose for a total of 3 naltrexone doses).

[†]Subject AN 0008 was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing.

²Subjects AN 0006 and AN 0011 were discontinued from the study by the Investigator on Day 1 of Period 3 (elbasvir + buprenorphine + naloxone) due to vomiting within 8 hours of dosing.

Subject AN 0008 was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing.

[†]The terminal elimination phase of buprenorphine could not be characterized for Subject AN 0012 following buprenorphine + naloxone alone; therefore, AUC_{0-∞} could not be calculated for this subject.

. = Missing value;

AM = Arithmetic mean; SD = Standard deviation; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (\text{SD}/\text{AM})$; Med = Median; Min = Minimum; Max = Maximum; GM = Geometric mean; GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: $100 \times \sqrt{(\exp(s^2) - 1)}$, where s^2 is the observed variance on the natural log-scale.

Table 4-Buprenorphine statistical analyses

Buprenorphine Pharmacokinetic Parameter	Buprenorphine + Naloxone Alone			Elbasvir + Buprenorphine + Naloxone			Elbasvir + Buprenorphine + Naloxone/ Buprenorphine + Naloxone Alone		Pseudo Within-Subject %CV ^{††}
	N [§]	GM	95% CI	N ^{††}	GM	95% CI	GMR	90% CI	
AUC _{0-∞} ^{†,‡‡} (ng•hr/mL)	14	38.4	(30.5, 48.4)	13	37.6	(31.4, 45.2)	0.98	(0.89, 1.08)	13.085
AUC _{0-last} [†] (ng•hr/mL)	15	37.5	(30.9, 45.5)	13	35.6	(29.7, 42.8)	0.95	(0.87, 1.03)	11.895
C _{max} [†] (ng/mL)	15	3.79	(3.05, 4.72)	13	3.57	(2.85, 4.48)	0.94	(0.82, 1.08)	19.729
C _{24h} [†] (ng/mL)	15	0.310	(0.248, 0.387)	13	0.303	(0.247, 0.372)	0.98	(0.88, 1.09)	15.947
T _{max} [†] (hr)	15	1.51	(0.75, 3.00)	13	1.49	(0.73, 2.99)			
Apparent terminal t _{1/2} ^{§,‡‡} (hr)	14	37.39	32.53	13	39.59	36.24			

Buprenorphine + Naloxone Alone: A single sublingual dose of 8 mg buprenorphine/2 mg naloxone (with naltrexone blockade administered as 50 mg naltrexone HCl q12h starting 14 hours prior to the buprenorphine/naloxone dose for a total of 3 naltrexone doses).

Elbasvir + Buprenorphine + Naloxone: A single oral dose of 50 mg elbasvir co-administered with a single sublingual dose of 8 mg buprenorphine/2 mg naloxone (with naltrexone blockade administered as 50 mg naltrexone HCl q12h starting 14 hours prior to the buprenorphine/naloxone dose for a total of 3 naltrexone doses).

[†]Pseudo Within-Subject %CV = $100 \times \sqrt{((\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2)}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

[§]Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.

[†]One (1) subject was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing.

^{††}Two (2) subjects were discontinued from the study by the Investigator on Day 1 of Period 3 (elbasvir + buprenorphine + naloxone) due to vomiting within 8 hours of dosing. One (1) subject was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing. Please refer to Section 10.4 for more details.

^{‡‡}The terminal elimination phase of buprenorphine could not be characterized for 1 subject following buprenorphine + naloxone alone; therefore, AUC_{0-∞} and apparent terminal t_{1/2} could not be calculated for this subject.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

B) Norbuprenorphine

Table 5-Norbuprenorphine pharmacokinetic parameters

	Norbuprenorphine Pharmacokinetic Parameters								
	AUC _{0-∞} (ng•hr/mL)			AUC _{0-last} (ng•hr/mL)			C _{max} (ng/mL)		
	Buprenorphine + Naloxone Alone ^{1,4,5}	Elbasvir + Buprenorphine + Naloxone ²	Elbasvir + Buprenorphine + Naloxone/ Buprenorphine + Naloxone Alone	Buprenorphine + Naloxone Alone ¹	Elbasvir + Buprenorphine + Naloxone ²	Elbasvir + Buprenorphine + Naloxone/ Buprenorphine + Naloxone Alone	Buprenorphine + Naloxone Alone ¹	Elbasvir + Buprenorphine + Naloxone ²	Elbasvir + Buprenorphine + Naloxone/ Buprenorphine + Naloxone Alone
N	14	13	13	15	13	13	15	13	13
AM	53.7	52.4	0.99	49.2	48.7	1.01	1.12	1.19	1.13
SD	25.0	20.1	0.23	20.9	18.6	0.22	0.622	0.586	0.27
ACV	46.5	38.4	23.4	42.4	38.3	21.8	55.4	49.1	24.2
Med	44.8	51.2	1.05	42.3	47.9	0.96	1.04	1.06	1.09
Min	28.8	19.9	0.63	26.2	18.3	0.70	0.507	0.363	0.72
Max	109	89.1	1.31	104	83.7	1.33	2.67	2.40	1.70
GM	49.4	48.3	0.97	45.7	45.0	0.98	0.992	1.06	1.10
GCV	43.1	46.2	25.1	39.7	46.0	22.5	53.5	56.3	23.7

Buprenorphine + Naloxone Alone: A single sublingual dose of 8 mg buprenorphine/2 mg naloxone (with naltrexone blockade administered as 50 mg naltrexone HCl q12h starting 14 hours prior to the buprenorphine/naloxone dose for a total of 3 naltrexone doses).
 Elbasvir + Buprenorphine + Naloxone: A single oral dose of 50 mg elbasvir co-administered with a single sublingual dose of 8 mg buprenorphine/2 mg naloxone (with naltrexone blockade administered as 50 mg naltrexone HCl q12h starting 14 hours prior to the buprenorphine/naloxone dose for a total of 3 naltrexone doses).
¹Subject AN 0008 was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing.
²Subjects AN 0006 and AN 0011 were discontinued from the study by the Investigator on Day 1 of Period 3 (elbasvir + buprenorphine + naloxone) due to vomiting within 8 hours of dosing.
³Subject AN 0008 was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing.
⁴The extrapolated portion of the AUC_{0-∞} for Subject AN 0010 following buprenorphine + naloxone alone was > 25% of the AUC_{0-∞}.
⁵The terminal elimination phase of norbuprenorphine could not be characterized for Subject AN 0011 following buprenorphine + naloxone alone; therefore, AUC_{0-∞} could not be calculated for this subject.
 = Missing value;
 AM = Arithmetic mean; SD = Standard deviation; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: 100 x (SD/AM); Med = Median; Min = Minimum; Max = Maximum; GM = Geometric mean; GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s²) - 1), where s² is the observed variance on the natural log-scale.

Table 6-Norbuprenorphine statistical analysis

Norbuprenorphine Pharmacokinetic Parameter	Buprenorphine + Naloxone Alone			Elbasvir + Buprenorphine + Naloxone			Elbasvir + Buprenorphine + Naloxone/ Buprenorphine + Naloxone Alone		Pseudo Within-Subject %CV ⁷
	N ⁶	GM	95% CI	N ¹¹	GM	95% CI	GMR	90% CI	
AUC _{0-∞} ^{2,3,11} (ng•hr/mL)	14	49.4	(38.9, 62.6)	13	47.7	(37.1, 61.4)	0.97	(0.86, 1.09)	17.463
AUC _{0-last} ^{2,3,11} (ng•hr/mL)	15	45.7	(37.0, 56.5)	13	45.0	(35.4, 57.1)	0.98	(0.88, 1.10)	15.716
C _{max} ² (ng/mL)	15	0.992	(0.751, 1.31)	13	1.09	(0.823, 1.44)	1.10	(0.98, 1.23)	16.474
C ₂₄ ² (ng/mL)	15	0.640	(0.511, 0.801)	13	0.622	(0.486, 0.796)	0.97	(0.87, 1.09)	15.590
AUC _{0-∞} Ratio ^{2,3,11,12}	13	1.40	(1.13, 1.74)	13	1.41	(1.10, 1.82)	1.01	(0.88, 1.16)	18.686
T _{max} ¹ (hr)	15	1.51	(0.50, 12.01)	13	1.01	(0.49, 11.98)			
Apparent terminal t _{1/2} ^{5,11,13} (hr)	14	38.81	33.64	13	33.92	33.27			

Buprenorphine + Naloxone Alone: A single sublingual dose of 8 mg buprenorphine/2 mg naloxone (with naltrexone blockade administered as 50 mg naltrexone HCl q12h starting 14 hours prior to the buprenorphine/naloxone dose for a total of 3 naltrexone doses).
 Elbasvir + Buprenorphine + Naloxone: A single oral dose of 50 mg elbasvir co-administered with a single sublingual dose of 8 mg buprenorphine/2 mg naloxone (with naltrexone blockade administered as 50 mg naltrexone HCl q12h starting 14 hours prior to the buprenorphine/naloxone dose for a total of 3 naltrexone doses).
¹Pseudo Within-Subject %CV = 100*sqrt((σ_A² + σ_B² - 2σ_{AB})/2), where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
²Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
³Median (Minimum, Maximum) reported for T_{max}.
⁴Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
⁵One (1) subject was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing.
⁶Two (2) subjects were discontinued from the study by the Investigator on Day 1 of Period 3 (elbasvir + buprenorphine + naloxone) due to vomiting within 8 hours of dosing. One (1) subject was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing. Please refer to Section 10.4 for more details.
⁷The extrapolated portion of the AUC_{0-∞} for 1 subject following buprenorphine + naloxone alone was > 25% of the AUC_{0-∞}.
⁸The terminal elimination phase of norbuprenorphine could not be characterized for 1 subject following buprenorphine + naloxone alone; therefore, AUC_{0-∞} and apparent terminal t_{1/2} could not be calculated for this subject.
⁹The terminal elimination phase of norbuprenorphine for 1 subject and buprenorphine for 1 subject could not be characterized following buprenorphine + naloxone alone; therefore, AUC_{0-∞} Ratio could not be calculated for 2 subjects.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio;
 AUC_{0-∞} Ratio = Molecular weight-adjusted AUC_{0-∞} ratio of norbuprenorphine/buprenorphine.

C) Naloxone

Table 7-Free naloxone pharmacokinetic parameters

AN	Free Naloxone Pharmacokinetic Parameters								
	AUC0-∞ (ng•hr/mL)			AUC0-last (ng•hr/mL)			Cmax (ng/mL)		
	Buprenorphine + Naloxone Alone ^{†,‡}	Elbasvir + Buprenorphine + Naloxone [‡]	Elbasvir + Buprenorphine + Naloxone/ Buprenorphine + Naloxone Alone	Buprenorphine + Naloxone Alone [†]	Elbasvir + Buprenorphine + Naloxone [‡]	Elbasvir + Buprenorphine + Naloxone/ Buprenorphine + Naloxone Alone	Buprenorphine + Naloxone Alone [†]	Elbasvir + Buprenorphine + Naloxone [‡]	Elbasvir + Buprenorphine + Naloxone/ Buprenorphine + Naloxone Alone
N	14	13	13	15	13	13	15	13	13
AM	0.512	0.470	0.91	0.494	0.450	0.91	0.179	0.157	0.93
SD	0.233	0.205	0.24	0.220	0.196	0.27	0.0927	0.0753	0.37
ACV	45.5	43.6	26.5	44.6	43.7	30.0	51.9	48.0	40.1
Med	0.418	0.409	0.89	0.404	0.404	0.94	0.152	0.151	1.01
Min	0.272	0.172	0.62	0.260	0.150	0.56	0.111	0.0524	0.25
Max	1.09	0.774	1.50	1.06	0.769	1.55	0.481	0.312	1.44
GM	0.470	0.426	0.88	0.455	0.406	0.88	0.165	0.141	0.84
GCV	43.5	50.6	25.7	42.7	52.1	30.3	39.4	52.8	55.2

Buprenorphine + Naloxone Alone: A single sublingual dose of 8 mg buprenorphine/2 mg naloxone (with naltrexone blockade administered as 50 mg naltrexone HCl q12h starting 14 hours prior to the buprenorphine/naloxone dose for a total of 3 naltrexone doses).
 Elbasvir + Buprenorphine + Naloxone: A single oral dose of 50 mg elbasvir co-administered with a single sublingual dose of 8 mg buprenorphine/2 mg naloxone (with naltrexone blockade administered as 50 mg naltrexone HCl q12h starting 14 hours prior to the buprenorphine/naloxone dose for a total of 3 naltrexone doses).
[†]Subject AN 0008 was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing.
[‡]Subjects AN 0006 and AN 0011 were discontinued from the study by the Investigator on Day 1 of Period 3 (elbasvir + buprenorphine + naloxone) due to vomiting within 8 hours of dosing. Subject AN 0008 was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing.
[§]The terminal elimination phase of free naloxone could not be characterized for Subject AN 0011 following buprenorphine + naloxone alone; therefore, AUC0-∞ could not be calculated for this subject.
 . = Missing value;
 AM = Arithmetic mean; SD = Standard deviation; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (SD/AM)$; Med = Median; Min = Minimum; Max = Maximum; GM = Geometric mean; GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: $100 \times \sqrt{\exp(s^2) - 1}$, where s^2 is the observed variance on the natural log-scale.

Table 8-Free naloxone statistical analysis

Free Naloxone Pharmacokinetic Parameter	Buprenorphine + Naloxone Alone			Elbasvir + Buprenorphine + Naloxone			Elbasvir + Buprenorphine + Naloxone/ Buprenorphine + Naloxone Alone		Pseudo Within-Subject %CV [†]
	N [‡]	GM	95% CI	N ^{††}	GM	95% CI	GMR	90% CI	
AUC0-∞ ^{‡,§} (ng•hr/mL)	14	0.470	(0.370, 0.598)	13	0.416	(0.316, 0.549)	0.88	(0.78, 1.00)	17.885
AUC0-last [‡] (ng•hr/mL)	15	0.455	(0.363, 0.571)	13	0.400	(0.305, 0.525)	0.88	(0.76, 1.02)	20.936
Cmax [‡] (ng/mL)	15	0.165	(0.133, 0.203)	13	0.139	(0.103, 0.188)	0.85	(0.66, 1.09)	36.263
C24 ^{‡‡} (ng/mL)	15	.	.	13
Tmax [‡] (hr)	15	0.75	(0.50, 1.51)	13	0.98	(0.49, 1.01)	.	.	.
Apparent terminal t _{1/2} ^{§,} (hr)	14	1.93	51.48	13	2.08	48.71	.	.	.

Buprenorphine + Naloxone Alone: A single sublingual dose of 8 mg buprenorphine/2 mg naloxone (with naltrexone blockade administered as 50 mg naltrexone HCl q12h starting 14 hours prior to the buprenorphine/naloxone dose for a total of 3 naltrexone doses).
 Elbasvir + Buprenorphine + Naloxone: A single oral dose of 50 mg elbasvir co-administered with a single sublingual dose of 8 mg buprenorphine/2 mg naloxone (with naltrexone blockade administered as 50 mg naltrexone HCl q12h starting 14 hours prior to the buprenorphine/naloxone dose for a total of 3 naltrexone doses).
[†]Pseudo Within-Subject %CV = $100 \times \sqrt{(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
^{‡‡}Median (Minimum, Maximum) reported for Tmax.
[§]Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
^{††}One (1) subject was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing.
^{‡‡‡}Two (2) subjects were discontinued from the study by the Investigator on Day 1 of Period 3 (elbasvir + buprenorphine + naloxone) due to vomiting within 8 hours of dosing. One (1) subject was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing. Please refer to Section 10.4 for more details.
^{||}Results were not presented for C24 because only 3 of 15 subjects had measurable C24 values following buprenorphine + naloxone alone, and only 1 of 13 subjects had measurable C24 values following elbasvir + buprenorphine + naloxone.
^{|||}The terminal elimination phase of free naloxone could not be characterized for 1 subject following buprenorphine + naloxone alone; therefore, AUC0-∞ and apparent terminal t_{1/2} could not be calculated for this subject.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

C) Elbasvir

Table 9-Elbasvir pharmacokinetic parameters

	Elbasvir Pharmacokinetic Parameters								
	AUC _{0-∞} (μM•hr)			AUC _{0-last} (μM•hr)			C _{max} (μM)		
	Elbasvir Alone [†]	Elbasvir + Buprenorphine + Naloxone [‡]	Elbasvir + Buprenorphine + Naloxone/ Elbasvir Alone	Elbasvir Alone [†]	Elbasvir + Buprenorphine + Naloxone [‡]	Elbasvir + Buprenorphine + Naloxone/ Elbasvir Alone	Elbasvir Alone [†]	Elbasvir + Buprenorphine + Naloxone [‡]	Elbasvir + Buprenorphine + Naloxone/ Elbasvir Alone
N	15	13	13	15	13	13	15	13	13
AM	2.38	2.85	1.37	2.30	2.74	1.36	0.117	0.126	1.32
SD	1.25	1.47	0.84	1.18	1.33	0.84	0.0586	0.0517	0.94
ACV	52.4	51.5	61.1	51.3	48.7	61.5	50.2	41.0	71.4
Med	2.27	2.64	0.97	2.25	2.51	0.97	0.123	0.113	0.93
Min	0.700	0.984	0.77	0.690	0.959	0.76	0.0317	0.0527	0.56
Max	5.60	6.82	3.84	5.38	6.25	3.85	0.282	0.216	4.11
GM	2.08	2.56	1.22	2.02	2.48	1.21	0.103	0.117	1.12
GCV	59.7	50.9	49.1	58.4	49.1	49.3	59.2	43.7	60.7

Elbasvir Alone: A single oral dose of 50 mg elbasvir.
 Elbasvir + Buprenorphine + Naloxone: A single oral dose of 50 mg elbasvir co-administered with a single sublingual dose of 8 mg buprenorphine/ 2 mg naloxone (with naltrexone blockade administered as 50 mg naltrexone HCl q12h starting 14 hours prior to the buprenorphine/naloxone dose for a total of 3 naltrexone doses).
[†]Subject AN 0008 was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of receiving the buprenorphine + naloxone dose.
[‡]Subjects AN 0006 and AN 0011 were discontinued from the study by the Investigator on Day 1 of Period 3 (elbasvir + buprenorphine + naloxone) due to vomiting within 8 hours of dosing. Subject AN 0008 was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing.
 . = Missing value;
 AM = Arithmetic mean; SD = Standard deviation; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (SD/AM)$; Med = Median; Min = Minimum; Max = Maximum;
 GM = Geometric mean; GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: $100 \times \sqrt{\exp(s^2) - 1}$, where s^2 is the observed variance on the natural log-scale.

Table 10-Elbasvir statistical analysis

Elbasvir Pharmacokinetic Parameter	Elbasvir Alone			Elbasvir + Buprenorphine + Naloxone			Elbasvir + Buprenorphine + Naloxone/ Elbasvir Alone		Pseudo Within-Subject %CV [†]
	N [‡]	GM	95% CI	N ^{††}	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (μM•hr)	15	2.08	(1.54, 2.83)	13	2.55	(1.94, 3.35)	1.22	(0.98, 1.52)	32.054
AUC _{0-last} [‡] (μM•hr)	15	2.02	(1.50, 2.73)	13	2.47	(1.89, 3.22)	1.22	(0.98, 1.52)	32.170
C _{max} [‡] (μM)	15	0.103	(0.0760, 0.139)	13	0.116	(0.0908, 0.149)	1.13	(0.87, 1.46)	38.342
C ₂₄ [‡] (nM)	15	32.5	(24.5, 43.1)	13	39.7	(30.2, 52.1)	1.22	(0.99, 1.51)	30.927
T _{max} [‡] (hr)	15	4.00	(2.00, 6.00)	13	3.01	(2.00, 6.05)			
Apparent terminal t _{1/2} [§] (hr)	15	18.46	17.34	13	18.60	18.92			

Elbasvir Alone: A single oral dose of 50 mg elbasvir.
 Elbasvir + Buprenorphine + Naloxone: A single oral dose of 50 mg elbasvir co-administered with a single sublingual dose of 8 mg buprenorphine/2 mg naloxone (with naltrexone blockade administered as 50 mg naltrexone HCl q12h starting 14 hours prior to the buprenorphine/naloxone dose for a total of 3 naltrexone doses).
[†]Pseudo Within-Subject %CV = 100*sqrt((σ_A² + σ_B² - 2σ_{AB})/2), where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
[¶]Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
^{††}One (1) subject was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing.
^{†††}Two (2) subjects were discontinued from the study by the Investigator on Day 1 of Period 3 (elbasvir + buprenorphine + naloxone) due to vomiting within 8 hours of dosing. One (1) subject was discontinued by the Investigator on Day 1 of Period 1 (buprenorphine + naloxone alone) due to vomiting within 3 hours of dosing. Please refer to Section 10.4 for more details.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

10.4 Safety Analysis

According to the trial report, no deaths or serious adverse events were reported for the trial.

11. Discussion and Conclusions

Based on the results from the P21 trial, the following conclusions can be made:

- When a single dose of 8 mg buprenorphine/2 mg naloxone was administered with a single dose of elbasvir 50 mg:
 - the buprenorphine C_{24h}, AUC_(0-inf) and C_{max} were decreased by 2%, 2% and 6%, respectively, and the 90% confidence intervals for C_{24h}, AUC_(0-inf) and C_{max} were within the standard limits of 80% to 125%.
 - the elbasvir C_{24h}, AUC_(0-inf) and C_{max} were increased by 22%, 22% and 13%, respectively, and the 90% confidence intervals for C_{24h}, AUC_(0-inf) and C_{max} were not within the standard limits of 80% to 125%.

The results support the absence of a clinically significant effect of elbasvir on buprenorphine exposure and the absence of a clinically significant effect of buprenorphine/naloxone on elbasvir exposure is supported by the available elbasvir exposure-safety information.

8742-023

1. Title

A Study to Evaluate the Drug-Drug Interaction Between Digoxin and MK-8742 (Elbasvir) in Healthy Volunteers

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted from October 23, 2014 (trial initiation) to December 9, 2014 (trial completion).

3. Objectives

The objectives of the trial included evaluating the effect of elbasvir on the exposure of digoxin.

4. Trial Design

023 was a clinical trial that enrolled healthy subjects 19 to 55 years old.

In period 1, subjects received a single dose of 0.25 mg digoxin on day 1. Subsequent to a washout period consisting of a minimum of 10 days, in period 2, subjects received multiple doses of 50 mg elbasvir once daily for 14 days with a single dose of 0.25 mg digoxin coadministered on day 10.

5. Excluded Medications, Restrictions or Exceptions

Medications, including nonprescription and herbal products, were not permitted within either 14 days (or 28 days for CYP or P-gp inducers) before the first digoxin dose and during the trial.

6. Dosage and Administration

The trial medications were administered under fasted conditions. This is consistent with the proposed U.S. prescribing information (USPI) recommendation for grazoprevir in combination with elbasvir (with or without food). The digoxin USPI does not include specific dosing recommendations with regards to food or meals.

7. Rationale for Doses Used in the Trial

The elbasvir dosing regimen of 50 mg once daily is consistent with the recommended dosage regimen in the proposed U.S. prescribing information for elbasvir and grazoprevir (50 mg of elbasvir with 100 mg of grazoprevir once daily). The dose of digoxin is consistent with the recommendations in the digoxin USPI.

8. Drugs Used in the Trial

The medications administered in trial 023 are displayed in Table 1.

Table 1-Medications administered in trial 023

Bulk Product Description	Manufacturing Lot Number
(b) (4) MK-8742 (elbasvir) (b) (4) 50 mg (b) (4) (b) (4) Oval) tablet	WL00055785
LANOXIN [®] (digoxin) USP 250 µg (0.25 mg) tablet [†]	Not Applicable
[†] LANOXIN [®] (digoxin) USP 0.25 mg tablet (lot number A94746; expiration date May-2016; (b) (4) was supplied by the Investigator.	

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included digoxin predose and postdose blood samples up to 120 hours in periods 1 and 2.

Bioanalysis

The method and bioanalysis of digoxin are acceptable.

Digoxin plasma samples were analyzed using a validated LC/MS/MS method in K₂EDTA anticoagulated plasma by (b) (4). The blood samples for analysis of digoxin appear to have been collected in tubes containing K₂EDTA as an anticoagulant.

For the plasma samples from the P23 trial that were analyzed for digoxin, the lower limit of quantification for digoxin was 10 pg/mL and the upper limit of quantification was 2500 pg/mL. There were no precision or accuracy issues identified for digoxin based on the bioanalytical report. For the P23 trial, precision and accuracy for digoxin were evaluated using plasma digoxin quality control (QC) samples at 30 pg/mL, 187.5 pg/mL, 1250 pg/mL, and 1875 ng/mL (the 187.5 ng/mL QC was not evaluated as part of the method validation). For digoxin, the corresponding inter-run accuracy values were -1.67% for 30 ng/mL, 0.68% for 187.5 pg/mL, 0.09% for 1250 pg/mL, and -6.62% for 1875 pg/mL. The corresponding digoxin inter-run precision values were 6.48% for 30 pg/mL, 7.99% for 187.5 pg/mL, 5.58% for 1250 pg/mL, and 5.66% for 1875 pg/mL.

Of the samples selected for incurred sample reanalysis for digoxin, two samples out of fifty eight samples were not within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of digoxin samples that were reanalyzed represents 7% of the total number of samples that were initially analyzed.

For the P23 trial, the bioanalytical report states that the maximum length of storage for the digoxin samples was 42 days at -20°C. For the P23 trial, long term digoxin stability data of 81 days at -20°C and -80°C in K₂EDTA anticoagulated plasma was generated by (b) (4) for a digoxin method validated for a calibration range of 10 ng/mL to 10000 ng/mL (the method used to analyze the P23 samples is a partial validation of this method). QC concentrations of 30 pg/mL and 7500 pg/mL were evaluated for the long term stability experiments. The long term stability data generated by (b) (4) appears sufficient based on the information provided in the submission (the bioanalytical report states that the date of last analysis

was December 14, 2014) if digoxin stability trends remain consistent below 7500 pg/mL.

Pharmacokinetic Assessments

Based on the information included in the trial report, noncompartmental analysis was performed using actual sampling times to derive digoxin plasma pharmacokinetic parameters.

Statistical Analysis

The statistical analyses included deriving 90% confidence intervals for relevant pharmacokinetic parameters comparing digoxin with concomitant use of digoxin and elbasvir (test arm) to the reference arm (digoxin alone).

10. Results

10.1 Subject Demographics

Table 2-P23 subject demographics

	All Subjects	
	N	(%)
Subjects in Study	18	
Gender		
Female	8	(44)
Male	10	(56)
Age (Years)		
0 to 19	0	(0)
20 to 39	6	(33)
40 to 59	12	(67)
Mean	40.7	
SD	8.48	
Median	42.5	
Range	21 to 53	
Race		
Asian	1	(6)
White	17	(94)
Ethnicity		
Hispanic or Latino	1	(6)
Not Hispanic or Latino	17	(94)
Height (cm)		
Mean	171.3	
Range	152 to 188	
Weight (kg)		
Mean	78.7	
Range	57.0 to 109.6	
BMI (kg/m²)		
Mean	26.6	
Range	21.69 to 31.46	

10.2 Concomitant Medications

The concomitant medications that were administered in the trial included acetaminophen. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Table 3-Digoxin pharmacokinetic parameters

	Digoxin Pharmacokinetic Parameters								
	AUC0-∞ [†] (ng•hr/mL)			AUC0-last (ng•hr/mL)			Cmax (ng/mL)		
	Digoxin Alone	Digoxin + Elbasvir	Digoxin + Elbasvir/ Digoxin Alone	Digoxin Alone	Digoxin +Elbasvir	Digoxin+ Elbasvir/ Digoxin Alone	Digoxin Alone	Digoxin +Elbasvir	Digoxin + Elbasvir/ Digoxin Alone
N	18	18	18	18	18	18	18	18	18
AM	20.3	22.0	1.14	17.2	19.1	1.16	1.24	1.77	1.59
SD	6.16	4.25	0.289	4.77	3.98	0.277	0.451	0.431	0.653
ACV	30.3	19.3	25.2	27.7	20.8	23.8	36.2	24.4	41.2
Med	19.6	21.3	1.03	16.7	18.6	1.04	1.28	1.80	1.38
Min	8.79	15.5	0.872	7.47	12.9	0.894	0.598	1.01	0.796
Max	30.6	31.5	1.94	23.8	28.6	1.96	2.20	2.66	3.15
GM	19.4	21.6	1.11	16.5	18.8	1.14	1.17	1.72	1.47
GCV	33.7	19.5	23.1	31.3	20.7	21.7	38.9	25.7	41.0

Digoxin Alone: A single oral dose of 0.25 mg digoxin (1 x 0.25 mg tablet) administered on Day 1 of Period 1 following an overnight fast.
 Digoxin + Elbasvir: Multiple oral doses of 50 mg elbasvir (1 x 50 mg tablet) administered every 24 hours for 14 days, co-administered with a single oral dose of 0.25 mg digoxin on Day 10 of Period 2 following an overnight fast.
[†]The extrapolated portion of AUC0-∞ was ≥ 25% (26.4%) of AUC0-∞ for Subject AN 0014 in Period 1, consequently, results for AUC0-∞ should be interpreted with caution.
 AM = Arithmetic mean; SD = Standard deviation; GM = Geometric mean; Med = Median;
 Min = Minimum; Max = Maximum; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: 100 x (SD/AM); GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s²) - 1), where s² is the observed variance on the natural log-scale.

Table 4-Digoxin statistical analyses

Digoxin Pharmacokinetic Parameters	Digoxin Alone			Digoxin + Elbasvir			Digoxin + Elbasvir/ Digoxin Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC0-∞ ^{†,‡} (ng•hr/mL)	18	19.4	(16.5, 22.8)	18	21.6	(19.6, 23.8)	1.11	(1.02, 1.22)	16.105
AUC0-last [†] (ng•hr/mL)	18	16.5	(14.2, 19.2)	18	18.8	(16.9, 20.8)	1.14	(1.04, 1.24)	15.153
Cmax [†] (ng/mL)	18	1.17	(0.968, 1.41)	18	1.72	(1.51, 1.95)	1.47	(1.25, 1.73)	27.857
Tmax [§] (hr)	18	1.00	(1.00, 2.00)	18	0.99	(0.49, 1.49)			
Apparent Terminal t _{1/2} ^{,¶} (hr)	18	45.10	21.70	18	41.96	18.73			

Digoxin Alone: A single oral dose of 0.25 mg digoxin (1 x 0.25 mg tablet) administered on Day 1 of Period 1 following an overnight fast.
 Digoxin + Elbasvir: Multiple oral doses of 50 mg elbasvir (1 x 50 mg tablet) administered every 24 hours for 14 days, co-administered with a single oral dose of 0.25 mg digoxin on Day 10 of Period 2 following an overnight fast.
[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for Tmax.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
[¶]The extrapolated portion of AUC0-∞ was ≥ 25% (26.4%) of AUC0-∞ for 1 subject in Period 1, consequently, results for AUC0-∞ should be interpreted with caution.
[#]Digoxin apparent terminal t_{1/2} values for the digoxin alone treatment were greater than ½ the time of the pharmacokinetic sampling duration (120 hours) and were greater than ⅓ the time of the pharmacokinetic sampling duration for 10 subjects. Digoxin apparent terminal t_{1/2} values for the digoxin + elbasvir treatment were greater than ⅓ the time of the pharmacokinetic sampling duration (120 hours) for 11 subjects.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

10.4 Safety Analysis

According to the trial report, no deaths or serious adverse events were reported for the trial.

11. Discussion and Conclusions

Based on the results from the P23 trial, the following conclusion can be made:

- When a single dose of digoxin 0.25 mg was administered with elbasvir 50 mg once daily:
 - the digoxin $AUC_{(0-inf)}$ and C_{max} were increased by 11% and 47%, respectively, and only the 90% confidence interval for $AUC_{(0-inf)}$ was within the standard limits of 80% to 125%.

In the proposed U.S. prescribing information for elbasvir and grazoprevir, no specific clinical recommendations are proposed by the applicant in section 7 for managing a drug interaction with concomitant use of digoxin and elbasvir/grazoprevir. Based on discussions with the cardiovascular clinical pharmacology review team, the applicant's approach is acceptable because the magnitude of increase in digoxin exposure is less than 20%.

Title: A Study to Evaluate the 2 Way interaction Multiple Doses of MK-5172 and Multiple Doses of a Reverse Transcriptase Inhibitor (Tenofovir Disoproxil Fumarate) and Multiple Doses of MK-5172 and Multiple Doses of an HIV Integrase Inhibitor (Raltegravir) in Healthy Adult Subjects

Study Initiation Date: 1-Nov-2012

Study Completion Date: 27-Dec-2012

Study Site: (b) (4)

Study Design

This was a 2-part study, each being a fixed-sequence, 3-period, open-label study in 24 healthy adult subjects to evaluate the 2-way interaction of multiple doses of MK-5172 and multiple doses of tenofovir disoproxil Fumarate (TDF), as well as multiple doses of MK-5172 and multiple doses of raltegravir (RAL). Subjects participated in only one part of the study. All doses were administered under fasting conditions.

Table 1. Study Design

	Period 1	Washout	Period 2	Period 3
Part 1	TDF 300 mg QD for 7 days PK sampling for tenofovir: up to 96 hours post-dose on Day 7	≥ 5 Days	MK-5172 200 mg QD for 7 days PK sampling for MK-5172: up to 24 hours post-dose on Day 7	TDF 300 mg QD and MK-5172 200 mg QD for 7 days PK sampling for tenofovir and MK-5172: up to 96 hours post-dose on Day 7
Part 2	Raltegravir 400 mg BID for 4 days, last dose administered in the morning of Day 4 PK sampling for raltegravir: up to 72 hours post-dose on Day 7	≥ 3 Days	MK-5172 200 mg QD for 7 days PK sampling for MK-5172: up to 24 hours post-dose on Day 7	Raltegravir 400 mg BID and MK-5172 200 mg QD for 7 days (last dose of raltegravir administered in the morning of Day 7) PK sampling for tenofovir and MK-5172: up to 72 hours post-dose on Day 7

Key Inclusion Criteria

- Healthy adult male and female volunteers, 19-55 years of age, inclusive
- BMI: 19- 32 kg/m², inclusive. Weigh at least 52 kg for males and 45 kg for females.
- Non-smokers (have not used nicotine-containing products for at least 3 months prior to the first dose)
- Medically healthy with no clinically significant history, physical exam, lab profiles. Liver function tests must be below the upper limit of normal for inclusion
- A female of childbearing potential must either sexually inactive or use acceptable 2 acceptable methods of birth control. Female subjects must demonstrate a serum beta human chorionic gonadotropin level consistent with nongravid state.
- Male subjects must use a condom (or abstain from sexual intercourse) and agree not to donate sperm from the first dose until 90 days after the last dose

Key Exclusion Criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 80 mL/min
- Consuming excessive amounts of alcohol or caffeine
- History of drug or alcohol abuse (within 1 year)
- Positive results at screening for HIV, hepatitis B, or hepatitis C, urine drug or cotinine screening
- Donation of blood or had significant blood loss within 4 weeks prior to the first dose of study drug or plasma donation within 7 days prior to the first dose of study drug.
- Participation in another clinical trial within 28 days prior to the first dose of study drug.
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients

Concomitant Medications and Diet Restrictions

No drugs were to be taken within 14 days (or 28 days for inducers or strong inhibitors of CYP or P-gp and/or strong inhibitors or substrates of OATP1B transporters) or 5 half-lives of the compound, whichever is longer, prior to the first dosing. Acetaminophen, up to 2 g per 24 hour period, may have been used for minor ailments without prior consultation with the Sponsor Clinical Monitor.

Identity of Clinical Supplies

Table 2. Identity of Clinical Supplies

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency	Site of Manufacture
MK-5172 [†]	100 mg	WL00044051	Tablet	WL00050369	98%	Merck & Co., Inc., West Point, PA
Tenofovir disoproxil fumarate [‡]	300 mg	001002	Tablet	NA	NA	NA
Raltegravir [§]	400 mg	H017532	Tablet	NA	NA	NA

[†]MK-5172 (a product manufactured for Merck & Co., Inc.). The batch number was WL00044051. CoA Number A-11-1175.

[‡]Tenofovir disoproxil fumarate (Viread[®]) (a product manufactured for Gilead Sciences, Inc.) required for the study was purchased by the Investigator. The lot number was 001002; expiration date Apr-2017.

[§]Raltegravir (Isentress[®]) (a product manufactured by MSD International GmbH [Singapore Branch]) required for the study was purchased by the Investigator. The lot number was H017532; expiration date Dec-2014.

Pharmacokinetic Assessments

Blood samples for determination of study drug concentrations were collected as outlined in Study Design. C₁₂, C₂₄, and C_{trough} values were obtained using SAS (Version 9.1). All other pharmacokinetic parameters were calculated using the software WinNonlin Phoenix 6.3. C_{max} and T_{max} were generated by WinNonlin from each analytes plasma concentration-time data. All AUC parameters were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down).

Bioanalysis

Plasma sample analyses for MK-5172 and tenofovir were performed by (b) (4). Plasma sample analysis for raltegravir was performed by MSD (Oss, The Netherlands). The concentrations of these drugs were determined using validated LC/MS/MS methods. All methods were adequately validated and the standard curve and QC data indicated assays were acceptable. All samples were stored and processed in the time frame supported by the stability data.

Table 3. Summary of bioanalysis

Analyte	MK-5172	Tenofovir	Raltegravir
Internal standard	MK-5172-d ₆	Tenofovir -d ₆	Raltegravir- ¹³ C ₆
Matrix/Anticoagulant	Plasma/K ₂ EDTA	Plasma/K ₂ EDTA	Plasma/K ₂ EDTA
Extraction method	Liquid-liquid extraction	Protein precipitation	Liquid-liquid extraction
Calibration range	1- 1000 ng/mL	5 to 1000 ng/mL	2 to 1000 ng/mL
QC concentration	3, 75, and 750 ng/mL	10, 25, 75, 200 and 750 ng/mL	6, 75, and 750 ng/mL
Interday precision and accuracy	P: 3.81 to 4.91% A: - 6.57 to - 4.31%	P: 2.76 to 4.74% A: -4.01 to 1.93%	P: 4.22 to 5.65% A: 1.05 to 6.67%
Long term stability	397 Days at -20 °C	606 Days at - 20 °C	77 days at - 20 °C

RESULTS

Demographic and Baseline Characteristics

Twenty-four subjects were enrolled into the study, 12 subjects in Part 1 and 12 subjects in Part 2. One subject was discontinued in Part 2 due to a positive urine drug screen for cannabinoids in Period 1.

Table 4. Subject baseline demographics

	Part 1 N=12	Part 2 N=12
Age in Years , Mean (range)	36 (22 – 50)	
Sex , n (%)		
Female	3 (25%)	5 (42%)
Male;	9 (75%)	7 (58%)
BMI (kg/m²) , range	26.55 (20.29 – 31.02)	26.07 (20.82-31.38)
Height (cm) , range	173.3 (161.0 – 186.0)	173.8 (152.0 to 190.0)
Weight (kg) , range	80.1 (57.4 – 95.9)	79.7 (52.3 – 101.5)
Ethnicity , n (%)		
Hispanic or Latino:	0 (0%)	0 (0%)
Not Hispanic or Latino:	12 (100%)	12 (100%)
Race , n (%)		
White	10 (83%)	11 (92%)
African American/Black	2 (17%)	1 (8%)

Concomitant Therapy

One subject (PN015) received pseudoephedrine and ibuprofen at screening. It is unlikely to have an effect on the assessment of the study objectives.

PHARMACOKINETIC RESULTS

Part 1. Drug interactions between MK-5172 and TDF

The co-administration of TDF decreased AUC_{0-24hr} , C_{max} , and C_{24hr} of MK-5172 by 14%, 22%, and 11%, respectively. The co-administration of MK-5172 increased AUC_{0-24hr} , C_{max} , and C_{24hr} of MK-5172 by 18%, 14%, and 24%, respectively. These changes are not considered clinically relevant.

Table 5. MK-5172 plasma pharmacokinetics with or without the co-administration of TDF

Pharmacokinetic Parameter	MK-5172 Alone (Period 2)			Tenofovir + MK-5172 (Period 3)			Tenofovir + MK-5172/ MK-5172		Pseudo Within Subject %CV [‡]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC_{0-24}^{\dagger} (μM·hr)	12	2.07	(1.45, 2.96)	12	1.77	(1.26, 2.49)	0.86	(0.65, 1.12)	36.895
C_{max}^{\dagger} (μM)	12	0.447	(0.267, 0.747)	12	0.348	(0.202, 0.599)	0.78	(0.51, 1.18)	56.689
C_{24}^{\dagger} (nM)	12	15.1	(11.5, 19.8)	12	13.4	(9.95, 18.1)	0.89	(0.78, 1.01)	17.277
T_{max}^{\parallel} (hr)	12	3.00	(2.00, 6.00)	12	3.51	(2.00, 6.00)			
Apparent terminal $t_{1/2}^{\S}$ (hr)				12	26.85	33.80			

MK-5172 Alone: 200 mg (2 x 100 mg tablets) q.d. oral doses of MK-5172 administered for 7 days (Days 1 to 7).
Tenofovir + MK-5172: 300 mg (1 x 300 mg tablet) q.d. oral doses of Tenofovir co-administered with 200 mg (2 x 100 mg tablets) q.d. oral doses of MK-5172 for 10 days (Days 1 to 10).
[†]Back-transformed least squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values.
[‡]Pseudo within-subject %CV = $100 \cdot \text{Sqrt}((\sigma_C^2 + \sigma_B^2 - 2 \cdot \sigma_{CB})/2)$, where σ_C^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{CB} is the corresponding estimated covariance, each obtained from the linear mixed effects model.
^{||}Median (minimum, maximum) reported for T_{max} .
[§]Geometric mean (percent geometric coefficient of variation) reported for terminal apparent $t_{1/2}$.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments

Table 6. Tenofovir plasma pharmacokinetics with or without the co-administration of MK-5172

Pharmacokinetic Parameter	Tenofovir Alone (Period 1)			Tenofovir + MK-5172 (Period 3)			Tenofovir + MK-5172/ Tenofovir		Pseudo Within Subject %CV [‡]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC_{0-24}^{\dagger} (ng/mL·hr)	12	2020	(1750, 2330)	12	2380	(2000, 2840)	1.18	(1.09, 1.28)	11.438
C_{max}^{\dagger} (ng/mL)	12	257	(223, 296)	12	293	(246, 348)	1.14	(1.04, 1.25)	13.029
C_{24}^{\dagger} (ng/mL)	12	43.1	(36.6, 50.6)	12	53.4	(45.0, 63.3)	1.24	(1.10, 1.39)	15.907
T_{max}^{\parallel} (hr)	12	0.77	(0.50, 1.50)	12	1.01	(0.52, 2.01)			
Apparent terminal $t_{1/2}^{\S}$ (hr)	12	19.75	18.90	12	21.13	17.95			

Tenofovir alone: 300 mg (1 x 300 mg tablet) q.d. oral doses of Tenofovir administered in Part 1 for 7 days (Days 1 to 7).
Tenofovir + MK-5172: 300 mg (1 x 300 mg tablet) q.d. oral doses of Tenofovir co-administered with 200 mg (2 x 100 mg tablets) q.d. oral doses of MK-5172 for 10 days (Days 1 to 10).
[†]Back-transformed least squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values.
[‡]Pseudo within-subject %CV = $100 \cdot \text{Sqrt}((\sigma_C^2 + \sigma_A^2 - 2 \cdot \sigma_{CA})/2)$, where σ_C^2 and σ_A^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{CA} is the corresponding estimated covariance, each obtained from the linear mixed effects model.
^{||}Median (minimum, maximum) reported for T_{max} .
[§]Geometric mean (percent geometric coefficient of variation) reported for terminal apparent $t_{1/2}$.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments

Part 2. Drug interactions between raltegravir and MK-5172

The co-administration of raltegravir decreased AUC_{24hr} , C_{max} , and C_{24hr} of MK-5172 by 11%, 15%, and 10%, respectively. The co-administration of MK-5172 increased AUC_{24hr} , C_{max} , and C_{24hr} of MK-5172 by 43%, 46%, and 47%, respectively. These changes are not considered clinically relevant.

Table 7. MK-5172 plasma pharmacokinetics with or without the co-administration of raltegravir

Pharmacokinetic Parameter	MK-5172 Alone (Period 2)			Raltegravir + MK-5172 (Period 3)			Raltegravir + MK-5172 / MK-5172		
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	Pseudo Within Subject %CV [‡]
AUC_{0-24}^{\dagger} ($\mu M \cdot hr$)	11	2.78	(1.71, 4.52)	11	2.46	(1.55, 3.92)	0.89	(0.72, 1.09)	26.418
C_{max}^{\dagger} (μM)	11	0.653	(0.334, 1.28)	11	0.555	(0.313, 0.984)	0.85	(0.62, 1.16)	40.450
C_{24}^{\dagger} (nM)	11	17.8	(12.9, 24.5)	11	16.1	(11.6, 22.2)	0.90	(0.82, 0.99)	12.310
T_{max}^{\parallel} (hr)	11	3.00	(1.51, 4.02)	11	3.01	(2.00, 6.00)			
Apparent terminal $t_{1/2}^{\S}$ (hr)				11	18.94	10.69			

MK-5172 Alone: 200 mg (2 x 100 mg tablets) q.d. oral doses of MK-5172 administered for 7 days (Days 1 to 7).
 Raltegravir + MK-5172: 400 mg (1 x 400 mg tablet) b.i.d. oral doses of raltegravir co-administered with 200 mg (2 x 100 mg tablets) q.d. oral doses of MK-5172 administered for 7 days (Days 1 to 7), with the last dose of raltegravir administered in the morning of Day 7.

[†]Back-transformed least squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values.
[‡]Pseudo within-subject %CV = $100 \cdot \text{Sqrt}((\sigma_E^2 + \sigma_B^2 - 2 \cdot \sigma_{EB})/2)$, where σ_E^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{EB} is the corresponding estimated covariance, each obtained from the linear mixed effects model.
^{||}Median (minimum, maximum) reported for T_{max} .
[§]Geometric mean, (percent geometric coefficient of variation) reported for terminal apparent $t_{1/2}$.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments

Table 8. Raltegravir plasma pharmacokinetics with or without the co-administration of MK-5172

Pharmacokinetic Parameter	Raltegravir Alone (Period 1)			Raltegravir + MK-5172 (Period 3)			Raltegravir + MK-5172 / Raltegravir		
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	Pseudo Within Subject %CV [‡]
AUC_{0-12}^{\dagger} ($\mu g/mL \cdot hr$)	11	6.07	(3.18, 11.6)	11	8.67	(4.86, 15.5)	1.43	(0.89, 2.30)	61.385
C_{max}^{\dagger} ($\mu g/mL$)	11	1.84	(0.809, 4.18)	11	2.69	(1.30, 5.54)	1.46	(0.78, 2.73)	80.814
C_{12}^{\dagger} (ng/mL)	11	54.0	(36.9, 79.0)	11	79.4	(48.8, 129)	1.47	(1.085, 1.998)	39.497
T_{max}^{\parallel} (hr)	11	1.00	(0.50, 4.00)	11	1.50	(0.00, 4.01)			
Apparent terminal $t_{1/2}^{\S}$ (hr)	10 [†]	12.44	86.97	11	12.70	118.51			

Raltegravir Alone: 400 mg (1 x 400 mg tablet) b.i.d. oral doses of raltegravir administered for 4 days (Days 1 to 4) with the last dose administered in the morning of Day 4.
 Raltegravir + MK-5172: 400 mg (1 x 400 mg tablet) b.i.d. oral doses of raltegravir co-administered with 200 mg (2 x 100 mg tablets) q.d. oral doses of MK-5172 administered for 7 days (Days 1 to 7), with the last dose of raltegravir administered in the morning of Day 7.

[†]Back-transformed least squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values.
[‡]Pseudo within-subject %CV = $100 \cdot \text{Sqrt}((\sigma_E^2 + \sigma_D^2 - 2 \cdot \sigma_{ED})/2)$, where σ_E^2 and σ_D^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{ED} is the corresponding estimated covariance, each obtained from the linear mixed effects model.
^{||}Median (minimum, maximum) reported for T_{max} .
[§]Geometric mean (percent geometric coefficient of variation) reported for terminal apparent $t_{1/2}$.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatments
[†]Subject AN 0020 apparent terminal $t_{1/2}$ in Period 1 was excluded from summary statistics because it was considered an outlier.

Conclusion

The exposure of MK-5172 was slightly decreased by the co-administration of TDF or raltegravir. The exposures of tenofovir or raltegravir were slightly increased by the co-administration of MK-5172. These changes are not clinically relevant. MK-5172 can be administered with raltegravir or TDF without a dose adjustment.

Title: A Study to Characterize the Two-Way Pharmacokinetic Interaction Between MK-5172 (Grazoprevir) and Lopinavir/ritonavir, Atazanavir/ritonavir, and Darunavir/ritonavir in Healthy Subjects (PN029)

Study Initiation Date: 14-Dec-2012

Study Completion Date: 26-Jan-2013

Study Site: (b) (4)

Study Design

This was a 3-part study, each part being a fixed-sequence, 3-treatment, 3-period, open-label study in 39 healthy adult subjects. Thirteen subjects were enrolled in each part of the study, with a minimum of 3 females per part, with the expectation that at least 10 subjects would complete each part of the study. No subjects participated in more than one part. Within each part, subjects received in fixed sequence treatments (Table 1). There was a washout period of at least 7 days separated the last dose of Period 1 and the first dose of Period 2. There was no washout period between Period 2 and Period 3.

Table 1. Study Design

Period	Part 1	Part 2	Part 3
1	Multiple oral doses of 200 mg MK-5172 administered q.d. for 7 days (MK-5172 Alone)		
2	Multiple oral doses of 300 mg atazanavir and 100 mg ritonavir q.d. for 14 days (ATV/r Alone)	Multiple oral doses of 400 mg lopinavir and 100 mg ritonavir b.i.d. for 14 days (LPV/r Alone)	Multiple oral doses of 600 mg darunavir and 100 mg ritonavir b.i.d. for 14 days (DRV/r Alone)
3	Multiple oral doses of 300 mg atazanavir, 100 mg ritonavir and 200 mg MK-5172 co-administered q.d. for 7 days (ATV/r + MK-5172)	Multiple oral doses of 400 mg lopinavir, 100 mg ritonavir b.i.d. and 200 mg MK-5172 co-administered q.d. for 7 days (LPV/r + MK-5172)	Multiple oral doses of 600 mg darunavir, 100 mg ritonavir b.i.d. and 200 mg MK-5172 co-administered q.d. for 7 days (DRV/r + MK-5172)

Plasma samples for full pharmacokinetic assessments of MK-5172 and (Periods 1 and 3) and protease inhibitors (Periods 2 and 3) were collected at specified time points pre-dose and post-dose on Days 7 (Periods 1 and 3) and on Day 14 (Period 2). On the days of plasma PK sample collection, all drugs were administered under fed conditions (a moderate-fat breakfast containing approximately 550 calories and 25 - 35% of fat) was consumed within 30 minutes. When protease inhibitors were self-administered at home, subjects were instructed to take drugs under fed conditions.

Key Inclusion Criteria

- Healthy adult male and female volunteers, 18-55 years of age, inclusive
- BMI: 18.5-30 kg/m², inclusive. Weigh at least 52 kg for males and 45 kg for females.
- Non-smokers (have not used nicotine-containing products for at least 3 months prior to the first dose)

- Medically healthy with no clinically significant history, physical exam, lab profiles. Liver function tests must be below the upper limit of normal for inclusion
- A female of childbearing potential must either sexually inactive or use acceptable birth control methods.
- Male subjects must use a condom (or abstain from sexual intercourse) and agree not to donate sperm from the first dose until 90 days after the last dose

Key Exclusion Criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 80 mL/min
- History of alcoholism or drug abuse (within 2 years)
- History of diabetes mellitus or hyperglycemia
- Female subjects who are pregnant or lactating
- Positive results at screening for HIV, hepatitis B, or hepatitis C, urine drug or cotinine screening
- Donation of blood or had significant blood loss within 56 days prior to the first dose of study drug or plasma donation within 7 days prior to the first dose of study drug.
- Participation in another clinical trial within 28 days prior to the first dose of study drug.
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients

Identity of Investigational Products

Table 2. Identity of investigational products

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency (N = X)	Site of Manufacture
MK-5172	100 mg	WL00044049	Tablet	WL00050479	98.0%	Merck & Co., Inc., West Point, PA
Reyataz [®] (atazanavir sulfate) [†]	300 mg	MR-4907	Capsule	NA	NA	NA
Norvir [®] Ritonavir [‡]	100 mg	NA	Tablet	NA	NA	NA
Kaletra [®] (Lopinavir/Ritonavir) [§]	200/50 mg	NA	Tablet	NA	NA	NA
Prezista [®] (darunavir)	600 mg	NA	Tablet	NA	NA	NA

[†]Reyataz[®] (a registered product of Bristol-Meyers Squibb Company) was purchased by the Investigator. The lot number was 2J5079A; expiration date Sep-2014.

[‡]Norvir[®] (a registered product of Abbott Laboratories) was purchased by the Investigator. The lot number was 200922E; expiration date 07-May-2014

[§]Kaletra[®] (a registered product of Abbott Pharmaceuticals PR Ltd.) required for the study was purchased by the Investigator. The lot number was 20415AA; expiration date 07-Aug-2015.

^{||}Prezista[®] (a registered product of Jansses Ortho LLC) required for the study was purchased by the Investigator. The lot number was 2KG331; expiration date Aug-2014.

Concomitant medications

No subject was to take medication (including over-the-counter products, especially proton-pump inhibitor and antacids), herbal products or vitamin supplements for the 14 days (or 28 days for CYP or P-gp inducers) or 5 half-lives of the medication(s), whichever was longer, prior to the first dose of the study and until the end of the study. During the study, acetaminophen (up to 2 g per 24 hours) could have been administered at the discretion of the Investigator.

Pharmacokinetic assessments

Plasma samples for MK-5172 concentrations were collected at predose and specified time points over 96 hours post-dose in Period 1 and Period 3. Plasma samples for protease inhibitors' (ATV, LPV, or DRV) concentrations were collected over 24 hours and 96 hours on Day 14 of Period 2 (protease inhibitor alone) and on Day 7 of Period 3 (protease inhibitor + MK-5172), respectively.

C_{12} , C_{24} , and C_{trough} values were obtained using SAS (Version 9.1). All other pharmacokinetic parameters were calculated using the software WinNonlin Phoenix 6.3. C_{max} and T_{max} were generated by WinNonlin from each analytes plasma concentration-time data. All AUC parameters were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down).

Reviewer comments: Plasma samples for ritonavir were also collected but the data will not be reviewed as changes in ritonavir concentrations have minimal clinical implications.

Bioanalysis

Blood samples (~ 4mL for MK-5172 in K₂EDTA-coated containers and ~2mL for HIV protease inhibitors in K₃EDTA-coated containers) were collected for bioanalysis. Bioanalyses for plasma concentrations of MK-5172 and protease inhibitors were conducted by (b) (4). The concentrations of these drugs were determined using validated LC/MS/MS methods. All methods were adequately validated and the standard curve and QC data indicated assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data.

Table 3. Summary of Bioanalysis (PN029)

Analyte	Darunavir	Lopinavir	Atazanavir	MK-5172
Internal standard	Darunavir-d ₉	Lopinavir-d ₈	Atazanavir-d ₅	MK-5172-d ₆
Matrix/Anticoagulant	Plasma/K ₃ EDTA	Plasma/K ₃ EDTA	Plasma/K ₃ EDTA	Plasma/K ₂ EDTA
Extraction method	Protein precipitation followed by filtration	Protein precipitation followed by filtration	Liquid-liquid extraction	Liquid-liquid extraction
Calibration range and regression method	10- 10000 ng/mL 1/x ² regression	10- 10000 ng/mL 1/x ² regression	10- 10000 ng/mL 1/x ² regression	1- 1000 ng/mL 1/x ² regression
QC concentration	30, 75, 300, 1200 and 7500 ng/mL	30, 75, 300, 1200 and 7500 ng/mL	30, 75, 300, 1200 and 7500 ng/mL	3, 75, and 750 ng/mL
Interday precision and accuracy	P: 1.7 to 4.8% A: -1.3 to 10.3%	P: 2.5 to 12.4% A: 4.6 to 10.8%	P: 3.9 to 5.5% A: -4.0 to 5.3%	P: 4.2 to 6.8% A: -7.9 to 7.0%

Storage stability	309 days at – 20°C	1060 days at – 20°C	699 days at – 20°C	397 days at – 20°C
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Results

Demographic information and baseline characteristics

Table 4. Subject baseline demographics

	Part 1 N=13	Part 2 N=13	Part 3 N=13
Number of subjects completed the study	11	13	11
Number of subjects discontinued	2 AN 0001 (adverse event in Period 2; rash); AN0008 (non-attendance to return visit on Day 3 of Period 1)	None	2 AN0041 (positive drug screen in Period 3) AN0044 (lab adverse event; ALT increase in washout after Period 1*)
Age in Years, Mean (range)	40 (25-49)	37 (19-47)	44 (28-55)
Sex, n (%)			
Female	4 (31%)	6	4 (31%)
Male;	9 (69%)	7	9 (69%)
BMI (kg/m²), range	25.8 (20.4-29.5)	27.3 (24.2-29.7)	26.6 (22.4-39.8)
Height (cm), range	17.02 (156.0-189.0)	162.0 (146.0-170.0)	167.2 (153.0-185.0)
Weight (kg), range	75.0 (53.4-96.9)	72.2 (51.7-85.5)	74.8 (54.0-72.3)
Ethnicity, n (%)			
Hispanic or Latino:	11 (85%)	13 (100%)	12 (92%)
Not Hispanic or Latino:	3 (15%)		1 (8%)
Race, n (%)			
White	11 (84%)	13 (100%)	12 (92%)
African American/Black	1 (8%)	0 (0%)	1 (8%)
Asian	1 (8%)	0 (0%)	0 (0%)

*An ALT increase (2.4XULN) was observed 16 days after the completion of Period 1(MK-5172 only). The event was considered resolved approximately 6 days later. The event was considered by the investigator to be not related to the study treatment. The subject was discontinued from the study.

Concomitant medications

Three subjects received acetaminophen as needed. One subject received a topical steroid (fluocinolone acetonide) to treat vitiligo (not due to adverse experience). These medications were judged not to have an effect on the assessment of the pharmacokinetics of study drugs.

Pharmacokinetic Results

Part 1 (drug interactions between MK-5172 and ATV/r)

MK-5172 exposures were markedly increased by the co-administration of ATV/r; AUC_{24hr}, C_{max}, and C_{24hr} of MK-5172 were increased by 10.6-fold, 6.2-fold, and 11.6-fold, respectively, by the co-administration of ATV/rtv 300 mg/100 mg once daily for 7 days (Table 5). MK-5172 slightly increased ATV AUC and C_{max} but the magnitude of the increase is not considered clinically significant (Table 6).

Table 5. Steady-state pharmacokinetics of MK-5172 with or without the co-administration of atazanavir/ritonavir 300 mg/100 mg QD for 7 days

MK-5172 Pharmacokinetic Parameter	MK-5172 Alone			ATV/r + MK-5172			ATV/r + MK-5172 / MK-5172 Alone		Pseudo Within Subject %CV ¹
	N [†]	GM	95% CI	N ^{††}	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [†] (μM•hr)	12	3.38	(2.26, 5.05)	11	35.7	(26.1, 49.0)	10.58	(7.78, 14.39)	40.497
C _{max} [†] (μM)	12	0.952	(0.573, 1.58)	11	5.94	(4.48, 7.87)	6.24	(4.42, 8.81)	46.122
C ₂₄ [†] (nM)	12	14.7	(10.7, 20.2)	11	171	(104, 280)	11.64	(7.96, 17.02)	48.944
T _{max} [‡] (hr)	12	2.50	(2.00, 5.00)	11	3.00	(2.00, 4.00)			
Apparent terminal t _{1/2} [§] (hr)	12	27.67	27.4	11	25.94	29.3			

MK-5172 Alone: Multiple oral doses of 200 mg MK-5172 q.d. for 7 consecutive days.
ATV/r + MK-5172: Multiple oral doses of 300 mg atazanavir/100 mg ritonavir and 200 mg MK-5172 co-administered q.d. for 7 consecutive days.
¹Pseudo Within-Subject %CV = 100* $\sqrt{(\sigma^2_A + \sigma^2_B - 2*\sigma_{AB})/2}$, where σ^2_A and σ^2_B are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[†]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[‡]Median (min, max) reported for T_{max}.
[§]Geometric mean and percent geometric coefficient of variation (GCV) reported for apparent terminal t_{1/2}.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval
[†]Subject AN 0008 was discontinued by the Investigator on Day 3 of Period 1 due to non-attendance to return visits.
^{††}Subject AN 0001 was discontinued by the Investigator due to an adverse experience on Day 13 of Period 2.

Table 6. Steady-state pharmacokinetics of atazanavir with or without the co-administration of MK-5172 QD for 7 days

Pharmacokinetic Parameter	ATV/r Alone			ATV/r + MK-5172			ATV/r + MK-5172 / ATV/r Alone		Pseudo Within Subject %CV ¹
	N [†]	GM	95% CI	N ^{††}	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [†] (ng•hr/mL)	11	42400	(32300, 55600)	11	60600	(45800, 80300)	1.43	(1.30, 1.57)	12.045
C _{max} [†] (ng/mL)	11	4560	(3650, 5680)	11	5100	(4330, 6000)	1.12	(1.01, 1.24)	13.203
C ₂₄ [†] (ng/mL)	11	798	(544, 1170)	11	983	(670, 1440)	1.23	(1.13, 1.34)	11.253
T _{max} [‡] (hr)	11	4.00	(2.00, 5.00)	11	3.00	(3.00, 4.02)			

ATV/r Alone: Multiple oral doses of 300 mg atazanavir and 100 mg ritonavir q.d. for 14 consecutive days.
ATV/r + MK-5172: Multiple oral doses of 300 mg atazanavir/100 mg ritonavir and 200 mg MK-5172 co-administered q.d. for 7 consecutive days.
¹Pseudo Within-Subject %CV = 100* $\sqrt{(\sigma^2_A + \sigma^2_B - 2*\sigma_{AB})/2}$, where σ^2_A and σ^2_B are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[†]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[‡]Median (min, max) reported for T_{max}.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval
[†]Subject AN 0008 was discontinued by the Investigator on Day 3 of Period 1 due to non-attendance to return visits.
^{††}Subject AN 0001 was discontinued by the Investigator due to an adverse experience on Day 13 of Period 2.

Part 2 (drug interactions between MK-5172 and LPV/r)

MK-5172 exposures were markedly increased by the co-administration of LPV/r; AUC_{24hr}, C_{max}, and C_{24hr} of MK-5172 were increased by 12.8-fold, 7.3-fold, and 21.7-fold, respectively by the co-administration of LPV/r 400 mg/100 mg twice daily for 7 days. LPV exposures were not altered by the co-administration of MK-5172 (Table 8).

Table 7. Steady-state pharmacokinetics of MK-5172 with or without the co-administration of lopinavir/ritonavir 400 mg/100 mg BID for 7 days

MK-5172 Pharmacokinetic Parameter	MK-5172 Alone			LPV/r + MK-5172			LPV/r + MK-5172/ MK-5172 Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [†] (μM·hr)	13	3.63	(2.37, 5.56)	13	46.7	(30.1, 72.5)	12.86	(10.25, 16.13)	32.424
C _{max} [†] (μM)	13	0.954	(0.568, 1.60)	13	6.97	(5.30, 9.16)	7.31	(5.65, 9.45)	36.796
C ₂₄ [†] (nM)	13	15.1	(11.7, 19.5)	13	327	(149, 721)	21.70	(12.99, 36.25)	73.378
T _{max} [‡] (hr)	13	3.00	(1.00, 6.03)	13	3.02	(2.00, 6.01)			.
Apparent terminal t _{1/2} [§] (hr)	13	35.03	26.4	13	24.63	19.9			.

MK-5172 Alone: Multiple oral doses of 200 mg MK-5172 q.d. for 7 consecutive days.
 LPV/r + MK-5172: Multiple oral doses of 400/100 mg lopinavir/ritonavir b.i.d. co-administered with multiple oral doses of 200 mg of MK-5172 q.d. for 7 consecutive days.
[†]Pseudo Within-Subject %CV = 100* $\sqrt{(\sigma^2_A + \sigma^2_B - 2*\sigma_{AB})/2}$, where σ^2_A and σ^2_B are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max}.
[§]Geometric mean and percent geometric coefficient of variation (GCV) reported for apparent terminal t_{1/2}.
 GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval

Table 8. Steady-state pharmacokinetics of lopinavir with or without the co-administration of MK-5172 QD for 7 days

Pharmacokinetic Parameter	LPV/r Alone			LPV/r + MK-5172			LPV/r + MK-5172 /LPV/r Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₁₂ [†] (ng·hr/mL)	13	103000	(81600, 131000)	13	107000	(93800, 121000)	1.03	(0.92, 1.16)	16.401
C _{max} [†] (ng/mL)	13	12600	(10500, 15100)	13	12300	(11200, 13400)	0.97	(0.88, 1.08)	14.608
C ₁₂ [†] (ng/mL)	13	5220	(3520, 7740)	13	5040	(3680, 6910)	0.97	(0.81, 1.15)	25.211
T _{max} [‡] (hr)	13	4.00	(2.00, 5.05)	13	4.01	(2.00, 10.03)			.
Apparent terminal t _{1/2} [§] (hr)	13	7.61	117.1	13	7.12	85.3			.

LPV/r Alone: Multiple oral doses of 400/100 mg lopinavir/ritonavir b.i.d. for 14 consecutive days.
 LPV/r + MK-5172: Multiple oral doses of 400/100 mg lopinavir/ritonavir b.i.d. co-administered with multiple oral doses of 200 mg of MK-5172 q.d. for 7 consecutive days.
[†]Pseudo Within-Subject %CV = 100* $\sqrt{(\sigma^2_A + \sigma^2_B - 2*\sigma_{AB})/2}$, where σ^2_A and σ^2_B are the estimated variances on the log scale for the 2 treatment, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max}.
[§]Geometric mean and percent geometric coefficient of variation (GCV) reported for apparent terminal t_{1/2}.
 GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval

Part 3 (drug interactions between MK-5172 and DRV/r)

MK-5172 exposures were markedly increased by the co-administration of DRV/r; AUC_{24hr}, C_{max}, and C_{24hr} of MK-5172 were increased by 7.5-fold, 5.3-fold, and 8.5-fold, respectively by the co-administration of DRV/r 600 mg/100 mg twice daily for 7 days (Table 9). DRV exposures were not altered by the co-administration of MK-5172 (Table 10).

Table 9. Steady-state pharmacokinetics of MK-5172 with or without the co-administration of atazanavir/ritonavir 600 mg/100 mg BID for 7 days

MK-5172 Pharmacokinetic Parameter	MK-5172 Alone			DRV/r + MK-5172			DRV/r + MK-5172 / MK-5172 Alone		Pseudo Within Subject %CV ²
	N	GM	95% CI	N ^{††}	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [†] (μM•hr)	13	3.31	(2.25, 4.86)	11	24.8	(18.7, 32.9)	7.50	(5.92, 9.51)	32.176
C _{max} [†] (μM)	13	0.824	(0.502, 1.35)	11	4.34	(3.27, 5.75)	5.27	(4.04, 6.86)	36.854
C ₂₄ [†] (nM)	13	15.7	(12.2, 20.1)	11	126	(91.0, 175)	8.05	(6.33, 10.24)	30.933
T _{max} [‡] (hr)	13	3.02	(1.00, 5.03)	11	4.00	(2.00, 5.03)			
Apparent terminal t _½ [§] (hr)	13	29.33	30.4	11	25.61	22.1			

MK-5172 Alone: Multiple oral doses of 200 mg MK-5172 q.d. for 7 consecutive days.
DRV/r + MK-5172: Multiple oral doses of 600/100 mg darunavir/ritonavir b.i.d. co-administered with multiple oral doses of 200 mg of MK-5172 q.d. for 7 consecutive days.
²Pseudo Within-Subject %CV = 100* $\sqrt{(\sigma^2_A + \sigma^2_B - 2*\sigma_{AB})/2}$, where σ^2_A and σ^2_B are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[†]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[‡]Median (min, max) reported for T_{max}.
[§]Geometric mean and percent geometric coefficient of variation (GCV) reported for apparent terminal t_½.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval
[†]Subject AN 0041 was discontinued by the Investigator due to a positive drug screen on Day 6 of Period 3.
^{††}Subject AN 0044 was discontinued by the Investigator due to a laboratory adverse experience on Day 1 of Period 2.

Table 10. Steady-state pharmacokinetics of Darunavir with or without the co-administration of MK-5172 for 7 days

Pharmacokinetic Parameter	DRV/r Alone			DRV/r + MK-5172			DRV/r + MK-5172 / DRV/r Alone		Pseudo Within Subject %CV ²
	N ^{††}	GM	95% CI	N [†]	GM	95% CI	GMR	90% CI	
AUC ₀₋₁₂ [†] (ng•hr/mL)	12	68900	(59700, 79500)	11	76400	(67700, 86300)	1.11	(0.99, 1.24)	15.023
C _{max} [†] (ng/mL)	12	8660	(7790, 9610)	11	9480	(8430, 10700)	1.10	(0.96, 1.25)	17.055
C ₁₂ [†] (ng/mL)	12	3680	(2950, 4600)	11	3690	(2980, 4580)	1.00	(0.85, 1.18)	21.468
T _{max} [‡] (hr)	12	4.02	(2.02, 5.00)	11	3.01	(1.99, 6.00)			
Apparent terminal t _½ [§] (hr)	12	7.05	27.4	11	5.66	17.7			

DRV/r Alone: Multiple oral doses of 600 mg darunavir and 100 mg ritonavir b.i.d. for 14 consecutive days.
DRV/r + MK-5172: Multiple oral doses of 600 mg darunavir/100 mg ritonavir b.i.d. and 200 mg MK-5172 co-administered q.d. for 7 consecutive days.
²Pseudo Within-Subject %CV = 100* $\sqrt{(\sigma^2_A + \sigma^2_B - 2*\sigma_{AB})/2}$, where σ^2_A and σ^2_B are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[†]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[‡]Median (min, max) reported for T_{max}.
[§]Geometric mean and percent geometric coefficient of variation (GCV) reported for apparent terminal t_½.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval
[†]Subject AN 0041 was discontinued by the Investigator due to a positive drug screen on Day 6 of Period 3
^{††}Subject AN 0044 was discontinued by the Investigator due to a laboratory adverse experience on Day 1 of Period 2.

Reviewer comments

Significant increases in MK-5172 exposures by ATV/r, LPV/r, and DRV/r are likely due to the inhibition of OATP1B. When MK-5172 was co-administered with ritonavir 100 mg BID (without protease inhibitors), MK-5172 AUC was increased by ~ 2-fold (Study PN006). Therefore, the increases in MK-5172 exposures are mainly driven by individual protease inhibitors, not by ritonavir. The co-

administration with OATP1B inhibitors and MK-5172 should be contraindicated as the significant increases in MK-5172 exposures may increase the risk of late AST/ALT elevations.

Conclusion

- MK-5172 exposures were markedly increased by the co-administration of ATV/r, LPV/r, or DRV/r. The co-administration with MK-5172 and these HIV protease inhibitors should be contraindicated
- ATV AUC_{24hr} was increased by 43% by the co-administration of MK-5172. LPV and DRV exposures were not altered by the co-administration of MK-5172.

5172-030

1. Title

A Study to Evaluate the Effect of Grazoprevir on the Pharmacokinetics of Methadone and Buprenorphine/Naloxone

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted from October 1, 2012 (trial initiation) to December 27, 2012 (trial completion).

3. Objectives

The objectives of the trial included evaluating the effect of multiple dosing of grazoprevir on the exposure of methadone or buprenorphine.

4. Trial Design

030 was a clinical trial that enrolled subjects 18 to 55 years old that were receiving a stable regimen of methadone or buprenorphine/naloxone. The trial was divided into two panels. As designed, in panel A, methadone dosage regimens ranging from 20 mg to 150 mg once daily were administered on day 1 and on days 2 to 11, grazoprevir 200 mg once daily were administered with 20 mg to 150 mg once daily of methadone and in panel B, buprenorphine/naloxone dosage regimens ranging from 8 mg/2 mg to 24 mg/6 mg once daily were administered on day 1 and on days 2 to 11, grazoprevir 200 mg once daily was administered with buprenorphine/naloxone dosage regimens ranging from 8 mg/2 mg to 24 mg/6 mg once daily.

5. Excluded Medications, Restrictions or Exceptions

Specific medications were not permitted during the trial, including certain CYP3A inhibitors and inducers, and certain CYP3A substrates. Oral contraceptives were also not permitted.

6. Dosage and Administration

The trial medications were administered under fasted conditions. This is consistent with the proposed U.S. prescribing information (USPI) recommendation for grazoprevir in combination with elbasvir (with or without food). Both the methadone USPI and the buprenorphine/naloxone USPI do not include specific dosing recommendations with regards to food or meals.

7. Rationale for Doses Used in the Trial

The dosing regimen of 200 mg once daily is higher than the recommended dosage regimen in the proposed U.S. prescribing information for elbasvir and grazoprevir (100 mg with 50 mg of elbasvir once daily). Based on the information provided by the applicant, greater than dose proportional changes in exposure and time dependent pharmacokinetics were observed with grazoprevir. According to the applicant, the rationale for dosing 200 mg once daily is that grazoprevir steady state exposure is approximately twice as high in hepatitis C infected subjects when compared to healthy subjects. For opioid dependence detoxification, the methadone USPI states that typical stable doses occur between 80 mg to 120 mg/day. The doses of buprenorphine/naloxone are consistent with the recommendations in the

buprenorphine/naloxone USPL.

8. Drugs Used in the Trial

The medications administered in trial 030 are displayed in Table 1.

Table 1-Medications administered in trial 030

Bulk Product Description	Manufacturing Lot Number
Grazoprevir 100 mg Oral (b) (4) Tablet	WL00044049
Methadone 20 – 150 mg Liquid or Tablet [†]	N/A
Buprenorphine/naloxone 8/2 – 24/6 mg Sublingual disc or film [‡]	N/A

[†]Methadone (lot number 0527U83120; expiration date Mar-2016; Mallinckrodt) was supplied by the Investigator.

[‡]Suboxone (Buprenorphine/Naloxone) (lot number g12GW104; expiration date Dec-2013 and lot number C12GW109; expiration date Aug-2013; Reckitt Benckiser) was supplied by the Investigator.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included methadone, buprenorphine, and naloxone predose and postdose blood samples up to 24 hours on day 1 and day 11 and grazoprevir blood samples at predose and up to 72 hours postdose on day 11 for both panels.

Bioanalysis

The method and bioanalysis of buprenorphine are acceptable.

Buprenorphine plasma samples were analyzed using a validated LC/MS/MS method in K₃EDTA anticoagulated plasma by (b) (4) (a combined method was used to analyze buprenorphine, norbuprenorphine and naloxone). The blood samples for analysis of buprenorphine appear to have been collected in tubes containing K₃EDTA as an anticoagulant.

For the plasma samples from the P30 trial that were analyzed for buprenorphine, the lower limit of quantification for buprenorphine was 20 pg/mL and the upper limit of quantification was 10000 pg/mL. There were no precision or accuracy issues identified for buprenorphine based on the bioanalytical report. For the P30 trial, precision and accuracy were evaluated using plasma buprenorphine quality control (QC) samples at 50 pg/mL, 120 pg/mL, 450 pg/mL, 1600 pg/mL and 7500 pg/mL. The corresponding buprenorphine inter-run accuracy values were -4.35% for 50 pg/mL, -6.17% for 120 pg/mL, -4.35% for 450 pg/mL, -2.33% for 1600 pg/mL and -4.78% for 7500 pg/mL. The buprenorphine inter-run precision values were 1.84% for 50 pg/mL, 1.98% for 120 pg/mL, 2% for 450 pg/mL, 1.42% for 1600 pg/mL and 2.18% for 7500 pg/mL.

The P30 bioanalytical report for buprenorphine, norbuprenorphine and naloxone does not provide information regarding whether incurred sample reanalysis for buprenorphine was conducted for the P30 trial.

For the P30 trial, the bioanalytical report states that the maximum length of storage for the buprenorphine samples was 126 days at -20°C. Specific information regarding whether current reference standards were used as part of the stability evaluations was not provided by (b) (4). For the P30 trial, the long term buprenorphine stability data of 200 days at -20°C and -70°C in K₃EDTA anticoagulated plasma generated by (b) (4) appears sufficient based on the information provided in the submission (the bioanalytical report states that the date of last analysis for buprenorphine, norbuprenorphine and naloxone samples was February 20, 2013).

Bioanalytical information for norbuprenorphine or naloxone is not provided in this review because the applicant is not proposing to include exposure information for either analyte in the proposed USPI for elbasvir and grazoprevir.

The method and bioanalysis of methadone are acceptable.

Methadone plasma samples were analyzed using a validated LC/MS/MS method in K₃EDTA anticoagulated plasma by (b) (4). The method was validated to measure the R and S enantiomers of methadone, not total methadone. The blood samples for analysis of methadone appear to have been collected in tubes containing K₃EDTA as an anticoagulant.

For the plasma samples from the P30 trial that were analyzed for methadone, the lower limit of quantification for R-methadone and S-methadone was 5 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for methadone based on the bioanalytical report. For the P30 trial, precision and accuracy for R methadone and S methadone were evaluated using plasma methadone quality control (QC) samples at 10 ng/mL, 25 ng/mL, 70 ng/mL, 200 ng/mL and 750 ng/mL. For R-methadone, the corresponding methadone inter-run accuracy values were -2.59% for 10 ng/mL, -0.826% for 25 ng/mL, -0.639% for 70 ng/mL, -0.364% for 200 ng/mL and -0.875% for 750 ng/mL. The corresponding methadone inter-run precision values were 3.22% for 10 ng/mL, 5.27% for 25 ng/mL, 4.13% for 70 ng/mL, 2.71% for 200 ng/mL and 2.17% for 750 ng/mL. For S-methadone, the corresponding methadone inter-run accuracy values were 1.61% for 10 ng/mL, 0.398% for 25 ng/mL, -3.54% for 70 ng/mL, -0.4% for 200 ng/mL and -1.46% for 750 ng/mL. The corresponding methadone inter-run precision values were 5.14% for 10 ng/mL, 2.11% for 25 ng/mL, 6.61% for 70 ng/mL, 2.69% for 200 ng/mL and 3.43% for 750 ng/mL.

Incurred sample reanalysis for methadone was not conducted for the P30 trial.

For the P30 trial, the bioanalytical report states that the maximum length of storage for the methadone samples was 144 days at -20°C that includes 73 days of -70°C storage. Specific information regarding whether current reference standards were used as part of the stability evaluations was not provided by (b) (4). For the P30 trial, the long term R-methadone and S-methadone stability data of 280 days at -70°C and 365 days at -20°C in K₃EDTA anticoagulated plasma generated by (b) (4) appears sufficient based on the information provided in the submission (the bioanalytical report states that the date of last analysis was March 23, 2013).

The bioanalysis of grazoprevir was acceptable.

Grazoprevir plasma samples were analyzed using a LC/MS/MS method in K₂EDTA anticoagulated plasma by (b) (4) (556 V1.01). The method validation information, including the long term stability data,

for grazoprevir was not reviewed because the method is being used for multiple trials. The blood samples for analysis of grazoprevir appear to have been collected in tubes containing K₂EDTA as an anticoagulant.

For the plasma samples from the P30 trial that were analyzed for grazoprevir, the lower limit of quantification for grazoprevir was 1 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for grazoprevir based on the bioanalytical report. For the P30 trial, precision and accuracy were evaluated using plasma grazoprevir quality control (QC) samples at 3 ng/mL, 75 ng/mL and 750 ng/mL. The corresponding grazoprevir inter-run accuracy values were -6.19% for 3 ng/mL, -7.03% for 75 ng/mL and -7.55% for 750 ng/mL. The grazoprevir inter-run precision values were 3.32% for 3 ng/mL, 2.02% for 75 ng/mL and 2.41% for 750 ng/mL.

Incurred sample reanalysis for grazoprevir was not conducted for the P30 trial.

For the P30 trial, the bioanalytical report states that the maximum length of storage for the grazoprevir samples was 105 days (including 36 days of -70°C storage for the first shipped samples). For the P30 trial, the bioanalytical report states that for grazoprevir, long term stability data for 397 days at -20°C (provided by the applicant) and 69 days at -70°C (generated by (b) (4)) are available. The long term stability data appears sufficient if the grazoprevir long term stability data used to support the analysis of the P30 trial samples is acceptable (the bioanalytical report states that the date of last analysis was January 29, 2013) and grazoprevir plasma samples were stored at -20°C or at -70°C.

Pharmacokinetic Assessments

Based on the information included in the trial report, noncompartmental analysis was performed using actual sampling times to derive buprenorphine, norbuprenorphine, naloxone, R-methadone, S-methadone, and grazoprevir plasma pharmacokinetic parameters. The trial report states that the 24 hour samples for methadone, buprenorphine, norbuprenorphine, and naloxone were collected prior to the 24 hour time point and the AUC_{0-last} was substituted for the AUC_(0-24 hours) and reported as AUC_(0-24 hours). Total methadone concentrations were derived based on adding together the R and S methadone plasma concentrations. Dose normalized pharmacokinetic parameters were derived by dividing by the subject's dose for R-methadone, S-methadone, total methadone buprenorphine, and norbuprenorphine, and naloxone (for R and S methadone the doses were half of the total methadone dose).

Statistical Analysis

The statistical analyses included deriving 90% confidence intervals for the following comparisons: a) methadone (R, S, and total methadone): concomitant use of methadone and grazoprevir (test arm) to the reference arm (methadone alone), and b) buprenorphine, norbuprenorphine or naloxone: concomitant use of buprenorphine/naloxone and grazoprevir (test arm) to the reference arm (buprenorphine/naloxone alone).

Additionally, with concomitant use of either methadone or buprenorphine/naloxone, statistical analyses were conducted for grazoprevir by comparing to historical data (MK-5172 P001: Part 2- 200 mg multiple dosing).

10. Results

10.1 Subject Demographics

Table 2-P30 subject demographics

	Panel A		Panel B	
	n	(%)	n	(%)
Subjects in population	12		12	
Gender				
Male	9	(75.0)	9	(75.0)
Female	3	(25.0)	3	(25.0)
Age (Years)				
0 to 17	0	(0.0)	0	(0.0)
18 to 55	12	(100.0)	12	(100.0)
>55	0	(0.0)	0	(0.0)
Mean	32.8		29.6	
SD	10.4		6.7	
Median	30.0		29.0	
Range	21 to 53		22 to 47	
Race				
Native Hawaiian Or Other Pacific Islander	1	(8.3)	0	(0.0)
White	11	(91.7)	12	(100.0)
Ethnicity				
Hispanic Or Latino	2	(16.7)	2	(16.7)
Not Hispanic Or Latino	10	(83.3)	10	(83.3)
Panel A: Subjects in Panel A (AN 000001 - 000012) received a single daily dose of methadone 20 - 150 mg QD on Days 1 through 11 and a single daily dose of MK-5172 200 mg on Days 2 through 11.				
Panel B: Subjects in Panel B (AN 000020 - 000031) received a single daily dose of buprenorphine/naloxone 8/2 - 24/6 mg QD on Days 1 through 11 and a single daily dose MK-5172 200 mg on Days 2 through 11.				

10.2 Concomitant Medications

The concomitant medications that were administered in the trial included acetaminophen. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

10.3 Dosage regimens of methadone or buprenorphine/naloxone administered in the trial

Table 3-Methadone dosage regimens

Methadone Hydrochloride	14 Days	Total Subjects	Duration Range	Mean Duration
Any Dose	12	12	14 to 14 days	14.0 days
25 mg	1	1	14 to 14 days	14.0 days
70 mg	1	1	14 to 14 days	14.0 days
85 mg	1	1	14 to 14 days	14.0 days
94 mg	1	1	14 to 14 days	14.0 days
98 mg	1	1	14 to 14 days	14.0 days
100 mg	1	1	14 to 14 days	14.0 days
110 mg	1	1	14 to 14 days	14.0 days
120 mg	3	3	14 to 14 days	14.0 days
127 mg	1	1	14 to 14 days	14.0 days
150 mg	1	1	14 to 14 days	14.0 days

Each subject who received Methadone hydrochloride is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to Methadone hydrochloride.

Each subject is counted again on 1 or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.

Table 4-Buprenorphine/naloxone dosage regimens

Buprenorphine 8 mg/Naloxone 2 mg	14 Days	Total Subjects	Duration Range	Mean Duration
Any Dose	12	12	14 to 14 days	14.0 days
1 count	6	6	14 to 14 days	14.0 days
1.5 count	1	1	14 to 14 days	14.0 days
2 count	3	3	14 to 14 days	14.0 days
3 count	2	2	14 to 14 days	14.0 days

Each subject who received Buprenorphine 8 mg/Naloxone 2 mg is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to Buprenorphine 8 mg/Naloxone 2 mg.

Each subject is counted again on 1 or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.

Note: 1 count = 1 sublingual film

10.4 Pharmacokinetic and Statistical Analysis

A) Methadone

Table 5A R-methadone pharmacokinetic parameters

	R-Methadone Pharmacokinetic Parameters												
	AUC ₀₋₂₄ /D (ng•hr/mL/mg)			C _{max} /D (ng/mL/mg)			C ₂₄ /D (ng/mL/mg)			T _{max} (hr)		Apparent Terminal t _{1/2} [†] (hr)	
	Methadone Alone	Methadone + Grazoprevir	Methadone + Grazoprevir /Methadone Alone	Methadone Alone	Methadone + Grazoprevir	Methadone + Grazoprevir /Methadone Alone	Methadone Alone	Methadone + Grazoprevir	Methadone + Grazoprevir /Methadone Alone	Methadone Alone	Methadone + Grazoprevir	Methadone Alone	Methadone + Grazoprevir
N	12	12	12	12	12	12	12	12	12	12	12	9	11
AM	91.8	101	1.10	5.90	6.14	1.04	3.28	3.38	1.06	2.63	2.42	28.86	31.49
SD	19.5	24.6	0.15	1.19	1.55	0.16	0.87	0.91	0.25	1.03	0.77	10.36	12.18
ACV	21.2	24.4	13.5	20.2	25.3	15.1	26.7	27.0	23.5	39.1	31.7	35.9	38.7
Med	89.0	93.8	1.07	5.59	5.50	1.00	3.05	3.23	1.07	2.50	2.00	24.74	27.63
Min	56.6	72.9	0.86	4.04	4.43	0.85	1.72	2.27	0.47	1.00	1.50	19.43	22.11
Max	127	158	1.31	7.88	9.00	1.39	4.84	5.10	1.45	4.02	4.00	51.10	63.76
GM	89.9	98.2	1.09	5.79	5.98	1.03	3.17	3.27	1.03	2.43	2.31	27.46	29.90
GCV	21.7	23.2	13.6	20.3	24.4	14.6	28.3	26.9	29.3	45.3	31.8	33.2	32.4

Methadone Alone: 20 – 150 mg methadone on Day 1
Methadone + Grazoprevir: Co-administration of 20 – 150 mg methadone QD with 200 mg grazoprevir QD on Days 2 to 11
[†]No apparent terminal t_{1/2} could be calculated for Subjects AN 0001, AN 0006, and AN 0008 following administration of methadone alone and for Subject AN 0008 following co-administration of methadone and grazoprevir, due to the lack of data in the terminal phase.
AM = Arithmetic mean; D = Dose normalized; SD = Standard deviation; GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum;
ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: 100 x (SD/AM); GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s²) - 1), where s² is the observed variance on the natural log-scale.

Table 5B S-methadone pharmacokinetic parameters

	S-Methadone Pharmacokinetic Parameters												
	AUC ₀₋₂₄ /D (ng•hr/mL/mg)			C _{max} /D (ng/mL/mg)			C ₂₄ /D (ng/mL/mg)			T _{max} (hr)		Apparent Terminal t _{1/2} [†] (hr)	
	Methadone Alone	Methadone + Grazoprevir	Methadone + Grazoprevir /Methadone Alone	Methadone Alone	Methadone + Grazoprevir	Methadone + Grazoprevir /Methadone Alone	Methadone Alone	Methadone + Grazoprevir	Methadone + Grazoprevir /Methadone Alone	Methadone Alone	Methadone + Grazoprevir	Methadone Alone	Methadone + Grazoprevir
N	12	12	12	12	12	12	12	12	12	12	12	10	12
AM	95.2	117	1.25	7.04	8.17	1.17	3.01	3.56	1.26	3.45	1.77	26.86	20.12
SD	37.7	45.7	0.22	2.48	3.03	0.19	1.45	1.62	0.34	4.03	0.52	16.83	3.64
ACV	39.6	39.2	17.3	35.2	37.1	15.9	48.2	45.4	27.2	116.6	29.5	62.7	18.1
Med	92.9	95.5	1.25	6.25	6.76	1.14	2.85	2.87	1.26	2.50	1.75	18.07	19.17
Min	50.7	69.6	0.79	4.33	5.15	0.92	1.27	1.75	0.46	1.00	1.00	12.94	15.01
Max	171	214	1.64	10.8	13.3	1.62	5.90	6.69	1.96	15.93	3.00	58.06	26.76
GM	88.5	109	1.23	6.67	7.69	1.15	2.69	3.24	1.20	2.53	1.70	22.97	19.82
GCV	41.6	38.7	18.5	35.2	37.2	15.1	53.8	47.6	35.2	80.6	29.5	62.1	18.1

Methadone Alone: 20 – 150 mg methadone on Day 1
Methadone + Grazoprevir: Co-administration of 20 – 150 mg methadone QD with 200 mg grazoprevir QD on Days 2 to 11
[†]No apparent terminal t_{1/2} could be calculated for Subjects AN 0006 and AN 0008 following administration of methadone alone due to the lack of data in the terminal phase.
AM = Arithmetic mean; D = Dose normalized; SD = Standard deviation; GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum;
ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: 100 x (SD/AM); GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s²) - 1), where s² is the observed variance on the natural log-scale.

Table 5C Total methadone pharmacokinetic parameters

	Total Methadone Pharmacokinetic Parameters												
	AUC ₀₋₂₄ /D (ng•hr/mL/mg)			C _{max} /D (ng/mL/mg)			C ₂₄ /D (ng/mL/mg)			T _{max} (hr)		Apparent Terminal t _{1/2} [†] (hr)	
	Methadone Alone	Methadone + Grazoprevir	Methadone + Grazoprevir /Methadone Alone	Methadone Alone	Methadone + Grazoprevir	Methadone + Grazoprevir /Methadone Alone	Methadone Alone	Methadone + Grazoprevir	Methadone + Grazoprevir /Methadone Alone	Methadone Alone	Methadone + Grazoprevir	Methadone Alone	Methadone + Grazoprevir
N	12	12	12	12	12	12	12	12	12	12	12	10	11
AM	93.5	109	1.17	6.43	7.11	1.11	3.15	3.47	1.15	2.54	2.02	25.51	29.00
SD	27.4	34.0	0.17	1.79	2.24	0.16	1.11	1.21	0.28	1.01	0.69	11.43	18.96
ACV	29.3	31.3	14.4	27.9	31.5	14.3	35.3	34.9	24.2	39.8	34.1	44.8	65.4
Med	89.7	93.4	1.16	5.88	5.94	1.06	3.10	2.93	1.12	3.00	2.00	19.65	21.34
Min	54.1	77.3	0.82	4.26	4.89	0.95	1.50	2.11	0.46	1.00	1.00	16.09	19.54
Max	149	186	1.46	9.10	11.1	1.49	5.29	5.90	1.61	4.00	3.03	47.58	84.66
GM	89.9	104	1.16	6.21	6.81	1.10	2.97	3.29	1.11	2.34	1.91	23.63	25.97
GCV	30.0	29.7	15.1	27.7	30.7	13.4	37.7	34.8	31.4	47.4	36.6	41.2	44.8

Methadone Alone: 20 – 150 mg methadone on Day 1
Methadone + Grazoprevir: Co-administration of 20 – 150 mg methadone QD with 200 mg grazoprevir QD on Days 2 to 11.
[†]No apparent terminal t_{1/2} could be calculated for Subjects AN 0006 and AN 0008 following administration of methadone alone and for Subject AN 0008 following co-administration of methadone and grazoprevir, due to the lack of data in the terminal.
AM = Arithmetic mean; D = Dose normalized; SD = Standard deviation; GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum;
ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: 100 x (SD/AM); GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s²) - 1), where s² is the observed variance on the natural log-scale.

Table 6A R-methadone statistical analyses

R-Methadone Pharmacokinetic Parameter	Methadone Alone			Methadone + Grazoprevir			Methadone + Grazoprevir /Methadone Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ /D [‡] (ng•hr/mL/mg)	12	89.9	(78.5, 103)	12	98.2	(84.9, 114)	1.09	(1.02, 1.17)	9.561
C _{max} /D [‡] (ng/mL/mg)	12	5.79	(5.10, 6.58)	12	5.98	(5.13, 6.97)	1.03	(0.96, 1.11)	10.260
T _{max} [§] (hr)	12	2.50	(1.00, 4.02)	12	2.00	(1.50, 4.00)			
Apparent Terminal t _{1/2} (hr)	9	27.46	33.22	11	29.90	32.36			

Methadone Alone: 20 – 150 mg methadone on Day 1
Methadone + Grazoprevir: Co-administration of 20 – 150 mg methadone QD with 200 mg grazoprevir QD on Days 2 to 11
[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
[¶]No apparent terminal t_{1/2} could be calculated for 3 subjects following administration of methadone alone and for 1 subject following co-administration of methadone with grazoprevir, due to the lack of data in the terminal phase.
D = Dose normalized; GM = Geometric mean; CI = Confidence interval; GMR = Geometric mean ratio

Table 6B S-methadone statistical analyses

S-Methadone Pharmacokinetic Parameter	Methadone Alone			Methadone + Grazoprevir			Methadone + Grazoprevir /Methadone Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ /D [‡] (ng•hr/mL/mg)	12	88.5	(68.7, 114)	12	109	(86.0, 138)	1.23	(1.12, 1.35)	12.964
C _{max} /D [‡] (ng/mL/mg)	12	6.67	(5.37, 8.29)	12	7.69	(6.12, 9.67)	1.15	(1.07, 1.25)	10.608
T _{max} [§] (hr)	12	2.50	(1.00, 15.93)	12	1.75	(1.00, 3.00)			
Apparent Terminal t _{1/2} (hr)	10	22.97	62.10	12	19.82	18.11			

Methadone Alone: 20 – 150 mg methadone on Day 1
Methadone + Grazoprevir: Co-administration of 20 – 150 mg methadone QD with 200 mg grazoprevir QD on Days 2 to 11
[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
[¶]No apparent terminal t_{1/2} could be calculated for 2 subjects following administration of methadone alone due to the lack of data in the terminal phase.
D = Dose normalized; GM = Geometric mean; CI = Confidence interval; GMR = Geometric mean ratio

Table 6C-Total methadone statistical analyses

Total Methadone Pharmacokinetic Parameter	Methadone Alone			Methadone + Grazoprevir			Methadone + Grazoprevir/ Methadone Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ /D [‡] (ng•hr/mL/mg)	12	89.9	(74.6, 108)	12	104	(86.7, 125)	1.16	(1.07, 1.25)	10.624
C _{max} /D [‡] (ng/mL/mg)	12	6.21	(5.22, 7.38)	12	6.81	(5.63, 8.25)	1.10	(1.02, 1.18)	9.421
T _{max} [§] (hr)	12	3.00	(1.00, 4.00)	12	2.00	(1.00, 3.03)			
Apparent Terminal t _{1/2} [¶] (hr)	10	23.63	41.20	11	25.97	44.84			

Methadone Alone: 20 – 150 mg methadone on Day 1
Methadone + Grazoprevir: Co-administration of 20 – 150 mg methadone QD with 200 mg grazoprevir QD on Days 2 to 11
[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
[¶]Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
^{¶¶}No apparent terminal t_{1/2} could be calculated for 2 subjects following administration of methadone alone and for 1 subject following co-administration of methadone with grazoprevir, due to the lack of data in the terminal.
D = Dose normalized; GM = Geometric mean; CI = Confidence interval; GMR = Geometric mean ratio

B) Buprenorphine

Table 7-Buprenorphine pharmacokinetic parameters

	Buprenorphine Pharmacokinetic Parameters								
	AUC ₀₋₂₄ /D (pg•hr/mL/mg)			C _{max} /D (pg/mL/mg)			C ₂₄ /D (pg/mL/mg)		
	Buprenorphine/ Naloxone Alone	Buprenorphine/ Naloxone + Grazoprevir	Buprenorphine/ Naloxone + Grazoprevir/ Buprenorphine/ Naloxone Alone	Buprenorphine/ Naloxone Alone	Buprenorphine/ Naloxone + Grazoprevir	Buprenorphine/ Naloxone + Grazoprevir/ Buprenorphine/ Naloxone Alone	Buprenorphine/ Naloxone Alone	Buprenorphine/ Naloxone + Grazoprevir	Buprenorphine/ Naloxone + Grazoprevir/ Buprenorphine/ Naloxone Alone
N	12	12	12	12	12	12	12	12	12
AM	5000	5050	1.05	864	824	0.94	63.6	71.5	1.18
SD	2060	2210	0.39	391	437	0.29	26.0	32.6	0.48
ACV	41.3	43.8	37.3	45.3	53.0	30.7	40.9	45.5	40.9
Med	4370	4750	1.01	784	654	0.92	59.8	59.6	1.04
Min	2540	1760	0.49	486	291	0.45	29.1	22.8	0.61
Max	9870	8780	1.89	1900	1690	1.43	119	124	2.01
GM	4650	4570	0.98	802	722	0.90	58.9	64.4	1.09
GCV	40.3	51.7	38.8	40.0	59.1	34.0	43.3	53.0	42.1

Buprenorphine/naloxone Alone: 8/2 – 24/6 mg buprenorphine/naloxone on Day 1
Buprenorphine/naloxone + Grazoprevir: Co-administration of 8/2 – 24/6 mg buprenorphine/naloxone QD with 200 mg grazoprevir QD on Days 2 to 11
AM = Arithmetic mean; D = Dose normalized; SD = Standard deviation; GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum;
ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: 100 x (SD/AM); GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt((exp(s²) - 1), where s² is the observed variance on the natural log-scale

Table 8-Buprenorphine statistical analysis

Buprenorphine Pharmacokinetic Parameter	Buprenorphine/Naloxone Alone			Buprenorphine/Naloxone + Grazoprevir			Buprenorphine/Naloxone + Grazoprevir/Buprenorphine/Naloxone Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ /D [‡] (pg•hr/mL/mg)	12	4650	(3640, 5950)	12	4570	(3350, 6230)	0.98	(0.81, 1.19)	26.462
C _{max} /D [‡] (pg/mL/mg)	12	802	(628, 1020)	12	722	(509, 1020)	0.90	(0.76, 1.07)	23.389
T _{max} [§] (hr)	12	1.99	(1.00, 3.00)	12	2.01	(1.00, 4.00)			
Apparent Terminal t _{1/2} (hr)	10	10.71	73.09	11	13.43	30.71			

Buprenorphine/Naloxone Alone: 8/2 – 24/6 mg buprenorphine/naloxone on Day 1
 Buprenorphine/Naloxone + Grazoprevir: Co-administration of 8/2 – 24/6 mg buprenorphine/naloxone QD with 200 mg grazoprevir QD on Days 2 to 11

[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.

[¶]No apparent terminal t_{1/2} could be calculated for 2 subjects following administration of buprenorphine/naloxone alone and for 1 subject following co-administration of buprenorphine/naloxone with grazoprevir, due to the lack of data in the terminal phase.

D = Dose normalized; GM = Geometric mean; CI = Confidence interval; GMR = Geometric mean ratio

C) Norbuprenorphine

Table 9-Norbuprenorphine pharmacokinetic parameters

	Norbuprenorphine Pharmacokinetic Parameters								
	AUC ₀₋₂₄ /D (pg•hr/mL/mg)			C _{max} /D (pg/mL/mg)			C ₂₄ /D (pg/mL/mg)		
	Buprenorphine/Naloxone Alone	Buprenorphine/Naloxone + Grazoprevir	Buprenorphine/Naloxone + Grazoprevir/Buprenorphine/Naloxone Alone	Buprenorphine/Naloxone Alone	Buprenorphine/Naloxone + Grazoprevir	Buprenorphine/Naloxone + Grazoprevir/Buprenorphine/Naloxone Alone	Buprenorphine/Naloxone Alone	Buprenorphine/Naloxone + Grazoprevir	Buprenorphine/Naloxone + Grazoprevir/Buprenorphine/Naloxone Alone
N	12	12	12	12	12	12	12	12	12
AM	3940	4520	1.17	258	282	1.13	127	147	1.15
SD	1770	1990	0.33	139	131	0.28	49.2	69.2	0.32
ACV	44.9	44.1	28.0	54.0	46.6	24.7	38.6	46.9	27.9
Med	3860	5370	1.15	216	305	1.08	130	164	1.20
Min	1490	1060	0.70	73.1	63.1	0.74	53.6	39.5	0.54
Max	6580	7680	1.62	481	508	1.65	210	255	1.84
GM	3530	3990	1.13	223	246	1.10	117	129	1.11
GCV	55.0	63.0	30.3	64.6	66.3	24.8	47.6	62.6	32.0

Buprenorphine/naloxone Alone: 8/2 – 24/6 mg buprenorphine/naloxone on Day 1
 Buprenorphine/naloxone + Grazoprevir: Co-administration of 8/2 – 24/6 mg buprenorphine/naloxone QD with 200 mg grazoprevir QD on Days 2 to 11

AM = Arithmetic mean; D = Dose normalized; SD = Standard deviation; GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum;
 ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: 100 x (SD/AM); GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt((exp(s²) - 1), where s² is the observed variance on the natural log-scale

Table 10-Norbuprenorphine statistical analysis

Norbuprenorphine Pharmacokinetic Parameter	Buprenorphine/Naloxone Alone			Buprenorphine/Naloxone + Grazoprevir			Buprenorphine/Naloxone + Grazoprevir/ Buprenorphine/Naloxone Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ /D [‡] (pg•hr/mL/mg)	12	3530	(2550, 4900)	12	3990	(2760, 5760)	1.13	(0.97, 1.32)	20.951
C _{max} /D [‡] (pg/mL/mg)	12	223	(153, 324)	12	246	(167, 360)	1.10	(0.97, 1.25)	17.247
T _{max} [§] (hr)	12	3.00	(1.00, 12.00)	12	3.00	(1.50, 6.00)			
Apparent Terminal t _½ [¶] (hr)	5	16.13	26.12	8	33.87	49.98			

Buprenorphine/Naloxone Alone: 8/2 – 24/6 mg buprenorphine/naloxone on Day 1
 Buprenorphine/Naloxone + Grazoprevir: Co-administration of 8/2 – 24/6 mg buprenorphine/naloxone QD with 200 mg grazoprevir QD on Days 2 to 11

[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

[¶]Geometric mean and geometric coefficient of variation reported for apparent terminal t_½.

[¶]No apparent terminal t_½ could be calculated for 7 subjects following administration of buprenorphine/naloxone alone and for 4 subjects following co-administration of buprenorphine/naloxone with grazoprevir, due to the lack of data in the terminal phase.

D = Dose normalized; GM = Geometric mean; CI = Confidence interval; GMR = Geometric mean ratio

D) Naloxone

Table 11-Naloxone pharmacokinetic parameters

	Naloxone Pharmacokinetic Parameters								
	AUC ₀₋₂₄ /D (pg•hr/mL/mg)			C _{max} /D (pg/mL/mg)			C ₂₄ /D (pg/mL/mg)		
	Buprenorphine/Naloxone Alone	Buprenorphine/Naloxone + Grazoprevir	Buprenorphine/Naloxone + Grazoprevir/Buprenorphine/Naloxone Alone	Buprenorphine/Naloxone Alone	Buprenorphine/Naloxone + Grazoprevir	Buprenorphine/Naloxone + Grazoprevir/Buprenorphine/Naloxone Alone	Buprenorphine/Naloxone Alone	Buprenorphine/Naloxone + Grazoprevir	Buprenorphine/Naloxone + Grazoprevir/Buprenorphine/Naloxone Alone
N	12	12	12	12	12	12	12	12	6
AM	394	453	1.30	164	165	1.11	0.58	0.64	0.82
SD	201	226	0.97	82.7	72.8	0.56	0.76	0.58	0.66
ACV	51.0	49.9	74.2	50.6	44.0	50.4	130.	90.7	80.7
Med	349	465	0.89	132	148	0.98	0.28	0.57	0.86
Min	164	92.2	0.56	92.5	62.0	0.57	0.00	0.00	0.00
Max	813	779	3.99	364	262	2.37	2.10	1.75	1.89
GM	352	387	1.10	149	149	1.00	.	.	0.83
GCV	52.7	72.5	60.7	45.0	51.8	47.2	.	.	80.0

Buprenorphine/naloxone Alone: 8/2 – 24/6 mg buprenorphine/naloxone on Day 1
 Buprenorphine/naloxone + Grazoprevir: Co-administration of 8/2 – 24/6 mg buprenorphine/naloxone QD with 200 mg grazoprevir QD on Days 2 to 11

. = Missing or Not reportable

AN = Allocation Number; AM = Arithmetic mean; D = Dose normalized; SD = Standard deviation; GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum;
 ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: 100 x (SD/AM); GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt((exp(s²) - 1), where s² is the observed variance on the natural log-scale

Table 12-Naloxone statistical analysis

Naloxone Pharmacokinetic Parameter	Buprenorphine/Naloxone Alone			Buprenorphine/Naloxone + Grazoprevir			Buprenorphine/Naloxone + Grazoprevir/ Buprenorphine/Naloxone Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ /D [‡] (pg•hr/mL/mg)	12	352	(257, 482)	12	387	(256, 584)	1.10	(0.82, 1.47)	39.597
C _{max} /D [‡] (pg/mL/mg)	12	149	(113, 196)	12	149	(110, 204)	1.00	(0.80, 1.27)	31.697
T _{max} [§] (hr)	12	0.75	(0.50, 3.00)	12	1.24	(0.50, 2.02)			
Apparent Terminal t _½ (hr)	10	3.33	92.14	12	5.20	107.25			

Buprenorphine/Naloxone Alone: 8/2 – 24/6 mg buprenorphine/naloxone on Day 1
 Buprenorphine/Naloxone + Grazoprevir: Co-administration of 8/2 – 24/6 mg buprenorphine/naloxone QD with 200 mg grazoprevir QD on Days 2 to 11

[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_½.

^{||}No apparent terminal t_½ could be calculated for 2 subjects following administration of buprenorphine/naloxone alone due to the lack of data in the terminal phase.

D = Dose normalized; GM = Geometric mean; CI = Confidence interval; GMR = Geometric mean ratio

E) Grazoprevir

Table 13-Grazoprevir pharmacokinetic parameters with concomitant use of methadone

		Grazoprevir Pharmacokinetic Parameters						
		AUC _{0-∞} (μM•hr)	AUC _{0-last} (μM•hr)	AUC ₀₋₂₄ (μM•hr)	C _{max} (μM)	C ₂₄ (nM)	T _{max} (hr)	Apparent Terminal t _½ (hr)
Methadone + Grazoprevir	N	12	12	12	12	12	12	12
	AM	3.48	3.34	3.00	0.704	14.8	3.34	24.26
	SD	2.10	2.04	1.94	0.655	5.07	1.66	5.12
	ACV	60.4	61.1	64.7	93.0	34.3	49.6	21.1
	Med	3.13	2.98	2.56	0.461	15.8	3.50	24.23
	Min	0.970	0.921	0.835	0.129	6.81	1.00	15.68
	Max	7.58	7.31	6.69	2.14	26.2	6.00	34.04
	GM	2.89	2.76	2.41	0.476	13.9	2.90	23.76
	GCV	73.7	75.6	81.8	118.3	37.1	64.7	22.0

Methadone + Grazoprevir: Co-administration of 20 – 150 mg methadone QD with 200 mg grazoprevir QD on Days 2 to 11

AM = Arithmetic mean; SD = Standard deviation; GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: 100 x (SD/AM); GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s²) - 1), where s² is the observed variance on the natural log-scale.

Table 14-Grazoprevir statistical analysis with concomitant use of methadone

Grazoprevir Pharmacokinetic Parameter	Grazoprevir Alone			Methadone + Grazoprevir			Methadone + Grazoprevir/Grazoprevir Alone		rMSE [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µM•hr)	6	2.27	(1.20, 4.29)	12	2.33	(1.50, 3.63)	1.03	(0.53, 1.97)	0.706
C _{max} [‡] (µM)	6	0.516	(0.216, 1.23)	12	0.454	(0.248, 0.831)	0.88	(0.36, 2.14)	0.964
C ₂₄ [‡] (nM)	6	17.8	(13.2, 23.9)	12	13.6	(11.1, 16.7)	0.77	(0.56, 1.04)	0.331
T _{max} [§] (hr)	6	4.00	(2.00, 4.00)	12	3.50	(1.00, 6.00)			.
Apparent Terminal t _{1/2} (hr)	6	20.86	20.17	12	23.76	21.99			.

Grazoprevir Alone: 200 mg grazoprevir QD administered Days 1 and 3 to 10, with 100 mg grazoprevir administered on Day 2 (historical data from MK-5172 P001)

Methadone + Grazoprevir: Co-administration of 20 – 150 mg methadone QD with 200 mg grazoprevir QD on Days 2 to 11

[†]rMSE - Square root of conditional mean squared error (residual error) from the linear model.

rMSE*100% approximates the between-subject %CV on the raw scale.

[‡]Back-transformed least squares mean and confidence interval from the linear model performed on natural log-transformed values, with treatment as fixed effect and age as a covariate.

[§]Median (Minimum, Maximum) reported for T_{max}.

^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.

GM = Geometric mean; CI = Confidence interval; GMR = Geometric mean ratio

Table 15-Grazoprevir pharmacokinetic parameters with concomitant use of buprenorphine/naloxone

		Grazoprevir Pharmacokinetic Parameters						
		AUC _{0-∞} (µM•hr)	AUC _{0-4hr}} (µM•hr)	AUC ₀₋₂₄ (µM•hr)	C _{max} (µM)	C ₂₄ (nM)	T _{max} (hr)	Apparent Terminal t _{1/2} (hr)
Buprenorphine/Naloxone + Grazoprevir	N	12	12	12	12	12	12	12
	AM	2.77	2.67	2.34	0.547	14.8	4.08	21.99
	SD	1.40	1.36	1.24	0.322	7.20	1.62	3.55
	ACV	50.5	51.1	53.0	58.8	48.8	39.7	16.2
	Med	2.29	2.19	1.89	0.476	12.0	4.00	21.15
	Min	0.853	0.824	0.680	0.0802	7.25	2.00	16.98
	Max	5.03	4.90	4.42	1.05	30.4	6.00	30.05
	GM	2.45	2.36	2.04	0.445	13.4	3.76	21.74
	GCV	56.8	57.5	60.5	85.8	46.4	46.3	15.7

Buprenorphine/Naloxone + Grazoprevir: Co-administration of 8/2 – 24/6 mg buprenorphine/naloxone QD with 200 mg grazoprevir QD on Days 2 to 11

AM = Arithmetic mean; SD = Standard deviation; GM = Geometric mean; Med = Median; Min = Minimum; Max = Maximum; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: 100 x (SD/AM); GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s²) - 1), where s² is the observed variance on the natural log-scale.

Table 16-Grazoprevir statistical analysis with concomitant use of buprenorphine/naloxone

Grazoprevir Pharmacokinetic Parameter	Grazoprevir Alone			Buprenorphine/Naloxone + Grazoprevir			Buprenorphine/Naloxone + Grazoprevir/ Grazoprevir Alone		rMSE [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µM·hr)	6	2.39	(1.59, 3.60)	12	1.92	(1.44, 2.56)	0.80	(0.53, 1.22)	0.464
C _{max} [‡] (µM)	6	0.544	(0.291, 1.02)	12	0.414	(0.267, 0.641)	0.76	(0.40, 1.44)	0.706
C ₂₄ [‡] (nM)	6	18.6	(14.6, 23.6)	12	12.8	(10.8, 15.1)	0.69	(0.54, 0.88)	0.269
T _{max} [§] (hr)	6	4.00	(2.00, 4.00)	12	4.00	(2.00, 6.00)			
Apparent Terminal t _½ (hr)	6	20.86	20.17	12	21.74	15.74			

Grazoprevir Alone: 200 mg grazoprevir QD administered Days 1 and 3 to 10, with 100 mg grazoprevir administered on Day 2 (historical data from MK-5172 P001)

Buprenorphine/Naloxone + Grazoprevir: Co-administration of 8/2 – 24/6 mg buprenorphine/naloxone QD with 200 mg grazoprevir QD on Days 2 to 11

[†]rMSE - Square root of conditional mean squared error (residual error) from the linear model.
rMSE*100% approximates the between-subject %CV on the raw scale.

[‡]Back-transformed least squares mean and confidence interval from the linear model performed on natural log-transformed values, with treatment as fixed effect and age as a covariate.

[§]Median (Minimum, Maximum) reported for T_{max}.

^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_½.

GM = Geometric mean; CI = Confidence interval; GMR = Geometric mean ratio

10.4 Safety Analysis

According to the trial report, no deaths or serious adverse events were reported for the trial and the most common adverse event was headache that occurred in three subjects.

11. Discussion and Conclusions

Based on the results from the P30 trial, the following conclusions can be made:

- With concomitant use of methadone once daily and grazoprevir 200 mg once daily:
 - the dose normalized R-methadone AUC_(0-24hr) and C_{max} were increased by 9% and 3%, respectively, and the 90% confidence intervals for AUC_(0-24hr) and C_{max} were within the standard limits of 80% to 125%.
 - the dose normalized S-methadone AUC_(0-24hr) and C_{max} were increased by 23% and 15%, respectively, and only the 90% confidence interval for C_{max} was within the standard limits of 80% to 125%.
 - the dose normalized total methadone AUC_(0-24hr) and C_{max} were increased by 16% and 10%, respectively, and only the 90% confidence interval for AUC_(0-24hr) and C_{max} were within the standard limits of 80% to 125%.
- With concomitant use of buprenorphine/naloxone once daily and grazoprevir 200 mg once daily:
 - the dose normalized buprenorphine AUC_(0-24hr) and C_{max} were decreased by 2% and 10%, respectively, and only the 90% confidence interval for AUC_(0-24hr) was within the standard limits of 80% to 125%.
 - the dose normalized norbuprenorphine AUC_(0-24hr) and C_{max} were increased by 13% and 10%, respectively, and only the 90% confidence interval for C_{max} was within the standard limits of 80% to 125%.

- the dose normalized naloxone $AUC_{(0-24hr)}$ and C_{max} were increased by 10% and 0%, respectively, and the 90% confidence intervals for $AUC_{(0-24hr)}$ and C_{max} were not within the standard limits of 80% to 125%.

The results support the absence of a clinically significant effect of grazoprevir on: a) buprenorphine (and norbuprenorphine or naloxone) exposure, and b) R-methadone, S-methadone or total methadone exposure.

Additionally, the analyses that were conducted for grazoprevir exposure compared to historical data indicate that an ALT/AST exposure-safety issue is not anticipated with concomitant use of either buprenorphine/naloxone or methadone.

Title: A 2- Part, Open-Label, 3-Period, Fixed-Sequence Study to Evaluate the 1-Way Interaction of Rifampin on MK-5172 (Part 1), and the 2-Way Interaction of MK-5172 and Efavirenz (Part 2) in Healthy Adult Subjects (PN017)

Study Initiation Date: 25-Jan-2013

Study Completion Date: 11-Apr-2013

Study Site: (b) (4)

Study Design

This was a 2-part study, each part being a fixed-sequence, 3-treatment, 3-period, open-label study. Twelve healthy subjects (with at least 3 females) were enrolled in each part of the study for a total of 24 subjects. On PK Sampling days, subjects were required to fast overnight at least 10 hours before dosing and for at least 4 hours following dosing. For all other doses, subjects were required to fast for at least 1 hour before dosing and for at least 2 hours following the dosing.

Table 1. Study design

Study Part	Period 1	Washout	Period 2	Period 3
Part 1: Drug interactions with rifampin	<p>MK-5172 single dose + IV rifampin A single dose of MK-5172 was administered immediately after the end of the 30-minute IV infusion of 600 mg rifampin</p> <p><i>MK-5172 PK sample collection: on Day 1</i></p>	≥ 7 days	<p>MK-5172 alone Subjects received a single dose of MK-5172 on Day 1, did not receive a dose on Day 2, and then received MK-5172 once daily on Days 3-9.</p> <p><i>MK-5172 PK sample collection: on Day 1 and on Day 9</i></p>	<p>MK-5172 + PO rifampin Once daily doses of MK-5172 continued from Period 2 for 14 days co-administered with multiple 600 mg oral doses of rifampin once daily.</p> <p><i>MK-5172 PK sample collection: on Day 1 and on Day 14</i></p>
Part 2: Drug interactions with efavirenz	<p>MK-5172 alone MK-5172 were administered once daily for 7 days</p> <p><i>MK-5172 PK sample collection: on Day 7</i></p>	≥ 7 days	<p>Efavirenz alone Efavirenz (600 mg) was administered once daily for 14 days.</p> <p><i>Efavirenz PK sample collection: on Day 14</i></p>	<p>Efavirenz + MK-5172 Once daily doses of efavirenz continued from Period 2 for 7 days were co-administered with MK-5172 once daily.</p> <p><i>MK-5172 and efavirenz PKsample collection: On day 7</i></p>

All MK-5172 doses were 200mg

Key inclusion criteria

- Healthy adult male and female volunteers, 19-55 years of age, inclusive
- BMI: 18.5-32 kg/m², inclusive. Weigh at least 52 kg for males and 45 kg for females.
- Have not used nicotine-containing products for at least 3 months prior to the first dose
- Medically healthy with no clinically significant history, physical exam, lab profiles.

- A female of childbearing potential must either sexually inactive or use acceptable birth control methods (part 1 only)
- Male subjects must use a condom (or abstain from sexual intercourse) and agree not to donate sperm from the first dose until 90 days after the last dose

Key exclusion criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study
- History of alcoholism or drug abuse within the past 2 years
- A female of childbearing potential (Part 2 only)
- History of seizure (Part 2 only)
- Estimated creatinine clearance less than 80 mL/min
- Female subjects who are pregnant or lactating
- Positive results at screening for HIV, hepatitis B, hepatitis C, or urine drug
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients
- Have been on a special diet (for whatever reasons) within the 28 days prior to the first dose of study drugs.

Identity of Clinical Supplies

Table 2. Identity of Clinical Supplies

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency	Site of Manufacture
MK-5172	100 mg	WL00044049	Tablet	WL00051231	96.9%	Merck & Co., Inc., West Point, PA
Rifampin Powder for Injection ¹	600 mg vial	NA	Injection	12R1F3A	NA	Akorn, Inc.
Rifampin ²	300 mg	NA	Capsule	70313A	NA	West-ward Pharmaceutical Corp
Efavirenz ³	600 mg	NA	Tablet	2D71550B	NA	Bristol Myers Squibb Pharma Company

¹Rifampin Powder for Injection (a product of Akorn, Inc.) was purchased by the Investigator. The lot number was 12R1F3A; expiration date May-2014.

²Rifampin 300 mg capsules (a product of West-ward Pharmaceutical Corp) were purchased by the Investigator. The lot number was 70313A; expiration date Jul-2014.

³Sustiva® (efavirenz) 600 mg tablets (a product of Bristol Myers Squibb Pharma Company) were purchased by the Investigator. The lot number was 2D71550B; expiration date May-2015.

Concomitant medications and diet restrictions

No subject was to take medication for the 14 days (or 28 days for CYP or P-gp inducers) or 5 half-lives of the medication(s), whichever was longer, prior to the first dose of the study and until the end of the study. During the study, acetaminophen (up to 2 g per 24 hours) could have been administered. Consumption of foods and beverages containing the following substances were prohibited.

Pharmacokinetic assessments

Blood samples for MK-5172 pharmacokinetic assessments were collected at predose and over 24 hours

postdose on Day 1 in Period 1, Day 9 in Period 2, and Day 1 in Period 3, over 48 hours postdose on Day 1 in Period 2, and over 96 hours postdose on Day 14 in Period 3. In Part 2, blood samples for MK-5172 and efavirenz analysis were collected at predose and up to 96 hours following administration of study doses. All other pharmacokinetic parameters were calculated using the software WinNonlin Phoenix 6.3 except that C₂₄ values were obtained using SAS (Version 9.1). C_{max} and T_{max} were generated by WinNonlin from each analyte's plasma concentration-time data. All AUC parameters were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down).

Reviewer comments: Blood samples for rifampin were also collected at the end of infusion on Day 1 of Period 1, predose on Day 10 of Period 2 and predose on Days 5, 13, and 14 of Period 3. However, no statistical or descriptive analyses were performed, thus rifampin pharmacokinetics will not be reviewed in this document.

Bioanalysis

Bioanalyses for plasma concentrations of MK-5172 and efavirenz were conducted by (b) (4) respectively. The concentrations of these drugs were determined using validated LC/MS/MS methods. All methods were adequately validated and the standard curve and QC data indicated assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data.

Table 3. Summary of bioanalysis

Analyte	MK-5172	Efavirenz
Internal standard	MK-5172-d ₆	Efavirenz-d ₅
Matrix/Anticoagulant	Plasma/K ₂ EDTA	Plasma/K ₂ EDTA
Extraction method	Liquid-liquid extraction	Liquid-liquid extraction
Calibration range	1- 1000 ng/mL	20- 4000 ng/mL
QC concentration	3, 75, and 750 ng/mL	60, 400, 2000, and 2800 ng/mL
Interday precision and accuracy	P: 3.10 to 9.31% A: -4.36 to -1.46%	P: 2.62 to 3.76% A: -0.19 to -11.47%
Long term stability	397 days at - 20°C	113 days at - 20°C

Results

Demographic and other baseline characteristics

Table 4. Subject baseline demographics

	Part 1 (interactions with rifampin) N=12	Part 2 (interactions with efavirenz) N=12 [#]
Age in Years, Mean (range)	37 (22-55)	42 (23-52)
Sex, n (%)		
Female	4 (33%)	3 (25%)
Male	8 (67%)	9 (75%)

BMI (kg/m²), range	27.42 (24.24-31.94)	27.08 (23.59-29.72)
Height (cm), range	172.3 (154.0-186.0)	173.6 (159.0-186.0)
Weight (kg), range	82.0 (60.2-108.9)	81.9 (65.8-98.7)
Ethnicity, n (%)		
Hispanic or Latino:	0 (0%)	1 (8%)
Not Hispanic or Latino:	12 (100%)	11 (92%)
Race, n (%)		
White	10 (83%)	11 (92%)
African American/Black	2 (17%)	0
Others	0 (0%)	1 (8%, American Indian/Alaska native)

Subject AN 0031 withdrew consent from Part 2 of the study and received all MK-5172 doses in Period 1 and only 2 doses of efavirenz (Days 1 and 2) in Period 2 of Part 2.

PHARMACOKINETIC RESULTS

Part 1. The effects of rifampin on the pharmacokinetics of MK-5172

The co-administration of a single IV dose of rifampin increased MK-5172 AUC_{inf}, C_{max}, and C_{24hr} by 10.2-fold, 11.0-fold, and 1.77-fold, respectively (Table 5). The co-administration of a single oral dose of rifampin increased MK-5172 AUC_{inf}, C_{max}, and C_{24hr} by 8.35-fold, 6.52-fold, and 1.62-fold, respectively (Table 6). When MK-5172 was co-administered with oral doses of rifampin for 7 days, MK-5172 AUC₂₄ and C_{max} were not altered but C₂₄ was significantly decreased (a 90% decrease; Table 7).

Table 5. MK-5172 pharmacokinetics following single dose administration with or without the co-administration of a single IV dose of rifampin.

Pharmacokinetic Parameter	MK-5172 + IV Rifampin			MK-5172 Alone			MK-5172 + IV Rifampin /MK-5172 Alone		
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	Pseudo Within Subject %CV [†]
AUC _{0-∞} [‡] (μM•hr)	12	9.94	(6.86, 14.4)	12	0.973	(0.700, 1.35)	10.21	(8.68, 12.00)	22.036
AUC ₀₋₄₈ [‡] (μM•hr)	12	9.93	(6.85, 14.4)	12	0.900	(0.633, 1.28)	11.03	(9.44, 12.89)	21.240
AUC ₀₋₂₄ [‡] (μM•hr)	12	9.84	(6.78, 14.3)	12	0.781	(0.533, 1.14)	12.61	(10.83, 14.67)	20.664
C ₂₄ [‡] (nM)	12	12.0	(8.88, 16.2)	12	6.76	(5.33, 8.58)	1.77	(1.40, 2.24)	31.908
C _{max} [‡] (μM)	12	1.72	(1.11, 2.67)	12	0.157	(0.0932, 0.266)	10.94	(8.92, 13.43)	27.913
T _{max} [§] (hr)	12	3.50	(2.98, 5.00)	12	3.00	(2.00, 5.04)	.	.	.
Apparent terminal t _{1/2} ^{††} (hr)	12	5.00	49.8	12	16.87	22.9	.	.	.

MK-5172 Alone: Single oral dose of 200 mg of MK-5172 (2 x 100 mg tablets) administered on Day 1 and multiple oral doses of 200 mg of MK-5172 (2 x 100 mg tablets) once daily for 7 consecutive days (Days 3 to 9).
MK-5172 + IV Rifampin: Single oral dose of 200 mg of MK-5172 (2 x 100 mg tablets) administered immediately after the end of the 30-minute IV infusion of 600 mg of rifampin
[†]Pseudo Within-subject %CV = 100*sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max}.
^{||}Geometric mean and geometric CV were reported for apparent terminal t_{1/2}.
^{††}Apparent terminal t_{1/2} may not be representative of the true terminal phase due to BLQ values after 32 hours in Period 1, MK-5172 + IV Rifampin.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio;
"." = Not Applicable

Table 6. MK-5172 pharmacokinetics following single dose administration with or without the co-administration of a single oral dose of rifampin.

Pharmacokinetic Parameter	MK-5172 + PO Rifampin			MK-5172 Alone			MK-5172 + PO Rifampin /MK-5172 Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µM·hr)	12	19.0	(13.8, 26.1)	12	2.27	(1.53, 3.37)	8.35	(7.38, 9.45)	16.906
C ₂₄ ^{‡†} (nM)	12	17.0	(13.2, 21.7)	12	10.5	(8.36, 13.1)	1.62	(1.32, 1.98)	27.396
C _{max} [‡] (µM)	12	3.75	(2.64, 5.32)	12	0.575	(0.332, 0.995)	6.52	(5.16, 8.24)	31.860
T _{max} [§] (hr)	12	2.00	(2.00, 5.00)	12	3.00	(1.00, 4.00)	.	.	.

MK-5172 Alone: Single oral dose of 200 mg of MK-5172 (2 x 100 mg tablets) administered on Day 1 and multiple oral doses of 200 mg of MK-5172 (2 x 100 mg tablets) once daily for 7 consecutive days (Days 3 to 9).
 MK-5172 + Rifampin: Multiple oral doses of 600 mg of rifampin (2 x 300 mg capsules) and 200mg of MK-5172 (2 x 100 mg tablets) co-administered once daily for 14 consecutive days (Days 1 to 14).
[†]Pseudo Within-subject %CV = 100*sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max}.
^{||}Apparent terminal t_{1/2} could not be characterized do to sampling for only 24 hours in Period 2 and BLQ values after 16 hours in Period 3.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio;
 “.” = Not Applicable

Table 7. Steady-state MK-5172 pharmacokinetics with or without the co-administration of multiple oral doses of rifampin (QD for 7 days)

Pharmacokinetic Parameter ^{††}	MK-5172 + PO Rifampin			MK-5172 Alone			MK-5172 + PO Rifampin /MK-5172 Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µM·hr)	12	2.12	(1.40, 3.22)	12	2.27	(1.53, 3.37)	0.93	(0.75, 1.17)	30.595
C ₂₄ ^{‡†} (nM)	12	1.01	(0.747, 1.37)	12	10.5	(8.36, 13.1)	0.10	(0.07, 0.13)	37.789
C _{max} [‡] (µM)	12	0.669	(0.422, 1.06)	12	0.575	(0.332, 0.995)	1.16	(0.82, 1.65)	47.881
T _{max} [§] (hr)	12	2.00	(1.00, 4.00)	12	3.00	(1.00, 4.00)	.	.	.

MK-5172 Alone: Single oral dose of 200 mg of MK-5172 (2 x 100 mg tablets) administered on Day 1 and multiple oral doses of 200 mg of MK-5172 (2 x 100 mg tablets) once daily for 7 consecutive days (Days 3 to 9).
 MK-5172 + PO Rifampin: Multiple oral doses of 600 mg of rifampin (2 x 300 mg capsules) and 200 mg of MK-5172 (2 x 100 mg tablets) co-administered once daily for 14 consecutive days (Days 1 to 14).
[†]Pseudo Within-subject %CV = 100*sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max}.
^{||}Geometric mean and geometric CV were reported for apparent terminal t_{1/2}.
^{††}For the summary of C₂₄, BLQ values were set to ½ LLOQ (0.65 nM).
^{†††}Apparent terminal t_{1/2} could not be reported due to quantifiable data for only 24 hours postdose following each treatment.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio;
 “.” = Not Applicable

Reviewer comments

Significant increases in MK-5172 exposures caused by the coadministration of a single dose rifampin is likely due to the inhibition of OATP1B-mediated hepatic uptake of MK-5172. It is reasonable to conclude that the role of intestinal transport for MK-5172 uptake is minimal based on comparison of the MK-5172 exposures following a single IV or oral dose of rifampin.

A much shorter apparent half-life of MK-5172 was observed when MK-5172 was co-administered with a single dose of rifampin. It is likely due to changes in volume of distribution rather than changes in metabolism as observed by Grover et al, 2009 (AAPS J, 2009). A similar change (a shorter half-life of a victim drug due to OATP-mediated drug interactions) was observed when a single IV dose of rifampin was co-administered with atorvastatin (Lau et al, Clin Pharmacol Ther, 2007).

Due to mixed effects of rifampin on OATP1B (inhibition) and CYP3A4 (induction) at steady-state of rifampin, a significant decrease was observed only in C_{24} , but not in AUC or C_{max} of MK-5172. The magnitude of decrease in MK-5172 C_{24} may be clinically relevant.

Part 2. Drug interactions between efavirenz and MK-5172

The co-administration of multiple doses of efavirenz (600 mg QD for 7 days) significantly decreased MK-5172 exposures (Table 8); AUC_{24hr} , C_{max} , and C_{24hr} of MK-5172 were decreased by 83%, 87%, and 69%, respectively, by the co-administration of efavirenz. The exposures of efavirenz were not altered by the co-administration of MK-5172 (Table 9).

Table 8. Steady-state pharmacokinetics of MK-5172 with or without the co-administration of efavirenz (600 mg QD for 7 days)

Pharmacokinetic Parameter	Efavirenz + MK-5172			MK-5172 Alone			Efavirenz + MK-5172 /MK-5172 Alone		Pseudo Within Subject %CV [†]
	N ^{††}	GM	95% CI	N ^{††}	GM	95% CI	GMR	90% CI	
AUC_{0-24}^{\ddagger} (µM•hr)	11	0.582	(0.412, 0.821)	12	3.34	(2.25, 4.95)	0.17	(0.13, 0.24)	43.197
C_{24}^{\ddagger} (nM)	11	5.04	(3.53, 7.19)	12	16.3	(11.6, 22.8)	0.31	(0.25, 0.38)	27.394
C_{max}^{\ddagger} (µM)	11	0.0992	(0.0605, 0.163)	12	0.776	(0.529, 1.14)	0.13	(0.09, 0.19)	52.551
T_{max}^{\S} (hr)	11	2.00	(1.00, 5.05)	12	3.00	(2.00, 4.01)			
Apparent terminal $t_{1/2}^{\parallel}$ (hr)	11	14.41	34.6	12	26.93	25.0			

MK-5172 Alone: Multiple oral doses of 200 mg of MK-5172 (2 x 100 mg tablets) once daily for 7 consecutive days (Days 1 to 7).
Efavirenz + MK-5172: Multiple oral doses of 600 mg efavirenz (1 x 600 mg Sustiva[®] tablet), and 200 mg of MK-5172 (2 x 100 mg tablets) co-administered once daily for 7 consecutive days (Days 1 to 7).
[†] Pseudo Within-subject %CV = $100 \cdot \sqrt{[(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2]}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡] Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values.
[§] Median (Min, Max) reported for T_{max} .
^{||} Geometric mean and geometric CV were reported for apparent terminal $t_{1/2}$.
[¶] The apparent terminal $t_{1/2}$ may not represent the terminal phase due to BLQ values in Period 3 (Efavirenz + MK-5172).
^{††} Subject AN 0031 withdrew on Day 2 of Period 2 due to adverse experiences and had no efavirenz data.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio; “.” = Not Applicable.

Table 9. Steady-state efavirenz pharmacokinetics with or without the co-administration of MK-5172 (200 mg QD for 7 days).

Pharmacokinetic Parameter	Efavirenz + MK-5172			Efavirenz Alone			Efavirenz + MK-5172 / Efavirenz Alone		Pseudo Within Subject %CV [†]
	N ^{††}	GM	95% CI	N ^{††}	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [†] (µg•hr/mL)	11	50.8	(41.4, 62.3)	11	50.6	(42.3, 60.6)	1.00	(0.96, 1.05)	5.912
C ₂₄ [‡] (µg/mL)	11	1.42	(1.11, 1.81)	11	1.53	(1.22, 1.92)	0.93	(0.88, 0.98)	7.376
C _{max} [‡] (µg/mL)	11	3.70	(3.12, 4.39)	11	3.59	(3.00, 4.30)	1.03	(0.99, 1.08)	5.643
T _{max} [§] (hr)	11	3.01	(2.00, 5.01)	11	3.01	(2.00, 5.02)	.	.	.
Apparent terminal t _½ (hr)	11	71.75	27.1

Efavirenz Alone: Multiple oral doses of 600 mg of efavirenz (1 x 600 mg Sustiva[®] tablet) once daily for 14 consecutive days (Days 1 to 14).
Efavirenz + MK-5172: Multiple oral doses of 600 mg efavirenz (1 x 600 mg Sustiva[®] tablet), and 200 mg of MK-5172 (2 x 100 mg tablets) co-administered once daily for 7 consecutive days (Days 1 to 7).
[†]Pseudo Within-subject %CV = 100*sqrt[(σ_A² + σ_B² - 2σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values.
[§]Median (Min, Max) reported for T_{max}.
^{||}Geometric mean and geometric CV were reported for apparent terminal t_½.
^{††}The apparent terminal t_½ may not represent the terminal phase due to BLQ values in Period 3 (Efavirenz + MK-5172).
^{†††}Subject AN 0031 withdrew on Day 2 of Period 2 due to adverse experiences and had no efavirenz data.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio;
“.” = Not Applicable.

Reviewer comments

A significant decrease in MK-5172 exposures caused by the co-administration of efavirenz is likely due to CYP3A4 induction. The magnitude of interaction (more than a 50% decrease) is considered clinically relevant based on MK-5172 exposure-response relationship for efficacy. The co-administration may result in the loss of MK-5172 efficacy, thus co-administration should be contraindicated.

Conclusion

- The co-administration of a single oral or IV dose of rifampin significantly increased MK-5172 exposures. The co-administration of multiple oral doses of rifampin significantly decreased MK-5172 C_{24hr} but did not alter MK-5172 AUC or C_{max}.
- The co-administration of efavirenz significantly decreased MK-5172 exposures.
- Significant decreases in MK-5172 exposures caused by the co-administration of multiple doses of efavirenz or rifampin may result in the loss of MK-5172 efficacy. Co-administration of either drug with MK-5172 should be contraindicated.

Study Title: A Multi-Part Study to Evaluate the Effect of Multiple Doses of MK-5172 on the Single Dose Pharmacokinetics of Midazolam, Atorvastatin, and Pitavastatin

Study Initiation Date: 07-Nov-2012

Study Completion Date: 09-Jan-2013

Study Site: (b) (4)

Study Design

This study was conducted in 3 parts. The study parts were conducted concurrently. Each part was conducted as an open-label, fixed-sequence study in healthy subjects. A total of 29 subjects were enrolled for this multi-part study, 11 subjects in Part 1 and 9 subjects in each of Parts 2 and 3. Each subject participated in only 1 study part. All doses of study drug were administered in the fasted state.

Part 1 (Midazolam)

Eleven subjects received a single oral dose of 2 mg midazolam on Day 1 and 200 mg MK-5172 once daily on Days 2 – 8, with co-administration of a single oral dose of 2 mg midazolam on Day 8. Serial plasma samples were obtained from predose to 24 hours postdose for midazolam pharmacokinetics.

Part 2 (Atorvastatin)

Nine subjects received a single oral dose of 20 mg atorvastatin on Day 1. Following a washout period on Days 2 – 5, subjects received 200 mg MK-5172 once daily on Days 6 – 13, with co-administration of a single oral dose of 20 mg atorvastatin on Day 11. Plasma samples were obtained from predose to 72 hours postdose for the pharmacokinetic analysis of atorvastatin and its metabolites on Days 1 and 11. A 24-hour plasma pharmacokinetic profile was obtained following Day 10 dosing for assessment of MK-5172 following MK-5172 alone and following Day 11 dosing for assessment of MK-5172 when MK-5172 was co-administered with atorvastatin.

Part 3 (Pitavastatin)

Nine subjects received a single oral dose of 1 mg pitavastatin on Day 1. Following a washout period on Days 2 – 3, subjects received 200 mg MK-5172 once daily on Days 4 – 12, with co-administration of a single oral dose of 1 mg pitavastatin on Day 10. Serial plasma samples were obtained from predose to 72 hours postdose for the pharmacokinetic analysis of pitavastatin and pharmacokinetic analysis of pitavastatin lactone on Days 1 and 10. A 24-hour plasma pharmacokinetic profile was obtained following Day 9 dosing for assessment of MK-5172 following MK-5172 alone and following Day 10 dosing for assessment of MK-5172 when MK-5172 was co-administered with pitavastatin.

Rationale for Study

MK-5172 is a reversible inhibitor of CYP3A4 with an IC_{50} value of 73 μ M. The IC_{50} is higher than the C_{max} (0.2 μ M) of MK-5172 following the administration of clinical doses (100 mg QD) in patients. However, MK-5172 is expected to accumulate in the liver by OATP1B-mediated transport, thus intrahepatic concentrations of MK-5172 may be significantly higher than plasma concentrations. Also, considering the theoretical maximum concentration of MK-5172 in the gut (~ 500 μ M), MK-5172 may inhibit intestinal CYP3A4. Therefore, the sponsor evaluated the effect of MK-5172 on the

pharmacokinetics of midazolam, a sensitive CYP3A4 substrate. MK-5172 also inhibited OATP1B1 *in vitro* (IC₅₀ = 0.7 μM). Therefore, the sponsor evaluated the effects of MK-5172 on the pharmacokinetics of atorvastatin and pitavastatin.

Key Inclusion Criteria

- Healthy adult male and female volunteers, 18-55 years of age, BMI: 19-32 kg/m², inclusive
- Have not used nicotine-containing products for at least 3 months prior to the first dose
- Medically healthy with no clinically significant history, physical exam, lab profiles.
- A female of childbearing potential must either sexually inactive or use acceptable birth control methods.

Key Exclusion Criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 80 mL/min
- Female subjects who are pregnant or lactating
- Positive results at screening for HIV, hepatitis B, hepatitis C, or urine drug screening
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients
- Consuming excessive alcohols or caffeinated beverages
- Subject has had major surgery, donated or lost blood within 8 weeks prior to the screen
- Subject has participated in another investigational study within 4 weeks prior to Day1
- Male subjects who are not using an acceptable form of birth control or who are unable to refrain from donating sperm during the conduct of the study and for 90 days postdose.
- Unable to refrain from the use of any medication for the 14 days (28 days prior to, if CYP or P-gp inducers) prior to the first dose of study medications and throughout the study.

Identity of Clinical Supplies

Table 1. Identity of Clinical Supplies

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency	Site of Manufacture
MK-5172	100 mg	WL00044049	Tablet	WL00047031	96.9%	Merck & Co., Inc., West Point, PA
Midazolam hydrochloride ¹	2 mg/mL	NA	Syrup	NA	NA	NA
Lipitor® (atorvastatin calcium) ²	20 mg	NA	Tablet	NA	NA	NA
Livalo® (pitavastatin) ³	1 mg	NA	Tablet	NA	NA	NA
¹ Midazolam hydrochloride (a product of Roxane Laboratories, Inc.) was purchased (b) (4) by the Investigator. The lot number was 259803A; expiration date Jun-2014.						
² Lipitor® (a product of Parke-Davis, Division of Pfizer Inc.) was purchased (b) (4) by the Investigator. The lot number was V121097; expiration date Jun-2015.						
³ Livalo® (a product of Kowa Pharmaceuticals America, Inc.) was purchased (b) (4) by the Investigator. The lot number was 3100852; expiration date Apr-2015.						

Pharmacokinetic assessments

Plasma samples for midazolam, atorvastatin, pitavastatin, and metabolites of these drugs were collected as described in Study Design. C_{12} , C_{24} , and C_{trough} values were obtained using SAS (Version 9.1). All other pharmacokinetic parameters were calculated using the software WinNonlin Phoenix 6.3. C_{max} and T_{max} were generated by WinNonlin from each analytes plasma concentration-time data. All AUC parameters were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down).

Bioanalysis

Bioanalyses for MK-5172 and midazolam were conducted by (b) (4) Bioanalyses for atorvastatin and its metabolites were conducted by (b) (4). Bioanalyses for pivavastatin and pitavastatin lactone were conducted by (b) (4). The concentrations of these drugs were determined using validated LC/MS/MS methods. All methods were adequately validated. Standard curves and QC data indicated assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data.

Table 2. Summary of bioanalysis

Analyte	Midazolam	Atorvastatin	<i>O</i> -hydroxy-atorvastatin	<i>P</i> -hydroxy-atorvastatin	Pitavastatin	Pitavastatin lactone	MK-5172
Internal standard	Midazolam-d ₄	Atorvastatin-d ₅	<i>O</i> -hydroxy-atorvastatin d ₅	<i>P</i> -hydroxy-atorvastatin d ₅	Pitavastatin-d ₅	Pitavastatin lactone d ₅	MK-5172-d ₆
Matrix/Anticoagulant	Na+heparin	Plasma /K ₂ EDTA	Plasma /K ₂ EDTA	Plasma /K ₂ EDTA	Plasma /K ₂ EDTA	Plasma /K ₂ EDTA	Plasma /K ₂ EDTA
Extraction method	Liquid-liquid extraction	Liquid-liquid extraction	Liquid-liquid extraction	Liquid-liquid extraction	Liquid-liquid extraction	Liquid-liquid extraction	Liquid-liquid extraction
Calibration range	0.1 to 100 ng/mL	50 to 10000 pg/mL	50 to 10000 pg/mL	50 to 5000 pg/mL	1 to 200 ng/mL	1 to 200 ng/mL	1 to 1000 ng/mL
QC concentration	0.3, 0.8, 4, 13, and 75 ng/mL	150, 5000, 5000, and 7000 pg/mL	150, 5000, 5000, and 7000 pg/mL	150, 250, 2500, and 3500 pg/mL	2, 5, 15, 40, and 150 ng/mL	2, 5, 15, 40, and 150 ng/mL	3, 75, and 750 ng/mL
Interday precision and accuracy	P: 2.22 to 4.06% A: -7.70 to 6.65%	P: 1.97 to 7.46% A: -4.25 to -0.37%	P: 1.51 to 7.52% A: -2.02 to 5.12%	P: 5.55 to 8.34% A: -5.11 to 0.55%	P: 1.41 to 9.70% A: -3.08 to 3.23%	P: 2.97 to 10.3% A: 5.02 to 10.4%	P: 1.87 to 2.60% A: -8.68 to -6.21%
Storage stability	363 days at -20 °C	120 days at -20 °C	120 days at -20 °C	120 days at -20 °C	122 days at -70 °C	122 days at -70 °C	397 days at -20 °C

Results

Demographic and baseline characteristics

A total of 29 healthy subjects were enrolled and 28 subjects completed the study per protocol. One subject (AN 0007) withdrew consent on Day 3 of Period 1 in Part 1 of the study due to an adverse event (headache).

Table 3. Subject baseline demographics

Part	Part 1 (N=11)	Part 2 (N=9)	Part 3 (N=9)
Age in Years, Mean (range)	33 (20 - 49)	35 (18 - 46)	39 (19 - 54)
Sex, n (%)			
Female:	8 (73%)	7 (78%)	7 (78%)
Male:	3 (27%)	2 (22%)	2 (22%)
BMI (kg/m ²), range	26.18 (21.39 to 29.19)	27.76 (21.36-32.02)	25.84 (19.38 to 30.29)
Height (cm), range	159.2 (149.0 to 175.0)	161.0 (151.0 to 176.0)	160.06 (149.0 to 179.0)
Weight (kg), range	66.7 (47.7 to 85.4)	72.0 (54.5 to 89.4)	66.3 (54.6 to 80.5)
Ethnicity, n (%)			
Hispanic or Latino:	9 (82%)	9 (100%)	9 (100%)
Not Hispanic or Latino:	2 (18%)	0 (0%)	0 (0%)
Race, n (%)			
White	11 (100%)	9 (100%)	9 (100%)

Pharmacokinetic Results

Part 1. The effects of MK-5172 on the pharmacokinetics of midazolam.

The co-administration of multiple doses of MK-5172 (200 mg QD for 7 days) increased midazolam C_{max} and AUC_{inf} by 15% and 34%, respectively, following a single oral dose of 2 mg midazolam administration.

Table 4. Plasma pharmacokinetics of midazolam with or without the co-administration of MK-5172

Pharmacokinetic Parameter	Midazolam Alone			Midazolam + MK-5172			Midazolam + MK-5172/ Midazolam Alone		Pseudo Within-Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (ng•hr/mL)	11	36.6	(31.1, 43.0)	10	49.0	(42.5, 56.5)	1.34	(1.29, 1.39)	4.796
C _{max} [‡] (ng/mL)	11	13.7	(11.0, 17.1)	10	15.7	(12.6, 19.6)	1.15	(1.01, 1.31)	16.103
C ₂₄ ^{§¶} (ng/mL)	11	0.135	(0.00, 0.222)	10	0.232	(0.00, 0.337)			
T _{max} [§] (hr)	11	0.50	(0.50, 1.01)	10	0.50	(0.50, 1.01)			
Apparent terminal t _½ (hr)	11	5.92	30.11	10	6.50	25.63			

Midazolam Alone: Single oral dose of 2 mg midazolam administered on Day 1.
Midazolam + MK-5172: 200 mg MK-5172 QD on Days 2 – 8 co-administered with a single oral dose of 2 mg midazolam on Day 8.
[†]Pseudo Within-Subject %CV = 100*sqrt[(σ²_{A1} + σ²_{A2} - 2σ_{A1A2})/2], where σ²_{A1} and σ²_{A2} are the estimated variances on the log scale for the 2 treatment groups, and σ_{A1A2} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for C₂₄ and T_{max}.
[¶]Three (3) subjects had BLQ C₂₄ values following midazolam alone, and 1 subject had a BLQ C₂₄ value following midazolam + MK-5172, which were all set to 0. As such, log transformation and the statistical model-based comparison were not performed.
^{||}Geometric mean and percent geometric CV reported for apparent terminal t_½.
^{††}Subject AN 0007 withdrew consent on Day 3 of Period 1 due to an adverse event and did not receive Midazolam + MK-5172.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

Reviewer comments: As the sponsor proposed, it is potentially due to the inhibition of intestinal CYP3A4. However, definitive conclusions cannot be made without IV midazolam data. The results suggest that MK-5172 is a weak CYP3A4 inhibitor for sensitive CYP3A4 substrates.

Part 2. Drug interactions between atorvastatin and MK-5172

The co-administration of multiple doses of MK-5172 (200 mg QD for 7 days) increased atorvastatin C_{max} and AUC_{inf} by 5.7-fold and 3.0-fold, respectively, following a single oral dose of 20 mg atorvastatin (Table 5). C_{max} and AUC_{inf} of orthohydroxyatorvastatin (a major active metabolite of atorvastatin) were also increased by 6.93-fold and 2.30-fold, respectively, by the co-administration of MK-5172 (Table 6). C_{max} of parahydroxyatorvastatin was also significantly increased by the co-administration of MK-5172 (Table 7). Due to the quantitation limits, changes in parahydroxyatorvastatin could not be reliably determined. The co-administration of a single dose of atorvastatin slightly increased MK-5172 exposures but this is not considered clinically relevant (Table 8).

Table 5. Atorvastatin plasma pharmacokinetics with or without the co-administration of MK-5172

Pharmacokinetic Parameter	Atorvastatin Alone			Atorvastatin + MK-5172			Atorvastatin + MK-5172/ Atorvastatin Alone		Pseudo Within-Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$ (ng•hr/mL)	9	31.9	(24.1, 42.1)	9	95.7	(58.8, 156)	3.00	(2.42, 3.72)	24.584
AUC_{0-last} (ng•hr/mL)	9	31.0	(23.4, 41.1)	9	95.3	(58.6, 155)	3.07	(2.48, 3.80)	24.385
AUC_{0-12} (ng•hr/mL)	9	23.0	(17.6, 30.0)	9	94.6	(58.2, 154)	4.12	(3.30, 5.15)	25.355
C_{max} (ng/mL)	9	7.27	(5.30, 9.97)	9	41.2	(22.7, 74.6)	5.66	(3.39, 9.45)	58.491
C_{24} ^{§¶} (pg/mL)	9	196	(65.4, 543)						
T_{max} [§] (hr)	9	0.50	(0.50, 6.00)	9	1.50	(1.50, 3.00)			
Apparent terminal $t_{1/2}$ (hr)	9	8.38	29.72	9	3.40	70.58			

Atorvastatin alone: Single oral dose of 20 mg atorvastatin administered on Day 1.
Atorvastatin + MK-5172: Co-administration of 200 mg QD of MK 5172 on Days 6 - 13 with a single oral dose of 20 mg atorvastatin on Day 11.
[†]Pseudo Within-Subject %CV = $100 \cdot \sqrt{(\sigma^2_{B1} + \sigma^2_{B2} - 2\sigma_{B1B2})/2}$, where σ^2_{B1} and σ^2_{B2} are the estimated variances on the log scale for the 2 treatment groups, and σ_{B1B2} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for C_{24} and T_{max} .
[¶]Geometric mean and Geometric CV reported for apparent terminal $t_{1/2}$.
^{¶¶}Only Subject AN 0026 had a measurable C_{24} concentration following atorvastatin + MK-5172.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

Table 6. Orthohydroxyatorvastatin plasma pharmacokinetics with or without the co-administration of MK-5172

Pharmacokinetic Parameter	Atorvastatin Alone			Atorvastatin + MK-5172			Atorvastatin + MK-5172/ Atorvastatin Alone		Pseudo Within-Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$ (ng•hr/mL)	9	44.4	(36.2, 54.5)	9	102	(68.3, 152)	2.30	(1.90, 2.77)	21.463
AUC_{0-last} (ng•hr/mL)	9	43.2	(35.1, 53.2)	9	101	(67.8, 152)	2.35	(1.95, 2.83)	21.426
AUC_{0-12} (ng•hr/mL)	9	27.5	(21.7, 34.7)	9	96.6	(63.8, 146)	3.51	(2.81, 4.39)	25.453
$AUC_{0-12_{ortho}}/AUC_{0-12_{ator}}$ [‡]	9	1.16	(0.937, 1.44)	9	0.992	(0.775, 1.27)	0.85	(0.77, 0.94)	11.157
C_{max} (ng/mL)	9	4.43	(3.16, 6.21)	9	30.7	(17.7, 53.3)	6.93	(4.44, 10.82)	50.767
C_{24} (pg/mL)	9	383	(302, 487)	9	125	(96.8, 163)	0.33	(0.28, 0.38)	17.383
T_{max} (hr)	9	1.00	(0.50, 2.50)	9	2.01	(1.50, 3.00)			
Apparent terminal $t_{1/2}$ (hr)	9	10.99	25.06	9	6.15	24.26			

Atorvastatin Alone: Single oral dose of 20 mg atorvastatin administered on Day 1.
Atorvastatin + MK-5172: Co-administration of 200 mg QD of MK-5172 on Days 6 - 13 with a single oral dose of 20 mg atorvastatin on Day 11.
[†]Pseudo Within-Subject %CV = $100 \cdot \sqrt{(\sigma^2_{B1} + \sigma^2_{B2} - 2\sigma_{B1B2})/2}$, where σ^2_{B1} and σ^2_{B2} are the estimated variances on the log scale for the 2 treatment groups, and σ_{B1B2} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max} .
[¶]Geometric mean and Geometric CV reported for apparent terminal $t_{1/2}$.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.
 $AUC_{0-12_{ortho}}/AUC_{0-12_{ator}}$ = Ratio of AUC_{0-12} for orthohydroxyatorvastatin to AUC_{0-12} for atorvastatin, multiplied by ratio of molecular weight of atorvastatin to molecular weight of orthohydroxyatorvastatin (558.64/574.64).

Table 7. Parahydroxyatorvastatin plasma pharmacokinetics with or without the co-administration of MK-5172

Pharmacokinetic Parameter	Atorvastatin Alone			Atorvastatin + MK-5172			Atorvastatin + MK-5172/ Atorvastatin Alone		Pseudo Within-Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (ng•hr/mL)	4 ^{††}	7.31	(3.95, 13.5)	4	10.3	(3.31, 31.8)			
AUC _{0-last} [§] (ng•hr/mL)	7 ^{‡‡}	2.59	(1.48, 4.53)	9	15.6	(9.12, 26.8)	6.04	(5.19, 7.02)	12.785
AUC ₀₋₁₂ [§] (ng•hr/mL)	7 ^{‡‡}	0.772	(0.518, 1.15)	9	14.9	(8.76, 25.2)	19.24	(16.69, 22.17)	14.397
AUC _{0-12_{par}} /AUC _{0-12_{ator}} [§]	7 ^{‡‡}	0.0339	(0.0275, 0.0418)	9	0.153	(0.123, 0.189)	4.50	(4.00, 5.07)	11.527
C _{max} [§] (ng/mL)	9	0.113	(0.0778, 0.163)	9	4.98	(2.67, 9.31)	44.24	(30.48, 64.22)	42.514
C ₂₄ ^{§§} (pg/mL)	9	65.7	(0.00, 99.1)						
T _{max} (hr)	9	5.00	(0.50, 12.00)	9	2.50	(2.00, 5.00)			
Apparent terminal t _{1/2} [¶] (hr)	4 ^{††}	38.65	41.21	4	3.62	137.50			

Atorvastatin alone: Single oral dose of 20 mg atorvastatin administered on Day 1.
 Atorvastatin + MK-5172: Co-administration of 200 mg QD of MK-5172 on Days 6 - 13 with a single oral dose of 20 mg atorvastatin on Day 11.

[†]Pseudo Within-Subject %CV = 100*sqrt[(σ²_{B1} + σ²_{B2} - 2σ_{B1B2})/2], where σ²_{B1} and σ²_{B2} are the estimated variances on the log scale for the 2 treatment groups, and σ_{B1B2} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Due to small number of observations for which AUC_{0-∞} could be estimated the model did not converge and non-model based geometric mean and 95% confidence interval reported.
[§]Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
^{||}Median (min, max) reported for C₂₄ and T_{max}.
[¶]Geometric mean and geometric CV reported for apparent terminal t_{1/2}.
^{††}AUC_{0-∞}, apparent terminal t_{1/2} could not be estimated for Subjects AN 0022 and AN 0026 - AN 0029 following atorvastatin alone, and Subjects AN 0021 - AN 0023, AN 0025, and AN 0029 following atorvastatin + MK-5172. Therefore, non-model based geometric means and 95% confidence intervals were reported, and GMR with 90% CIs were not calculated.
^{‡‡}AUC_{0-last}, AUC₀₋₁₂, and AUC_{0-12_{par}}/AUC_{0-12_{ator}} could not be estimated for Subjects AN 0027 and AN 0028 following atorvastatin alone.
^{§§}Only Subjects AN 0021 and AN 0026 had measurable C₂₄ concentrations following atorvastatin + MK-5172.
 GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.
 AUC_{0-12_{par}}/AUC_{0-12_{ator}} = Ratio of AUC₀₋₁₂ for parahydroxyatorvastatin to AUC₀₋₁₂ for atorvastatin, multiplied by ratio of molecular weight of atorvastatin to molecular weight of parahydroxyatorvastatin (558.64/574.64).
 Subjects AN 0027 and AN 0028 were excluded from statistical analysis for all AUC parameters for atorvastatin alone.

Table 8. MK-5172 plasma pharmacokinetic with or without the co-administration of a single dose atorvastatin

Pharmacokinetic Parameter	MK-5172 Alone			MK-5172 + Atorvastatin			MK-5172 + Atorvastatin/ MK-5172 Alone		Pseudo Within-Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (μM•hr)	9	2.59	(1.59, 4.23)	9	3.27	(2.22, 4.83)	1.26	(0.97, 1.64)	30.164
C _{max} [‡] (μM)	9	0.729	(0.389, 1.37)	9	0.916	(0.542, 1.55)	1.26	(0.83, 1.90)	47.417
C ₂₄ [‡] (nM)	9	11.8	(8.78, 15.9)	9	13.1	(10.4, 16.4)	1.11	(1.00, 1.23)	12.012
T _{max} [§] (hr)	9	3.00	(2.00, 6.00)	9	3.00	(2.00, 6.00)			

MK-5172 Alone: Once daily oral doses of 200 mg MK-5172 on Days 6 - 10.
 MK-5172 + Atorvastatin: Once daily oral doses of 200 mg MK-5172 on Days 6 - 13, with co-administration of a single oral dose of 20 mg atorvastatin on Day 11.

[†]Pseudo Within-Subject %CV = 100*sqrt[(σ²_{B1} + σ²_{B2} - 2σ_{B1B2})/2], where σ²_{B1} and σ²_{B2} are the estimated variances on the log scale for the 2 treatment groups, and σ_{B1B2} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max}.
 GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

Reviewer comments:

Refer to the review of study 076 (drug interactions with atorvastatin and MK-5172/MK-8742) for the possible mechanism of drug interaction and clinical implications. A significant increase in parahydroxyatorvastatin C_{max} was observed, particularly. As most of C_{max} values in the reference group (atorvastatin only) are barely above the quantitation limit, the fold-increase in C_{max} may not be reliable.

The clinical significance of the increase in parahydroxyatorvastatin is largely unknown. However, the C_{max} of parahydroxyatorvastatin (geometric mean: 4.9 ng/mL) is much lower than that of atorvastatin (geometric mean: 41.2 ng/mL) or orthohydroxyatorvastatin (30.7 ng/mL) in the presence of MK-5172 thus it would unlikely affect the safety and efficacy of atorvastatin.

Part 3. Drug interactions between MK-5172 and pitavastatin

The co-administration of multiple doses of MK-5172 (200 mg QD for 7 days) slightly increased the C_{max} and AUC_{inf} of pitavastatin (27% and 11%, respectively, Table 9). the C_{max} and AUC_{inf} of pitavastatin lactone (the major metabolite of pitavastatin) were not changed by the co-administration of MK-5172 (Table 10). The co-administration of a single dose of pitavastatin 1 mg slightly decreased MK-5172 exposures (Table 11).

Table 9. Pitavastatin plasma pharmacokinetics with or without the co-administration of MK-5172

Pharmacokinetic Parameter ^{††}	Pitavastatin Alone			Pitavastatin + MK-5172			Pitavastatin + MK-5172/ Pitavastatin Alone		Pseudo Within-Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$ (ng•hr/mL)	9	39.2	(26.2, 58.6)	9	43.4	(32.0, 58.9)	1.11	(0.91, 1.34)	21.867
C_{max} (ng/mL)	9	19.2	(13.5, 27.4)	9	24.4	(17.0, 35.1)	1.27	(1.07, 1.52)	20.086
T_{max} [§] (hr)	9	1.00	(0.50, 1.50)	9	0.50	(0.50, 2.00)			
Apparent terminal $t_{1/2}$ (hr)	9	3.20	63.40	9	2.36	48.83			

Pitavastatin Alone: Single oral dose of 1 mg pitavastatin administered on Day 1.
Pitavastatin + MK-5172: Co-administration of 200 mg QD of MK-5172 on Days 4 - 12 with a single oral dose of 1 mg pitavastatin on Day 10.
[†]Pseudo Within-Subject %CV = $100 \cdot \sqrt{(\sigma^2_{C1} + \sigma^2_{C2} - 2\sigma_{C1C2})/2}$, where σ^2_{C1} and σ^2_{C2} are the estimated variances on the log scale for the 2 treatment groups, and σ_{C1C2} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max} .
^{||}Geometric mean and geometric CV reported for apparent terminal $t_{1/2}$.
^{††} C_{24} was BLQ for all subjects for both treatments and therefore not reported.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

Table 10. Pitavastatin lactone plasma pharmacokinetics with or without the co-administration of MK-5172

Pharmacokinetic Parameter	Pitavastatin Alone			Pitavastatin + MK-5172			Pitavastatin + MK-5172/ Pitavastatin Alone		Pseudo Within-Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$ (ng•hr/mL)	9	145	(112, 187)	9	130	(103, 165)	0.90	(0.82, 0.99)	10.556
C_{max} (ng/mL)	9	12.1	(9.83, 14.9)	9	12.8	(10.7, 15.2)	1.05	(0.94, 1.18)	13.042
C_{24} ^{§†} (ng/mL)	9	2.32	(1.12, 3.14)	9	1.88	(0.00, 2.45)			
T_{max} [§] (hr)	9	2.00	(1.50, 3.00)	9	2.00	(1.50, 3.00)			
Apparent terminal $t_{1/2}$ (hr)	9	12.20	41.35	9	12.08	31.34			

Pitavastatin Alone: Single oral dose of 1 mg pitavastatin administered on Day 1.
Pitavastatin + MK-5172: Co-administration of 200 mg QD of MK-5172 on Days 4 - 12 with a single oral dose of 1 mg pitavastatin on Day 10.
[†]Pseudo Within-Subject %CV = $100 \cdot \sqrt{(\sigma^2_{C1} + \sigma^2_{C2} - 2\sigma_{C1C2})/2}$, where σ^2_{C1} and σ^2_{C2} are the estimated variances on the log scale for the 2 treatment groups, and σ_{C1C2} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for C_{24} and T_{max} .
[†]One (1) subject had a BLQ C_{24} value following pitavastatin + MK-5172, which was set to 0. As such, log transformation and the statistical model-based comparison were not performed.
^{||}Geometric mean and geometric CV reported for apparent terminal $t_{1/2}$.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

Table 11. MK-5172 plasma pharmacokinetics with or without the co-administration of a single dose pitavastatin

Pharmacokinetic Parameter	MK-5172 Alone			MK-5172 + Pitavastatin			MK-5172 + Pitavastatin/ MK-5172 Alone		Pseudo Within-Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µM•hr)	9	3.40	(1.86, 6.21)	9	2.76	(1.53, 4.99)	0.81	(0.70, 0.95)	17.867
C _{max} [‡] (µM)	9	0.827	(0.388, 1.76)	9	0.599	(0.307, 1.17)	0.72	(0.57, 0.92)	26.790
C ₂₄ [‡] (nM)	9	14.6	(10.3, 20.7)	9	13.3	(9.51, 18.5)	0.91	(0.82, 1.01)	11.780
T _{max} [§] (hr)	9	2.00	(2.00, 4.00)	9	4.00	(2.00, 4.00)			

MK-5172 Alone: Once daily oral doses of 200 mg MK-5172 on Days 4 - 9.
MK-5172 + Pitavastatin: Once daily oral doses of 200 mg MK-5172 on Days 4 - 12, with co-administration of a single oral dose of 1 mg pitavastatin on Day 10.
[†]Pseudo Within-Subject %CV = 100*sqrt[(σ²_{C1} + σ²_{C2} - 2σ_{C1C2})/2], where σ²_{C1} and σ²_{C2} are the estimated variances on the log scale for the 2 treatment groups, and σ_{C1C2} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max}.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

Reviewer comments

The sponsor concluded that MK-5172 is not a clinically relevant inhibitor of OATP1B as pitavastatin exposures were not significantly increased by the co-administration of MK-5172. However, pitavastatin does not appear to be a sensitive OATP1B substrate in vivo even though it is commonly used as an OATP1B substrate in vitro; pitavastatin AUCs were not significantly increased by known OATP1B inhibitors such as atazanavir (a 30% increase) or lopinavir/ritonavir (a 20% decrease) (LIVALO® USPI). Therefore, the study results do not rule out the possibility of OATP1B inhibition by MK-5172.

Conclusion

- The co-administration of MK-5172 increased midazolam C_{max} and AUC_{inf} by 15% and 34%, respectively.
- The co-administration of MK-5172 increased atorvastatin C_{max} and AUC_{inf} by 5.7-fold and 3.0-fold, respectively. The exposures of metabolites were also increased. Please refer to review of study PN076 for clinical recommendations regarding the coadministration of atorvastatin with the combination of MK-5172 and MK-8742.
- No clinically relevant interactions were observed between MK-5172 and pitavastatin

5172-046

1. Title

A Study to Assess the Effects of Multiple Oral Doses of MK-5172 on the Single-Dose Pharmacokinetics of an Oral Contraceptive (Ethinyl Estradiol and Levonorgestrel) in Healthy Adult Female Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted from March 22, 2013 (trial initiation) to May 12, 2013 (trial completion).

3. Objectives

The objectives of the trial included evaluating the effect of multiple dosing of MK-5172 (grazoprevir) on the exposure of a single dose of ethinyl estradiol and levonorgestrel (Nordette 28).

4. Trial Design

046 was a clinical trial that enrolled healthy female postmenopausal or oophorectomized subjects 18 to 65 years old. In period 1, a single dose of 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel (Nordette 28) was administered. Between period 1 and period 2, there was a washout period consisting of at least 7 days. In period 2, 200 mg once daily of MK-5172 was administered for 10 days and a single dose of 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel (Nordette 28) was administered on day 7.

5. Excluded Medications, Restrictions or Exceptions

Medications, including nonprescription and herbal products, were not permitted within either 14 days (or 28 days for CYP or P-gp inducers) or 5 half lives, depending on which was longer, before the first dose.

6. Dosage and Administration

The trial medications were administered under fasted conditions. This is consistent with the proposed U.S. prescribing information (USPI) recommendation for grazoprevir in combination with elbasvir (with or without food). The Nordette 28 USPI recommends dose administration after the evening meal or at bedtime and at the same time each day.

7. Rationale for Doses Used in the Trial

The dosing regimen of 200 mg once daily is higher than the recommended dosage regimen in the proposed U.S. prescribing information for elbasvir and grazoprevir (100 mg with 50 mg of elbasvir once daily). Based on the information provided by the applicant, greater than dose proportional changes in exposure and time dependent pharmacokinetics were observed with grazoprevir. According to the applicant, the rationale for dosing 200 mg once daily is that grazoprevir steady state exposure is approximately twice as high in hepatitis C infected subjects when compared to healthy subjects. The doses of ethinyl estradiol and levonorgestrel are consistent with Nordette 28.

8. Drugs Used in the Trial

The medications administered in trial 046 are displayed in Table 1.

Table 1-Medications administered in trial 046

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency (N = X)	Site of Manufacture
MK-5172	100 mg	WL00044049	Tablet	WL00051661	98.0%	Merck, Sharp & Dohme Corp West Point, PA
Nordette [®] -28 (levonorgestrel/ ethinyl estradiol) [†]	0.15 mg/0.03 mg	NA	Tablet	NA	NA	Teva Women's Health, Inc.,
[†] Nordette [®] -28 (a product manufactured by Teva Women's Health, Inc., subsidiary of Teva Pharmaceuticals USA, Inc.) was purchased by the Investigator. The lot number was 33803617A; expiration date Jan-2014.						

(Note: the trial report states that either use of Nordette 28 or a generic equivalent was permitted)

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included ethinyl estradiol and levonorgestrel predose and postdose blood samples up to 96 hours in period 1 and period 2.

Bioanalysis

The method and bioanalysis of ethinyl estradiol are acceptable.

Ethinyl estradiol plasma samples were analyzed using a validated LC/MS/MS method in K₂EDTA anticoagulated plasma by (b) (4). The blood samples for analysis of ethinyl estradiol appear to have been collected in tubes containing K₂EDTA as an anticoagulant.

For the plasma samples from the P46 trial that were analyzed for ethinyl estradiol, the lower limit of quantification for ethinyl estradiol was 1 pg/mL and the upper limit of quantification was 200 pg/mL. There were no precision or accuracy issues identified for ethinyl estradiol based on the bioanalytical report. However, not all of the plasma quality control samples that were evaluated as part of the P46 bioanalysis were included in the QC concentrations that were validated. In the method validation, QC concentrations of 3.01 g/mL, 70.14 pg/mL and 150.30 pg/mL were validated. For the P46 trial, precision and accuracy were evaluated using plasma ethinyl estradiol quality control (QC) samples at 3 pg/mL, 10 pg/mL, 100 pg/mL, and 150 pg/mL. The corresponding ethinyl estradiol inter-run accuracy values were -2.47% for 3 pg/mL, -2.51% for 10 pg/mL, -1.92% for 100 pg/mL and -6.34% for 150 pg/mL. The ethinyl estradiol inter-run precision values were 2.10% for 3 pg/mL, 1.65% for 10 pg/mL, 1.20% for 100 pg/mL and 1.05% for 150 pg/mL.

Incurred sample reanalysis for ethinyl estradiol was not conducted for the P46 trial.

For the P46 trial, no information was provided regarding either the duration or the storage temperature for the ethinyl estradiol plasma samples. Specific information regarding whether fresh calibration standards were used as part of the stability evaluations was not provided by (b) (4). For the P46 trial, the long term ethinyl estradiol stability data (fortified with 4960 pg/mL of levonorgestrel) of 273 days at -20°C and -80°C in K₂EDTA anticoagulated plasma generated by (b) (4) appears sufficient if the information

in section 2 is correct (the bioanalytical report states that the date of last analysis was May 12, 2013) and samples were stored at either -20°C or -80°C.

The method and bioanalysis of levonorgestrel are acceptable.

Levonorgestrel plasma samples were analyzed using a validated LC/MS/MS method in K₂EDTA anticoagulated plasma by (b) (4). The blood samples for analysis of levonorgestrel appear to have been collected in tubes containing K₂EDTA as an anticoagulant.

For the plasma samples from the P46 trial that were analyzed for levonorgestrel, the lower limit of quantification for levonorgestrel was 25 pg/mL and the upper limit of quantification was 5000 pg/mL. There were no precision or accuracy issues identified for levonorgestrel based on the bioanalytical report. However, not all of the plasma quality control samples that were evaluated as part of the P46 bioanalysis were included in the QC concentrations that were validated. In the method validation, QC concentrations of 75.45 pg/mL, 1760.50 pg/mL and 3772.5 pg/mL were validated. For the P46 trial, precision and accuracy were evaluated using plasma levonorgestrel quality control (QC) samples at 75 pg/mL, 375 pg/mL, 2500 pg/mL, and 3750 pg/mL. The corresponding levonorgestrel inter-run accuracy values were -3.43% for 75 pg/mL, -0.38% for 375 pg/mL, 0.45% for 2500 pg/mL, and -1% for 3750 pg/mL. The levonorgestrel inter-run precision values were 3.88% for 75 pg/mL, 2.65% for 375 pg/mL, 1.58% for 2500 pg/mL, and 1.08% for 3750 pg/mL.

Incurred sample reanalysis for levonorgestrel was not conducted for the P46 trial.

For the P46 trial, no information was provided regarding either the duration or the storage temperature for the levonorgestrel plasma samples. Specific information regarding whether current reference standards were used as part of the stability evaluations was not provided by (b) (4). For the P46 trial, the long term levonorgestrel stability data (fortified with 201 pg/mL of ethinyl estradiol) of 101 days at -20°C and -80°C in K₂EDTA anticoagulated plasma generated by (b) (4) appears sufficient if the information in section 2 is correct (the bioanalytical report states that the date of last analysis was May 11, 2013) and samples were stored at either -20°C or -80°C.

Pharmacokinetic Assessments

Based on the information included in the trial report, noncompartmental analysis was performed using actual sampling times to derive ethinyl estradiol and levonorgestrel plasma pharmacokinetic parameters, including C_{max} and AUC_(0-inf).

Statistical Analysis

The statistical analyses included deriving 90% confidence intervals for ethinyl estradiol and levonorgestrel pharmacokinetic parameters comparing the test arm (concomitant use of ethinyl estradiol and levonorgestrel [Nordette 28] with grazoprevir to the reference arm (concomitant use of ethinyl estradiol and levonorgestrel [Nordette 28] alone).

10. Results

10.1 Subject Demographics

Table 2-P46 subject demographics

AN	Gender	Race	Ethnicity	Age (yr)	Height (cm)	Weight (kg)	Body Mass Index (kg/m ²)
0001	Female	White	Not Hispanic or Latino	64	166.0	65.7	23.80
0002	Female	White	Not Hispanic or Latino	59	162.0	73.7	27.96
0003	Female	White	Not Hispanic or Latino	59	160.0	77.1	30.02
0004	Female	White	Hispanic or Latino	65	157.0	76.3	30.96
0005	Female	White	Hispanic or Latino	55	158.0	64.6	25.96
0006	Female	White	Not Hispanic or Latino	63	156.0	72.9	29.99
0007	Female	White	Not Hispanic or Latino	51	168.0	68.6	24.18
0008	Female	White	Not Hispanic or Latino	50	157.0	55.4	22.42
0009	Female	White	Not Hispanic or Latino	53	158.0	58.7	23.36
0010	Female	White	Hispanic or Latino	53	160.0	75.6	29.51
0011	Female	White	Hispanic or Latino	47	158.0	78.4	31.50
0012	Female	White	Hispanic or Latino	54	164.0	76.8	28.63
0013	Female	White	Not Hispanic or Latino	57	167.0	62.9	22.64
0014	Female	White	Hispanic or Latino	52	160.0	63.0	24.78
0015	Female	White	Hispanic or Latino	44	164.0	58.8	21.90
0016	Female	White	Not Hispanic or Latino	51	168.0	82.9	29.50
0017	Female	White	Hispanic or Latino	54	165.0	70.5	25.78
0018	Female	White	Not Hispanic or Latino	50	162.0	66.8	25.43
0019	Female	White	Hispanic or Latino	49	150.0	68.7	30.37
0020	Female	Black or African American	Not Hispanic or Latino	54	165.0	74.2	27.14
Study Summary							
N:				20	20	20	20
Range:				44 to 65	150.0 to 168.0	55.4 to 82.9	21.90 to 31.50
Arithmetic Mean:				54	161.3	69.6	26.79
AN = Allocation number.							

10.2 Concomitant Medications

The concomitant medications that were administered in the trial included ibuprofen, diphenhydramine, topical hydrocortisone and topical bacitracin, neomycin and polymyxin. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Table 3-Ethinyl estradiol pharmacokinetic parameters

AN	AUC _{0-∞} (nM•hr)			C _{max} (nM)			T _{max} (hr)		Apparent terminal t _{1/2} (hr)	
	Nordette®-28 Alone	Nordette®-28 With MK-5172	Nordette®-28 With MK-5172/ Nordette®-28 Alone	Nordette®-28 Alone	Nordette®-28 With MK-5172	Nordette®-28 With MK-5172/ Nordette®-28 Alone	Nordette®-28 Alone	Nordette®-28 With MK-5172	Nordette®-28 Alone	Nordette®-28 With MK-5172
N	20	20	20	20	20	20	20	20	20	20
AM	3.00	3.29	1.10	0.251	0.263	1.06	1.48	1.27	19.95	20.58
SD	0.770	0.883	0.12	0.0592	0.0618	0.19	0.41	0.35	4.67	3.91
ACV	25.7	26.9	10.6	23.6	23.5	18.1	27.7	27.1	23.4	19.0
Med	3.03	3.30	1.07	0.250	0.267	1.07	1.50	1.00	18.28	20.32
Min	1.06	1.40	0.95	0.147	0.173	0.80	0.99	0.99	13.43	15.16
Max	4.48	5.38	1.34	0.348	0.410	1.53	2.04	2.01	29.28	30.77
GM	2.88	3.16	1.10	0.244	0.256	1.05	1.43	1.23	19.46	20.25
GCV	31.8	30.1	10.4	24.5	23.5	17.8	29.1	25.9	23.0	18.6

Nordette®-28 Alone: Single oral dose of 0.03 mg EE/0.15 mg LNG (1 Nordette®-28 tablet) on Day 1 of Period 1.
 Nordette®-28 With MK-5172: Multiple oral doses of 200 mg MK-5172 (2 X 100 mg tablets) qd on Days 1 - 10 of Period 2 and a single oral dose of 0.03 mg EE/0.15 mg LNG (1 Nordette®-28 tablet) on Day 7.
 AN = Allocation number; AM = Arithmetic mean; SD = Standard deviation; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: 100 x (SD/AM)
 Med = Median; Min = Minimum; Max = Maximum.
 GM = Geometric mean; GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s²) - 1), where s² is the observed variance on the natural log scale.

Table 4-Levonorgestrel pharmacokinetic parameters

AN	AUC _{0-∞} (nM•hr)			C _{max} (nM)			T _{max} (hr)		Apparent Terminal t _{1/2} (hr)	
	Nordette®-28 Alone	Nordette®-28 With MK-5172	Nordette®-28 With MK-5172/ Nordette®-28 Alone	Nordette®-28 Alone	Nordette®-28 With MK-5172	Nordette®-28 With MK-5172/ Nordette®-28 Alone	Nordette®-28 Alone	Nordette®-28 With MK-5172	Nordette®-28 Alone	Nordette®-28 With MK-5172
N	20	20	20	20	20	20	20	20	20	20
AM	122	156	1.25	8.18	7.35	0.96	1.47	2.03	40.59	45.80
SD	50.3	78.7	0.22	3.28	2.12	0.26	0.53	1.01	13.38	17.65
ACV	41.2	50.4	17.6	40.1	28.8	26.9	35.9	49.6	33.0	38.5
Med	114	149	1.21	7.30	7.02	0.89	1.51	2.00	37.57	41.53
Min	47.4	56.9	0.82	3.21	4.01	0.64	1.00	0.51	24.78	20.53
Max	281	413	1.64	14.7	11.4	1.41	2.99	4.01	76.20	88.78
GM	114	140	1.23	7.58	7.05	0.93	1.39	1.79	38.75	42.90
GCV	39.0	50.2	18.6	42.1	30.2	27.0	33.5	57.8	31.4	38.1

Nordette®-28 Alone: Single oral dose of 0.03 mg EE/0.15 mg LNG (1 Nordette®-28 tablet) on Day 1 of Period 1.
 Nordette®-28 With MK-5172: Multiple oral doses of 200 mg MK-5172 (2 X 100 mg tablets) qd on Days 1-10 of Period 2 and a single oral dose of 0.03 mg EE/0.15 mg LNG (1 Nordette®-28 tablet) on Day 7.
 AN = Allocation number; AM = Arithmetic mean; SD = Standard deviation; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: 100 x (SD/AM)
 Med = Median; Min = Minimum; Max = Maximum.
 GM = Geometric mean; GCV = Geometric coefficient of variation is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s²) - 1), where s² is the observed variance on the natural log scale.
 Note: For Levonorgestrel, the AUC_{0-∞,pred} was ≥ 25% for Subjects AN 0005, AN 0010, and AN 0012 of Period 1 and Subjects AN 0004, AN 0005, AN 0010, AN 0012, AN 0013, and AN 0020 of Period 2. However, the AUC_{0-∞} values for all subjects were included in the summary statistics.

Table 5-Ethinyl estradiol and levonorgestrel statistical analyses

		Nordette®-28 Alone			Nordette®-28 With MK-5172			Nordette®-28 With MK-5172/ Nordette®-28 Alone		Pseudo Within Subject %CV [†]
Nordette®-28 Component	Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
Ethinyl Estradiol	AUC _{0-∞} [‡] (nM•hr)	20	2.88	(2.49, 3.33)	20	3.16	(2.76, 3.63)	1.10	(1.05, 1.14)	7.328
	C _{max} [‡] (nM)	20	0.244	(0.218, 0.274)	20	0.256	(0.230, 0.286)	1.05	(0.98, 1.12)	12.476
	T _{max} [§] (hr)	20	1.50	(0.99, 2.04)	20	1.00	(0.99, 2.01)	.	.	.
	Apparent terminal t _{1/2} (hr)	20	19.46	23.00	20	20.25	18.63	.	.	.
Levonorgestrel	AUC _{0-∞} [‡] (nM•hr)	20	114	(95.5, 136)	20	140	(112, 175)	1.23	(1.15, 1.32)	13.044
	C _{max} [‡] (nM)	20	7.58	(6.28, 9.16)	20	7.05	(6.14, 8.10)	0.93	(0.84, 1.03)	18.748
	T _{max} [§] (hr)	20	1.51	(1.00, 2.99)	20	2.00	(0.51, 4.01)	.	.	.
	Apparent terminal t _{1/2} (hr)	20	38.75	31.38	20	42.90	38.08	.	.	.

Nordette®-28 Alone: Single oral dose of 0.03 mg EE/0.15 mg LNG (1 Nordette®-28 tablet) on Day 1 of Period 1.
 Nordette®-28 With MK-5172: Multiple oral doses of 200 mg MK-5172 (2 X 100 mg tablets) qd on Days 1 - 10 of Period 2 and a single oral dose of 0.03 mg EE/0.15 mg LNG (1 Nordette®-28 tablet) on Day 7.
[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (min, max) reported for T_{max}.
^{||}Geometric mean and geometric CV reported for apparent terminal t_{1/2}.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio
 Note: For Levonorgestrel, the AUC_{0-∞} predicted was ≥ 25% for Subjects AN 0005, AN 0010, and AN 0012 of Period 1 and Subjects AN 0004, AN 0005, AN 0010, AN 0012, AN 0013, and AN 0020 of Period 2. However, the AUC_{0-∞} values for all subjects were included in the ANOVA.

10.4 Safety Analysis

According to the trial report, no deaths or serious adverse events or laboratory abnormalities were reported for the trial and the most common adverse events were nausea and headache that occurred in two subjects.

11. Discussion and Conclusions

Based on the results from the P46 trial, the following conclusions can be made:

- When a single dose of 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel (Nordette 28) was administered with grazoprevir 200 mg once daily:
 - the ethinyl estradiol AUC_(0-∞) and C_{max} were increased by 10% and 5%, respectively, and the 90% confidence intervals were within the standard limits of 80% to 125% for both parameters
 - the levonorgestrel AUC_(0-∞) was increased by 23% (the 90% confidence intervals were not within the standard limits of 80% to 125%) and C_{max} was decreased by 7% (the 90% confidence intervals were within the standard limits of 80% to 125%)

The results support the absence of a clinically significant effect of grazoprevir on ethinyl estradiol or levonorgestrel exposure.

Study Title: A Study to Evaluate the Interaction of MK-5172 and MK-8742 with Rilpivirine in Healthy Subjects

Study Initiation Date: 03-Jan-2014

Study Completion Date: 25-Mar-2014

Study Site: (b) (4)

Primary Objective: To assess the effect of multiple oral doses of MK-5172 and MK-8742 on the steady state pharmacokinetics of rilpivirine and the effect of multiple oral doses of rilpivirine on the steady state pharmacokinetics of MK-5172 and MK-8742.

Study Design

This was an open-label, 3-period, fixed-sequence study to assess the effect of multiple oral doses of MK-5172 and MK-8742 on the steady-state pharmacokinetics of rilpivirine, and the effect of multiple oral doses of rilpivirine on the steady-state pharmacokinetics of MK-5172 and MK-8742. Twenty healthy subjects were enrolled.

In Period 1, oral doses of 200 mg MK-5172 and 50 mg MK-8742 were co-administered QD from Days 1 to 8. In Period 2, oral doses of 25 mg rilpivirine were administered QD from Days 1 to 11. In Period 3, oral doses of 200 mg MK-5172, 50 mg MK-8742, and 25 mg rilpivirine were co-administered QD from Days 1 to 9. There was a washout period of 9 days between the last dose of MK-5172 and MK-8742 in Period 1 and the first dose of rilpivirine in Period 2. There was no washout period between the last dose of rilpivirine in Period 2 and the first dose of MK-5172, MK-8742, and rilpivirine in Period 3. Study medication was administered under fed conditions, approximately 30 minutes after the start of a normal-fat breakfast. Dosing was scheduled to occur at approximately the same time in the morning each day.

Key Inclusion Criteria

- Healthy adult male and female volunteers, 19-55 years of age, inclusive
- BMI: 19- 32 kg/m², inclusive. Weigh at least 52 kg for males and 45 kg for females.
- Have not used nicotine-containing products for at least 3 months prior to the first dose)
- Medically healthy with no clinically significant history, physical exam, lab profiles. Liver function test results must be at or lower than ULN.
- For females of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using acceptable birth control methods. Male subjects must use a condom (or abstain from sexual intercourse) and agree not to donate sperm from the first dose until 90 days after the last dose

Key Exclusion Criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 80 mL/min
- History of drug or alcohol abuse (within 2 years)
- Female subjects who are pregnant or lactating

- Positive results at screening for HIV, hepatitis B, or hepatitis C
- Positive results for urine drug, urine cotinine, or alcohol screening or check in
- Unable to refrain from or anticipates the use of any drug beginning 14 days (28 days for CYP/P-gp inducers) prior to the first dose of study drug and throughout the study.
- Donation of blood or had significant blood loss within 4 weeks prior to the first dose of study drug or plasma donation within 7 days prior to the first dose of study drug.
- Participation in another clinical trial within 28 days prior to the first dose of study drug.
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients

Concomitant medications

Subjects were not allowed to take medication (including over-the-counter products), herbal products or vitamin supplements for the 14 days (or 28 days for CYP or P-gp inducers) prior to the first dose of the study and throughout the study. This prohibition did not include hormonal contraceptives and hormone replacement therapy or acetaminophen administered on study, as judged by the attending physician.

Identity of Investigational Product

Table 1. Identity of Investigational Products

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency	Site of Manufacture
MK-5172	100 mg	WL00047516	Tablet	WL00055721	98.6 %	(b) (4)
MK-8742	10 mg	DL00018432	(b) (4)	WL00055722	102.9 %	(b) (4)
Rilpivirine [†] (EDURANT [®])	25 mg	NA	Tablet	NA	NA	NA
[†] Rilpivirine (EDURANT [®] , a product manufactured by Janssen-Cilag SpA) was purchased by the Investigator. The lot number was DCL5402; expiration date Aug-2015.						

Pharmacokinetic assessments

In Period 1, blood samples for the determination of MK-5172 and MK-8742 plasma concentrations were obtained predose on Days 1, 6, 7, 8, and at specified time points up to 24 hours postdose on Day 8. In Period 2, blood samples for the determination of rilpivirine plasma concentration were collected on Days 1, 9, 10, 11, and at specified time points up to 24 hours postdose on Day 11. In Period 3, blood samples for the determination of MK-5172, MK-8742 and rilpivirine plasma concentrations were obtained predose on Days 1, 7, 8, 9, and at specified time points up to 24 hours postdose on Day 9.

With the exception of C₂ and C₂₄ which were obtained using SAS[®] (Version 9.3), all of the pharmacokinetic parameters were calculated using the software Phoenix[®] WinNonlin[®] (Version 6.3). C_{max} and T_{max} were generated by WinNonlin[®] from each analyte's plasma concentration-time data. AUC was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down).

Bioanalysis

Plasma samples collected for rilpivirine quantitation were analyzed by (b) (4)

Plasma samples collected for MK-5172 and MK-8742 quantitation were analyzed by Merck (Oss, The Netherlands). The concentrations of these drugs were determined using validated LC/MS/MS methods. All methods were adequately validated. The standard curve and QC data indicated assays were acceptable. All samples were stored and processed in the time frame supported by the stability data.

Table 2. Summary of Bioanalysis

Analyte	MK-5172	MK-8742	Rilpivirine
Internal standard	MK-5172-d ₆	MK-8742-d ₆	Rilpivirine-d ₆
Matrix/Anticoagulant	Plasma/ K ₂ EDTA	Plasma/ K ₂ EDTA	Plasma/ K ₂ EDTA
Calibration range	1 to 1000 ng/mL	0.25 to 500 ng/mL	0.5 to 500 ng/mL
QC concentration	3, 20, 75, and 750 ng/mL	0.75, 75, and 375 ng/mL	1.5, 25, 250, and 375 ng/mL
Interday precision and accuracy	P: 3.3 to 4.3% A: -5.2 to -4%	P: 3.2 to 4.7% A: 4.5 to 10.9%	P: 1.4 to 2.0% A: - 7.2 to -1.3%
Storage stability	825 days at – 20 °C	651 days at – 20 °C	113 days at – 20 °C

RESULTS

Subject disposition and baseline characteristics

Twenty subjects were enrolled into the study and 18 subjects completed the study per protocol (Table 3) . Subject AN 0007 received all doses in the study as per protocol but was lost to follow-up. One subject (AN 0010) withdrew from the study due to personal reasons prior to Day 8 dosing in Period 1. This subject received 7 doses of MK-5172 and MK-8742 in Period 1

Concomitant medications

The concomitant medications that were administered in the trial included acetaminophen, ibuprofen, and vitamins. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

Table 3. Subject baseline demographics

AN	Gender	Race	Ethnicity	Age (yr)	Height (cm)	Weight (kg)	Body Mass Index (kg/m ²)
0001	Female	White	Not Hispanic or Latino	38	165.0	62.8	23.17
0002	Male	White	Not Hispanic or Latino	42	179.0	92.7	29.00
0003	Female	White	Not Hispanic or Latino	26	156.0	60.1	24.69
0004	Female	White	Hispanic or Latino	52	158.0	63.8	25.49
0005	Male	White, Black or African American	Hispanic or Latino	29	173.0	89.9	30.12
0006	Male	White	Not Hispanic or Latino	21	184.0	103.2	30.61
0007	Female	White	Not Hispanic or Latino	34	171.0	87.5	30.02
0008	Female	White	Not Hispanic or Latino	28	159.0	55.9	22.03
0009	Male	White	Not Hispanic or Latino	49	177.0	81.0	25.76
0010	Male	Black or African American	Not Hispanic or Latino	25	178.0	83.2	26.18
0011	Male	White	Not Hispanic or Latino	37	186.0	84.0	24.37
0012	Male	White	Not Hispanic or Latino	28	178.0	99.0	31.13
0013	Female	White	Not Hispanic or Latino	25	165.0	83.5	30.71
0014	Male	White	Not Hispanic or Latino	21	186.0	107.4	31.14
0015	Female	White	Unknown	23	160.0	57.9	22.55
0016	Male	White	Not Hispanic or Latino	44	180.0	98.3	30.48
0017	Female	White	Not Hispanic or Latino	27	163.0	57.7	21.85
0018	Male	White	Not Hispanic or Latino	28	173.0	89.4	29.87
0019	Female	White	Not Hispanic or Latino	55	183.0	77.3	23.11
0020	Female	White	Not Hispanic or Latino	30	162.0	58.4	22.30
Study Summary							
N:				20	20	20	20
Range:				21 to 55	156.0 to 186.0	55.9 to 107.4	21.85 to 31.14
Arithmetic Mean:				33	171.8	79.7	26.73
Female N:				10	10	10	10
Female Range:				23 to 55	156.0 to 183.0	55.9 to 87.5	21.85 to 30.71
Female Arithmetic Mean:				34	164.2	66.5	24.59
Male N:				10	10	10	10
Male Range:				21 to 49	173.0 to 186.0	81.0 to 107.4	24.37 to 31.14
Male Arithmetic Mean:				32	179.4	92.8	28.87
AN = Allocation Number.							
Program: /CA13143/sas_prg/stsas/intext/cdem.sas 03APR2014 15:34							

Pharmacokinetic Results

The exposures of MK-5172 and MK-8742 were not altered by the co-administration of rilpivirine (Table 4-5). The exposure of rilpivirine was not altered by the co-administration of MK-5172 and MK-8742 (Table 6).

Table 4. MK-5172 plasma pharmacokinetics with or without the co-administration of rilpivirine

MK-5172 Pharmacokinetic Parameter	MK-5172 + MK-8742			Rilpivirine + MK-5172 + MK-8742			Rilpivirine + MK 5172 + MK-8742 / MK-5172 + MK-8742		
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	Pseudo Within Subject %CV [†]
AUC ₀₋₂₄ [‡] (μM•hr)	19	3.61	(2.67, 4.87)	19	3.53	(2.58, 4.83)	0.98	(0.89, 1.07)	16.373
C _{max} [‡] (μM)	19	1.04	(0.749, 1.44)	19	1.01	(0.689, 1.49)	0.97	(0.83, 1.14)	28.049
C ₂ [‡] (μM)	19	0.337	(0.181, 0.626)	19	0.333	(0.148, 0.748)	0.99	(0.56, 1.74)	100.114
C ₂₄ [‡] (nM)	19	16.4	(12.6, 21.3)	19	16.3	(12.6, 21.1)	1.00	(0.93, 1.07)	12.924
T _{max} [§] (hr)	19	3.00	(1.50, 5.01)	19	3.00	(1.50, 8.01)			

MK-5172 + MK-8742: 200 mg MK-5172 QD and 50 mg MK-8742 QD on Days 1 to 8 of Period 1
Rilpivirine + MK-5172 + MK-8742: 200 mg MK-5172 QD, 50 mg MK-8742 QD, and 25 mg rilpivirine on Days 1 to 9 of Period 3.
[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma^2_A + \sigma^2_B - 2*\sigma_{AB})/2}$, where σ^2_A and σ^2_B are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.
^{||}Subject AN 0010 dropped from study before dosing on Day 8 of Period 1, this subject was removed from statistical analysis.
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Table 5. MK-8742 plasma pharmacokinetics with or without the co-administration of rilpivirine

MK-8742 Pharmacokinetic Parameter	MK-5172 + MK-8742			Rilpivirine + MK-5172 + MK-8742			Rilpivirine + MK 5172 + MK-8742 / MK-5172 + MK-8742		
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	Pseudo Within Subject %CV [†]
AUC ₀₋₂₄ [‡] (μM•hr)	19	2.86	(2.44, 3.36)	19	3.07	(2.62, 3.61)	1.07	(1.00, 1.15)	11.952
C _{max} [‡] (μM)	19	0.186	(0.156, 0.221)	19	0.200	(0.170, 0.234)	1.07	(0.99, 1.16)	13.754
C ₂ [‡] (μM)	19	0.0844	(0.0714, 0.0998)	19	0.0943	(0.0792, 0.112)	1.12	(0.99, 1.26)	21.306
C ₂₄ [‡] (nM)	19	88.7	(75.3, 104)	19	92.3	(78.3, 109)	1.04	(0.98, 1.11)	11.473
T _{max} [§] (hr)	19	5.02	(4.00, 8.01)	19	5.00	(4.00, 6.02)			

MK-5172 + MK-8742: 200 mg MK-5172 QD and 50 mg MK-8742 QD on Days 1 to 8 of Period 1.
Rilpivirine + MK-5172 + MK-8742: 200 mg MK-5172 QD, 50 mg MK-8742 QD, and 25 mg rilpivirine on Days 1 to 9 of Period 3.
[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma^2_A + \sigma^2_B - 2*\sigma_{AB})/2}$, where σ^2_A and σ^2_B are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.
^{||}Subject AN 0010 dropped from study before dosing on Day 8 of Period 1, this subject was removed from statistical analysis.
Program: /CA13143/sas_prg/pksas/stats-it_old.sas 25JUN2014 11:06

Table 6. Rilpivirine plasma pharmacokinetics with or without the co-administration of MK-5172 and MK-8742

Rilpivirine Pharmacokinetic Parameter	Rilpivirine			Rilpivirine + MK-5172 + MK-8742			Rilpivirine + MK 5172 + MK-8742 / Rilpivirine		
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	Pseudo Within Subject %CV [†]
AUC ₀₋₂₄ [‡] (µg•hr/mL)	19	3.16	(2.79, 3.58)	19	3.58	(3.09, 4.15)	1.13	(1.07, 1.20)	10.508
C _{max} [‡] (ng/mL)	19	199	(176, 226)	19	212	(184, 245)	1.07	(0.97, 1.17)	16.621
C ₂₄ [‡] (ng/mL)	19	124	(106, 146)	19	144	(120, 173)	1.16	(1.09, 1.23)	10.582
T _{max} [§] (hr)	19	4.00	(4.00, 16.00)	19	5.00	(4.00, 16.04)			

Rilpivirine alone: 25 mg rilpivirine QD on Days 1 to 11 of Period 2.
Rilpivirine + MK-5172 + MK-8742: 200 mg MK-5172 QD, 50 mg MK-8742 QD, and 25 mg rilpivirine on Days 1 to 9 of Period 3.

[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least squares mean and confidence interval from linear mixed effect model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

G = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

^{||}Subject AN 0010 dropped from study before dosing on Day 8 of Period 1, this subject was removed from statistical analysis.

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Conclusion

No drug interaction was observed between rilpivirine and MK-5172/MK-8742. Rilpivirine and MK-5172/MK-8742 can be co-administered.

Title: A Two-Part Study to Evaluate the Effect of Multiple Doses of MK-5172 and MK-8742 on the Single Dose Pharmacokinetics of Rosuvastatin and Pravastatin (PN054)

Study Initiation Date: 30-Dec-2013

Study Completion Date: 20-Feb-2014

Study Site: (b) (4)

Primary Study Objective: To determine the effect of steady-state MK-5172 and MK-8742 on the pharmacokinetics of single-dose rosuvastatin or pravastatin in healthy subjects.

Study design

This was an open-label, 2-part, fixed-sequence study to evaluate the effect of MK-5172 and MK-8742 on the single-dose pharmacokinetics of rosuvastatin and pravastatin. A total of 24 healthy adult subjects (12 subjects in each part), with at least 4 female subjects in each part, were enrolled in the study. Subjects fasted overnight for at least 8 hours prior to drug administration on PK sample collections days. On all other days, subjects fasted for at least 1 hour prior to dosing.

Table 1. Study design

Study Part	Period 1	Period 2	Period 3
1	Rosuvastatin 10 mg (single dose) on Day 1 <i>PK sampling: on Day 1</i>	MK-5172 200 mg QD for 9 days and rosuvastatin 10mg single dose on Day 7 <i>PK sampling: on Days 6 and Day 7</i>	MK-5172 200 mg QD and MK-8742 50 mg QD for 11 days and rosuvastatin 10mg single dose on Day 9 <i>PK sampling: on Days 8 and 9</i>
2	Pravastatin 40 mg on Day 1 <i>PK sampling: on Day 1</i>	MK-5172 200 mg QD and MK-8742 50 mg QD for 9 days Rosuvastatin 10mg single dose on Day 9 <i>PK sampling: on Days 8 and 9</i>	None

Key inclusion criteria

- Healthy adult male and female subjects, 19-55 years of age, inclusive
- BMI: 19-32 kg/m², inclusive
- Have not used nicotine-containing products for at least 3 months prior to the first dose
- Medically healthy with no clinically significant history, physical exam, lab profiles
- A female of childbearing potential must either sexually inactive or use acceptable birth control methods.
- Male subjects must agree not to donate sperm from the first dose until 90 days after the last dose

Key exclusion criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 90 mL/min
- History of alcoholism or drug abuse (within 2 years)
- History of myopathy or rhabdomyolysis
- Positive results at screening for HIV, hepatitis B, hepatitis C, urine drug, urine cotinine, or alcohol screening
- Donation of blood or had significant blood loss within 56 days prior to the first dose of study drug or plasma donation within 7 days prior to the first dose of study drug.
- Participation in another clinical trial within 28 days prior to the first dose of study drug.
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients

Identity of clinical supplies

Table 2. Identity of clinical supplies

Bulk Product Description	Manufacturing Lot Number
(b) (4) MK-5172 (b) (4) 100 mg	WL00047516
MK-8742 (b) (4) 10 mg	DL00018432
Rosuvastatin 10 mg Tablet [†]	NA
Pravastatin 40 mg Tablet [‡]	NA
[†] Crestor [®] (Rosuvastatin calcium), manufactured by Corden Pharma GmbH., was purchased by the Investigator. The lot number was BN0138; expiration date May-2016. [‡] Pravachol [®] (Pravastatin sodium), manufactured by Bristol-Myers Squibb Company, was purchased by the Investigator. The lot number was 2K71785A; expiration date Oct-2015.	

Concomitant medications and dietary restrictions

No subjects were to take medication for the 14 days (or 28 days for CYP or P-gp inducers) prior to the first dose of the study. Consumption of foods and beverages containing the following substances was prohibited. During the study, acetaminophen (up to 2 g per 24 hours) may have been administered at the discretion of the Investigator.

Xanthines/Caffeine: 24 hours before first dosing and throughout the study

- Alcohol: 48 hours before first dosing and throughout the study
- Vegetables from the mustard green family and charbroiled meats: 14 days before first dosing and throughout the study
- Fruit Juice: 72 hours before first dosing and throughout the study.
- Grapefruit/Seville orange: 14 days before first dosing and throughout the study.

Pharmacokinetic assessments

In Part 1, blood samples for rosuvastatin pharmacokinetics were collected at predose and over 72 hours on Day 1 of Period 1, Day 7 of Period 2, and Day 9 of Period 3. Blood samples for the determination of

plasma MK-5172 were obtained at predose and over 24 hours on Days 6 and 7 of Period 2, and Days 8 and 9 of Period 3. Blood samples for the determination of plasma MK-8742 were obtained at predose and over 24 hours on Days 8 and 9 of Period 3. In Part 2, blood samples for the determination of plasma pravastatin were collected at predose and over 24 hours on Day 1 of Period 1 and Day 9 of Period 2. Blood samples for the determination of plasma MK-5172 and MK-8742 were collected up to 24 hours on Days 8 and 9 of Period 2.

C₂ and C₂₄ values were obtained using SAS (Version 9.3). All other pharmacokinetic parameters were calculated using the software WinNonlin Phoenix 6.3. C_{max} and T_{max} were generated by WinNonlin from each analyte's plasma concentration-time data. All AUC parameters were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down).

Bioanalysis

Rosuvastatin and pravastatin bioanalyses were conducted by (b) (4) MK-5172 and MK-8742 bioanalyses were conducted by Merck Sharp & Dohme (The Netherlands). The concentrations of these drugs were determined using validated LC/MS/MS methods. All methods were adequately validated. The standard curve and QC data indicated that assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data.

Table 3. Summary of bioanalysis

Analyte	Rosuvastatin	Pravastatin	MK5172	MK-8742
Internal standard	Rosuvastatin-d ₆	Pravastatin-d ₂	MK-5172-d ₆	MK-8742-d ₆
Matrix/Anticoagulant	Plasma/K ₂ EDTA	Plasma/K ₂ EDTA	Plasma/K ₂ EDTA	Plasma/K ₂ EDTA
Extraction method	Liquid-liquid extraction	Liquid-liquid extraction	Liquid-liquid extraction	Liquid-liquid extraction
Calibration range and regression method	0.1 to 60 ng/mL Quadratic, 1/conc	0.2 to 400 ng/mL Quadratic, 1/conc	1 to 1000 ng/mL 1/x ² regression	0.25 to 500 ng/mL 1/x ² regression
QC concentration	0.3, 28, and 50 ng/mL	0.6, 15, 200, and 350 ng/mL	3, 20, 75, and 750 ng/mL	0.75, 75, and 375 ng/mL
Interday precision and accuracy	P: 2.1 to 3.0% A: 2.2 to 4.7%	P: 2.0 to 5.2% A: 1.7 to 4.5%	P: 2.5 to 2.8 % A: -3.2 to -1.5%	P:3.8 to 6.9% A:4.3 to 9.7%
Storage stability	40 Days at - 80 °C	498 Days at - 80 °C	825 Days - 20 °C	651 Days - 80 °C

Results

Trial subjects and baseline demographics

Twenty-four subjects were enrolled in the study and 23 subjects completed the study per protocol. One subject (AN002) was discontinued on Day 6 of Period 2 due to elevated creatinine phosphokinase (considered by the Investigator not be related to study drug).

Table 4. Subject baseline demographics

	Part 1 N=12	Part 2 N=12
Age in Years, Mean (range)	41 (28-49)	39 (23-50)
Sex, n (%)		
Female	5 (42%)	5 (42%)
Male	7 (58%)	7 (58%)
BMI (kg/m ²), range	26.65 (21.76-31.73)	26.40 (20.74-29.93)
Height (cm), range	161.4 (152.0 – 170.0)	165.5 (155.0 – 184.0)
Weight (kg), range	69.7 (50.5 – 90.8)	71.9 (64.6 – 80.8)
Ethnicity, n (%)		
Hispanic or Latino:	12 (100%)	11 (92%)
Not Hispanic or Latino:	0 (0%)	1 (8%)
Race, n (%)		
White	12 (100%)	11 (92%)
African American/Black	0	1 (8%)

Pharmacokinetic results

1. The effects of MK-5172 and MK-8742 co-administration on rosuvastatin exposures

The co-administration of MK-5172 and MK-8742 increased C_{max} and AUC_{inf} of rosuvastatin by 5.49-fold and 2.26-fold (Table 5). When rosuvastatin and MK-5172 (without MK-8742) was co-administered, rosuvastatin AUC_{inf} and C_{max} were increased by 1.59-fold and 4.25-fold, respectively (Table 6).

Therefore, the major contribution to the increase in rosuvastatin exposure appears to be from MK-5172. The co-administration of single dose rosuvastatin did not alter the pharmacokinetic profiles of MK-5172 or MK-8742 (Table 7 and Table 8)

Table 5. Rosuvastatin plasma pharmacokinetics with or without the co-administration of MK-5172 and MK-8742

Pharmacokinetic Parameter	Rosuvastatin Alone			Rosuvastatin + MK-5172 + MK-8742			Rosuvastatin + MK-5172 + MK-8742/ Rosuvastatin Alone		Pseudo Within Subject %CV [†]
	N [‡]	GM	95% CI	N ^{‡††}	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$ [‡] (ng/mL·hr)	8	60.5	(44.8, 81.6)	8	136	(107, 174)	2.26	(1.89, 2.69)	18.293
AUC_{0-24} [‡] (ng/mL·hr)	12	40.0	(29.3, 54.6)	11	107	(83.5, 137)	2.68	(2.26, 3.17)	22.545
C_{max} [‡] (ng/mL)	12	4.92	(3.51, 6.91)	11	27.1	(20.4, 35.9)	5.49	(4.29, 7.04)	33.423
C_{24} [‡] (ng/mL)	12	0.431	(0.349, 0.533)	11	0.421	(0.336, 0.528)	0.98	(0.84, 1.13)	19.421
CL/F [‡] (L/hr)	8	165	(123, 223)	8	73.3	(57.4, 93.7)	0.44	(0.37, 0.53)	18.293
V_z/F [‡] (L)	8	4330	(3010, 6220)	8	1720	(1330, 2230)	0.40	(0.29, 0.54)	32.404
T_{max} [§] (hr)	12	5.00	(3.00, 6.00)	11	2.00	(1.00, 3.00)			
Apparent terminal $t_{1/2}$ (hr)	8	18.24	27.88	8	16.60	24.04			
Alpha $t_{1/2}$ (hr)	12	3.47	13.03	11	2.18	20.96			

Rosuvastatin alone: 10 mg rosuvastatin at Hour 0 on Day 1, Period 1.
Rosuvastatin + MK-5172 + MK-8742: 200 mg MK-5172 QD and 50 mg MK-8742 QD on Days 1 to 11, and 10 mg rosuvastatin co-administered on Day 9, Period 3 (pharmacokinetic sampling on Day 9).
[†]Pseudo Within-Subject %CV = $100 \cdot \sqrt{(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max} .
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal $t_{1/2}$.
^{††}Terminal phases were not well characterized, as evidenced by poor correlation of linear regression ($R^2 < 0.80$) for Subject AN 0008 in Period 1 and for Subjects AN 0003, AN 0010, and AN 0011 in Periods 1 and 3. Consequently, $AUC_{0-\infty}$, CL/F, V_z/F , and the apparent terminal $t_{1/2}$ were only evaluable for 8 out of 12 subjects for Rosuvastatin Alone and for 8 out of 11 subjects for Rosuvastatin + MK-5172 + MK-8742.
^{†††}Subject AN 0002 was dropped from study on Day 6 of Period 2 due to elevated creatine phosphokinase and had no data available for Rosuvastatin + MK-5172 + MK-8742.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 6. Rosuvastatin plasma pharmacokinetics with or without the co-administration of MK-5172

Pharmacokinetic Parameter	Rosuvastatin Alone			Rosuvastatin + MK-5172			Rosuvastatin + MK-5172/ Rosuvastatin Alone		Pseudo Within Subject %CV [†]
	N [‡]	GM	95% CI	N ^{‡††}	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (ng/mL•hr)	8	60.5	(44.8, 81.6)	8	96.1	(78.5, 118)	1.59	(1.33, 1.89)	18.246
AUC ₀₋₂₄ [‡] (ng/mL•hr)	12	40.0	(29.3, 54.6)	11	73.8	(56.8, 95.9)	1.85	(1.56, 2.19)	22.647
C _{max} [‡] (ng/mL)	12	4.92	(3.51, 6.91)	11	20.9	(14.8, 29.7)	4.25	(3.25, 5.56)	36.122
C ₂₄ [‡] (ng/mL)	12	0.431	(0.349, 0.533)	11	0.344	(0.287, 0.412)	0.80	(0.70, 0.91)	17.816
CL/F [‡] (L/hr)	8	165	(123, 223)	8	104	(85.0, 127)	0.63	(0.53, 0.75)	18.246
V _z /F [‡] (L)	8	4330	(3010, 6220)	8	2950	(2180, 4010)	0.68	(0.50, 0.94)	34.133
T _{max} [§] (hr)	12	5.00	(3.00, 6.00)	11	2.00	(2.00, 3.00)			
Apparent terminal t _{1/2} (hr)	8	18.24	27.88	8	20.01	28.96			
Alpha t _{1/2} (hr)	12	3.47	13.03	11	2.38	17.73			

Rosuvastatin alone: 10 mg rosuvastatin at Hour 0 on Day 1, Period 1.
Rosuvastatin + MK-5172: 200 mg MK-5172 QD on Days 1 to 9 with 10 mg rosuvastatin co-administered on Day 7, Period 2 (pharmacokinetic sampling on Day 7).
[†]Pseudo Within-Subject %CV = 100*sqrt((σ_A² + σ_B² - 2σ_{AB})/2), where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
[¶]Terminal phases were not well characterized, as evidenced by poor correlation of linear regression (R² < 0.80) for Subject AN 0008 in Period 1 and for Subjects AN 0003, AN 0010, and AN 0011 in Periods 1 and 2. Consequently, AUC_{0-∞}, CL/F, V_z/F, and the apparent terminal t_{1/2} were only evaluable for 8 out of 12 subjects for Rosuvastatin Alone and for 8 out of 11 subjects for Rosuvastatin + MK-5172.
^{††}Subject AN 0002 was dropped from study on Day 6 of Period 2 due to elevated creatine phosphokinase and had no data available for Rosuvastatin + MK-5172.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 7. Steady-state MK-5172 plasma pharmacokinetics with or without the co-administration of a single dose rosuvastatin 20 mg

Pharmacokinetic Parameter	MK-5172 Alone			Rosuvastatin + MK-5172			Rosuvastatin + MK-5172/ MK-5172 Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (μM•hr)	11	2.40	(1.68, 3.41)	11	2.79	(1.92, 4.05)	1.16	(0.94, 1.44)	28.681
C _{max} [‡] (μM)	11	0.592	(0.367, 0.953)	11	0.668	(0.386, 1.16)	1.13	(0.77, 1.65)	50.279
C ₂ [‡] (μM)	11	0.264	(0.121, 0.576)	11	0.530	(0.283, 0.991)	2.01	(1.06, 3.80)	85.500
C ₂₄ [‡] (nM)	11	13.3	(9.67, 18.4)	11	12.4	(9.15, 16.9)	0.93	(0.84, 1.03)	13.590
T _{max} [§] (hr)	11	3.00	(2.00, 5.00)	11	3.01	(2.00, 5.01)			

MK-5172 alone: 200 mg MK-5172 QD on Days 1 to 6, Period 2 (pharmacokinetic sampling on Day 6).
Rosuvastatin + MK-5172: 200 mg MK-5172 QD on Days 1 to 9 with 10 mg rosuvastatin co-administered on Day 7, Period 2 (pharmacokinetic sampling on Day 7).
[†]Pseudo Within-Subject %CV = 100*sqrt((σ_A² + σ_B² - 2σ_{AB})/2), where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
^{||}Subject AN 0002 was dropped from study on Day 6 of Period 2 due to elevated creatine phosphokinase and has no data available for this analysis.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 8. Steady-state 8742 plasma pharmacokinetics with or without the co-administration of a single dose rosuvastatin 20 mg

Pharmacokinetic Parameter	MK-5172 + MK-8742			Rosuvastatin + MK-5172 + MK-8742			Rosuvastatin + MK-5172 + MK-8742/ MK-5172 + MK-8742		Pseudo Within Subject %CV [†]
	N [‡]	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (μM•hr)	11	2.14	(1.46, 3.13)	11	2.33	(1.78, 3.06)	1.09	(0.98, 1.21)	13.671
C _{max} [‡] (μM)	11	0.164	(0.114, 0.237)	11	0.183	(0.144, 0.233)	1.11	(0.99, 1.26)	15.615
C ₂ [‡] (μM)	11	0.112	(0.0666, 0.188)	11	0.144	(0.108, 0.190)	1.28	(0.96, 1.71)	37.163
C ₂₄ [‡] (nM)	11	59.4	(38.6, 91.3)	11	57.1	(41.4, 78.8)	0.96	(0.86, 1.08)	15.103
T _{max} [§] (hr)	11	4.00	(3.00, 5.00)	11	4.00	(3.01, 5.01)			

MK-5172 + MK-8742: 200 mg MK-5172 QD with 50 mg MK-8742 QD on Days 1 to 8, Period 3 (pharmacokinetic sampling on Day 8).
Rosuvastatin + MK-5172 + MK-8742: 200 mg MK-5172 QD and 50 mg MK-8742 QD on Days 1 to 11, and 10 mg rosuvastatin co-administered on Day 9, Period 3 (pharmacokinetic sampling on Day 9).

[†]Pseudo Within-Subject %CV = 100*sqrt((σ_A² + σ_B² - 2σ_{AB})/2), where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
[‡]Subject AN 0002 was dropped from study on Day 6 of Period 2 due to elevated creatine phosphokinase and has no data available for this analysis.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

Reviewer comments

The sponsor stated that the effects are mainly due to inhibition of BCRP by MK-5172. However, the possibility of OATP1B inhibition by MK-5172 cannot be ruled out as atorvastatin exposures were also increased by the co-administration of MK-5172.

The magnitude of interaction may be clinically significant and a dose reduction of rosuvastatin is recommended. The sponsor proposed a max daily dose of 10 mg. This is in line with the clinical recommendations for other drugs (lopinavir/ritonavir, atazanavir/ritonavir) that are mentioned in Crestor ® USPI.

2. The effects of MK-5172 and MK-8742 co-administration on pravastatin exposures

The co-administration of MK-5172 and MK-8742 increased pravastatin AUC_{inf} and C_{max} by 33% and 28%, respectively (Table 9). The magnitude of interaction is not considered clinically relevant. The co-administration of a single dose of 40 mg pravastatin slightly increased AUC_{inf} and C_{max} of MK-5172 (24% and 42%, respectively) but did not alter MK-8742 exposures (Table 10 and Table 11). No dose adjustment of pravastatin is necessary when pravastatin is co-administered with MK-5172/MK-8742.

Table 9. Pravastatin pharmacokinetics with or without the co-administration of MK-5172/MK-8742

Pharmacokinetic Parameter	Pravastatin Alone			Pravastatin + MK-5172 + MK-8742			Pravastatin + MK-5172 + MK-8742/ Pravastatin Alone		Pseudo Within Subject %CV [†]
	N [‡]	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (ng/mL•hr)	10	191	(131, 278)	11	254	(199, 325)	1.33	(1.09, 1.64)	24.001
AUC ₀₋₂₄ [‡] (ng/mL•hr)	12	187	(130, 268)	12	238	(176, 322)	1.28	(1.08, 1.51)	23.112
C _{max} [‡] (ng/mL)	12	86.8	(57.9, 130)	12	111	(79.3, 155)	1.28	(1.05, 1.55)	26.794
C ₂₄ [§] (ng/mL)	12	0.11	(0.00, 0.58)	12	0.10	(0.00, 0.28)			
CL/F [‡] (L/hr)	10	210	(144, 306)	11	157	(123, 201)	0.75	(0.61, 0.92)	24.001
V _z /F [‡] (L)	10	1530	(754, 3110)	11	843	(618, 1150)	0.55	(0.36, 0.84)	47.568
T _{max} (hr)	12	1.00	(1.00, 1.50)	12	1.27	(0.51, 2.50)			
Apparent terminal t _{1/2} [¶] (hr)	10	3.93	55.88	11	3.67	53.47			
Alpha t _{1/2} [¶] (hr)	12	1.22	29.26	12	1.10	27.05			

Pravastatin alone: 40 mg pravastatin at Hour 0 on Day 1, Period 1
Pravastatin + MK-5172 + MK-8742: 200 mg MK-5172 QD and 50 mg MK-8742 QD on Days 1 to 9 with 40 mg pravastatin co-administered on Day 9, Period 2 (pharmacokinetic sampling on Day 9).

[†]Pseudo Within-Subject %CV = 100*sqrt((σ_A² + σ_B² - 2σ_{AB})/2), where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for C₂₄ as 6 out of 12 subjects for each treatment (50% of subjects) have BLQ C₂₄ concentrations.

^{||}Median (Minimum, Maximum) reported for T_{max}.

[¶]Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.

^{‡‡} Terminal phases were not well characterized, as evidenced by poor correlation of linear regression (R² < 0.80) for Subjects AN 0014 and AN 0015 in Period 1 and for Subject AN 0022 in Period 2. Consequently, AUC_{0-∞}, CL/F, V_z/F, and the apparent terminal t_{1/2} were only evaluable in 10 out of 12 subjects for Pravastatin Alone and in 11 out of 12 subjects for Pravastatin + MK-5172 + MK-8742.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 10. Steady-state MK-5172 plasma pharmacokinetics with or without the co-administration of a single dose of 40 mg pravastatin

Pharmacokinetic Parameter	MK-5172 + MK-8742			Pravastatin + MK-5172 + MK-8742			Pravastatin + MK-5172 + MK-8742/ MK-5172 + MK-8742		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (μM•hr)	12	2.39	(1.49, 3.81)	12	2.96	(1.83, 4.80)	1.24	(1.00, 1.53)	28.898
C _{max} [‡] (μM)	12	0.406	(0.224, 0.735)	12	0.578	(0.323, 1.03)	1.42	(1.00, 2.03)	48.247
C ₂ [‡] (μM)	12	0.206	(0.0972, 0.438)	12	0.221	(0.0940, 0.518)	1.07	(0.72, 1.59)	54.061
C ₂₄ [‡] (nM)	12	20.0	(13.8, 28.9)	12	21.4	(14.9, 30.8)	1.07	(0.99, 1.16)	10.238
T _{max} [§] (hr)	12	3.50	(2.00, 5.00)	12	3.04	(2.00, 5.00)			

MK-5172 + MK-8742: 200 mg MK-5172 QD with 50 mg MK-8742 QD on Days 1 to 8, Period 2 (pharmacokinetic sampling on Day 8).
Pravastatin + MK-5172 + MK-8742: 200 mg MK-5172 QD and 50 mg MK-8742 QD on Days 1 to 9 with 40 mg pravastatin co-administered on Day 9, Period 2 (pharmacokinetic sampling on Day 9).

[†]Pseudo Within-Subject %CV = 100*sqrt((σ_A² + σ_B² - 2σ_{AB})/2), where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 11. Steady-state MK-8742 plasma pharmacokinetics with or without the co-administration of a single dose of 40 mg pravastatin

Pharmacokinetic Parameter	MK-5172 + MK-8742			Pravastatin + MK-5172 + MK-8742			Pravastatin + MK-5172 + MK-8742 / MK-5172 + MK-8742		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (μM•hr)	12	2.75	(2.32, 3.26)	12	2.68	(2.23, 3.22)	0.98	(0.93, 1.02)	6.511
C _{max} [‡] (μM)	12	0.202	(0.174, 0.234)	12	0.195	(0.160, 0.239)	0.97	(0.89, 1.05)	11.274
C ₂ [‡] (μM)	12	0.156	(0.131, 0.186)	12	0.160	(0.130, 0.197)	1.02	(0.94, 1.11)	11.339
C ₂₄ [‡] (nM)	12	75.8	(61.5, 93.4)	12	73.3	(60.7, 88.6)	0.97	(0.92, 1.02)	7.430
T _{max} [§] (hr)	12	3.50	(2.99, 4.00)	12	4.00	(3.01, 5.00)			

MK-5172 + MK-8742: 200 mg MK-5172 QD with 50 mg MK-8742 QD on Days 1 to 8, Period 2 (pharmacokinetic sampling on Day 8).
Pravastatin + MK-5172 + MK-8742: 200 mg MK-5172 QD and 50 mg MK-8742 QD on Days 1 to 9 with 40 mg pravastatin co-administered on Day 9, Period 2 (pharmacokinetic sampling on Day 9).
[†]Pseudo Within-Subject %CV = 100*sqrt((σ_A² + σ_B² - 2σ_{AB})/2), where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Conclusion

- The co-administration of MK-5172 and MK-8742 increased C_{max} and AUC_{inf} of rosuvastatin by 5.49-fold and 2.26-fold, respectively. A dose reduction (maximum daily dose of 10 mg) of rosuvastatin is recommended when rosuvastatin is co-administered with MK-5172/MK-8742.
- The co-administration of MK-5172 and MK-8742 increased pravastatin AUC_{inf} and C_{max} by 33% and 28%, respectively. No dose adjustment is recommended when pravastatin is co-administered with MK-5172/MK-8742.

Title: A Study to Evaluate the Effect of Sevelamer Carbonate and Calcium Acetate on MK-8742 (Elbasvir) and MK-5172 (Grazoprevir) Pharmacokinetics in Healthy Subjects

Primary Objectives

- To evaluate the pharmacokinetic profile of MK-5172 and MK-8742 after a single staggered dose of calcium acetate or sevelamer (administered 1 hour after the co-administration of MK-8742 and MK-5172) in healthy subjects.
- To evaluate the effect of a single dose of calcium acetate or sevelamer on the single dose pharmacokinetic profile of co-administered MK-5172 and MK-8742 in healthy subjects.

Study Initiation Date: 06-DEC-2013

Trial Completion Date: 17-Feb-2014

Trial Site: (b) (4)

Study Design

This was an open-label, 2-part, 3-period, fixed-sequence study to evaluate the effect of single oral doses of sevelamer carbonate and calcium acetate (phosphate binder) on the single dose pharmacokinetics of MK-8742 and MK-5172 in healthy subjects. A total of 24 healthy adult subjects (12 subjects for each part), with at least 4 individuals of each gender, were enrolled in each part. The 2 parts of the study were conducted concurrently.

Table 1. Study design

	Part 1 (calcium acetate)	Part 2 (sevelamer carbonate)
Period 1	MK-5172/MK-8742 100 mg/50 mg single dose administration	
Period 2	Simultaneous administration of single doses of MK-5172/MK-8742 with a phosphate binder	
Period 3	1 hour staggered dosing (single doses of MK-5172/MK-8742 100 mg/50 mg single dose administration 1 hour prior phosphate binder administration)	

A low fat/renal diet breakfast (limited potassium, phosphate, sodium and fluids) was given in each study period. An example of renal diet is ¾ cup of rice cereal, 1 packet of sugar, 1 English muffin, 1 egg patty, 1 pack of margarine, 1 apple and 1 cup of 1% milk.

In Period 1, subjects consumed a low-fat renal diet breakfast and MK-5172 and MK-8742 were administered within 30 minutes. In Period 2, single oral doses of 100 mg MK-5172 and 50 mg MK-8742 were co-administered with a phosphate binder with the same breakfast administration procedures outlined in Period 1. In Period 3, single oral doses of 100 mg MK-5172 and 50 mg MK-8742 were administered under fasted conditions then subjects continued to fast for an additional 30 minutes at which point a low-fat renal diet breakfast was consumed 30 minutes prior to calcium acetate (Part 1) or sevelamer carbonate (Part 2) administration. There was a washout period of at least 10 days between doses of MK-5172/MK-8742.

Rationale for study

Many patients with chronic kidney disease receive phosphate binders such as sevelamer carbonate and calcium acetate with each meal. Phosphate binders are known to perpetrate drug interactions via binding to and preventing absorption of numerous medications. This study evaluated the effect of both calcium acetate and sevelamer carbonate on the pharmacokinetics of MK-5172 + MK-8742 when co-administered at the same time. An hour stagger in dosing was chosen as the minimum time needed to mitigate potential negative effects of phosphate binders on the bioavailability of MK-5172 or MK-8742.

The dose of 2668 mg of calcium acetate was chosen as most patients require 3 - 4 capsules (i.e., 2001 to 2668 mg of calcium acetate) with each meal, as per the monograph for PhosLo® gel capsules. The dose of 2400 mg of sevelamer carbonate was chosen because it is the highest starting dose administered with a meal for dialysis patients switching from calcium acetate to sevelamer carbonate, as indicated in the monograph of Renvela® tablets.

Key inclusion criteria

- Healthy adult male and female volunteers, 18-55 years of age, inclusive.
- BMI: 18.5-32 kg/m², inclusive. Weigh at least 52 kg for males and 45 kg for females.
- Have not used nicotine-containing products for at least 3 months prior to the first dose).
- Medically healthy with no clinically significant history, physical exam, lab profiles. Liver function tests must be below the upper limit of normal for inclusion.
- A female of childbearing potential must either sexually inactive or use acceptable birth control methods.
- Male subjects must use a condom (or abstain from sexual intercourse) and agree not to donate sperm from the first dose until 90 days after the last dose.

Key exclusion criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study.
- Estimated creatinine clearance less than 90 mL/min.
- History of alcoholism or drug abuse (within 2 years).
- History of hypophosphatemia, hypercalcemia, dysphagia, or severe gastrointestinal motility disorders.
- Female subjects who are pregnant or lactating.
- Positive results at screening for HIV, hepatitis B, hepatitis C, urine drug or cotinine screening.
- Donation of blood or had significant blood loss within 56 days prior to the first dose of study drug or plasma donation within 7 days prior to the first dose of study drug.
- Participation in another clinical trial within 28 days prior to the first dose of study drug.
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients.
- Have been on a special diet (for whatever reason) within 28 days prior to the first dose
- Unable to refrain from the use of any medication for the 14 days (28 days prior to, if CYP or P-gp inducers) prior to the first dose of study medications and throughout the study. Hormonal

contraceptives and hormone replacement therapy (HRT) were allowed and acetaminophen (up to 2 g per 24-hour period) may be permitted during the study.

Identity of Investigational Products

Table 2. Identity of Investigational Products

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency (N = X)	Site of Manufacture ^{(b) (4)}
MK-5172	100 mg	WL00047516	Tablet	WL00055356	98.6%	
MK-8742	50 mg	WL00052481	Tablet	WL00055357	98.3%	
Calcium acetate [†]	667 mg	NA	Gel Capsule	NA	NA	NA
Sevelamer carbonate [‡]	800 mg	NA	Tablet	NA	NA	NA

[†]Calcium acetate[®], manufactured for Fresenius Medical Care North America, was purchased by the Investigator. The lot number was 13074; expiration date Sep-2018.

[‡]Renvela[®] (sevelamer carbonate), manufactured by Genzyme Ireland Ltd., was purchased by the Investigator. The lot number was B3356B01, expiration date May-2016.

Pharmacokinetic assessments

Plasma samples were collected at predose and at specified time points over 72 hours following MK-5172 and MK-8742 dose in each treatment period.

C₁₂, C₂₄, and C_{trough} values were obtained using SAS (Version 9.3). All other pharmacokinetic parameters were calculated using the software WinNonlin Phoenix 6.3. C_{max} and T_{max} were generated by WinNonlin from each analytes plasma concentration-time data. AUC values were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down).

Bioanalysis

Bioanalyses for plasma concentrations of MK-5172 and MK-8742 were conducted by Merck Research Laboratories (The Netherlands). The concentrations of these drugs were determined using validated LC/MS/MS methods. All methods were adequately validated. Standard curves and QC data indicated that assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data.

Table 3. Summary of bioanalysis

Analyte	MK-5172	MK-8742
Internal standard	MK-5172-d ₆	MK-8742-d ₆
Matrix/Anticoagulant	Plasma/K ₂ DTA	Plasma/K ₂ DTA
Extraction method	Liquid-liquid extraction	Liquid-liquid extraction
Calibration range and regression method	1- 1000 ng/mL 1/x ² regression	0.25-500 ng/mL 1/x ² regression

QC concentration	3, 20, 75, and 750 ng/mL	0.75, 75, and 375 ng/mL
Interday precision and accuracy	P: 3.1 to 4.3% A: -4.5 to -1.5%	P: 4.1 to 7.7% A: 1.1 to 2.9%
Long term stability	825 days at – 20°C	651 days at – 20°C

Results

Demographic and baseline characteristics information

Demographic and baseline characteristics are summarized in Table 4.

Table 4. Demographic and baseline characteristics

	Part 1 (Calcium acetate) N=12	Part 2 (Sevelamer Carbonate) N=12
Number of subjects completed the study	11 [#]	11 [#]
Age in Years, Mean (range)	46 (36-52)	43 (34-54)
Sex, n (%)		
Female	6 (50%)	6 (50%)
Male	6 (50%)	6 (50%)
BMI (kg/m²), range	28.14 (24.90-31.28)	27.42 (22.14-31.50)
Height (cm), range	166.8 (152.0-190.0)	164.5 (148.0-179.0)
Weight (kg), range	78.1 (64.5-95.3)	74.3 (53.0-90.2)
Ethnicity, n (%)		
Hispanic or Latino:	10 (83%)	10 (83%)
Not Hispanic or Latino:	2 (17%)	2 (17%)
Race, n (%)		
White	12 (100%)	11 (92%)
African American/Black	0 (0%)	1 (8%)

[#]Subject AN 0002 was withdrawn from the study prior to Period 2 due to an adverse event (increased ALT/ALT). Subject AN 0017 withdrew from the study on Day 3 of Period 2 due to personal reasons.

Pharmacokinetic Results

1. Drug interactions with phosphate binders and MK-5172

The simultaneous administration of MK-5172 and calcium acetate decreased C_{max} , AUC_{inf} , and C_{24} of MK-5172 by 33%, 34%, and 37%, respectively (Table 5). This drug interaction was mitigated to some extent by a 1 hour staggered dosing (administering MK-5172 one hour prior to administering calcium acetate). When calcium acetate was administered 1 hour after MK-5172 administration, MK-5172 C_{max} , AUC_{inf} , and C_{24} were decreased by 29%, 13%, and 22%, respectively (Table 6).

The simultaneous administration of sevelamer carbonate also decreased the exposures of MK-5172 (C_{max} , AUC_{inf} , and C_{24} by 47%, 18%, and 16%, respectively, Table 7). A 1 hour staggered dosing mitigated the effect of sevelamer on MK-5172 C_{max} (a 20% decrease) but AUC and C_{24} were the same as simultaneous administration (Table 8).

Table 5. MK-5172 plasma pharmacokinetics with or without simultaneous administration of calcium acetate

MK-5172 Pharmacokinetic Parameter	(MK-5172 + MK-8742) Alone			(MK-5172 + MK-8742) + Calcium Acetate			(MK-5172 + MK-8742) + Calcium Acetate/ (MK-5172 + MK-8742) Alone		P-value ^e	Pseudo Within Subject %CV ^f
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI		
AUC _{0-∞} [‡] (μM·hr)	12	0.688	(0.515, 0.919)	9	0.543	(0.409, 0.720)	0.79	(0.68, 0.91)	<0.0001	17.795
C _{max} [‡] (μM)	12	0.0766	(0.0516, 0.114)	11	0.0439	(0.0269, 0.0717)	0.57	(0.40, 0.83)		48.155
C ₂ [§] (μM)	12	0.0356	(0.00141, 0.102)	11	0.0226	(0.00, 0.0612)				
C ₂₄ [‡] (nM)	12	6.87	(5.24, 9.01)	11	5.32	(3.59, 7.89)	0.77	(0.61, 0.99)		32.101
T _{max} [§] (hr)	12	1.50	(1.00, 3.02)	11	2.00	(0.50, 12.00)				
Apparent Terminal t _{1/2} (hr)	12	31.15	30.78	8	39.68	30.59				

(MK-5172 + MK-8742) Alone: Co-administration of 100 mg MK-5172 and 50 mg MK-8742 at Hour 0 on Day 1, Period 1 under fed conditions
(MK-5172 + MK-8742) + Calcium Acetate: Co-administration of 100 mg MK-5172 and 50 mg MK-8742 with 2668 mg calcium acetate at Hour 0 on Day 1, Period 2 under fed conditions
[‡]Pseudo within-subject %CV = 100*sqrt((σ_A² + σ_B² - 2 σ_{AB})/2), where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[§]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
^{||}Median (Minimum, Maximum) reported for T_{max} and C₂.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
^eP-value is from a one-sided test of the GMR compared to 0.5 (Null hypothesis: GMR = 0.5; alternative hypothesis: GMR > 0.5).
^fSubjects AN 0008 and AN 0010 in Period 2 had BLQ values for C₂, and therefore, the BLQ values were set to zero for descriptive statistics.
Note: For Subject AN 0011 in Period 2 ((MK-5172 + MK-8742) + Calcium Acetate), the apparent terminal t_{1/2} was not well characterized and removed from descriptive statistics.
Subject AN 0002 was withdrawn from the study after Period 1.
Note: For Subjects AN 0003 and AN 0006 in Period 2, the terminal elimination phase was not well defined. Therefore, AUC_{0-∞} and the apparent terminal t_{1/2} could not be calculated.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 6. MK-5172 plasma pharmacokinetics with or without a 1 hour delayed administration of calcium acetate

MK-5172 Pharmacokinetic Parameter	(MK-5172 + MK-8742) Alone			(MK-5172 + MK-8742) + Calcium Acetate (Staggered)			(MK-5172 + MK-8742) + Calcium Acetate (Staggered)/ (MK-5172 + MK-8742) Alone		P-value ^e	Pseudo Within Subject %CV ^f
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI		
AUC _{0-∞} [‡] (μM·hr)	12	0.688	(0.515, 0.919)	10	0.597	(0.414, 0.861)	0.87	(0.73, 1.03)	<0.0001	21.609
C _{max} [‡] (μM)	12	0.0766	(0.0516, 0.114)	11	0.0547	(0.0369, 0.0811)	0.71	(0.52, 0.99)		42.753
C ₂ [§] (μM)	12	0.0356	(0.00141, 0.102)	11	0.0300	(0.0173, 0.136)				
C ₂₄ [‡] (nM)	12	6.87	(5.24, 9.01)	11	5.37	(3.71, 7.77)	0.78	(0.62, 0.99)		30.477
T _{max} [§] (hr)	12	1.50	(1.00, 3.02)	11	1.00	(1.00, 2.00)				
Apparent terminal t _{1/2} (hr)	12	31.15	30.78	10	34.91	17.52				

(MK-5172 + MK-8742) Alone: Co-administration of 100 mg MK-5172 and 50 mg MK-8742 at Hour 0 on Day 1, Period 1, under fed conditions
(MK-5172 + MK-8742) + Calcium Acetate (Staggered): Co-administration of 100 mg MK-5172 and 50 mg MK 8742 at Hour 0 on Day 1 under fasting conditions with 2668 mg calcium acetate administered at Hour 1 on Day 1, Period 3 under fed conditions
[‡]Pseudo within-subject %CV = 100*sqrt((σ_A² + σ_B² - 2 σ_{AB})/2), where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[§]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
^{||}Median (Minimum, Maximum) reported for T_{max} and C₂.
^eP-value is from a one-sided test of the GMR compared to 0.5 (Null hypothesis: GMR = 0.5; alternative hypothesis: GMR > 0.5).
^fSubject AN 0002 was withdrawn from the study after Period 1.
For Subject AN 0011 in Period 3, the terminal elimination phase was not well defined. Therefore, AUC_{0-∞} and the apparent terminal t_{1/2} could not be calculated.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 7. MK-5172 plasma pharmacokinetics with or without the simultaneous administration of sevelamer carbonate

MK-5172 Pharmacokinetic Parameter	(MK-5172 + MK-8742) Alone			(MK-5172 + MK-8742) + Sevelamer Carbonate			(MK-5172 + MK-8742) + Sevelamer Carbonate/ (MK-5172 + MK-8742) Alone		P-value [§]	Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI		
AUC _{0-∞} [‡] (μM•hr)	12	0.585	(0.476, 0.720)	10	0.479	(0.425, 0.540)	0.82	(0.68, 0.99)	0.0002	25.748
C _{max} [‡] (μM)	12	0.0660	(0.0452, 0.0965)	12	0.0348	(0.0246, 0.0491)	0.53	(0.37, 0.76)		
C ₂₄ ^{‡††} (μM)	12	0.0442	(0.00, 0.0865)	12	0.0171	(0.00, 0.0755)				
C ₂₄ [‡] (nM)	12	5.40	(4.42, 6.60)	12	4.52	(3.69, 5.55)	0.84	(0.71, 0.99)		
T _{max} [§] (hr)	12	2.00	(1.00, 3.01)	12	2.00	(1.00, 4.00)				
Apparent Terminal t _{1/2} (hr)	12	28.77	38.07	10	35.22	40.05				

(MK-5172 + MK-8742) Alone: Co-administration of 100 mg MK-5172 and 50 mg MK-8742 at Hour 0 on Day 1, Period 1 under fed conditions
(MK-5172 + MK-8742) + Sevelamer Carbonate: Co-administration of 100 mg MK-5172 and 50 mg MK-8742 with 2400 mg sevelamer carbonate at Hour 0 on Day 1, Period 2 under fed conditions
[‡]Pseudo within-subject %CV = 100*sqrt((σ_A² + σ_B² - 2 σ_{AB})/2), where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
^{‡††}Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max} and C₂.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
[†]P-value is from a one-sided test of the GMR compared to 0.5 (Null hypothesis: GMR = 0.5; alternative hypothesis: GMR > 0.5).
^{††}Subjects AN 0013 and AN 0022 in Period 2 and Subject AN 0022 in Period 1 had BLQ values for C₂, and therefore, the BLQ values were set to zero for descriptive statistics and the median (min, max) was reported in the summary statistics.
Note: For Subjects AN 0015 and AN 0017 (withdrew on Day 3 of Period 2) in Period 2, the terminal elimination phase was not well defined. Therefore, AUC_{0-∞} and apparent terminal t_{1/2} could not be calculated.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 8. MK-5172 plasma pharmacokinetics with or without a 1-hour delayed administration of sevelamer carbonate

MK-5172 Pharmacokinetic Parameter	(MK-5172 + MK-8742) Alone			(MK-5172 + MK-8742) + Sevelamer Carbonate (Staggered)			(MK-5172 + MK-8742) + Sevelamer Carbonate (Staggered)/ (MK-5172 + MK-8742) Alone		P-value [§]	Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI		
AUC _{0-∞} [‡] (μM•hr)	12	0.585	(0.476, 0.720)	11	0.471	(0.377, 0.587)	0.80	(0.63, 1.02)	0.0021	32.560
C _{max} [‡] (μM)	12	0.0660	(0.0452, 0.0965)	11	0.0529	(0.0414, 0.0676)	0.80	(0.58, 1.11)		
C ₂₄ ^{‡††} (μM)	12	0.0442	(0.00, 0.0865)	11	0.0322	(0.0134, 0.0580)				
C ₂₄ [‡] (nM)	12	5.40	(4.42, 6.60)	11	4.77	(3.79, 6.01)	0.88	(0.74, 1.06)		
T _{max} [§] (hr)	12	2.00	(1.00, 3.01)	11	1.01	(1.00, 2.01)				
Apparent Terminal t _{1/2} (hr)	12	28.77	38.07	11	32.67	28.12				

(MK-5172 + MK-8742) Alone: Co-administration of 100 mg MK-5172 and 50 mg MK-8742 at Hour 0 on Day 1, Period 1 under fed conditions
(MK-5172 + MK-8742) + Sevelamer carbonate (Staggered): Co-administration of 100 mg MK-5172 and 50 mg MK 8742 at Hour 0 on Day 1 under fasting conditions with 2400 mg sevelamer carbonate administered at Hour 1 on Day 1, Period 3 under fed conditions
[‡]Pseudo within-subject %CV = 100*sqrt((σ_A² + σ_B² - 2 σ_{AB})/2), where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
^{‡††}Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max} and C₂.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
[†]P-value is from a one-sided test of the GMR compared to 0.5 (Null hypothesis: GMR = 0.5; alternative hypothesis: GMR > 0.5).
^{††}Subject AN 0022 in Period 1 had BLQ value for C₂, and therefore, the BLQ value was set to zero for descriptive statistics.
Subject AN 0017 withdrew from the study after Period 2.
Note: Subject AN 0023 in Period 3 had a predose concentration above the LLOQ, however, less than 5% of its C_{max}. No adjustment was made.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Reviewer comments: Although MK-5172 exposures were decreased by simultaneous administration of either calcium acetate or sevelamer carbonate, the magnitude of interaction is not considered clinically relevant. Phosphate binders are to be taken with meals and food increases the absorption of MK-5172. When MK-5172 exposures following simultaneous administration with phosphate binders and food were compared to MK-5172 exposures under fasted conditions, MK-5172 exposures were still higher following simultaneous administration with phosphate binders.

Table 9. MK-5172 plasma pharmacokinetic parameters under fasted conditions following a single dose administration of MK-5172 100 mg in healthy volunteer (Study 045 and 055)

	AUC _∞ (μM·hr)	C _{max} (μM)	C ₂₄
Number of Subjects	46	61	61
Geometric mean (95% CI)	0.479 (0.400-0.74)	0.031 (0.025-0.038)	4.87 (4.15-5.70)

2. Drug interactions with phosphate binders and MK-8742

Simultaneous administration of phosphate binders and MK-8742 minimally altered MK-8742 exposures (Table 10 and Table 12). A 1 hour dose staggering (administering MK-5172 one hour prior to administering a phosphate binder) unexpectedly decreased the exposures of MK-8742 (Table 11 and Table 13).

Table 10. MK-8742 plasma pharmacokinetics with or without the simultaneous administration of calcium acetate

MK-8742 Pharmacokinetic Parameter	(MK-5172 + MK-8742) Alone			(MK-5172 + MK-8742) + Calcium Acetate			(MK-5172 + MK-8742) + Calcium Acetate/ (MK-5172 + MK-8742) Alone		P-value [†]	Pseudo Within Subject %CV [‡]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI		
AUC _{0-∞} [‡] (μM·hr)	12	2.21	(1.70, 2.88)	11	2.04	(1.49, 2.78)	0.92	(0.75, 1.14)	<0.0001	27.783
C _{max} [‡] (μM)	12	0.124	(0.0917, 0.167)	11	0.106	(0.0835, 0.135)	0.86	(0.71, 1.04)		26.116
C ₂ [§] (μM)	12	0.0353	(0.0101, 0.154)	11	0.0554	(0.00190, 0.138)				
C ₂₄ [‡] (nM)	12	36.2	(27.5, 47.7)	11	31.6	(23.3, 43.0)	0.87	(0.70, 1.09)		29.281
T _{max} [§] (hr)	12	4.00	(3.00, 6.02)	11	3.07	(2.00, 6.00)				
Apparent Terminal t _{1/2} (hr)	12	17.42	14.51	11	17.92	15.85				

(MK-5172 + MK-8742) Alone: Co-administration of 100 mg MK-5172 and 50 mg MK-8742 at Hour 0 on Day 1, Period 1 under fed conditions
(MK-5172 + MK-8742) + Calcium Acetate: Co-administration of 100 mg MK-5172 and 50 mg MK-8742 with 2668 mg calcium acetate at Hour 0 on Day 1, Period 2 under fed conditions
[‡]Pseudo within-subject %CV = 100*sqrt((σ_A² + σ_B² - 2 σ_{AB})/2), where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max} and C₂.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
[†]P-value is from a one-sided test of the GMR compared to 0.5 (Null hypothesis: GMR = 0.5; alternative hypothesis: GMR > 0.5). Subject AN 0002 was withdrawn from the study after Period 1.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 11. MK-8742 plasma pharmacokinetics with or without a 1 hour delayed administration of calcium acetate

MK-8742 Pharmacokinetic Parameter	(MK-5172 + MK-8742) Alone			(MK-5172 + MK-8742) + Calcium Acetate (Staggered)			(MK-5172 + MK-8742) + Calcium Acetate (Staggered)/ (MK-5172 + MK-8742) Alone		P-value [§]	Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI		
AUC _{0-∞} [‡] (μM•hr)	12	2.21	(1.70, 2.88)	11	1.47	(1.08, 1.99)	0.66	(0.54, 0.82)	0.0158	27.513
C _{max} [‡] (μM)	12	0.124	(0.0917, 0.167)	11	0.0832	(0.0640, 0.108)	0.67	(0.55, 0.82)		
C ₂ [‡] (μM)	12	0.0353	(0.0101, 0.154)	11	0.0653	(0.0273, 0.115)				
C ₂₄ [‡] (nM)	12	36.2	(27.5, 47.7)	11	22.8	(16.7, 31.1)	0.63	(0.50, 0.79)		
T _{max} [§] (hr)	12	4.00	(3.00, 6.02)	11	3.00	(2.00, 4.00)				
Apparent Terminal t _{1/2} (hr)	12	17.42	14.51	11	16.88	12.72				

(MK-5172 + MK-8742) Alone: Co-administration of 100 mg MK-5172 and 50 mg MK-8742 at Hour 0 on Day 1, Period 1, under fed conditions
(MK-5172 + MK-8742) + Calcium Acetate (Staggered): Co-administration of 100 mg MK-5172 and 50 mg MK 8742 at Hour 0 on Day 1 under fasting conditions with 2668 mg calcium acetate administered at Hour 1 on Day 1, Period 3 under fed conditions
[†]Pseudo within-subject %CV = 100*sqrt((σ_A² + σ_B² - 2 σ_{AB})/2), where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max} and C₂.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
[§]P-value is from a one-sided test of the GMR compared to 0.5 (Null hypothesis: GMR = 0.5; alternative hypothesis: GMR > 0.5). Subject AN 0002 was withdrawn from the study after Period 1.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 12. MK-8742 plasma pharmacokinetics with or without the simultaneous administration of sevelamer carbonate

MK-8742 Pharmacokinetic Parameter	(MK-5172 + MK-8742) Alone			(MK-5172 + MK-8742) + Sevelamer Carbonate			(MK-5172 + MK-8742) + Sevelamer Carbonate/ (MK-5172 + MK-8742) Alone		P-value [§]	Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI		
AUC _{0-∞} [‡] (μM•hr)	12	2.81	(2.25, 3.52)	11	3.19	(2.41, 4.23)	1.13	(0.94, 1.37)	<0.0001	24.649
C _{max} [‡] (μM)	12	0.153	(0.125, 0.187)	12	0.163	(0.129, 0.207)	1.07	(0.88, 1.29)		
C ₂ [‡] (μM)	12	0.0799	(0.00351, 0.167)	12	0.0501	(0.000520, 0.131)				
C ₂₄ [‡] (nM)	12	43.7	(35.4, 53.9)	12	53.1	(41.1, 68.5)	1.22	(1.02, 1.45)		
T _{max} [§] (hr)	12	3.01	(2.00, 4.00)	12	4.00	(3.00, 8.00)				
Apparent Terminal t _{1/2} (hr)	12	18.49	15.32	11	17.76	14.39				

(MK-5172 + MK-8742) Alone: Co-administration of 100 mg MK-5172 and 50 mg MK-8742 at Hour 0 on Day 1, Period 1 under fed conditions
(MK-5172 + MK-8742) + Sevelamer Carbonate: Co-administration of 100 mg MK-5172 and 50 mg MK-8742 with 2400 mg sevelamer carbonate at Hour 0 on Day 1, Period 2 under fed conditions
[†]Pseudo within-subject %CV = 100*sqrt((σ_A² + σ_B² - 2 σ_{AB})/2), where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max} and C₂.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
[§]P-value is from a one-sided test of the GMR compared to 0.5 (Null hypothesis: GMR = 0.5; alternative hypothesis: GMR > 0.5).
Note: For Subject AN 0017 (withdrew on Day 3, Period 2) in Period 2, the terminal elimination phase was not well defined. Therefore, AUC_{0-∞} and apparent terminal t_{1/2} could not be calculated.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 13. MK-8742 plasma pharmacokinetics with or without a 1-hour delayed administration of sevelamer carbonate

MK-8742 Pharmacokinetic Parameter	(MK-5172 + MK-8742) Alone			(MK-5172 + MK-8742) + Sevelamer Carbonate (Staggered)			(MK-5172 + MK-8742) + Sevelamer Carbonate (Staggered)/ (MK-5172 + MK-8742) Alone		P-value [§]	Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI		
AUC _{0-∞} [‡] (μM•hr)	12	2.81	(2.25, 3.52)	11	1.94	(1.57, 2.39)	0.69	(0.59, 0.81)	0.0012	20.932
C _{max} [‡] (μM)	12	0.153	(0.125, 0.187)	11	0.0927	(0.0693, 0.124)	0.61	(0.49, 0.75)		
C ₂ [§] (μM)	12	0.0799	(0.00351, 0.167)	11	0.0831	(0.0364, 0.122)				20.490
C ₂₄ [‡] (nM)	12	43.7	(35.4, 53.9)	11	30.6	(25.1, 37.2)	0.70	(0.60, 0.81)		
T _{max} [§] (hr)	12	3.01	(2.00, 4.00)	11	3.00	(2.00, 4.00)				
Apparent Terminal t _{1/2} (hr)	12	18.49	15.32	11	18.61	12.71				

(MK-5172 + MK-8742) Alone: Co-administration of 100 mg MK-5172 and 50 mg MK-8742 at Hour 0 on Day 1, Period 1 under fed conditions
(MK-5172 + MK-8742) + Sevelamer carbonate (Staggered): Co-administration of 100 mg MK-5172 and 50 mg MK 8742 at Hour 0 on Day 1 under fasting conditions with 2400 mg sevelamer carbonate administered at Hour 1 on Day 1, Period 3 under fed conditions
[†]Pseudo within-subject %CV = 100*sqrt((σ_A² + σ_B² - 2 σ_{AB})/2), where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max} and C₂.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
^{††}P-value is from a one-sided test of the GMR compared to 0.5 (Null hypothesis: GMR = 0.5; alternative hypothesis: GMR > 0.5).
Subject AN 0017 withdrew from the study after Period 2.
Note: Subject AN 0023 in Period 3 had a predose concentration above the lower limit of quantitation (LLOQ), however, less than 5% of the C_{max}. No adjustment was made.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Reviewer comments

Decreased exposures of MK-8742 following a 1 hour dose staggering of a phosphate binder were unexpected as dose staggering usually mitigates drug interactions. A confounder in this analysis is the timing of food. In Period 1 (MK-5172/8742 alone), drugs were administered within 30 minute after eating a meal. In Period 3, drugs were administered under fasted conditions but food was given 30 min after drug administration. This confounder may play a role in this unexpected interaction. The magnitude of interaction is not considered clinically relevant based on the exposure-response relationship for efficacy.

Conclusion

- MK-5172 exposures were decreased by the simultaneous administration of phosphate binders. A 1 hour dose staggering mitigated this effect to some extent but did not completely remove the interaction. The magnitude of decrease (following either simultaneous or staggered dosing) in MK-5172 exposures is not considered clinically relevant.
- Simultaneous administration of MK-8742 and phosphate binders minimally altered MK-8742 exposures. A 1 hour dose staggering unexpectedly resulted in further decreases in MK-8742 exposures, but the magnitude of interaction is not considered clinically relevant.

Study Title: A study to Evaluate the Interaction of MK-5172 and MK-8742 with Dolutegravir in Healthy Subjects

Primary Objectives: To assess the effect of multiple oral doses of MK-5172 and MK-8742 on the pharmacokinetics of a single oral dose of dolutegravir.

Study Initiation Date: 27-Jan-2014

Study Completion Date: 01-Mar-2014

Study Site: (b) (4)

Study Design

This was a randomized, open-label, 2-period, fixed-sequence study to assess the effect of multiple oral doses of MK-5172 and MK-8742 on the pharmacokinetics of a single oral dose of dolutegravir. Twelve healthy subjects were enrolled.

In Period 1, a single oral dose of 50 mg dolutegravir was administered on Day 1. In Period 2, an oral dose of 200 mg MK-5172 and 50 mg MK-8742 was co-administered QD from Days 1 - 11, inclusive. On Day 9, a single oral dose of 50 mg dolutegravir was co-administered with the dose of MK-5172 and MK-8742. There was a washout period of 3 days between the dose of dolutegravir in Period 1 and first dose of MK-5172 and MK-8742 in Period 2. Subjects fasted overnight for at least 8 hours prior to dosing on Day 1 of Period 1 and Days 8 and 9 of Period 2. On all other days, subjects fasted for 1 hour prior to dosing and remained fasted for at least 2 hours postdose.

Key Inclusion Criteria

- Healthy adult male and female (at least 4) volunteers, 19-55 years of age, inclusive.
- BMI: 19- 32 kg/m², inclusive. Weigh at least 52 kg for males and 45 kg for females.
- Non-smokers (have not used nicotine-containing products for at least 3 months prior to the first dose)
- Medically healthy with no clinically significant history, physical exam, lab profiles. Liver function test results must be at or lower than ULN.
- For females of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using acceptable birth control methods. Male subjects must use a condom (or abstain from sexual intercourse) and agree not to donate sperm from the first dose until 90 days after the last dose

Key Exclusion Criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 90 mL/min
- History of drug or alcohol abuse (within 2 years)
- Female subjects who are pregnant or lactating
- Positive results at screening for HIV, hepatitis B, or hepatitis C
- Positive results for urine drug, urine cotinine, or alcohol screening or check in

- Unable to refrain from or anticipates the use of any drug beginning 14 days (28 days for CYP/P-gp inducers) prior to the first dose of study drug and throughout the study.
- Donation of blood or had significant blood loss within 4 weeks prior to the first dose of study drug or plasma donation within 7 days prior to the first dose of study drug.
- Participation in another clinical trial within 28 days prior to the first dose of study drug.
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients

Concomitant medications

Subjects were not allowed to take medication for the 14 days (or 28 days for CYP or P-gp inducers) prior to the first dose of the study and throughout the study. This prohibition did not include hormonal contraceptives and hormone replacement therapy or acetaminophen.

Identity of Investigational Product

Table 1. Identity of Investigational Products

Drug	Potency	Formulation No.	Dosage Form	Control No.	Assay Potency	Site of Manufacture ^{(b) (4)}
MK-5172	100 mg	WL00047516	Tablet	WL00055894	98.6	[REDACTED]
MK-8742	10 mg	DL00018432	[REDACTED] ^{(b) (4)}	WL00055895	102.9	
Dolutegravir (TIVICAY [®]) [†]	50 mg	NA	Tablet	NA	NA	NA

[†]Dolutegravir (TIVICAY[®]) (a product manufactured by GlaxoSmithKline) was purchased by the Investigator. The lot number was 3ZP0820; expiration date Aug-2015.

Pharmacokinetic assessments

Blood samples for the determination of plasma dolutegravir concentrations were collected predose and at specified time points over 72 hours following administration of dolutegravir alone on Day 1 of Period 1, and MK-5172 + MK-8742 + dolutegravir on Day 9 of Period 2. Blood samples for the determination of MK-5172 and MK-8742 plasma concentrations were collected predose on Day 1, Days 6 through 9 of Period 2, and at specified time points over 24 hours following administration of MK-5172 + MK-8742 on Day 8 of Period 2, and MK-5172 + MK-8742 + dolutegravir on Day 9 of Period 2.

With the exception of C₂₄, which was obtained using SAS[®] (Version 9.3), all the pharmacokinetic parameters were calculated by noncompartmental analysis using the software Phoenix[®] WinNonlin[®] (Version 6.3). C_{max} and T_{max} were generated by Phoenix[®] WinNonlin[®] from the plasma dolutegravir concentration-time data. AUC_{0-∞} was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down).

Bioanalysis

Plasma samples collected for MK-8742 and MK-5172 assays were analyzed by [REDACTED] ^{(b) (4)}. The concentrations of these drugs were determined using LC/MS/MS methods. All methods were adequately validated. The standard curve and QC data indicated assays were acceptable. All samples were stored and processed in the time frame supported by the stability data

Table 2. Summary of Bioanalysis

Analyte	MK-5172	MK-8742	Dolutegravir
Internal standard	MK-5172-d ₆	MK-8742-d ₆	ERC-349572-d ₇ , ¹⁵ N
Matrix/Anticoagulant	Plasma/ K ₂ EDTA	Plasma/ K ₂ EDTA	Plasma/ K ₂ EDTA
Calibration range	1 to 1000 ng/mL	0.25 to 500 ng/mL	20 to 20000 ng/mL
QC concentration	3, 20, 75, and 750 ng/mL	0.75, 75, and 375 ng/mL	60, 160, 640, 2400, and 15200 ng/mL
Interday precision and accuracy	P: 4.6 to 5.2% A: -6.4 to -3.7%	P: 4.4 to 7.5% A: -1.6 to 4.4%	P: 1.1 to 6.1% A: -6.4 to 5.8%
Storage stability	825 days at -20 °C	651 days at -20 °C	558 days at -20 °C

RESULTS

Subject disposition and baseline characteristics

Twelve healthy adult male and female subjects were enrolled into the study and all 12 subjects completed the study per protocol

Table 3. Subject baseline demographics

AN	Gender	Race	Ethnicity	Age (yr)	Height (cm)	Weight (kg)	Body Mass Index (kg/m ²)
0001	Male	Black or African American	Not Hispanic or Latino	38	185.0	80.7	23.55
0002	Male	White	Not Hispanic or Latino	28	195.0	94.4	24.81
0003	Male	White	Not Hispanic or Latino	30	180.0	87.8	27.22
0004	Male	White	Not Hispanic or Latino	27	182.0	66.5	20.04
0005	Male	White	Not Hispanic or Latino	35	184.0	98.0	28.97
0006	Male	White	Not Hispanic or Latino	52	181.0	84.1	25.70
0007	Male	White/Asian	Not Hispanic or Latino	36	181.0	80.6	24.58
0008	Male	White	Not Hispanic or Latino	29	188.0	97.2	27.58
0009	Female	White	Not Hispanic or Latino	31	158.0	57.2	22.84
0010	Female	White	Not Hispanic or Latino	47	165.0	59.2	21.73
0011	Female	White	Not Hispanic or Latino	47	162.0	62.6	23.84
0012	Female	Asian	Not Hispanic or Latino	28	161.0	81.2	31.21
Study Summary							
N:				12	12	12	12
Range:				27 to 52	158.0 to 195.0	57.2 to 98.0	20.04 to 31.21
Arithmetic Mean:				36	176.8	79.1	25.17
Female N:				4	4	4	4
Female Range:				28 to 47	158.0 to 165.0	57.2 to 81.2	21.73 to 31.21
Female Arithmetic Mean:				38	161.5	65.1	24.91
Male N:				8	8	8	8
Male Range:				27 to 52	180.0 to 195.0	66.5 to 98.0	20.04 to 28.97
Male Arithmetic Mean:				34	184.5	86.2	25.31
AN = Allocation Number.							
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Concomitant Therapy

The concomitant medications that were administered in the trial included acetaminophen, cephalexin, vitamins, ibuprofen, and diphenhydramine hydrochloride. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

Pharmacokinetic Results

The co-administration of MK-5172 and MK-8742 slightly increased AUC_{inf} (16%) and C_{max} (22%) of dolutegravir (Table 4). The co-administration of dolutegravir decreased C_{max} and AUC_{24hr} of MK-5172 by 36% and 19%, respectively (Table 5). These changes are not considered clinically relevant. MK-8742 exposure was not altered by the co-administration of dolutegravir (Table 6).

Table 4. Dolutegravir plasma pharmacokinetics with or without the co-administration of MK-5172/MK-8742

Pharmacokinetic Parameter	Dolutegravir Alone			MK-5172 + MK-8742 + Dolutegravir			MK-5172 + MK-8742 + Dolutegravir/ Dolutegravir Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (μg/mL•hr)	12	57.6	(47.8, 69.4)	12	66.7	(56.7, 78.5)	1.16	(1.00, 1.34)	19.781
C ₂₄ [‡] (ng/mL)	12	898	(726, 1110)	12	1020	(851, 1220)	1.14	(0.95, 1.36)	24.535
C _{max} [‡] (μg/mL)	12	2.67	(2.21, 3.23)	12	3.25	(2.80, 3.78)	1.22	(1.05, 1.40)	19.477
CL/F [‡] (L/hr)	12	0.869	(0.721, 1.05)	12	0.750	(0.637, 0.883)	0.86	(0.75, 1.00)	19.781
T _{max} [§] (hr)	12	2.00	(0.50, 5.00)	12	2.01	(1.01, 5.01)			
Apparent terminal t _{1/2} (hr)	12	15.08	17.3	12	15.56	24.8			

Dolutegravir Alone: A single oral dose of 50 mg dolutegravir administered on Day 1 of Period 1.
MK-5172 + MK-8742 + Dolutegravir: Co-administration of 200 mg MK-5172 and 50 mg MK-8742 on Days 1 to 11 of Period 2 with 50 mg dolutegravir co-administered on Day 9.
[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A² + σ_B² - 2*σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares means ratio.
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Table 5. MK-5172 plasma pharmacokinetics with or without the co-administration of dolutegravir

Pharmacokinetic Parameter	MK-5172 + MK-8742			MK-5172 + MK-8742 + Dolutegravir			MK-5172 + MK-8742 + Dolutegravir/ MK-5172 + MK-8742		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (μM•hr)	12	1.97	(1.48, 2.62)	12	1.59	(1.03, 2.45)	0.81	(0.67, 0.97)	25.108
C _{max} [‡] (μM)	12	0.441	(0.326, 0.597)	12	0.284	(0.155, 0.519)	0.64	(0.44, 0.93)	50.409
C ₂ [‡] (μM)	12	0.250	(0.146, 0.427)	12	0.131	(0.0625, 0.273)	0.52	(0.28, 0.97)	83.700
C ₂₄ [‡] (nM)	12	11.8	(9.15, 15.3)	12	10.1	(8.02, 12.8)	0.86	(0.79, 0.93)	10.711
T _{max} [§] (hr)	12	3.00	(2.00, 5.00)	12	4.00	(1.00, 5.00)			

MK-5172 + MK-8742: Co-administration of 200 mg MK-5172 and 50 mg MK-8742 on Days 1 to 8 of Period 2. Pharmacokinetic parameters calculated on Day 8 of Period 2.
MK-5172 + MK-8742 + Dolutegravir: Co-administration of 200 mg MK-5172 and 50 mg MK-8742 on Days 1 to 11 of Period 2 with 50 mg dolutegravir co-administered on Day 9. Pharmacokinetic parameters calculated on Day 9 of Period 2.
[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A² + σ_B² - 2*σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares means ratio.
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Table 6. MK-8742 plasma pharmacokinetics with or without the co-administration of dolutegravir

Pharmacokinetic Parameter	MK-5172 + MK-8742			MK-5172 + MK-8742 + Dolutegravir			MK-5172 + MK-8742 + Dolutegravir/ MK-5172 + MK-8742		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µM•hr)	12	2.37	(2.01, 2.79)	12	2.33	(1.98, 2.75)	0.98	(0.93, 1.04)	6.981
C _{max} [‡] (µM)	12	0.187	(0.164, 0.214)	12	0.181	(0.155, 0.212)	0.97	(0.89, 1.05)	11.244
C ₂ [‡] (µM)	12	0.142	(0.120, 0.166)	12	0.139	(0.112, 0.172)	0.98	(0.86, 1.11)	16.993
C ₂₄ [‡] (nM)	12	60.4	(49.9, 73.2)	12	59.2	(48.9, 71.7)	0.98	(0.93, 1.03)	6.900
T _{max} [§] (hr)	12	4.00	(3.00, 4.00)	12	4.00	(2.00, 5.00)			

MK-5172 + MK-8742: Co-administration of 200 mg MK-5172 and 50 mg MK-8742 on Days 1 to 8 of Period 2. Pharmacokinetic parameters calculated on Day 8 of Period 2.

MK-5172 + MK-8742 + Dolutegravir: Co-administration of 200 mg MK-5172 and 50 mg MK-8742 on Days 1 to 11 of Period 2 with 50 mg dolutegravir co-administered on Day 9. Pharmacokinetic parameters calculated on Day 9 of Period 2.

[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A² + σ_B² - 2*σ_{AB})/2], where σ_A² and σ_B² are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares means ratio.

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Conclusion

When MK-5172 and MK-8742 were co-administered with dolutegravir, no clinically relevant drug interactions were observed.

Study Title: A Study to Evaluate the Interaction of MK-5172 and MK-8742 with Sofosbuvir in Healthy Subjects (PN063).

Study Initiation Date: 01-May-2014

Study Completion Date: 01-Jul-2014

Study Site: (b) (4)

Primary: To assess the effect of multiple oral doses of MK-5172 and MK-8742 on the pharmacokinetics of a single oral dose of sofosbuvir as reflected in the concentrations of sofosbuvir and its metabolite GS-331007.

Study Design

This was an open-label, 2-period, fixed-sequence study to assess the effect of multiple oral doses of MK-5172 and MK-8742 on the pharmacokinetics of a single oral dose of sofosbuvir. Sixteen healthy adult male and female subjects were enrolled. In Period 1, subjects received a single dose of 400 mg sofosbuvir on Day 1. In Period 2, 200 mg MK-5172 and 50 mg MK-8742 were co-administered once daily (QD) from Days 1 to 15, inclusive. On Day 11, a single dose of 400 mg sofosbuvir was co-administered with MK-5172 and MK-8742. There was a washout period of 8 days between the dose of sofosbuvir in Period 1 and the first dose of MK-5172 and MK-8742 in Period 2. Subjects fasted overnight for at least 8 hours prior to each study drug administration.

Key Inclusion Criteria

- Healthy adult male and female volunteers, 18-55 years of age, BMI: 19-32 kg/m², inclusive
- Have not used nicotine-containing products for at least 3 months prior to the first dose
- Medically healthy with no clinically significant history, physical exam, lab profiles.
- A female of childbearing potential must either sexually inactive for 14 days prior the first dose or use acceptable birth control methods. Non-vasectomized male subjects must agree to use a condom with spermicide or abstain from sexual intercourse from the first dose until 90 days after stopping the study drug. Male subjects must agree not to donate sperm from the first dose until 90 days after the last dose of study medication.

Key Exclusion Criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study including liver disease
- Estimated creatinine clearance less than 80 mL/min
- Female subjects who are pregnant or lactating
- Positive results at screening for HIV, hepatitis B, hepatitis C, or urine drug screening
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients
- History of alcoholism and drug abuse within 2 years
- Subject has had major surgery, donated or lost blood within 8 weeks prior to the screen
- Have been on a diet incompatible with the on-study diet
- Subject has participated in another investigational study within 4 weeks prior to Day1

Identity of Clinical Supplies

Table 1. Identity of Clinical Supplies

Bulk Product Description	Manufacturing Lot Number
Tablet MK-5172 100 mg	WL00047521
Tablet MK-8742 50 mg	WL00052481
Tablet Sovaldi™ (Sofosbuvir) 400 mg	002459A
Sovaldi™ (sofosbuvir) 400 mg (Lot number 002459A; expiration date Oct-2015; Gilead Sciences, Inc.) was supplied by McKesson.	

Concomitant medications and dietary restrictions

Consumption of foods and beverages containing the following substances was prohibited

- Xanthines/Caffeine: 24 hours before dosing on the first dose and throughout the study Alcohol: 72 hours before dosing on Day 1 of Period 1 and throughout the study.
- Grapefruit/Seville orange: 14 days before the first dose on Day 1 of Period 1 and throughout the study
- Vegetables from the mustard green family and charbroiled meats: 7 days before dosing on Day 1 of Period 1 and throughout the study.
- Fruit Juice: 72 hours before dosing on Day 1 of Period 1 and throughout the study.

Subjects were not allowed to take drugs (including over-the-counter products), herbal products, or vitamin supplements for the 14 days prior to dosing (or 28 days for CYP and/or P-gp inducers including St. John's Wort) and throughout the study. During the study, acetaminophen (up to 2 g per 24 hours) may have been administered.

Pharmacokinetic assessments

Plasma samples for the determination of sofosbuvir and its metabolite GS-331007 were obtained at predose and specified time points up to 120 hours postdose. With the exception of C_{24} values which were obtained using SAS® (Version 9.3), all of the pharmacokinetic parameter values were calculated using the software Phoenix® WinNonlin® (Version 6.3). C_{max} and T_{max} were generated by Phoenix® WinNonlin® from each analyte's plasma concentration-time data. AUCs were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down).

Bioanalysis

Plasma sofosbuvir and GS-331007 concentrations were determined by [REDACTED] (b) (4) using a validated LC/MS/MS method. All methods were adequately validated. The standard curve and QC data indicated assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data.

Table 2. Summary of Bioanalysis

Analyte	Sofosbuvir	GS-331007
Internal standard	Zidovudine	Zidovudine
Matrix/Anticoagulant	Plasma/K ₂ EDTA	Plasma/K ₂ EDTA
Extraction method	Protein precipitation	Protein precipitation
Calibration range	10 – 2000 ng/mL	10 – 3000 ng/mL
QC concentration	30, 150, 1000, and 1500 ng/mL	30, 225, 1500, and 2250 ng/mL
Interday precision and accuracy	P: 1.50 to 3.64% A: - 1.52% to 1.7%	P: 3.55 to 4.37% A: - 4.28 to 0.23%
Long term stability	91 Days at – 80 °C	91 Days at – 80 °C

RESULTS**Demographic and Other Subject Characteristics****Table 3. Subject Baseline Demographics**

AN	Gender	Race	Ethnicity	Age (yr)	Height (cm)	Weight (kg)	Body Mass Index (kg/m ²)
0001	Female	White	Hispanic or Latino	34	173.0	70.3	23.57
0002	Female	White	Hispanic or Latino	42	156.0	76.1	31.29
0003	Male	White	Hispanic or Latino	31	163.0	64.2	24.08
0004	Female	White	Hispanic or Latino	33	142.0	55.4	27.40
0005	Female	White	Hispanic or Latino	51	155.0	72.8	30.34
0006	Female	White	Hispanic or Latino	39	160.0	68.2	26.64
0007	Female	White	Hispanic or Latino	49	154.0	73.5	31.01
0008	Female	White	Hispanic or Latino	35	157.0	49.9	20.25
0009	Male	White	Hispanic or Latino	22	169.0	74.3	25.96
0010	Female	White	Hispanic or Latino	32	161.0	70.9	27.24
0011	Female	White	Hispanic or Latino	50	150.0	70.7	31.57
0012	Female	White	Hispanic or Latino	34	155.0	66.7	27.68
0013	Male	White	Not Hispanic or Latino	52	188.0	95.5	27.04
0014	Male	White	Hispanic or Latino	42	173.0	78.7	26.40
0015	Female	White	Hispanic or Latino	26	156.0	71.5	29.49
0016	Male	White	Hispanic or Latino	28	166.0	62.3	22.59
Study Summary							
N:				16	16	16	16
Range:				22 to 52	142.0 to 188.0	49.9 to 95.5	20.25 to 31.57
Arithmetic Mean:				38	161.1	70.1	27.03
Female N:				11	11	11	11
Female Range:				26 to 51	142.0 to 173.0	49.9 to 76.1	20.25 to 31.57
Female Arithmetic Mean:				39	156.3	67.8	27.86
Male N:				5	5	5	5
Male Range:				22 to 52	163.0 to 188.0	62.3 to 95.5	22.59 to 27.04
Male Arithmetic Mean:				35	171.8	75.0	25.21
AN = Allocation Number.							

Pharmacokinetic Results

The co-administration of MK-5172 and MK-8742 increased the exposure of sofosbuvir (Table 4). AUC_{inf} and C_{max} of a single dose of sofosbuvir were increased by 2.43-fold and 2.27-fold, respectively, by the co-administration of MK-5172 and MK-8742. The AUC_{inf} and C_{24hr} of GS-331007 were increased by 13%

and 53%, respectively, by the co-administration of MK-5172 and MK-8742 (Table 5). In contrast, the C_{max} of GS-310007 was slightly decreased (13%) by the co-administration of MK-5172 and MK-8742.

Table 4. Sofosbuvir plasma pharmacokinetics with or without the co-administration of MK-5172/MK-8742

Pharmacokinetic Parameter	Sofosbuvir Alone			Sofosbuvir + MK-5172 + MK-8742			Sofosbuvir + MK-5172 + MK-8742/ Sofosbuvir Alone		
	N [¶]	GM	95% CI	N ^{††}	GM	95% CI	GMR	90% CI	Pseudo Within Subject %CV [†]
AUC _{0-∞} [‡] (ng•hr/mL)	12	583	(465, 733)	14	1420	(1270, 1580)	2.43	(2.12, 2.79)	18.822
AUC _{0-last} [‡] (ng•hr/mL)	16	539	(436, 666)	16	1400	(1260, 1560)	2.59	(2.28, 2.94)	20.461
C _{max} [‡] (ng/mL)	16	490	(338, 711)	16	1110	(903, 1370)	2.27	(1.72, 2.99)	44.493
T _{max} [§] (hr)	16	0.75	(0.25, 3.50)	16	0.75	(0.25, 3.00)			
Apparent terminal t _½ (hr)	12	0.43	39.88	14	0.39	14.60			

Sofosbuvir Alone: 400 mg (1 x 400 mg tablet) sofosbuvir on Day 1, Period 1.
Sofosbuvir + MK-5172 + MK-8742: Co-administration of 400 mg sofosbuvir on Day 11, Period 2, with 200 mg [2 x 100 mg tablets] MK-5172 + 50 mg [1 x 50 mg tablet] MK-8742 QD on Days 1 to 15, Period 2.
[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_½.
[¶]The apparent terminal phase was not well characterized for 4 subjects in Period 1. Consequently, AUC_{0-∞} and apparent terminal t_½ were only calculated for 12 out of 16 subjects for Sofosbuvir Alone. See [9.5.4] for details.
^{††}The apparent terminal phase was not well characterized for two subjects in Period 2. Consequently, AUC_{0-∞} and apparent terminal t_½ were only calculated for 14 out of 16 subjects for Sofosbuvir + MK-5172 + MK-8742. See [9.5.4] for details.
Note: C₂₄ values were not reported due to all values being below the limit of quantification (BLQ) for all subjects in both treatments.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 5. GS-331007 plasma pharmacokinetics with or without the co-administration of MK-5172/MK-8742

GS-331007 Pharmacokinetic Parameter	Sofosbuvir Alone			Sofosbuvir + MK-5172 + MK-8742			Sofosbuvir + MK-5172 + MK-8742 / Sofosbuvir Alone		
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	Pseudo Within Subject %CV [†]
AUC _{0-∞} [‡] (ng•hr/mL)	16	13300	(12300, 14500)	16	15000	(13700, 16500)	1.13	(1.05, 1.21)	11.434
AUC _{0-last} [‡] (ng•hr/mL)	16	12700	(11600, 13900)	16	14300	(13100, 15700)	1.13	(1.04, 1.22)	12.897
C _{max} [‡] (ng/mL)	16	1440	(1270, 1630)	16	1250	(1100, 1410)	0.87	(0.78, 0.96)	16.209
C ₂₄ [‡] (ng/mL)	16	86.9	(74.7, 101)	16	133	(117, 150)	1.53	(1.43, 1.63)	10.176
T _{max} [§] (hr)	16	3.01	(1.51, 5.01)	16	3.00	(1.99, 5.00)			
Apparent terminal t _{1/2} (hr)	16	23.97	32.29	16	30.66	18.46			

Sofosbuvir Alone: 400 mg (1 x 400 mg tablet) sofosbuvir on Day 1, Period 1.
Sofosbuvir + MK-5172 + MK-8742: Co-administration of 400 mg sofosbuvir on Day 11, Period 2, with 200 mg (2 x 100 mg tablets) MK-5172 + 50 mg (1 x 50 mg tablet) MK-8742 QD on Days 1 to 15, Period 2.

[†]Pseudo within-subject %CV = 100* $\sqrt{[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least squares mean and confidence interval from linear mixed effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Reviewer Comments and

The increased sofosbuvir exposures by the co-administration of MK-5172 and MK-8742 are possibly due to the inhibition of intestinal BCRP. According to SOVALDI® (sofosbuvir) USPI, coadministration of SOVALDI with drugs that inhibit P-gp and/or BCRP may increase the plasma concentration of sofosbuvir without increasing the plasma concentration of GS-331007. SOVALDI may be coadministered with P-gp and/or BCRP inhibitors. The sponsor concluded that the magnitude of increase in the exposures of sofosbuvir and GS-331007 by MK-5172 and MK-8742 is not considered clinically relevant. The sponsor’s conclusion is in line with the sofosbuvir clinical recommendations outlined in SOVALDI ® USPI.

Conclusion

The co-administration of MK-5172 and MK-8742 increased the exposure of sofosbuvir (AUC_{inf} and C_{max} by 2.43-fold and 2.27-fold, respectively) and GS-331007 (AUC and C_{24hr} by 13% and 53%, respectively). This is not considered clinically significant. Sofosbuvir can be administered with MK-5172/MK-8742 without a dose adjustment.

5172-070

1. Title

A Study to Evaluate the One-Way Interaction of MK-5172 (grazoprevir) on Montelukast in Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted from June 17, 2014 (trial initiation) to July 30, 2014 (trial completion).

3. Objectives

The objectives of the trial included evaluating the effect of grazoprevir on the exposure of montelukast.

4. Trial Design

070 was a clinical trial that enrolled healthy subjects 19 to 55 years old.

In period 1, subjects received a single dose of 10 mg montelukast on day 1. Subsequent to a 4 day washout period, in period 2 subjects received multiple doses of 200 mg grazoprevir once daily for 10 days with a single dose of 10 mg montelukast coadministered on day 9.

5. Excluded Medications, Restrictions or Exceptions

Medications, including nonprescription and herbal products, were not permitted within either 14 days (or 28 days for CYP or P-gp inducers) before the first dose and during the trial.

6. Dosage and Administration

The trial medications were administered under fasted conditions. This is consistent with the proposed U.S. prescribing information (USPI) recommendation for grazoprevir in combination with elbasvir (with or without food). According to the montelukast medication guide, montelukast may be administered with or without food.

7. Rationale for Doses Used in the Trial

The dosing regimen of 200 mg once daily is higher than the recommended dosage regimen in the proposed U.S. prescribing information for elbasvir and grazoprevir (100 mg with 50 mg of elbasvir once daily). Based on the information provided by the applicant, greater than dose proportional changes in exposure and time dependent pharmacokinetics were observed with grazoprevir. According to the applicant, the rationale for dosing 200 mg once daily is that grazoprevir steady state exposure is approximately twice as high in hepatitis C infected subjects when compared to healthy subjects. The dose of montelukast is consistent with the recommendation in the montelukast USPI.

8. Drugs Used in the Trial

The medications administered in trial 070 are displayed in Table 1.

Table 1-Medications administered in trial 070

Bulk Product Description	Manufacturing Lot Number
Tablet MK-5172 (grazoprevir) 100 mg	WL00047521
Tablet Singulair [®] (montelukast sodium) 10 mg	K002902
Singulair [®] (montelukast sodium, lot number K002902; expiration date Nov-2015; Merck Sharp & Dohme Corp.) was supplied by the Investigator.	

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included montelukast predose and postdose blood samples up to 48 hours in periods 1 and 2.

Bioanalysis

The method and bioanalysis of the montelukast M6 metabolite was not reviewed because the applicant is not proposing to include data for the M6 metabolite from the 070 trial in the proposed U.S. prescribing information (USPI) for grazoprevir in combination with elbasvir.

The method and bioanalysis of montelukast are acceptable.

Montelukast plasma samples were analyzed using a validated LC/MS/MS method in K₂EDTA anticoagulated plasma by (b) (4). The blood samples for analysis of montelukast appear to have been collected in tubes containing K₂EDTA as an anticoagulant.

For the plasma samples from the P70 trial that were analyzed for montelukast, the lower limit of quantification for montelukast was 1 ng/mL and the upper limit of quantification was 1200 ng/mL. There were no precision or accuracy issues identified for montelukast based on the bioanalytical report. For the P70 trial, precision and accuracy for montelukast were evaluated using plasma montelukast quality control (QC) samples at 3 ng/mL, 600 ng/mL, and 1000 ng/mL. For montelukast, the corresponding inter-run accuracy values were -5% for 3 ng/mL, -3.2% for 600 ng/mL, and -1.5% for 1000 ng/mL. The corresponding montelukast inter-run precision values were 3% for 3 ng/mL, 2% for 600 ng/mL, and 3.1% for 1000 ng/mL.

Of the samples selected for incurred sample reanalysis for montelukast, all samples were within 20% using the percentage values of the repeat and original concentrations. According to the bioanalytical report, the number of incurred samples represents 10% of the total number of samples that were initially analyzed. The current FDA recommendation is 7%.

For the P70 trial, the bioanalytical report states that the maximum length of storage for the montelukast samples was 32 days at -80°C. For the P70 trial, long term montelukast stability data of 40 days at -80°C and 35 days at -80°C when combined with 200 ng/mL of grazoprevir in K₂EDTA anticoagulated plasma

was generated by (b) (4). The long term stability data generated by (b) (4) appears sufficient based on the information provided in the submission (the bioanalytical report states that the date of last analysis was July 30, 2014) if samples were stored at -80°C.

Pharmacokinetic Assessments

Based on the information included in the trial report, noncompartmental analysis was performed using actual sampling times to derive montelukast and M6 plasma pharmacokinetic parameters.

Statistical Analysis

The statistical analyses included deriving 90% confidence intervals for relevant pharmacokinetic parameters comparing digoxin with concomitant use of montelukast and grazoprevir (test arm) to the reference arm (montelukast alone).

10. Results

10.1 Subject Demographics

Table 2-P70 subject demographics

AN	Gender	Race	Ethnicity	Age (yr)	Height (cm)	Weight (kg)	Body Mass Index (kg/m ²)
0001	Female	White	Not Hispanic or Latino	37	171.0	67.5	22.98
0002	Female	White, American Indian/Alaska Native	Hispanic or Latino	54	163.0	64.0	24.13
0003	Male	White	Not Hispanic or Latino	32	180.0	79.9	24.70
0004	Female	White	Not Hispanic or Latino	47	166.0	60.2	21.90
0005	Female	White	Not Hispanic or Latino	43	156.0	56.0	22.94
0006	Female	White	Not Hispanic or Latino	54	170.0	88.2	30.46
0007	Male	White	Not Hispanic or Latino	43	186.0	83.4	24.12
0008	Male	Black or African American	Not Hispanic or Latino	32	181.0	87.1	26.49
0009	Male	White	Not Hispanic or Latino	25	178.0	83.1	26.36
0010	Female	White	Not Hispanic or Latino	33	163.0	81.5	30.65
0011	Male	Black or African American	Not Hispanic or Latino	24	182.0	86.6	26.27
0012	Male	Black or African American	Not Hispanic or Latino	34	170.0	69.0	23.77
0013	Female	White	Not Hispanic or Latino	20	167.0	64.1	23.09
0014	Female	White	Not Hispanic or Latino	25	166.0	67.1	24.39
0015	Female	White	Not Hispanic or Latino	29	157.0	59.5	24.21
0016	Male	White	Not Hispanic or Latino	39	174.0	84.1	27.63
0017	Male	White	Not Hispanic or Latino	28	182.0	71.0	21.40
0018	Female	White	Hispanic or Latino	30	156.0	68.7	28.33
0019	Female	White	Not Hispanic or Latino	49	170.0	65.4	22.57
0020	Male	White	Not Hispanic or Latino	49	184.0	102.0	29.99
0021	Male	American Indian/Alaska Native	Not Hispanic or Latino	37	180.0	83.6	25.70
0022	Female	White	Not Hispanic or Latino	26	166.0	80.4	29.31
0023	Male	White	Not Hispanic or Latino	24	168.0	73.6	25.94
Study Summary							
N:				23	23	23	23
Range:				20 to 54	156.0 to 186.0	56.0 to 102.0	21.40 to 30.65
Arithmetic Mean:				35	171.1	75.0	25.54
Female N:				12	12	12	12
Female Range:				20 to 54	156.0 to 171.0	56.0 to 88.2	21.90 to 30.65
Female Arithmetic Mean:				37	164.3	68.6	25.41
Male N:				11	11	11	11
Male Range:				24 to 49	168.0 to 186.0	69.0 to 102.0	21.40 to 29.99
Male Arithmetic Mean:				33	178.6	82.1	25.67
AN = Allocation Number.							

10.2 Concomitant Medications

The concomitant medications that were administered in the trial included acetaminophen. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Note: in the tables below the trial report states that C_{24h} was the plasma drug concentration 24 hours postdose. The montelukast M6 metabolite pharmacokinetic data and statistical analyses are provided for informational purposes only

Table 3-Montelukast pharmacokinetic parameters

	Montelukast Pharmacokinetics								
	AUC _{0-1st} (ng•hr/mL)			AUC _{0-∞} (ng•hr/mL)			C _{max} (ng/mL)		
	Montelukast Alone	Montelukast + Grazoprevir	Montelukast + Grazoprevir/ Montelukast Alone	Montelukast Alone	Montelukast + Grazoprevir	Montelukast + Grazoprevir/ Montelukast Alone	Montelukast Alone	Montelukast + Grazoprevir	Montelukast + Grazoprevir/ Montelukast Alone
N	23	22	22	23	22	22	23	22	22
AM	3050	3300	1.13	3080	3350	1.14	462	446	0.986
SD	1070	1150	0.256	1070	1150	0.247	170	213	0.360
ACV	35.2	34.9	22.5	34.8	34.2	21.7	36.7	47.9	36.5
Med	3050	3370	1.11	3130	3510	1.11	427	439	0.907
Min	1170	1530	0.669	1200	1590	0.721	193	161	0.482
Max	5200	5480	1.57	5220	5500	1.57	754	945	1.69
GM [‡]	2850	3090	1.11	2880	3150	1.11	431	398	0.924
GCV	40.2	40.2	23.7	39.7	39.3	22.4	40.4	52.9	38.5

Montelukast Alone: 10 mg montelukast (1 x 10 mg tablet) at Hour 0 on Day 1, following an overnight fast.
Montelukast + Grazoprevir: 200 mg grazoprevir (2 x 100 mg tablets) administered every 24 hours for 10 days (within ± 1 hour of dosing time on Day 1), with 10 mg of montelukast (1 x 10 mg tablet) co-administered at Hour 0 on Day 9, following an overnight fast.
[‡]Subject AN 0010 was dropped from the study prior to the start of Period 2 due to the use of a concomitant medication and had no available data for Montelukast + Grazoprevir.
[‡]GMs were calculated using all non-missing values.
AM = Arithmetic mean; SD = Standard deviation; GM = Geometric Mean; Med = Median; Min = Minimum; Max = Maximum;
ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (SD/AM)$; GCV = Geometric coefficient of variation is calculated in the natural log scale with the equation: $100 \times \sqrt{\exp(s^2) - 1}$, where s^2 is the observed variance on the natural log-scale.

Table 4-Montelukast statistical analyses

Pharmacokinetic Parameter	Montelukast Alone			Montelukast + Grazoprevir			Montelukast + Grazoprevir/ Montelukast Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC _{0-1st} [‡] (ng•hr/mL)	23	2850	(2410, 3370)	22	3140	(2650, 3720)	1.10	(1.01, 1.20)	16.570
AUC _{0-∞} [‡] (ng•hr/mL)	23	2880	(2440, 3400)	22	3200	(2710, 3770)	1.11	(1.02, 1.20)	15.680
C _{max} [‡] (ng/mL)	23	431	(364, 510)	22	398	(321, 494)	0.92	(0.81, 1.06)	26.244
C _{24h} [‡] (ng/mL)	23	12.7	(9.76, 16.6)	22	17.8	(13.7, 23.1)	1.39	(1.25, 1.56)	21.313
T _{max} [‡] (hr)	23	2.02	(1.03, 6.00)	22	3.50	(0.93, 6.00)			
Apparent terminal t _{1/2} [§] (hr)	23	6.36	25.86	22	6.84	41.28			

Montelukast Alone: 10 mg montelukast (1 x 10 mg tablet) at Hour 0 on Day 1, following an overnight fast.
Montelukast + Grazoprevir: 200 mg grazoprevir (2 x 100 mg tablets) administered every 24 hours for 10 days (within ± 1 hour of dosing time on Day 1), with 10 mg of montelukast (1 x 10 mg tablet) co-administered at Hour 0 on Day 9, following an overnight fast.
[†]Pseudo Within-Subject %CV = $100 \times \sqrt{(\sigma_A^2 + \sigma_B^2 - 2 \sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
[§]Median (Min, Max) reported for T_{max}.
[¶]Geometric mean and Geometric CV reported for apparent terminal t_{1/2}.
[‡]One (1) subject was dropped from the study prior to the start of Period 2 due to the use of a concomitant medication and had no available data for Montelukast + Grazoprevir.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

Table 5-Montelukast M6 metabolite pharmacokinetic parameters

	M6 Pharmacokinetics								
	AUC _{0-12h} (ng•hr/mL)			AUC _{0-∞} (ng•hr/mL)			C _{max} (ng/mL)		
	Montelukast Alone	Montelukast + Grazoprevir	Montelukast + Grazoprevir/ Montelukast Alone	Montelukast Alone	Montelukast + Grazoprevir	Montelukast + Grazoprevir/ Montelukast Alone	Montelukast Alone	Montelukast + Grazoprevir	Montelukast + Grazoprevir/ Montelukast Alone
N	23	22	22	23	22	22	23	22	22
AM	231	283	1.37	250	303	1.36	31.7	41.6	1.37
SD	117	133	0.476	129	142	0.445	12.4	23.2	0.628
ACV	50.5	47.2	34.8	51.5	46.7	32.7	39.0	55.7	45.8
Med	246	278	1.29	264	298	1.28	34.8	39.1	1.23
Min	36.5	72.3	0.668	44.1	81.9	0.725	7.76	9.07	0.434
Max	455	487	2.51	509	507	2.46	51.5	90.3	3.02
GM [†]	196	244	1.29	212	264	1.29	28.7	34.6	1.24
GCV	71.8	67.0	36.3	70.3	63.9	33.5	53.3	75.7	50.5

Montelukast Alone: 10 mg montelukast (1 x 10 mg tablet) at Hour 0 on Day 1, following an overnight fast.

Montelukast + Grazoprevir: 200 mg grazoprevir (2 x 100 mg tablets) administered every 24 hours for 10 days (within ± 1 hour of dosing time on Day 1), with 10 mg of montelukast (1 x 10 mg tablet) co-administered at Hour 0 on Day 9, following an overnight fast.

[†]Subject AN 0010 was dropped from the study prior to the start of Period 2 due to the use of a concomitant medication and had no available data for Montelukast + Grazoprevir.

[‡]GMs were calculated using all non-missing values.

AM = Arithmetic mean; SD = Standard deviation; GM = Geometric Mean; Med = Median; Min = Minimum; Max = Maximum; ACV = Arithmetic coefficient of variation is calculated in the original scale with the equation: $100 \times (SD/AM)$; GCV = Geometric coefficient of variation is calculated in the natural log scale with the equation: $100 \times \sqrt{(\exp(s^2) - 1)}$, where s^2 is the observed variance on the natural log-scale.

Table 6-Montelukast M6 metabolite statistical analyses

Pharmacokinetic Parameter	Montelukast Alone			Montelukast + Grazoprevir			Montelukast + Grazoprevir/ Montelukast Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC _{0-12h} [‡] (ng•hr/mL)	23	196	(149, 260)	22	252	(192, 329)	1.28	(1.13, 1.46)	24.937
AUC _{0-∞} [‡] (ng•hr/mL)	23	212	(162, 279)	22	273	(210, 353)	1.28	(1.14, 1.45)	23.120
C _{max} [‡] (ng/mL)	23	28.7	(23.2, 35.7)	22	35.5	(26.4, 47.7)	1.23	(1.04, 1.47)	33.719
C ₂₄ [§] (ng/mL)	23	1.49	(0.00, 5.02)	22	1.66	(0.00, 5.46)			
T _{max} [§] (hr)	23	3.55	(2.00, 6.00)	22	4.01	(2.00, 6.01)			
Apparent terminal t _{1/2} (hr)	23	5.02	40.16	22	6.01	35.21			

Montelukast Alone: 10 mg montelukast (1 x 10 mg tablet) at Hour 0 on Day 1, following an overnight fast.

Montelukast + Grazoprevir: 200 mg grazoprevir (2 x 100 mg tablets) administered every 24 hours for 10 days (within ± 1 hour of dosing time on Day 1), with 10 mg of montelukast (1 x 10 mg tablet) co-administered at Hour 0 on Day 9, following an overnight fast.

[†]Pseudo Within-Subject %CV = $100 \times \sqrt{(\sigma_A^2 + \sigma_B^2 - 2 \sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.

[§]Median (Min, Max) reported for C₂₄ and T_{max}.

^{||}Geometric mean and Geometric CV reported for apparent terminal t_{1/2}.

[¶]One (1) subject was dropped from the study prior to the start of Period 2 due to the use of a concomitant medication and had no available data for Montelukast + Grazoprevir.

^{††}Nine (9) subjects had M6 concentrations that were below the limit of quantitation (BLQ) 24 hours postdose for Montelukast Alone. In addition, 4 subjects had M6 concentrations that were BLQ 24 hours postdose for Montelukast + Grazoprevir. These BLQ values were imputed with a value of 0 for calculation of descriptive statistics.

GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

10.4 Safety Analysis

According to the trial report, no deaths or serious adverse events were reported for the trial.

11. Discussion and Conclusions

Based on the results from the P70 trial, the following conclusion can be made:

- When a single dose of montelukast 10 mg was administered with grazoprevir 200 mg once daily:
 - the montelukast $AUC_{(0-inf)}$ and C_{24h} were increased by 11% and 39%, respectively, the C_{max} was decreased by 8% and only the 90% confidence interval for C_{24h} was not within the standard limits of 80% to 125%.
 - the M6 metabolite $AUC_{(0-inf)}$ and C_{max} were increased by 28% and 23%, respectively, and the 90% confidence interval for $AUC_{(0-inf)}$ and C_{max} were not within the standard limits of 80% to 125%.

The results support the absence of a clinically significant effect of grazoprevir on montelukast exposure.

Study Title: A study to Evaluate the Effect of Famotidine and Pantoprazole on the Pharmacokinetics of Grazoprevir and Elbasvir following a Single Dose Administration of MK-5172A (Grazoprevir/Elbasvir Fixed-Dose Combination) in Healthy Subjects

Study Initiation Date: 19-Jun-2014 **Study Completion Date:** 06-Sep-2014

Study Site: (b) (4)

Study Design

This was an open label, 3-period, fixed-sequence study. Sixteen healthy subjects were enrolled. On Day 1 of Period 1, a single oral dose of MK-5172A [fixed dose combination tablet containing 100 mg grazoprevir (GZR) and 50 mg elbasvir (EBR)] was administered followed by pharmacokinetic sampling for GZR and EBR through 96 hours. There was a washout of at least 10 days between the dose in Period 1 and the first dose of Period 2. In Period 2, a single oral dose of 20 mg famotidine was administered approximately 10 hours (evening of Day -1) and 2 hours (morning of Day 1) prior to MK-5172A dosing on Day 1. Pharmacokinetic sampling for GZR and EBR were collected through 96 hours following MK-5172A dosing on Day 1. There was a washout of at least 10 days between the last dose in Period 2 and the first dose of Period 3. In Period 3, multiple oral doses of 40 mg pantoprazole were administered QD for 5 consecutive days followed by a single oral dose of MK-5172A administered approximately 2 hours after pantoprazole dosing on Day 5. Pharmacokinetic sampling for GZR and EBR were collected through 96 hours following MK-5172A dosing on Day 5.

Rationale for Study

The solubility of both GZR and EBR is pH dependent, and changes in stomach pH have the potential to affect absorption of these compounds. As such, the goal of the current study was to provide information on the potential pharmacokinetic effect of agents altering the stomach pH on MK-5172A as administered in the FDC formulation

Key Inclusion Criteria

- Healthy adult male and female volunteers, 19-55 years of age, inclusive
- BMI: 19- 32 kg/m², inclusive. Weigh at least 52 kg for males and 45 kg for females.
- Non-smokers
- Medically healthy with no clinically significant history, physical exam, lab profiles. Liver function test results must be at or lower than ULN.
- For females of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using acceptable birth control methods. Male subjects must use a condom (or abstain from sexual intercourse) and agree not to donate sperm from the first dose until 90 days after the last dose

Key Exclusion Criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 80 mL/min
- History of drug or alcohol abuse (within 2 years)

- Female subjects who are pregnant or lactating
- Positive results at screening for HIV, hepatitis B, or hepatitis C
- Positive results for urine drug, urine cotinine, or alcohol screening or check in
- Unable to refrain from or anticipates the use of any drug beginning 14 days (28 days for CYP/P-gp inducers) prior to the first dose of study drug and throughout the study.
- Donation of blood or had significant blood loss within 4 weeks prior to the first dose of study drug or plasma donation within 7 days prior to the first dose of study drug.
- Participation in another clinical trial within 28 days prior to the first dose of study drug.
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients
- Subject is unable to refrain from or anticipates the use of any medication beginning 2 weeks (or 5 half-lives of the compound, whichever is longer) prior to first dosing and throughout the study.

Concomitant medications

With the exception of oral contraceptives, no drugs were to be taken within 14 days prior to first dose (or 28 days for inducers of CYP enzymes and/or P-gp, including St. John’s Wort), without knowledge of the Investigator and approval by the Sponsor's Medical Monitor. No drugs of any kind were to be taken during the study unless required to treat an adverse experience. Acetaminophen (up to 2 g per 24 hours) could have been prescribed by the Investigator during the study for minor ailments. Hormonal contraceptives and hormone replacement therapy were not prohibited.

Identity of Investigational Product

Table 1. Identity of Investigational Products

Bulk Product Description	Manufacturing Lot Number
MK-5172A 100 mg/50 mg Tablet	WL00056641
[‡] Pepcid AC [®] Famotidine 20 mg Tablet	NA
[§] Protonix [®] (Pantoprazole Sodium) 40 mg Delayed-Release Tablets	NA
[‡] Pepcid AC [®] Famotidine 20 mg tablet (Lot number EDF003; Expiration date Dec-2015; McNeil Consumer Pharmaceuticals Co.)	
[§] Protonix [®] (pantoprazole sodium) 40 mg (Lot number 237693AN; Expiration date Aug-2016; Pfizer Inc.)	

Pharmacokinetic assessments

Blood samples for determination of GZR and EBR plasma concentrations were collected at predose and at specified time points over 96 hours following the GZR and EBR dose in each treatment period. With the exception of the C₂ and C₂₄ values which were obtained directly using SAS[®] (Version 9.3) from the observed plasma concentration-time data, all the pharmacokinetic parameter values were calculated using the software Phoenix[®] WinNonlin[®] (Version 6.3). C_{max} and T_{max} values were generated by WinNonlin[®] from the observed GZR and EBR plasma concentration-time data. AUCs were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down).

Bioanalysis

Plasma samples collected for EBR and GZR assays were analyzed by (b) (4). The concentrations of these drugs were determined using validated LC/MS/MS methods. All methods were adequately validated. The standard curve and QC data indicated assays were acceptable. All samples were stored and processed in the time frame supported by the stability data.

Table 2. Summary of Bioanalysis

Analyte	MK-5172 (GZR)	MK-8742 (EBR)
Internal standard	MK-5172-d ₆	MK-8742-d ₆
Matrix/Anticoagulant	Plasma/ K ₂ EDTA	Plasma/ K ₂ EDTA
Extraction method	Liquid-liquid extraction	Liquid-liquid extraction
Calibration range	1 to 1000 ng/mL	0.25 to 500 ng/mL
QC concentration	3, 50, 75, 500 and 750 ng/mL	0.75, 12.5, 75, 250 and 375 ng/mL
Interday precision and accuracy	P: 1.37 to 4.21% A: - 0.90 to 3.43%	P: 1.87 to 5.19 % A: - 2.75 to 2.17%
Storage stability	99 days at - 20 °C	83 days at - 20 °C

RESULTS

Subject disposition and baseline characteristics

Sixteen subjects were enrolled into the study and 12 subjects completed the study per protocol. Two subjects were discontinued by the Investigator due to non-drug related adverse events (one subject for genital swelling and perineal pain and one for ventricular extrasystoles). One subject was discontinued due to a protocol violation (positive drug screen for amphetamines) and one subject withdrew from the study due to a motorcycle accident.

Table 3. Subject baseline demographics

AN	Gender	Race	Ethnicity	Age (yr)	Height (cm)	Weight (kg)	Body Mass Index (kg/m ²)
0001	Female	White	Not Hispanic or Latino	33	154.0	51.4	21.69
0002	Male	White	Not Hispanic or Latino	52	181.0	82.5	25.23
0003	Male	White	Not Hispanic or Latino	46	175.0	86.1	28.11
0004	Female	White	Not Hispanic or Latino	41	173.0	91.8	30.50
0005	Male	White	Not Hispanic or Latino	48	171.0	80.3	27.39
0006	Female	White	Not Hispanic or Latino	31	168.0	77.5	27.42
0007	Male	White	Not Hispanic or Latino	32	168.0	88.0	31.11
0008	Female	White	Not Hispanic or Latino	45	171.0	85.0	29.11
0009	Female	Asian	Not Hispanic or Latino	34	165.0	78.2	28.58
0010	Male	White	Not Hispanic or Latino	28	183.0	89.4	26.58
0011	Female	White	Not Hispanic or Latino	31	171.0	66.8	22.78
0012	Male	White	Hispanic or Latino	23	166.0	75.5	27.45
0013	Female	White	Not Hispanic or Latino	19	160.0	68.0	26.55
0014	Female	White	Not Hispanic or Latino	55	173.0	62.7	20.95
0015	Male	White	Not Hispanic or Latino	23	174.0	71.8	23.57
0016	Male	White	Not Hispanic or Latino	29	172.0	67.0	22.74
Study Summary							
N:				16	16	16	16
Range:				19 to 55	154.0 to 183.0	51.4 to 91.8	20.95 to 31.11
Arithmetic Mean:				36	170.3	76.4	26.24
Female N:				8	8	8	8
Female Range:				19 to 55	154.0 to 173.0	51.4 to 91.8	20.95 to 30.50
Female Arithmetic Mean:				36	166.9	72.7	25.95
Male N:				8	8	8	8
Male Range:				23 to 52	166.0 to 183.0	67.0 to 89.4	22.74 to 31.11
Male Arithmetic Mean:				35	173.8	80.1	26.52
AN = Allocation number.							

Pharmacokinetic Results

1. The effects of the co-administration of famotidine on GZR and EBR exposures

The co-administration of famotidine did not significantly alter the pharmacokinetics of GZR or EBR (Table 4-5).

Table 4. GZR plasma pharmacokinetics with or without the co-administration of famotidine

Grazoprevir Pharmacokinetic Parameter	MK-5172A			MK-5172A + Famotidine			MK-5172A + Famotidine/ MK-5172A		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (μM•hr)	16	0.573	(0.465, 0.707)	14	0.633	(0.545, 0.735)	1.10	(0.95, 1.28)	23.104
AUC _{0-last} [‡] (μM•hr)	16	0.477	(0.382, 0.596)	14	0.519	(0.431, 0.625)	1.09	(0.93, 1.28)	24.681
C _{max} [‡] (nM)	16	39.4	(28.8, 54.0)	14	35.0	(28.6, 42.8)	0.89	(0.71, 1.11)	34.392
C ₂₄ [‡] (nM)	16	6.00	(4.86, 7.40)	14	6.72	(5.50, 8.21)	1.12	(0.97, 1.30)	22.525
C ₂ [‡] (nM)	16	21.9	(16.1, 29.7)	14	27.2	(21.3, 34.7)	1.24	(0.97, 1.60)	39.062
T _{max} [§] (hr)	16	1.50	(1.00, 12.00)	14	2.00	(1.00, 4.00)			
Apparent terminal t _{1/2} (hr)	16	33.80	35.41	14	35.47	32.09			

MK-5172A: Single oral dose of MK-5172A (1 x 100 mg grazoprevir/50 mg elbasvir tablet FDC).
 MK-5172A + Famotidine: Single oral doses of 20 mg famotidine (1 x 20 mg tablet) administered 10 hours (Day -1) and 2 hours (Day 1) prior to a single oral dose of MK-5172A (1 x 100 mg grazoprevir/50 mg elbasvir tablet FDC) on Day 1.
[‡]Pseudo within-subject %CV = $100 \times \sqrt{[(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2]}$, where σ_A^2 and σ_B^2 are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Min, Max) reported for T_{max}.
^{||}Geometric mean and Geometric CV reported for apparent terminal t_{1/2}.
[†]Two (2) subjects were dropped from the study on Day -1 of Period 2, and therefore, these subjects have no data available for MK-5172A + Famotidine. See Section 10.4 for details.
 GM = Geometric mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

Table 5. EBR plasma pharmacokinetics with or without the co-administration of famotidine

Elbasvir Pharmacokinetic Parameter	MK-5172A			MK-5172A + Famotidine			MK-5172A + Famotidine/ MK-5172A		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (μM•hr)	16	2.75	(2.38, 3.19)	14	2.88	(2.44, 3.41)	1.05	(0.92, 1.18)	18.627
AUC _{0-last} [‡] (μM•hr)	16	2.67	(2.32, 3.08)	14	2.80	(2.37, 3.31)	1.05	(0.92, 1.19)	18.776
C _{max} [‡] (μM)	16	0.140	(0.124, 0.158)	14	0.156	(0.131, 0.185)	1.11	(0.98, 1.26)	19.265
C ₂₄ [‡] (nM)	16	42.6	(37.0, 49.0)	14	43.9	(37.1, 51.9)	1.03	(0.91, 1.17)	19.190
C ₂ [‡] (nM)	16	105	(86.4, 126)	14	101	(82.1, 125)	0.97	(0.81, 1.16)	27.127
T _{max} [§] (hr)	16	3.50	(3.00, 4.00)	14	3.50	(3.00, 4.00)			
Apparent terminal t _{1/2} (hr)	16	19.27	10.85	14	18.48	15.17			

MK-5172A: Single oral dose of MK-5172A (1 x 100 mg grazoprevir/50 mg elbasvir tablet FDC).
 MK-5172A + Famotidine: Single oral doses of 20 mg famotidine (1 x 20 mg tablet) administered 10 hours (Day -1) and 2 hours (Day 1) prior to a single oral dose of MK-5172A (1 x 100 mg grazoprevir/50 mg elbasvir tablet FDC) on Day 1.
[‡]Pseudo within-subject %CV = $100 \times \sqrt{[(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2]}$, where σ_A^2 and σ_B^2 are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Min, Max) reported for T_{max}.
^{||}Geometric mean and Geometric CV reported for apparent terminal t_{1/2}.
[†]Two (2) subjects were dropped from the study on Day -1 of Period 2, and therefore, these subjects have no data available for MK-5172A + Famotidine. See Section 10.4 for details.
 GM = Geometric mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

2. The effects of the co-administration of pantoprazole on GZR and EBR exposures

The co-administration of pantoprazole did not significantly alter the pharmacokinetics of GZR or EBR (Table 6-7).

Table 6. GZR plasma pharmacokinetics with or without the co-administration of pantoprazole

Grazoprevir Pharmacokinetic Parameter	MK-5172A			MK-5172A + Pantoprazole			MK-5172A + Pantoprazole/ MK-5172A		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (μM•hr)	16	0.573	(0.465, 0.707)	12	0.640	(0.534, 0.767)	1.12	(0.96, 1.30)	21.926
AUC _{0-12hr}} [‡] (μM•hr)	16	0.477	(0.382, 0.596)	12	0.561	(0.459, 0.686)	1.18	(1.00, 1.38)	23.819
C _{max} [‡] (nM)	16	39.4	(28.8, 54.0)	12	43.5	(32.7, 57.9)	1.10	(0.89, 1.37)	31.511
C ₂₄ [‡] (nM)	16	6.00	(4.86, 7.40)	12	7.02	(5.83, 8.45)	1.17	(1.02, 1.34)	19.558
C ₂ [‡] (nM)	16	21.9	(16.1, 29.7)	12	29.0	(18.9, 44.4)	1.33	(0.94, 1.87)	49.159
T _{max} [§] (hr)	16	1.50	(1.00, 12.00)	12	1.50	(1.00, 4.00)			
Apparent terminal t _{1/2} (hr)	16	33.80	35.41	12	30.95	32.45			

MK-5172A: Single oral dose of MK-5172A (1 x 100 mg grazoprevir/50 mg elbasvir tablet FDC).
MK-5172A + Pantoprazole: Multiple oral doses of 40 mg pantoprazole (1 x 40 mg tablet) administered QD on Days 1 through 5 and a single oral dose of MK-5172A (1 x 100 mg grazoprevir/50 mg elbasvir tablet FDC) administered 2 hours after pantoprazole dosing on Day 5.

[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A² + σ_B² - 2 σ_{AB})/2], where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Min, Max) reported for T_{max}.
^{||}Geometric mean and Geometric CV reported for apparent terminal t_{1/2}.
[¶]Two (2) subjects were dropped from the study on Day -1 of Period 2, 1 subject was dropped between Periods 2 and 3, and 1 subject withdrew herself from the study on Day 1 of Period 3; therefore, these subjects have no data available for MK-5172A + Pantoprazole. See Section 10.4 for details.
GM = Geometric mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

Table 7. EBR plasma pharmacokinetics with or without the co-administration of pantoprazole.

Elbasvir Pharmacokinetic Parameter	MK-5172A			MK-5172A + Pantoprazole			MK-5172A + Pantoprazole/ MK-5172A		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (μM•hr)	16	2.75	(2.38, 3.19)	12	2.88	(2.42, 3.42)	1.05	(0.93, 1.18)	16.468
AUC _{0-last} [‡] (μM•hr)	16	2.67	(2.32, 3.08)	12	2.80	(2.36, 3.31)	1.05	(0.93, 1.18)	16.308
C _{max} [‡] (μM)	16	0.140	(0.124, 0.158)	12	0.143	(0.122, 0.169)	1.02	(0.92, 1.14)	15.405
C ₂₄ [‡] (nM)	16	42.6	(37.0, 49.0)	12	44.0	(37.3, 52.0)	1.03	(0.92, 1.17)	16.793
C ₂ [‡] (nM)	16	105	(86.4, 126)	12	112	(88.5, 143)	1.07	(0.88, 1.31)	27.929
T _{max} [§] (hr)	16	3.50	(3.00, 4.00)	12	3.50	(3.00, 4.00)			
Apparent terminal t _{1/2} (hr)	16	19.27	10.85	12	18.74	12.79			

MK-5172A: Single oral dose of MK-5172A (1 x 100 mg grazoprevir/50 mg elbasvir tablet FDC).
 MK-5172A + Pantoprazole: Multiple oral doses of 40 mg pantoprazole (1 x 40 mg tablet) administered QD on Days 1 through 5 and a single oral dose of MK-5172A (1 x 100 mg grazoprevir/50 mg elbasvir tablet FDC) administered 2 hours after pantoprazole dosing on Day 5.

[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A² + σ_B² - 2 σ_{AB})/2], where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.

[§]Median (Min, Max) reported for T_{max}.

^{||}Geometric mean and Geometric CV reported for apparent terminal t_{1/2}.

[¶]Two (2) subjects were dropped from the study on Day -1 of Period 2, 1 subject was dropped between Periods 2 and 3, and 1 subject withdrew herself from the study on Day 1 of Period 3; therefore, these subjects have no data available for MK-5172A + Pantoprazole. See Section 10.4 for details.

GM = Geometric mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

Reviewer comments

The effects of acid reducing agents on the absorption of EBR appear to be formulation-dependent; pantoprazole and famotidine did not alter the pharmacokinetics of EBR in this trial (using FDC2 formulation). However, famotidine decreased EBR AUC_{inf} by 53% following a single dose of the EBR-FFP formulation (formulation used in the early phase of the development). As the fixed-dose tablet formulation used in this trial is identical to the to-be-marketed formulation except for color coating, this formulation can be administered with acid-reducing agents.

Conclusion

The pharmacokinetics of GZR and EBR are not significantly altered by co-administration with famotidine or pantoprazole. Zepatier™ can be co-administered with famotidine, pantoprazole, and other acid reducing agents.

Study title: A four-part study to evaluate the interaction of grazoprevir and elbasvir with cyclosporine, tacrolimus, mycophenolate mofetil, and prednisone in healthy subjects (PN073)

Primary objective: To assess the effect of multiple oral doses of grazoprevir and elbasvir on the single-dose pharmacokinetics of cyclosporine, tacrolimus, MPA, MPAG, prednisone, or prednisolone

Trial center: (b) (4)

Study design

This was a 4-part multi-site study. In each part, single-dose pharmacokinetics for immunosuppressants (cyclosporine, tacrolimus, mycophenolate mofetil or prednisone), elbasvir (EBR) and grazoprevir (GZR) were determined. In each part, healthy adult, non-tobacco using, male and female subjects (at least 3 female subjects) were enrolled. Each subject participated in only 1 study part.

Table 1. Study design

	Part 1	Part 2	Part 3	Part 4
Period 1: immunosuppressant only	400 mg cyclosporine Single oral dose	2 mg tacrolimus Single oral dose	1 g mycophenolate mofetil (MMF) Single oral dose	40 mg prednisone Single oral dose
PK sampling in Period 1	Up to 72 hours post-dose	Up to 144 hours post-dose	Up to 96 hours post-dose	Up to 24 hours post-dose
Washout period	3 days	6 days	4 days	No washout period
Period 2 Co-administration of GZR/EBR and immunosuppressant (Multiple doses of GZR/EBR and a single oral dose of immunosuppressant)	200 mg GZR+50 mg EBR QD for 13 days A single dose of 400 mg cyclosporine on Day 11	200 mg GZR+50 mg EBR QD for 16 days A single dose of 2 mg of tacrolimus Day 11	200 mg GZR+50 mg EBR QD for 14 days A single dose of 1 g MMF on Day 11.	200 mg GZR+50 mg EBR QD for 11 days A single dose of 40 mg prednisone on Day 11.
PK sampling in Period 2	GZR/EBR: Up to 24 hours post-dose on Days 10 and 11 Cyclosporine: Up to 72 hours post-dose on Day 11	GZR/EBR: Up to 24 hours post-dose on Day 10 and 11 Tacrolimus: Up to 144 hours post-dose on Day 11	GZR/EBR: Up to 24 hours post-dose on Day 10 and 11 MMF: Up to 96 hours post-dose on Day 11	GZR/EBR: Up to 24 hours post-dose on Day 10 and 11 prednisone: Up to 24 hours post-dose on Day 11
Fasted/fed for PK sampling	Overnight fast	Overnight fast	Overnight fast	Overnight fast
# of subjects enrolled	14	16	14	14

Rationale for dosing regimen and pharmacokinetic endpoint

Cyclosporine (Part 1)

Cyclosporine is generally dosed 7 – 9 mg/kg/day divided twice daily in transplant patients. The applicant stated that a dose of 400 mg was considered to give a robust assessment of the perpetrator potential of cyclosporine on GZR via OATP, P-gp, CYP3A, and BCRP pathways, while providing a safety margin in the event that cyclosporine concentrations were significantly increased. Whole blood cyclosporine concentrations are typically determined as cyclosporine has a high affinity to erythrocytes and plasma concentrations can be varied. Therefore, whole blood cyclosporine concentrations were measured in this trial.

Tacrolimus (Part 2): Tacrolimus is generally dosed at 0.075 - 0.2 mg/kg/day divided twice daily. A dose of 2 mg tacrolimus was selected for this study to provide a safety margin in the event that tacrolimus concentrations increase due to CYP3A inhibition by GZR and EBR. Tacrolimus also has a high affinity to erythrocytes thus whole blood concentrations are typically measured.

MMF (Part 3): MMF is generally dosed at 1 g orally twice daily in renal transplant patients and 1.5 g twice weekly for use in adult cardiac or hepatic transplant patients. The applicant stated that up to 1.5 g MMF have been administered to healthy subjects from literature. Therefore, a dose of 1 g is expected to give a reasonable assessment of the perpetrator potential without posing safety concerns. Following oral and IV administration, MMF undergoes rapid and complete metabolism pre-systemically by carboxylesterase to MPA. MPA is metabolized into MPAG, MPA glucuronide by UGT1A and UGT2B7. MPAG is an inactive metabolite but it is converted MPA via enterohepatic recirculation resulting in secondary peaks in plasma MPA concentrations 6-12 hours post-dose. Therefore, both MPA and MPAG concentrations were determined in this study.

Prednisone (Part 4): Prednisone was administered as a single oral 40 mg dose. The usual dosage range is 5 – 60 mg per day depending on the condition that is being treated. Therefore, a dose of 40 mg was considered to give a reasonable assessment of the perpetrator and victim potential of prednisone and prednisolone. Prednisolone is an active metabolite of prednisone and prednisolone and prednisone are metabolically interconvertible. Therefore, plasma concentrations of both entities were determined.

Reviewer comments

Due to the potential safety concerns, a single low (or subtherapeutic) dose of tacrolimus was used in this trial. Therefore, the results may not reflect the worst case scenario. Please refer to the study results and discussions for detailed information.

Identity of investigational products

Table 2. Identify of investigational products

Bulk Product Description	Manufacturing Lot Number
(b) (4) MK-5172 (b) (4) 100 mg	WL00047521
MK-8742 50 mg (b) (4)	WL00055785
Oval) Neoral [®] Soft Gelatin Capsules 100 mg (Cyclosporine)	Not Applicable
Prograf [®] Capsules USP 1 mg (Tacrolimus)	Not Applicable
CellCept [®] Tablets 500 mg (Mycophenolate mofetil)	Not Applicable
Prednisone Tablets USP 20 mg	Not Applicable
Cyclosporine 100 mg (lot number F4161A; expiration date Oct-2015; Catalet Pharma Solutions, LLC) was supplied by the Investigator.	
Tacrolimus 1 mg (lot number 047661; expiration date Oct-2016; Astellas Pharma US, Inc.) was supplied by the Investigator.	
Mycophenolate mofetil 500 mg (lot number M3176; expiration date May-2016; Genentech [A member of the Roche Group]) was supplied by the Investigator.	
Prednisone Tablets USP 20 mg (lot number PV023B; expiration date May-2017; HIKMA Pharmaceuticals) was supplied by the Investigator.	

Key inclusion criteria

- Healthy adult male and female subjects, 19-55 years of age, inclusive
- BMI: 19-32 kg/m², inclusive
- Medically healthy with no clinically significant history, physical exam, lab profiles
- Female with non-childbearing potential or a female of childbearing potential must either sexually inactive or use acceptable birth control methods. A female of childbearing potential was excluded in Part 3 and Part 4
- Male subjects must agree not to donate sperm from the first dose until 90 days after the last dose

Key exclusion criteria

- History of any illness that might confound the results of the study or poses an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 90 mL/min
- History of alcoholism or drug abuse (within 2 years)
- Positive results at screening for HIV, hepatitis B, or hepatitis C
- Subjects who received any live or live attenuated vaccine within 30 days before dosing
- Subjects who received injectable corticoids in the 12 weeks prior to the first dose of study drug or any oral form of corticoids in the 30 days prior to the first dose of study drug
- Donation of blood or had significant blood loss within 56 days prior to the first dose of study drug or plasma donation within 7 days prior to the first dose of study drug
- Participation in another clinical trial within 28 days prior to the first dose of study drug.

- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients
- Unable to refrain from any drug including prescription and non-prescription medications. Acetaminophen (up to 2 g per 24-hour period) may be permitted during the study
- Any drugs known to be significant inducers of CYP enzymes and/or P gp, including St. John's Wort, for 28 days prior to the first dose of study drug and throughout the study
- History or presence of chronic infection
- History or presence of hereditary deficiency of hypoxanthine guanine phosphoribosyl transferase (Part 3 only)
- History or presence of atypical mycobacterial infection (Part 3 only)
- History or presence of glaucoma, hypothyroidism, stomach ulcer, ocular herpes simples (Part 4 only)
- History of ECG abnormalities, hypokalemia (Part 2 only)

Pharmacokinetic assessments

For all parts, blood samples for the determination of immunosuppressants, GZR, and EBR were collected as outlined under “study design”. Blood/plasma concentrations and actual sampling times relative to the time of the administered doses for each respective treatment were used to determine the pharmacokinetics of all drugs. Pharmacokinetic parameter values were determined from blood or plasma concentration-time data by employing a noncompartmental approach using Phoenix® WinNonlin® (Version 6.3). AUC values were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down).

Bioanalysis

Method validation and sample analyses were performed by (b) (4) except for GZR and EBR (b) (4). Validated methods and assay results are summarized in Table 3.

All methods were adequately validated. The standard curve, QC data, and ISR (incurred sample analyses) results met the predefined criteria and indicated assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data.

Table 1. Summary of bioanalysis

Analyte	Cyclosporin A	Tacrolimus	Mycophenolic acid (MPA)	MPA-glucuronide	Prednisone	Prednisolone	GZR	EBR
Internal standard	Cyclosporin D	Ascomycin	Mycophenolic acid cyclo-propane analogue	Mycophenolic acid cyclo-propane analog glucuronide	Dexamethasone	Dexamethasone	[² H ₆] GZR	[² H ₆]MK-8742
Matrix	Whole blood	Whole blood	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
Anticoagulant	K ₂ EDTA	K ₃ EDTA	K ₂ EDTA	K ₂ EDTA	K ₂ EDTA	K ₂ EDTA	K ₂ EDTA	K ₂ EDTA
Extraction methods	Liquid-liquid extraction	Liquid-liquid extraction	Protein precipitation	Protein precipitation	Liquid-liquid extraction	Liquid-liquid extraction	Liquid-liquid extraction	Liquid-liquid extraction
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
Calibration range	5-2500 ng/mL	0.25-25 ng/mL	50 to 40000 ng/mL ^(a)	0.5-200 µg/mL	1-50 ng/mL	5-250 ng/mL	1-1000 ng/mL	0.25- 500 ng/mL
QC conc	15, 125, 1250 , 1875 ng/mL	0.75, 1.88, 12.5, 18.75 ng/mL	90, 1200, 12000, 18000 ng/mL	1.5, 15, 100 and 150 µg/mL	3, 3.75, 25, 37.5 ng/mL	15, 18.75, 125, 187.5 ng/mL	3, 75, 750 ng/mL	0.75, 75, 375 ng/mL
Interday precision (P) accuracy (A)	P: 3.4% to 4.1% A:-10.5% to 4.6%	P: 1.8% to 7.5% A: -3.1% to 6.6%	P: 1.5% to 2.5% A:-5.5% to 1.2%	P: 2.9% to 4.5% A: 0% to 3.33%	P:1.7% to 3.1% A: -4.4% to 0.8 %	P: 1.9% to 3.1 % A: -5.4% to 1.6%	P: 3.2% to 6% A: -8.8% to 0.8%	P: 5.4% to 8.5% A: 2% to 7.1%
Dilution validation	Validated at 24995 ng/mL	Validated at 254 ng/mL	Validated at 120 µg/mL	Validated at 401.4 µg/mL	Validated at 251.5 ng/mL	Validated at 1250 ng/mL	Validated up to 50000 ng/mL	Validated up to 10000 ng/mL
Storage stability	52 days at -80°C	242 days at -20 °C	108 days at -80 °C	100 days at -20 °C	231 days at -20 °C	231 days at -20 °C	825 days at -20 °C	651 days at -20 °C
ISR (% samples analyzed)	13%	10%	10%	10%	15%	15%	None	None

(a): The validated calibration range is from 30.00 to 24000.00 ng/mL. A correction factor of 1.7 was applied to study samples to account for the addition of 2% phosphoric acid. This resulted in the determination of mycophenolic acid in human EDTA K2 plasma from 50 to 40000 ng/mL.

Pharmacokinetic results

Part 1: Drug interactions between GZR/EBR and cyclosporine

The effects of multiple daily doses of 200 mg GZR and 50 mg EBR on the whole blood pharmacokinetics of cyclosporine (a single 400 mg dose) are summarized in Table 5. GZR and EBR did not significantly alter the pharmacokinetics of cyclosporine.

The effects of a single dose of cyclosporine (400 mg) on the pharmacokinetics of GZR and EBR are summarized in Table 6 and 7. Cyclosporine significantly increased GZR exposure by approximately 15-fold, 17-fold, and 22-fold for AUC_{24hr} , C_{max} , and C_{24hr} , respectively. Cyclosporine also increased AUC_{24hr} , C_{max} , and C_{24hr} values of EBR by 1.98-fold, 1.95-fold, and 2.21-fold, respectively.

Table 5. Cyclosporine whole blood pharmacokinetics with and without the co-administration of EBR/GZR

Pharmacokinetic Parameter	Cyclosporine Alone			Grazoprevir + Elbasvir + Cyclosporine			Grazoprevir + Elbasvir + Cyclosporine / Cyclosporine Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$ [‡] (µg•hr/mL)	14	9.14	(7.95, 10.5)	13	8.77	(7.49, 10.3)	0.96	(0.90, 1.02)	8.776
AUC_{0-last} [‡] (µg•hr/mL)	14	8.87	(7.77, 10.1)	13	8.54	(7.34, 9.95)	0.96	(0.91, 1.02)	8.763
C_{max} [‡] (µg/mL)	14	1.35	(1.22, 1.50)	13	1.22	(1.08, 1.39)	0.90	(0.85, 0.97)	9.556
C_{12} [‡] (ng/mL)	14	165	(138, 197)	13	165	(134, 203)	1.00	(0.92, 1.08)	11.283
T_{max} [§] (hr)	14	1.50	(1.00, 5.00)	13	1.50	(1.00, 1.50)			
Apparent Terminal $t_{1/2}$ [¶] (hr)	14	18.08	16.6	13	16.89	19.8			

Cyclosporine Alone: A single oral dose of 400 mg cyclosporine administered on Day 1 of Period 1.
 Grazoprevir + Elbasvir + Cyclosporine: 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 - 13 with 400 mg cyclosporine co-administered on Day 11 of Period 2.

[†]Pseudo within-subject %CV = $100 \cdot \text{Sqrt}[(\sigma_A^2 + \sigma_B^2 - 2 \cdot \sigma_{AB})/2]$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max} .
[¶]Geometric mean and geometric coefficient of variation reported for apparent terminal $t_{1/2}$.
^{††}One (1) subject vomited and terminated early on Day 11. Therefore, this subject's Day 11 pharmacokinetic estimates were not calculated.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 6. GZR plasma pharmacokinetics with and without the co-administration of Cyclosporine

Pharmacokinetic Parameter	Grazoprevir + Elbasvir			Grazoprevir + Elbasvir + Cyclosporine			Grazoprevir + Elbasvir + Cyclosporine / Grazoprevir + Elbasvir		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC_{0-24} [‡] (µM•hr)	14	1.60	(1.26, 2.05)	13	24.4	(19.6, 30.3)	15.21	(12.83, 18.04)	24.669
C_{max} [‡] (µM)	14	0.306	(0.214, 0.439)	13	5.21	(4.44, 6.10)	17.00	(12.94, 22.34)	40.491
C_2 [‡] (µM)	14	0.124	(0.0694, 0.221)	13	2.84	(1.98, 4.08)	22.95	(12.69, 41.49)	87.655
C_{24} [‡] (nM)	14	13.7	(11.4, 16.5)	13	46.6	(33.1, 65.7)	3.39	(2.82, 4.09)	26.836
T_{max} [§] (hr)	14	3.00	(2.00, 5.03)	13	3.01	(2.00, 5.04)			

Grazoprevir + Elbasvir: 200 mg grazoprevir and 50 mg elbasvir co-administered QD on Days 1 - 10 of Period 2.
 Grazoprevir + Elbasvir + Cyclosporine: 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 - 13 with 400 mg cyclosporine co-administered on Day 11 of Period 2.

[†]Pseudo within-subject %CV = $100 \cdot \text{Sqrt}[(\sigma_A^2 + \sigma_B^2 - 2 \cdot \sigma_{AB})/2]$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max} .
[¶]One (1) subject vomited and terminated early on Day 11. Therefore, this subject's Day 11 pharmacokinetic estimates were not calculated.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 7. EBR plasma pharmacokinetics with and without the co-administration of Cyclosporine

Pharmacokinetic Parameter	Grazoprevir + Elbasvir			Grazoprevir + Elbasvir + Cyclosporine			Grazoprevir + Elbasvir + Cyclosporine/ Grazoprevir + Elbasvir		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µM•hr)	14	2.42	(1.94, 3.02)	13	4.80	(4.07, 5.67)	1.98	(1.84, 2.13)	10.626
C _{max} [‡] (µM)	14	0.171	(0.139, 0.211)	13	0.334	(0.283, 0.394)	1.95	(1.84, 2.07)	8.612
C ₂ [‡] (µM)	14	0.122	(0.0982, 0.152)	13	0.123	(0.100, 0.151)	1.00	(0.88, 1.14)	18.119
C ₂₄ [‡] (nM)	14	67.6	(52.4, 87.3)	13	150	(122, 183)	2.21	(1.98, 2.47)	15.907
T _{max} [§] (hr)	14	4.00	(3.00, 5.01)	13	5.00	(4.00, 6.00)			

Grazoprevir + Elbasvir: 200 mg grazoprevir and 50 mg elbasvir co-administered QD on Days 1 - 10 of Period 2.
Grazoprevir + Elbasvir + Cyclosporine: 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 – 13 with 400 mg cyclosporine co-administered on Day 11 of Period 2.
[†]Pseudo within-subject %CV = 100* $\sqrt{[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
[¶]One (1) subject vomited and terminated early on Day 11. Therefore, this subject's Day 11 pharmacokinetic estimates were not calculated.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Reviewer comments

A significant increase in the GZR exposure is likely due to OATP1B inhibition by cyclosporine. In vitro and drug interaction trial results (rifampin and protease inhibitors) suggest that GZR is a sensitive OATP1B substrate. A 2-fold increase in EBR exposure is likely the mixed effects of P-gp and OATP1B inhibition. The magnitude of the increase in GZR exposure is clinically relevant; a 15-fold increase in GZR exposure would result in an exposure comparable to GZR 400 mg in CHC patients. GZR 400 mg in CHC patients is associated with a significantly higher rate of late AST/ALT elevation, thus the use of that dose was disallowed during development.

Part 2: Drug interactions between GZR/EBR and tacrolimus

The effects of multiple daily doses of 200 mg GZR and 50 mg EBR on the whole blood pharmacokinetics of tacrolimus (2 mg single dose) are summarized in Table 8. The co-administration of EBR/GZR increased the AUC_{0-∞}, AUC_{last}, and C_{min} values of tacrolimus by 1.43, 1.51, and 1.70-fold, respectively.

The effects of a single dose tacrolimus (2 mg) on the pharmacokinetics of GZR and EBR are summarized in Table 9 and 10. The co-administration with tacrolimus and GZR/EBR did not alter the pharmacokinetic parameters of GZR or EBR.

Table 8. Tacrolimus whole blood pharmacokinetics with and without the co-administration of GZR/EBR

Pharmacokinetic Parameter	Tacrolimus Alone			Grazoprevir + Elbasvir + Tacrolimus			Grazoprevir + Elbasvir + Tacrolimus / Tacrolimus Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (ng•hr/mL)	16	108	(90.0, 129)	16	153	(134, 176)	1.43	(1.24, 1.64)	22.935
AUC _{0-last} [‡] (ng•hr/mL)	16	91.5	(74.3, 113)	16	138	(119, 159)	1.51	(1.28, 1.77)	26.227
C _{max} [‡] (ng/mL)	16	10.3	(8.71, 12.2)	16	6.18	(5.37, 7.10)	0.60	(0.52, 0.69)	21.991
C ₁₂ [‡] (ng/mL)	16	1.49	(1.24, 1.79)	16	2.53	(2.21, 2.91)	1.70	(1.49, 1.94)	21.176
T _{max} [§] (hr)	16	1.50	(1.00, 2.01)	16	3.00	(1.01, 6.00)			
Apparent Terminal t _{1/2} (hr)	16	33.30	19.8	16	35.82	22.7			

Tacrolimus Alone: A single oral dose of 2 mg tacrolimus administered on Day 1 of Period 1.
Grazoprevir + Elbasvir + Tacrolimus: 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 - 16 with 2 mg tacrolimus co-administered on Day 11 of Period 2.

[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Reviewer comments

The observed increase in tacrolimus exposure is, at least in part, potentially due to weak inhibition of CYP3A by GZR. The increased tacrolimus exposure following the co-administration of tacrolimus and GZR/EBR may be clinically relevant. In consultation with Division of Transplant and Ophthalmology Products, the review team concluded that frequent monitoring of tacrolimus whole blood concentrations, renal function and tacrolimus-related side effects are recommended upon initiating co-administration with ZEPATIER.

Table 9. GZR plasma pharmacokinetics with and without the co-administration of tacrolimus

Pharmacokinetic Parameter	Grazoprevir + Elbasvir			Grazoprevir + Elbasvir + Tacrolimus			Grazoprevir + Elbasvir + Tacrolimus / Grazoprevir + Elbasvir		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µM•hr)	16	1.90	(1.35, 2.68)	16	2.14	(1.57, 2.90)	1.12	(0.97, 1.30)	23.168
C _{max} [‡] (µM)	16	0.440	(0.288, 0.675)	16	0.469	(0.332, 0.662)	1.07	(0.83, 1.37)	40.962
C ₂ [‡] (µM)	16	0.135	(0.0586, 0.312)	16	0.177	(0.109, 0.288)	1.31	(0.69, 2.48)	103.137
C ₂₄ [‡] (nM)	16	14.6	(10.9, 19.5)	16	13.7	(10.9, 17.4)	0.94	(0.87, 1.02)	13.151
T _{max} [§] (hr)	16	3.50	(2.00, 5.00)	16	3.00	(2.00, 5.00)			

Grazoprevir + Elbasvir: 200 mg grazoprevir and 50 mg elbasvir co-administered QD on Days 1 - 10 of Period 2.
Grazoprevir + Elbasvir + Tacrolimus: 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 – 16 with 2 mg tacrolimus co-administered on Day 11 of Period 2.

[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 10. EBR plasma pharmacokinetics with and without the co-administration of tacrolimus

Pharmacokinetic Parameter	Grazoprevir + Elbasvir			Grazoprevir + Elbasvir + Tacrolimus			Grazoprevir + Elbasvir + Tacrolimus / Grazoprevir + Elbasvir		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µM•hr)	16	2.17	(1.78, 2.65)	16	2.12	(1.68, 2.66)	0.97	(0.90, 1.06)	13.234
C _{max} [‡] (µM)	16	0.162	(0.134, 0.196)	16	0.160	(0.123, 0.207)	0.99	(0.88, 1.10)	17.633
C ₂ [‡] (µM)	16	0.112	(0.0846, 0.147)	16	0.111	(0.0888, 0.140)	1.00	(0.85, 1.18)	26.508
C ₂₄ [‡] (nM)	16	57.8	(46.4, 71.9)	16	53.1	(41.7, 67.6)	0.92	(0.83, 1.02)	16.325
T _{max} [§] (hr)	16	4.02	(2.00, 6.01)	16	4.01	(2.03, 4.03)			

Grazoprevir + Elbasvir: 200 mg grazoprevir and 50 mg elbasvir co-administered QD on Days 1 - 10 of Period 2.
 Grazoprevir + Elbasvir + Tacrolimus: 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 - 16 with 2 mg tacrolimus co-administered on Day 11 of Period 2.
[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Part 3. Drug interactions between GZR/EBR and Mycophenolate Mofetil

The effects of multiple daily doses of 200 mg GZR and 50 mg EBR on the plasma pharmacokinetics of MPA and MPA-G are summarized in Table 11 and 12. The co-administration of EBR/GZR did not alter the pharmacokinetic parameters of MPA and MPAG.

The effects of the co-administration of a single dose MMF (1 g) on the pharmacokinetics of GZR and EBR are summarized in Table 13 and 14. MMF decreased C_{max} and AUC values of GZR by 42% and 26%. However, C_{min} of GZR was not decreased in the presence by the co-administration of MMF. The pharmacokinetic parameters of EBR were not altered by co-administration of MMF.

Table 11. MPA plasma pharmacokinetics with and without the co-administration of GZR/EBR

Pharmacokinetic Parameter	MMF Alone			Grazoprevir + Elbasvir + MMF			Grazoprevir + Elbasvir + MMF / MMF / MMF Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (µg•hr/mL)	14	62.1	(52.9, 72.7)	14	58.8	(50.4, 68.7)	0.95	(0.87, 1.03)	12.184
AUC _{0-last} [‡] (µg•hr/mL)	14	59.3	(49.8, 70.5)	14	56.4	(48.2, 66.0)	0.95	(0.88, 1.03)	11.749
C _{max} [‡] (µg/mL)	14	19.3	(14.0, 26.7)	14	16.4	(11.8, 22.8)	0.85	(0.67, 1.07)	34.560
T _{max} [§] (hr)	14	0.64	(0.50, 3.01)	14	0.51	(0.50, 2.00)			
Apparent Terminal t _{1/2} (hr)	14	12.52	36.3	14	12.99	24.1			

MMF Alone: A single oral dose of 1 g MMF administered on Day 1 of Period 1.
 Grazoprevir + Elbasvir + MMF: 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 - 14 with 1 g MMF co-administered on Day 11 of Period 2.
[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 12. MPAG plasma pharmacokinetics with and without the co-administration of EBR/GZR

Pharmacokinetic Parameter	MMF Alone			Grazoprevir + Elbasvir + MMF			Grazoprevir + Elbasvir + MMF / MMF Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (µg•hr/mL)	14	528	(462, 604)	14	487	(421, 563)	0.92	(0.88, 0.97)	6.897
AUC _{0-last} [‡] (µg•hr/mL)	14	501	(433, 578)	14	463	(401, 535)	0.92	(0.89, 0.96)	5.966
C _{max} [‡] (µg/mL)	14	37.4	(30.5, 46.0)	14	35.8	(28.8, 44.4)	0.96	(0.80, 1.14)	25.914
T _{max} [§] (hr)	14	1.50	(1.00, 5.00)	14	1.50	(1.00, 3.00)			
Apparent Terminal t _½ (hr)	14	13.16	33.6	14	13.72	22.6			

MMF Alone: A single oral dose of 1 g MMF administered on Day 1 of Period 1.
 Grazoprevir + Elbasvir + MMF: 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 - 14 with 1 g MMF co-administered on Day 11 of Period 2.

[†]Pseudo within-subject %CV = 100* $\sqrt{[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_½.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 13. GZR plasma pharmacokinetics with and without the co-administration with MMF

Pharmacokinetic Parameter	Grazoprevir + Elbasvir			Grazoprevir + Elbasvir + MMF			Grazoprevir + Elbasvir + MMF / Grazoprevir + Elbasvir		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µM•hr)	14	1.97	(1.35, 2.87)	14	1.46	(0.855, 2.48)	0.74	(0.60, 0.92)	32.157
C _{max} [‡] (µM)	14	0.360	(0.236, 0.547)	14	0.210	(0.104, 0.424)	0.58	(0.42, 0.82)	50.292
C ₂ [‡] (µM)	14	0.103	(0.0538, 0.198)	14	0.105	(0.0457, 0.243)	1.02	(0.63, 1.66)	72.624
C ₂₄ [‡] (nM)	14	12.8	(9.38, 17.5)	14	12.4	(9.22, 16.8)	0.97	(0.89, 1.06)	12.706
T _{max} [§] (hr)	14	4.00	(3.00, 5.00)	14	4.01	(2.01, 6.01)			

Grazoprevir + Elbasvir: 200 mg grazoprevir and 50 mg elbasvir co-administered QD on Days 1 - 10 of Period 2.
 Grazoprevir + Elbasvir + MMF: 200 mg grazoprevir and 50 mg elbasvir on Days 1 – 14 with 1 g MMF co-administered on Day 11 of Period 2.

[†]Pseudo within-subject %CV = 100* $\sqrt{[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 14. EBR plasma pharmacokinetics with and without the co-administration of MMF

Pharmacokinetic Parameter	Grazoprevir + Elbasvir			Grazoprevir + Elbasvir + MMF			Grazoprevir + Elbasvir + MMF / Grazoprevir + Elbasvir		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µM•hr)	14	2.25	(1.86, 2.72)	14	2.40	(2.06, 2.81)	1.07	(1.0003, 1.14)	10.001
C _{max} [‡] (µM)	14	0.172	(0.137, 0.215)	14	0.183	(0.154, 0.219)	1.07	(0.98, 1.16)	12.383
C ₂ [‡] (µM)	14	0.103	(0.0813, 0.129)	14	0.123	(0.0981, 0.153)	1.20	(1.0049, 1.42)	25.964
C ₂₄ [‡] (nM)	14	62.4	(52.0, 74.9)	14	65.4	(55.5, 77.1)	1.05	(0.97, 1.14)	12.067
T _{max} [§] (hr)	14	4.00	(3.01, 6.02)	14	4.01	(2.01, 5.01)			

Grazoprevir + Elbasvir: 200 mg grazoprevir and 50 mg elbasvir co-administered QD on Days 1 - 10 of Period 2.
 Grazoprevir + Elbasvir + MMF: 200 mg grazoprevir and 50 mg elbasvir on Days 1 - 14 with 1 g MMF co-administered on Day 11 of Period 2.

[†]Pseudo within-subject %CV = 100* $\sqrt{[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Reviewer comments

GZR AUC and Cmax values were decreased in the presence of MMF. The exact underlying mechanism is unknown but it seems to be absorption-related. The magnitude of decrease is not considered clinically relevant.

Part 4. Drug interactions with GZR/EBR and prednisone

The effects of multiple daily doses of 200 mg GZR and 50 mg EBR on the plasma pharmacokinetics of prednisone and prednisolone are summarized in Table 15 and 16. The co-administration of EBR/GZR did not alter the pharmacokinetic parameters of prednisone and prednisolone.

The effects of a single dose prednisone (40 mg) on the pharmacokinetics of GZR and EBR are summarized in Table 17 and Table 18. Slight increases in GZR and EBR C_{max} values (38% and 25%, respectively) were observed when GZR was co-administered with prednisone. However, AUC and C_{min} values of GZR and EBR were not altered by co-administration with prednisone.

Table 15. Prednisone plasma pharmacokinetics with and without the co-administration of EBR/GZR

Pharmacokinetic Parameter	Prednisone Alone			Grazoprevir + Elbasvir + Prednisone			Grazoprevir + Elbasvir + Prednisone/ Prednisone Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (ng•hr/mL)	13 [†]	358	(326, 392)	14	387	(356, 421)	1.08	(1.0003, 1.17)	11.169
AUC _{0-last} [‡] (ng•hr/mL)	14	311	(287, 337)	14	329	(309, 351)	1.06	(1.0032, 1.12)	7.971
C _{max} [‡] (ng/mL)	14	41.8	(37.8, 46.1)	14	43.9	(40.7, 47.3)	1.05	(1.0016, 1.10)	7.129
T _{max} [§] (hr)	14	2.50	(2.00, 6.00)	14	2.50	(1.50, 4.00)			
Apparent Terminal t _½ (hr)	13 [†]	3.34	25.9	14	3.59	26.0			

Prednisone Alone: A single oral dose of 40 mg prednisone administered on Day 1 of Period 1.
Grazoprevir + Elbasvir + Prednisone: 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 - 11 with 40 mg prednisone co-administered on Day 11 of Period 2.

[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_½.

^{††}No AUC_{0-∞} or apparent terminal t_½ could be calculated for one subject due to lack of data in the terminal phase after administration of prednisone alone.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 16. Prednisolone plasma pharmacokinetics with and without the co-administration of GZR/EBR.

Pharmacokinetic Parameter	Prednisone Alone			Grazoprevir + Elbasvir + Prednisone			Grazoprevir + Elbasvir + Prednisone/ Prednisone Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (µg•hr/mL)	13 [†]	2.37	(2.15, 2.63)	14	2.57	(2.35, 2.81)	1.08	(1.01, 1.16)	9.505
AUC _{0-last} [‡] (µg•hr/mL)	14	2.21	(2.02, 2.42)	14	2.39	(2.20, 2.60)	1.08	(1.02, 1.14)	8.387
C _{max} [‡] (ng/mL)	14	409	(378, 443)	14	424	(392, 458)	1.04	(0.99, 1.09)	7.158
T _{max} [§] (hr)	14	1.75	(1.00, 6.00)	14	2.00	(1.00, 4.00)			
Apparent Terminal t _½ (hr)	13 [†]	2.68	7.0	14	2.75	7.6			

Prednisone Alone: A single oral dose of 40 mg prednisone administered on Day 1 of Period 1.
Grazoprevir + Elbasvir + Prednisone: 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 - 11 with 40 mg prednisone co-administered on Day 11 of Period 2.

[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_½.

^{††}No AUC_{0-∞} or apparent terminal t_½ could be calculated for one subject due to lack of data in the terminal phase after administration of prednisone alone.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 17. GZR plasma pharmacokinetics with and without the co-administration of a single dose of 40 mg prednisone

Pharmacokinetic Parameter	Grazoprevir + Elbasvir			Grazoprevir + Elbasvir + Prednisone			Grazoprevir + Elbasvir + Prednisone / Grazoprevir + Elbasvir		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µM•hr)	14	3.21	(2.26, 4.55)	14	3.50	(2.64, 4.66)	1.09	(0.95, 1.25)	20.573
C _{max} [‡] (µM)	14	0.657	(0.407, 1.06)	14	0.878	(0.597, 1.29)	1.34	(1.10, 1.62)	28.867
C ₂ [‡] (µM)	14	0.291	(0.148, 0.569)	14	0.402	(0.216, 0.750)	1.38	(0.91, 2.12)	63.509
C ₂₄ [‡] (nM)	14	16.3	(12.9, 20.8)	14	15.3	(11.7, 19.9)	0.93	(0.87, 1.00)	10.449
T _{max} [§] (hr)	14	3.00	(2.00, 6.00)	14	3.01	(2.00, 5.00)			

Grazoprevir + Elbasvir: 200 mg grazoprevir and 50 mg elbasvir co-administered QD on Days 1 - 10 of Period 2.
Grazoprevir + Elbasvir + Prednisone: 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 – 11 with 40 mg prednisone co-administered on Day 11 of Period 2

[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Table 18. EBR plasma pharmacokinetics with and without the co-administration of a single dose of 40 mg prednisone

Pharmacokinetic Parameter	Grazoprevir + Elbasvir			Grazoprevir + Elbasvir + Prednisone			Grazoprevir + Elbasvir + Prednisone / Grazoprevir + Elbasvir		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC ₀₋₂₄ [‡] (µM•hr)	14	2.58	(2.14, 3.11)	14	3.02	(2.53, 3.62)	1.17	(1.11, 1.24)	7.748
C _{max} [‡] (µM)	14	0.194	(0.158, 0.238)	14	0.243	(0.205, 0.288)	1.25	(1.16, 1.35)	10.915
C ₂ [‡] (µM)	14	0.141	(0.114, 0.173)	14	0.168	(0.138, 0.205)	1.20	(1.08, 1.32)	14.615
C ₂₄ [‡] (nM)	14	70.6	(56.4, 88.4)	14	73.4	(59.5, 90.5)	1.04	(0.97, 1.12)	11.123
T _{max} [§] (hr)	14	4.00	(2.00, 5.01)	14	4.00	(3.00, 5.00)			

Grazoprevir + Elbasvir: 200 mg grazoprevir and 50 mg elbasvir co-administered QD on Days 1 - 10 of Period 2.
Grazoprevir + Elbasvir + Prednisone: 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 – 11 with 40 mg prednisone co-administered on Day 11 of Period 2

[†]Pseudo within-subject %CV = 100* $\sqrt{(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for T_{max}.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Conclusion

- The co-administration of cyclosporine and GZR/EBR increased GZR and EBR AUCs by 15-fold and 2-fold, respectively. Due to the significant increases in GZR exposures, the co-administration should be contraindicated.
- GZR and EBR increased the single-dose $AUC_{0-\infty}$ of tacrolimus by approximately 40%, but decreased C_{max} by approximately 40%. These effects may be clinically relevant. Frequent monitoring of tacrolimus whole blood concentrations, renal function and tacrolimus-related side effects are recommended upon initiating co-administration with ZEPATIER.
- No clinically relevant drug interactions were observed following multiple dose administration of GZR/EBR and single dose administration of MMF.
- No clinically relevant drug interactions were observed following multiple dose administration of GZR/EBR and single dose administration of prednisone.

Study title: A One-Way Interaction Study to Evaluate the Effect of Multiple Doses of Grazoprevir and Elbasvir on the Single-Dose Pharmacokinetics of Atorvastatin (PN076)

Trial initiation date: 04-AUG-2014 **Trial completion date:** 15-SEP-2014

Trial Site: (b) (4)

Study Design

This was an open-label, fixed-sequence, 2-period study. Sixteen healthy adult subjects were enrolled. On Day 1 of Period 1, a single oral dose of atorvastatin was administered followed by pharmacokinetic sampling for 72 hours. In Period 2, multiple oral doses of grazoprevir and elbasvir were administered once daily for 13 consecutive days with a single oral dose of atorvastatin co-administered on Day 11 followed by pharmacokinetic sampling for 72 hours. There was a washout of 3 days between the atorvastatin dose in Period 1 and the first dose of grazoprevir and elbasvir in Period 2. All study drugs were administered orally with approximately 240 mL of water. Subjects fasted overnight for at least 8 hours prior to each study drug administration in both periods.

Key Inclusion Criteria

- Healthy adult male and female subjects, 19-55 years of age, inclusive
- BMI: 19-32 kg/m², inclusive
- Non-smokers (have not used nicotine-containing products for at least 3 months prior to the first dose)
- Medically healthy with no clinically significant history, physical exam, lab profiles
- Female with non-childbearing potential or a female of childbearing potential must either sexually inactive or use acceptable birth control methods.
- Male subjects must agree not to donate sperm from the first dose until 90 days after the last dose

Key Exclusion Criteria

- History of any illness that might confound the results of the study or pose an additional risk to the subjects by their participation in the study
- Estimated creatinine clearance less than 90 mL/min
- History of alcoholism or drug abuse (within 2 years)
- Positive results at screening for HIV, hepatitis B, or hepatitis C
- Donation of blood or had significant blood loss within 56 days prior to the first dose of study drug or plasma donation within 7 days prior to the first dose of study drug.
- Participation in another clinical trial within 28 days prior to the first dose of study drug.
- History or presence of hypersensitivity or idiosyncratic reaction to the study drugs, related compounds, or inactive ingredients
- Unable to refrain from any drug including prescription and non-prescription medications. Acetaminophen (up to 2 g per 24-hour period) may be permitted during the study
- Any drugs known to be significant inducers of CYP enzymes and/or P-gp for 28 days prior to the first dose of study drug and throughout the study.

Identity of investigational products

Table 1. Identity of Investigational Products

Bulk Product Description	Manufacturing Lot Number
Grazoprevir 100 mg tablets	WL0004752
Elbasvir 50 mg tablets	WL00052481
Atorvastatin Calcium 10 mg tablets	Not Applicable
Atorvastatin 10 mg (Lipitor [®]) (lot number H79780; expiration date Dec-2016, Pfizer) was supplied by the Investigator.	

Pharmacokinetic assessments

Blood samples for atorvastatin and ortho-hydroxyatorvastatin, and para-hydroxyatorvastatin quantitation in plasma were collected from each subject at predose and at selected time points over 72 hours following administration of atorvastatin doses in each treatment. Plasma concentrations and actual sampling times relative to the time of the administered doses for each respective treatment were used to determine the pharmacokinetics of atorvastatin, ortho-hydroxyatorvastatin, and para-hydroxyatorvastatin.

Pharmacokinetic parameters were determined from plasma concentration-time data by employing a non-compartmental approach using Phoenix[®] WinNonlin[®] (Version 6.3).

Reviewer comments

According to LIPITOR[®] USPI, atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products (via CYP3A-mediated metabolism). In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. As such, the applicant determined concentrations of ortho- and parahydroxylated derivatives in this study.

Bioanalysis

Blood (4 mL) for determination of atorvastatin, orthohydroxyatorvastatin, and parahydroxyatorvastatin plasma concentrations was drawn in K₂EDTA containing tubes. Method validation and sample analyses were performed by ^{(b) (4)} Validated methods and assay results are summarized in Table 2. Overall, all methods were adequately validated. The standard curve, QC data, and ISR (incurred sample analyses) results met the predefined criteria and indicated assays were precise and accurate. All samples were stored and processed in the time frame supported by the stability data.

Table 2. Summary of bioanalysis

Analyte	Atorvastatin	O-hydroxyatorvastatin	p-hydroxyatorvastatin
I.S	Atorvastatin-d ₅	O-hydroxyatorvastatin-d ₅	p-hydroxyatorvastatin-d ₅
Matrix	Plasma/ K ₂ EDTA	Plasma/ K ₂ EDTA	Plasma/ K ₂ EDTA
Extraction method	Liquid-liquid extraction	Liquid-liquid extraction	Liquid-liquid extraction
Calibration range	10 to 50000 pg/mL	25 to 50000 pg/mL	25 to 5000 pg/mL
QC concentrations	30, 3750, 37500, 25000 pg/mL	75, 3750, 37500, 25000 pg/mL	75, 3750, 2500, 3750 pg/mL
Interday precision	A: -2.02 to 0.66%	A: -3.35 to -0.62%	A: -2.32 to 2.32%

and accuracy	P: 0.86 to 7.82%	P: 2.87 to 5.81%	P: 2.99 to 8.49%
Storage stability	53 days at – 80°C	53 days at – 80°C	53 days at – 80°C
ISR (samples analyzed)	10% (58/576)	10% (58/576)	6.4% (37/576)

Study results

Demographic and other subject characteristics

Table 3. Subject baseline demographics

AN	Gender	Race	Ethnicity	Age (yr)	Height (cm)	Weight (kg)	Body Mass Index (kg/m)
0001	Male	White	Not Hispanic or Latino	30	171.0	71.4	24.36
0002	Male	White	Hispanic or Latino	28	179.0	100.1	31.31
0003	Male	White	Not Hispanic or Latino	46	191.0	113.8	31.26
0004	Male	White	Hispanic or Latino	37	173.0	81.1	27.12
0005	Male	White	Not Hispanic or Latino	54	173.0	78.0	26.08
0006	Male	White	Not Hispanic or Latino	28	182.0	82.6	24.92
0007	Male	Black or African American	Not Hispanic or Latino	35	171.0	68.9	23.66
0008	Male	Black or African American	Not Hispanic or Latino	27	165.0	60.4	22.30
0009	Male	White	Not Hispanic or Latino	24	180.0	83.1	25.64
0010	Male	White	Not Hispanic or Latino	40	183.0	104.6	31.38
0011	Male	White	Not Hispanic or Latino	39	172.0	85.9	29.14
0012	Male	White	Not Hispanic or Latino	28	188.0	104.1	29.32
0013	Female	White	Hispanic or Latino	30	164.0	80.5	30.09
0014	Female	White	Hispanic or Latino	44	168.0	80.2	28.47
0015	Female	White	Hispanic or Latino	38	160.0	81.2	31.71
0016	Female	White	Hispanic or Latino	52	159.0	60.1	23.75
Study Summary							
N:				16	16	16	16
Range:				24 to 54	159.0 to 191.0	60.1 to 113.8	22.30 to 31.71
Arithmetic Mean:				36	173.7	83.5	27.53
Female N:				4	4	4	4
Female Range:				30 to 52	159.0 to 168.0	60.1 to 81.2	23.75 to 31.71
Female Arithmetic Mean:				41	162.8	75.5	28.51
Male N:				12	12	12	12
Male Range:				24 to 54	165.0 to 191.0	60.4 to 113.8	22.30 to 31.38
Male Arithmetic Mean:				35	177.3	86.2	27.21
AN = Allocation number							

Prior and concomitant therapy

None of the subjects in this study received prior or concomitant therapy.

Pharmacokinetic results

Atorvastatin, ortho-hydroxyatorvastatin, para-hydroxyatorvastatin pharmacokinetics following the administration of a single dose of 10 mg atorvastatin with and without the co-administration of multiple doses of 200 mg GZR and 50 mg EBR in healthy adult subjects are summarized in Table 4, Table 5, and Table 6, respectively.

Atorvastatin

GZR and EBR co-administration increased the 10 mg single-dose atorvastatin $AUC_{0-\infty}$ by approximately 2.0-fold and increased C_{max} by 4.3-fold, but decreased C_{24hr} by 79%. Median atorvastatin T_{max} appeared to

be delayed after co-administration of GZR/EBR (2.00 hours) compared to that after administration of atorvastatin alone (0.52 hours).

Reviewer comments:

The increased exposure of atorvastatin is likely due to inhibition of intestinal and hepatic transporters by GZR and EBR, such as BCRP or OATP (refer to QBR section 2.4.2.5). The increase in exposure observed in this study is comparable to the increase in atorvastatin exposures reported when coadministered with fosamprenavir (AUC: 2.5-fold increase, C_{max}: 2.8-fold increase) or clarithromycin (AUC: 4.4-fold increase, C_{max}: 5.4-fold increase). The atorvastatin product label recommends that the dose of atorvastatin is limited to 20 mg once daily when coadministered with fosamprenavir or clarithromycin. Therefore, a similar recommendation should be made when atorvastatin is co-administered with GZR/EBR. The primary concern with elevated atorvastatin exposures is the risk of myopathy.

While C_{max} and AUC values of atorvastatin are increased when co-administered with GZR/EBR, the C_{24hr} value is significantly decreased (geometric mean ratio: 0.21). This appears to be due to changes in the volume of distribution and apparent elimination half-life (see Table 4 and Fig 1). A similar trend (increases in AUC and C_{max} but a decrease in C_{24hr}) was also observed in a drug interaction study where the effect of GZR on atorvastatin 20 mg was evaluated (PN032).

Table 4. Atorvastatin pharmacokinetics following the administration of a single dose of 10 mg atorvastatin with and without the co-administration of multiple doses of 200 mg GZR and 50 mg EBR in healthy adult subjects

Atorvastatin Pharmacokinetic Parameter	Atorvastatin Alone			Grazoprevir + Elbasvir + Atorvastatin			Grazoprevir + Elbasvir + Atorvastatin/ Atorvastatin Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
AUC _{0-∞} [‡] (ng•hr/mL)	16	16.4	(12.0, 22.4)	15	32.0	(20.1, 50.9)	1.94	(1.63, 2.33)	28.066
AUC _{0-12h} [‡] (ng•hr/mL)	16	15.9	(11.6, 21.8)	16	32.1	(20.3, 50.6)	2.02	(1.70, 2.39)	27.168
AUC ₀₋₁₂ [‡] (ng•hr/mL)	16	9.55	(6.96, 13.1)	16	30.5	(19.1, 48.5)	3.19	(2.63, 3.87)	31.297
C ₂₄ [‡] (pg/mL)	16	165	(116, 233)	16	34.3	(22.9, 51.4)	0.21	(0.17, 0.26)	32.856
C _{max} [‡] (ng/mL)	16	2.38	(1.74, 3.25)	16	10.3	(5.89, 18.1)	4.34	(3.10, 6.07)	54.191
CL/F [‡] (L/hr)	16	609	(446, 831)	15	313	(197, 498)	0.51	(0.43, 0.62)	28.066
Vz/F [‡] (L)	16	11200	(8600, 14700)	15	3790	(2230, 6460)	0.34	(0.26, 0.44)	41.814
T _{max} [§] (hr)	16	0.52	(0.50, 3.00)	16	2.00	(0.50, 6.00)			
Apparent Terminal t _{1/2} (hr)	16	12.79	21.5	15	8.69	38.9			

Atorvastatin Alone: A single oral dose of 10 mg atorvastatin administered on Day 1, Period 1
Grazoprevir + Elbasvir + Atorvastatin: Multiple oral doses of 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 - 13, co-administered with a single oral dose of 10 mg atorvastatin on Day 11, Period 2.

[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A² + σ_B² - 2 σ_{AB})/2], where σ_A² and σ_B² are the estimated variance on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.

[§]Median (Minimum, Maximum) reported for T_{max}.

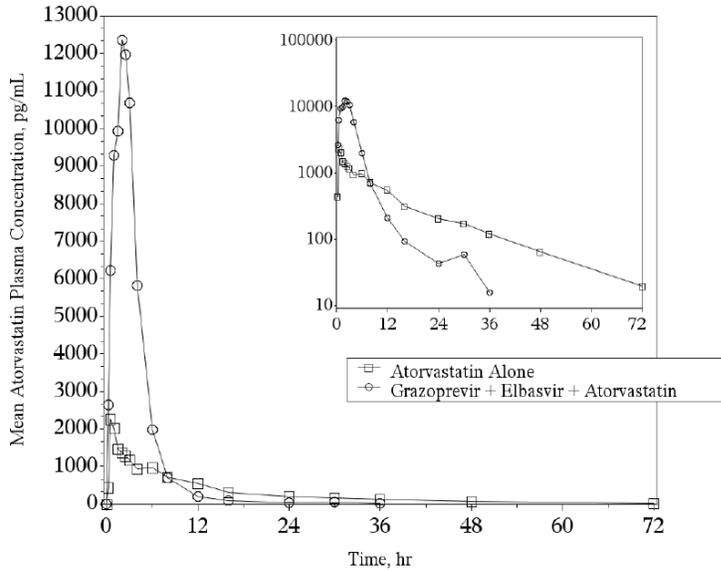
^{||}Geometric mean and geometric coefficient of variation reported for apparent terminal t_{1/2}.

[¶]Apparent terminal t_{1/2} and related parameters were not evaluable for one subject in Period 2 due to insufficient data in the terminal phase.

^{|||}One (1) subject had a C₂₄ which was BLQ after administration of Grazoprevir + Elbasvir + Atorvastatin; the value was imputed to 5.00 pg/mL (1/2 LLOQ of 10 pg/mL).

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Fig 1. Arithmetic mean plasma concentration-time profiles of following the administration of a single dose of 10 mg atorvastatin with and without the co-administration of multiple doses of 200 mg GZR and 50 mg EBR in healthy adult subjects



Orthohydroxyatorvastatin

GZR and EBR co-administration increased the orthohydroxyatorvastatin $AUC_{0-\infty}$ following the administration of 10 mg single-dose atorvastatin by approximately 1.9-fold and increased C_{max} by approximately 7.3-fold. Co-administration did not significantly change the metabolite-to-parent ratio, indicating the metabolism of atorvastatin was not significantly altered by GZR/EBR.

Table 5. Orthohydroxyatorvastatin pharmacokinetics following the administration of a single dose of 10 mg atorvastatin with and without the co-administration of multiple doses of 200 mg GZR and 50 mg EBR in healthy adult subjects

Orthohydroxyatorvastatin Pharmacokinetic Parameter	Atorvastatin Alone			Grazoprevir + Elbasvir + Atorvastatin			Grazoprevir + Elbasvir + Atorvastatin/ Atorvastatin Alone		Pseudo Within Subject %CV [†]
	N	GM	95% CI	N [‡]	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$ [‡] (ng•hr/mL)	16	17.7	(13.6, 23.2)	15	33.9	(23.3, 49.3)	1.91	(1.66, 2.20)	21.717
AUC_{0-12h} [‡] (ng•hr/mL)	16	16.1	(12.3, 21.0)	16	33.1	(22.8, 48.2)	2.06	(1.80, 2.35)	21.480
AUC_{0-12} [‡] (ng•hr/mL)	16	8.53	(6.47, 11.2)	16	30.0	(20.3, 44.1)	3.51	(2.99, 4.13)	26.149
C_{24} [‡] (pg/mL)	16	196	(149, 257)	16	74.8	(55.5, 101)	0.38	(0.34, 0.43)	19.614
C_{max} [‡] (ng/mL)	16	1.11	(0.835, 1.48)	16	8.16	(5.07, 13.1)	7.34	(5.74, 9.38)	39.610
$AUC_{0-\infty}$ Ratio (Metabolite/Parent) [‡]	16	1.05	(0.909, 1.22)	14	0.974	(0.812, 1.17)	0.93	(0.84, 1.02)	13.731
T_{max} [‡] (hr)	16	2.50	(0.50, 6.00)	16	2.00	(0.50, 6.00)			
Apparent Terminal $t_{1/2}$ [‡] (hr)	16	15.96	46.8	15	12.03	28.3			

Atorvastatin Alone: A single oral dose of 10 mg atorvastatin administered on Day 1, Period 1
 Grazoprevir + Elbasvir + Atorvastatin: Multiple oral doses of 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 - 13, co-administered with a single oral dose of 10 mg atorvastatin on Day 11, Period 2
[†]Pseudo within-subject %CV = $100 \times \sqrt{(\sigma_A^2 + \sigma_B^2 - 2 \sigma_{AB})/2}$, where σ_A^2 and σ_B^2 are the estimated variance on the log scale for the 2 treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[‡]Median (Minimum, Maximum) reported for T_{max} .
[‡]Geometric mean and geometric coefficient of variation reported for apparent terminal $t_{1/2}$.
[‡]Period 2 apparent terminal $t_{1/2}$ and related atorvastatin parameters were not evaluable for 1 subject due to insufficient data in the terminal phase. Apparent terminal $t_{1/2}$ and related orthohydroxyatorvastatin parameters were not evaluable for another subject in Period 2 due to insufficient data in the terminal phase.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.
 $AUC_{0-\infty}$ Ratio (Metabolite/Parent) = $(AUC_{0-\infty}$ Metabolite/ $AUC_{0-\infty}$ Parent) • (MW Parent/MW Metabolite)

Parahydroxyatorvastatin

Parahydroxyatorvastatin concentrations appear to be increased in the presence of GZR/EBR. However, The exact magnitude of the effect cannot be determined because the concentrations were mostly below the quantitation level when atorvastatin was administered alone.

Table 6. Parahydroxyatorvastatin pharmacokinetics following the administration of a single dose of 10 mg atorvastatin with and without the co-administration of multiple doses of 200 mg GZR and 50 mg EBR in healthy adult subjects

Parahydroxyatorvastatin Pharmacokinetic Parameter	Atorvastatin Alone			Grazoprevir + Elbasvir + Atorvastatin		
	N [§]	Median [†]	(Min, Max) [†]	N	Median [†]	(Min, Max) [†]
AUC ₀₋₁₂ (ng•hr/mL)	13 [§]	1.08	(0.00, 6.88)	16	4.73	(1.13, 51.5)
AUC ₀₋₁₂ (ng•hr/mL)	13 [§]	0.22	(0.00, 1.18)	16	4.31	(0.95, 49.6)
C ₂₄ (pg/mL)	16 [¶]	36.1	(0.00, 101)	- [§]	-	-
C _{max} (ng/mL)	13 [§]	0.0451	(0.00, 0.156)	16	1.05	(0.168, 15.5)
AUC ₀₋₁₂ Ratio (Metabolite/Parent)	13 [§]	0.01	(0.00, 0.04)	16	0.13	(0.07, 0.22)
T _{max} (hr)	8 [‡]	12.00	(2.00, 24.00)	16	2.52	(1.50, 6.00)
Apparent Terminal t _{1/2} (hr) [‡]	- [‡]	-	-	6 ^{††}	12.56	86.0

Atorvastatin Alone: A single oral dose of 10 mg atorvastatin administered on Day 1, Period 1
 Grazoprevir + Elbasvir + Atorvastatin: Multiple oral doses of 200 mg grazoprevir and 50 mg elbasvir QD on Days 1 - 13, co-administered with a single oral dose of 10 mg atorvastatin on Day 11, Period 2
[†]GMR, 90% CI, and Pseudo Within Subject %CV are not presented because 5 subjects had all BLQ concentrations after atorvastatin alone and 3 subjects had only 1 quantifiable concentration after atorvastatin alone. Median, minimum, and maximum values are presented instead.
[‡]Geometric mean and geometric coefficient of variation was reported for apparent terminal t_{1/2} and apparent terminal t_{1/2} was not calculated after atorvastatin alone due to lack of data in the terminal phase. AUC_{0-∞} was therefore missing after atorvastatin alone except where set to zero for 5 subjects who had all BLQ concentrations and therefore was not summarized in this table.
[§]N = 13 because 3 subjects had only 1 quantifiable concentration after atorvastatin alone so no parameters were calculated. Subjects who had all BLQ concentrations had AUC and C_{max} parameters set to 0 and T_{max} and apparent terminal t_{1/2} reported as missing.
[¶]N = 8 because 5 subjects had all BLQ concentrations and 3 subjects had only 1 quantifiable concentration after atorvastatin alone
[‡]After atorvastatin alone, parahydroxyatorvastatin at 24 hours was quantifiable only in 9 subjects so median, minimum, and maximum are presented after administration of grazoprevir + elbasvir + atorvastatin, parahydroxyatorvastatin at 24 hours was only quantifiable in 6 subjects so no statistics were presented.
^{††}N = 6 because only 6 subjects had evaluable data to estimate apparent terminal t_{1/2} after administration of grazoprevir + elbasvir + atorvastatin.
 GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.
 AUC₀₋₁₂Ratio (Metabolite/Parent) = (AUC₀₋₁₂ Metabolite/AUC₀₋₁₂ Parent) • (MW Parent/MW Metabolite)

Conclusion

GZR and EBR co-administration increased atorvastatin AUC_{0-∞} and C_{max} by 2.0-fold and 4.3-fold, respectively. GZR and EBR co-administration also increased orthohydroxyatorvastatin AUC_{0-∞} and C_{max} by 1.9-fold and 7.3-fold, respectively, but did not significantly change the metabolite-to-parent ratio. The magnitude of the increase observed in this study may be clinically relevant. The sponsor proposed that the dose of atorvastatin should not exceed a daily dose of 20 mg when co-administered with EBR and GZR. In consultation with the clinical pharmacology team for endocrinology-metabolism products, the review team concluded that this proposal is acceptable.

4.6 In vitro studies

Study Title: In vitro studies of MK-8742 (PK002, 03XZ42)

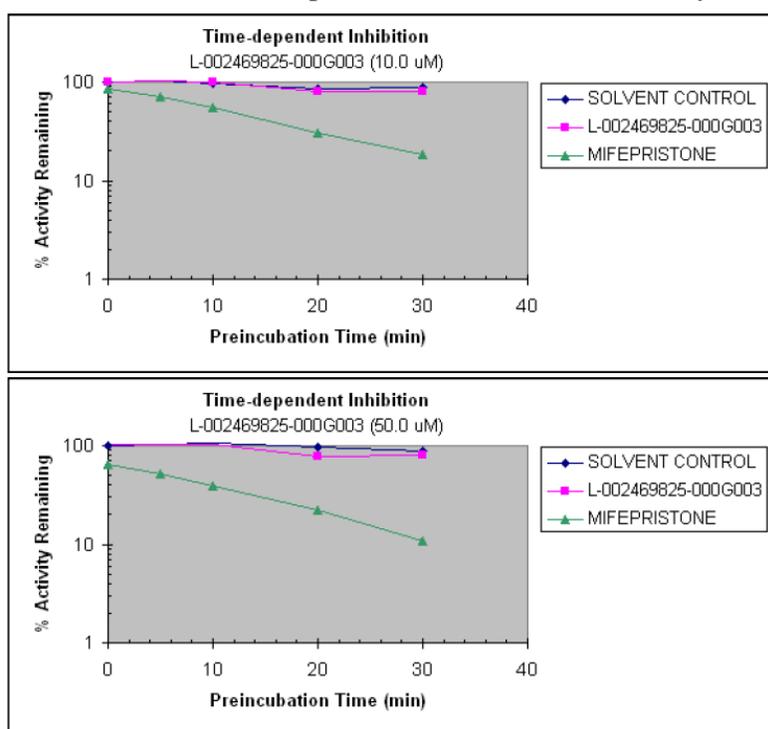
1. Time-dependent inhibition of CYP3A

Methods:

Pooled human liver microsomes (1 mg/mL) were pre-incubated at 37 °C with 10 and 50 μM of MK-8742 in 100 mM potassium phosphate buffer (pH 7.4) with an NADPH-generating system for a duration ranging from 5 to 30 min. The incubation mixtures (20 μL) were diluted 10-fold with the same buffer containing 250 μM testosterone and an NADPH-generating system. The incubation was continued for an additional 10 min to monitor the extent of testosterone 6β-hydroxylation. The reactions were terminated by adding 400 μL of 75/25 acetonitrile/water (v/v) containing 0.05% formic acid. This termination solution contained cortisone (0.15 μM) as the internal standard. The samples were spun in a centrifuge at 3,700 rpm for 15 min at 4°C, and 0.2 mL aliquots of the supernatants were transferred to new tubes which contained 0.1 mL of 0.05% formic acid in water. The resulting samples were subjected to LC-MS/MS analysis. The first order rate constants (k_{obs}) for inactivation at 10 and 50 μM were determined by plotting the decrease in natural logarithm of activity over time.

Results

Time dependent inhibition of CYP3A by MK-8742 (L-002469825)



Conclusion

MK-8742 is not a time-dependent CYP3A4 inhibitor at concentrations up to 50 μM in vitro.

2. In vitro plasma protein binding

Methods

Plasma protein binding of MK-8742 was determined using equilibrium dialysis with a 96-well equilibrium dialyzer plate (b) (4). Frozen human, Sprague-Dawley rat, CD-1 mouse, beagle dog, and cynomolgus monkey plasma (1 mL, (b) (4)) was spiked with MK-8742 to a final concentration of 10 μ M. MK-8742 was also tested at 1 μ M in human plasma. In addition, plasma protein binding of MK-8742 (1 and 10 μ M) was also measured in 10% human plasma (1:10 diluted with phosphate buffered saline (PBS) buffer, pH 7.4). Aliquots of plasma (200 μ L in four replicates) were transferred to one side of the 96-well equilibrium dialyzer, and 200 μ L of PBS buffer (pH 7.4) was transferred to the other side. The plate was incubated on a single-plate rotator at 37 °C inside a CO2 incubator. Aliquots (120 μ L) of each plasma and buffer sample were taken, quenched with three volumes of acetonitrile (containing 1 μ M of corticosterone as the internal standard), and compound concentrations in plasma (Cp) and buffer (Cb) were determined by LC-MS/MS.

Results

In Vitro Plasma Protein Binding of MK-8742 in Human, Sprague-Dawley Rat, CD-1 Mouse, Beagle Dog, and Cynomolgus Monkey Plasma

Concentration	%Unbound					
	Human	Human (10% plasma)	Rat	Mouse	Dog	Cynomolgus Monkey
1 μ M	<0.1	<0.1	-	-	-	-
10 μ M	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1

Conclusion

MK-8742 is highly plasma protein bound (> 99%) at 1 - 10 μ M in vitro.

3. Blood to plasma ratio

Methods:

[³H]MK-8742 was mixed with male human, Sprague-Dawley rat, beagle dog, and cynomolgus monkey blood to a final concentration of 0.1, 1, and 10 μ M (36, 38, and 37 μ Ci/mL, respectively). Aliquots (100 μ L) of blood were oxidized (b) (4) and then counted for radioactivity using a Tri-Carb 3100 TR liquid scintillation analyzer (b) (4). The rest of the blood samples were incubated at 37°C for 30 min. Then 100 μ L aliquots of incubated blood were oxidized and counted for radioactivity (normalized to weight, dpm/g). These counts provided the radioactivity number for the blood fraction. The remaining blood samples were centrifuged to obtain plasma. Aliquots (25 μ L) of plasma were then counted for radioactivity (normalized to weight, dpm/g). These counts provided the radioactivity number for the plasma fraction. The blood-to-plasma ratio was calculated by dividing the normalized radioactivity (dpm/g) in the blood fraction by the normalized radioactivity (dpm/g) in the plasma fraction.

Results

In Vitro Blood-to-Plasma Concentration Ratio of [3H]MK-8742 in Human, Sprague-Dawley Rat , Beagle Dog, and Cynomolgus Monkey

Concentration	Blood-to-Plasma Concentration Ratio			
	Human	Sprague-Dawley Rat	Beagle Dog	Cynomolgus Monkey
0.1 μ M	0.62	0.62	0.91	0.56
1 μ M	0.64	0.61	0.95	0.58
10 μ M	0.61	0.61	0.95	0.55
Mean	0.62	0.61	0.94	0.56
SD ^a	0.02	0.003	0.02	0.01
Hematocrit	45.0%	47.5%	50.5%	53.0%

Conclusion

MK-8742 did not preferentially partition into red blood cells in human blood. The blood-to-plasma ratio of MK-8742 was concentration independent from 0.1 to 10 μ M.

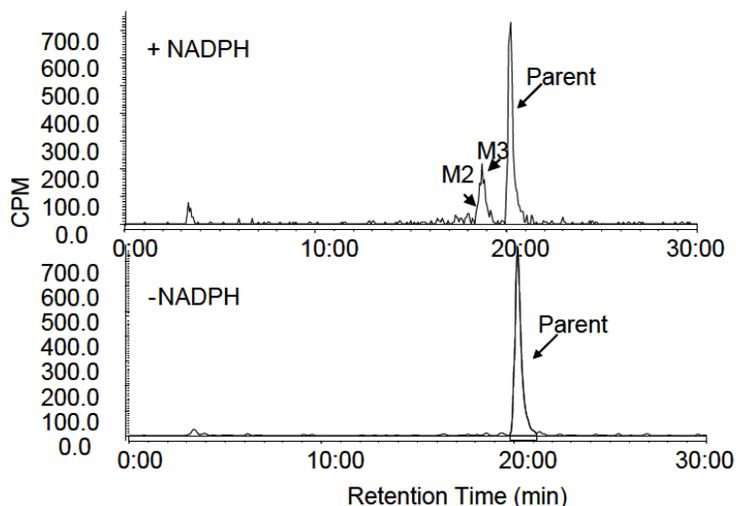
4. In vitro metabolism

Methods

[¹⁴C]MK-8742 (10 μ M, 1.2 μ Ci/mL) was incubated with human liver microsomes in the presence of NADPH. The incubations were carried out at 37° C for 2.5 hr in an incubation volume of 0.5 mL with a final concentration of 1.0 mg microsomal protein/mL, 100 mM potassium phosphate buffer (pH 7.4), and 1 mM NADPH. The reactions were quenched with the addition of a half volume of acetonitrile. Samples were centrifuged at 4 ° C for 10 min at 3,800 rpm. Supernatants were transferred for LC-MS/MS analysis with radiometric detection.

Results

Metabolite Profiles of [3H]MK-8742 in Incubations with Pooled Human Liver Microsomes in the Presence (Top) and Absence of NADPH (Bottom)



Conclusion: MK-8742 was minimally metabolized in liver microsomal incubation. Oxidative metabolites (M2, M3) of MK-8742 were detected in human liver microsomes.

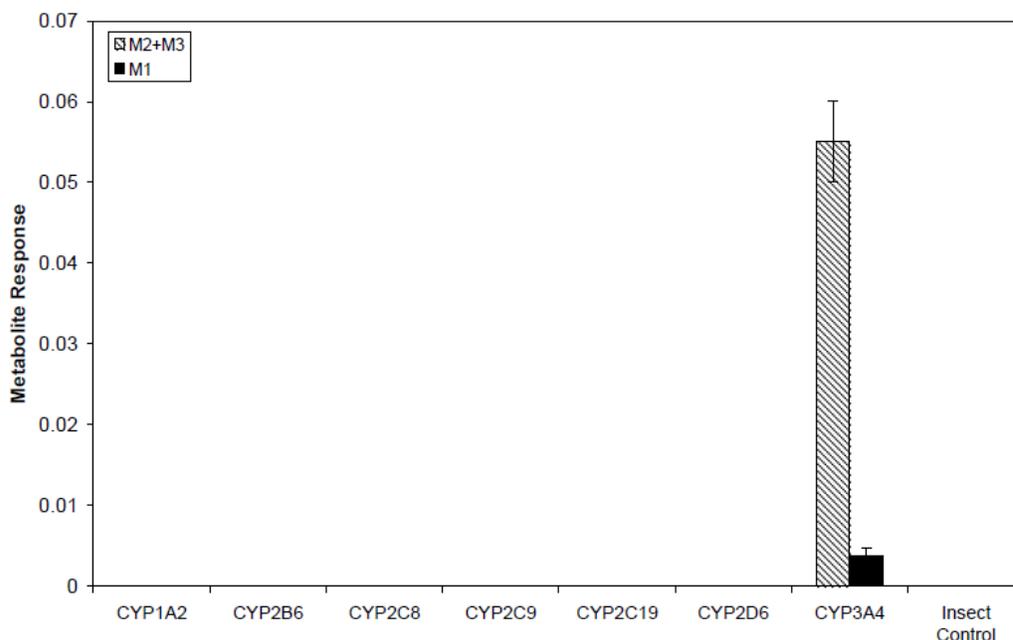
5. In vitro CYP reaction phenotyping

Methods

Recombinant human P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, 0.25 nmol P450/mL) and insect control microsomes were incubated with MK-8742 (1 μ M) for 90 min. The compound displayed significant non-specific binding such that in incubations with recombinant CYPs, low recovery of MK-8742 was detected at the low protein concentrations of the recombinant enzymes. Therefore protein concentrations of rCYPs were increased to the level of human liver microsomes (2.1 mg protein/mL) with the addition of insect control microsomes. The reactions were quenched with an equal volume of acetonitrile containing 1 μ M of 2-phenyl-4-quinoline-carboxylic acid (PQA) as the internal standard. The samples were centrifuged, and the supernatants were subject to LC-MS/MS quantification for parent and oxidative metabolites.

Results

Screening of MK-8742 for the Formation of Metabolites with Recombinant Human P450 Enzymes



Conclusion

Two oxidative metabolites of MK-8742 were formed by CYP3A4. CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 did not form metabolites of MK-8742 in vitro.

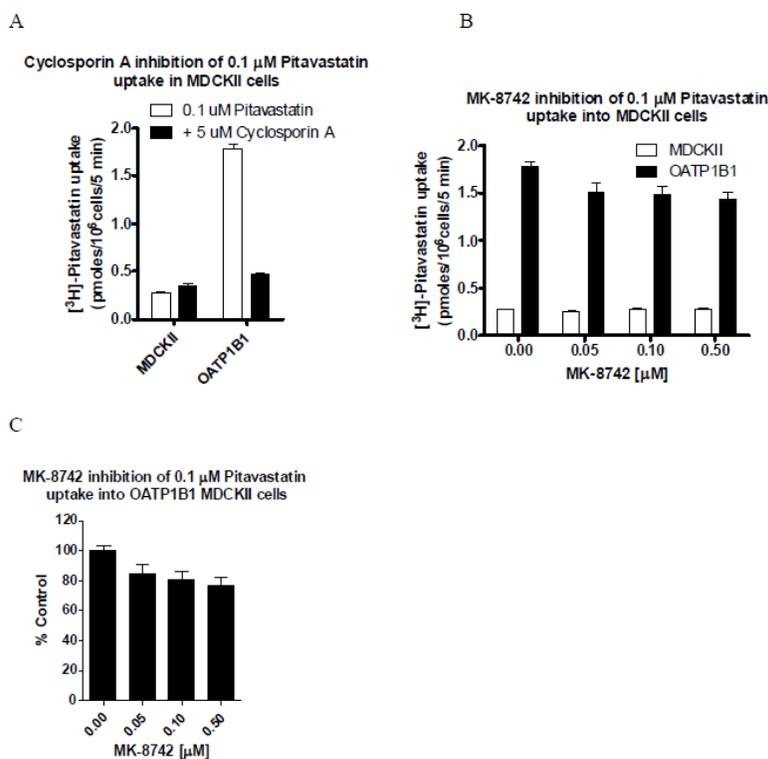
6. Inhibition of OATP1B1 in stably transfected MDCKII Cells

Methods

The inhibitory effect of MK-8742 on OATP1B1-mediated [³H]pitavastatin uptake was conducted in MDCKII cells and MDCKII cells stably transfected with an OATP1B1 cDNA (MDCKII-OATP1B1). Cells were dislodged with trypsin EDTA and re-suspended in HBSS with 10 mM HEPES, pH 7.4. Cells were then suspended in 96-deep well plates at a density of 0.4 x 10⁶ cells/well. Uptake was initiated by the addition of 0.1 μM [³H]pitavastatin (final concentration) containing various concentrations of MK-8742 or CsA (5 μM) dissolved in HBSS buffer with 10 mM HEPES, pH 7.4. Cells were then incubated for 5 minutes and uptake was stopped by the addition of ice cold PBS, immediate centrifugation for 2 minutes at 3000 rpm at 4°C followed by washing of the cell pellets with PBS, 4 times. Cell pellets were re-suspended in 50% acetonitrile (b) (4) and scintillation fluid was added (b) (4). Radioactivity was determined by liquid scintillation counting in an LS6500 Multipurpose Scintillation Counter.

Results

Inhibition of OATP1B1-mediated uptake of [³H]pitavastatin (0.1 μM) by cyclosporin A (CsA) and by MK-8742 in MDCKII and MDCKII-OATP1B1 cells



^a Inhibition of [³H]Pitavastatin (0.1 μM) uptake was studied in the presence of 5 μM of CsA or 0.05-0.5 μM of MK-8742 (L-002469825-000G003, SCH 2758362). The data are expressed as pmoles/10⁶ cells/5 min. All data points are mean ± standard error of the mean (n=3).

Conclusion: It appears that MK-8742 may be a weak inhibitor of OATP1B1 at higher concentrations (> 0.5 μM) but the IC₅₀ could not be determined due to solubility limitations.

Study Title: In vitro studies of MK-5172 (PK003;0436QZ)

1. P-glycoprotein uptake studies

Methods

LLC-PK1, L-MDR1, and L-mdr1a cells were plated at a density of 5.0×10^4 cells/0.15 mL/well on porous (0.4 μ m) polycarbonate membrane filters (b) (4) (b) (4) coated with MATRIGEL™ matrix (b) (4) in a feeder tray with 25 mL of culture medium. The transport experiment was then initiated by replacing the medium in each compartment with 0.15 mL of transport buffer with and without [3 H] MK-5172 at 0.5 and 1 μ M. Directional transport of [3 H]verapamil (1 μ M) was run in parallel as a positive control for Pgp activity. After incubating for three hours at 37°C, 50 μ L aliquots of both the [3 H]MK-5172 and [3 H]Verapamil were taken from the apical and basolateral sides and transferred to 96-well scintillation plate containing 0.1 mL scintillation cocktail (b) (4). The total radioactivity was measured by liquid scintillation. The apparent permeability coefficient (P_{app} in $\times 10^{-6}$ cm/s) was calculated with the following equation:

$$P_{app} = \frac{\text{Transported amounts (pmol/3-hrs/well)}}{\text{sum of the concentration in the donor and receiver compartments after 3-hrs incubation (nM)/surface area (0.11 cm}^2\text{/well) / incubation time (10800 s)}}$$

The basal-to-apical (BA) versus apical-to-basal (AB) ratio (BA/AB) was calculated as follows:

$$\text{BA/AB ratio} = \frac{\text{mean } P_{app} \text{ (BA)}}{\text{mean } P_{app} \text{ (AB)}}$$

Results

Transcellular transport of MK-5172 across human transfected MDR1, rat transfected Mdr1a, and control LLC-PK1 cell monolayers

(A) 1 μ M MK-5172, (B) 0.5 μ M MK-5172, and (C) Verapamil

	Human MDR1	Rat Mdr1a	Control LLC-PK1
(A) 1 μ M MK-5172			
B-A/A-B	101.8	29.9	1.1
P_{app} (cm/s* 10^{-6}) LLC-PK1			18.9
% Transport			15
(B) 0.5 μ M MK-5172			
B-A/A-B	76.5	91.7	1.5
P_{app} (cm/s* 10^{-6}) LLC-PK1			19.2
% Transport			15
(C) Verapamil			
B-A/A-B	3.8	6.3	1.1
P_{app} (cm/s* 10^{-6}) LLC-PK1			29.5
% Transport			23

B-A/A-B was calculated with the mean values of each P_{app} value.

Conclusion

Directional transport studies performed on [3 H]MK-5172 at 1 μ M showed B-A/A-B ratios of 101.8, 29.9, and 1.1 in LLC-PK1 cells expressing human and rat Pgp and in the parental LLC-PK1, respectively.

These results demonstrated that MK-5172 is a substrate of human and rat P-gp. The passive permeability in the LLC-PK1 cells was 19×10^{-6} cm/s, which suggests that MK-5172 has good passive permeability.

2. P-gp inhibition studies

Methods

Human *MDR1* transfectants (L-MDR1), transfectants and their parental cell line LLC-PK1 (porcine renal epithelial cells) were prepared. To assess the inhibitory effect of MK-5172 on bi-directional transport of [³H]digoxin (0.1 μM), [³H]Digoxin (0.1 μM) and MK-5172 at various concentrations were prepared in transport buffer (Hanks buffer with 10 mM HEPES, pH 7.4). Substrate solution (500 μL) was added to either the A or B compartment of the culture plate, and buffer (500 μL) was added to the compartment opposite to that containing [³H]digoxin. MK-5172 at various concentrations was added to both compartments. After 3 hours, 50 μL of sample was taken out from both sides and scintillant (200 μL, ^{(b) (4)}) was added. Radioactivity was determined by liquid scintillation counting.

Percent control was calculated as follows: $\% \text{ Control} = (R_1 / R_0) \times 100$

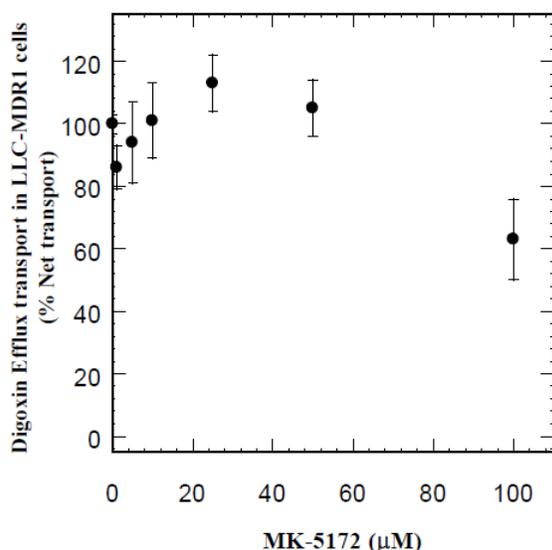
Where R_1 represents net transport of digoxin measured in the presence of various concentrations of inhibitor; R_0 represents the net transport of digoxin in the absence of inhibitor.

Net digoxin transport in L-MDR1 was calculated as follows

$$\text{Net digoxin transport} = (\% \text{ Transport B-A}) - (\% \text{ Transport A-B})$$

Results

The effect of MK-5172 on bi-directional transport of digoxin-d3 (0.1 μM) in LLC-MDR1 cells



Conclusion

MK-5172 was not a potent inhibitor of P-gp-mediated digoxin transport, with an $IC_{50} > 100 \mu M$.

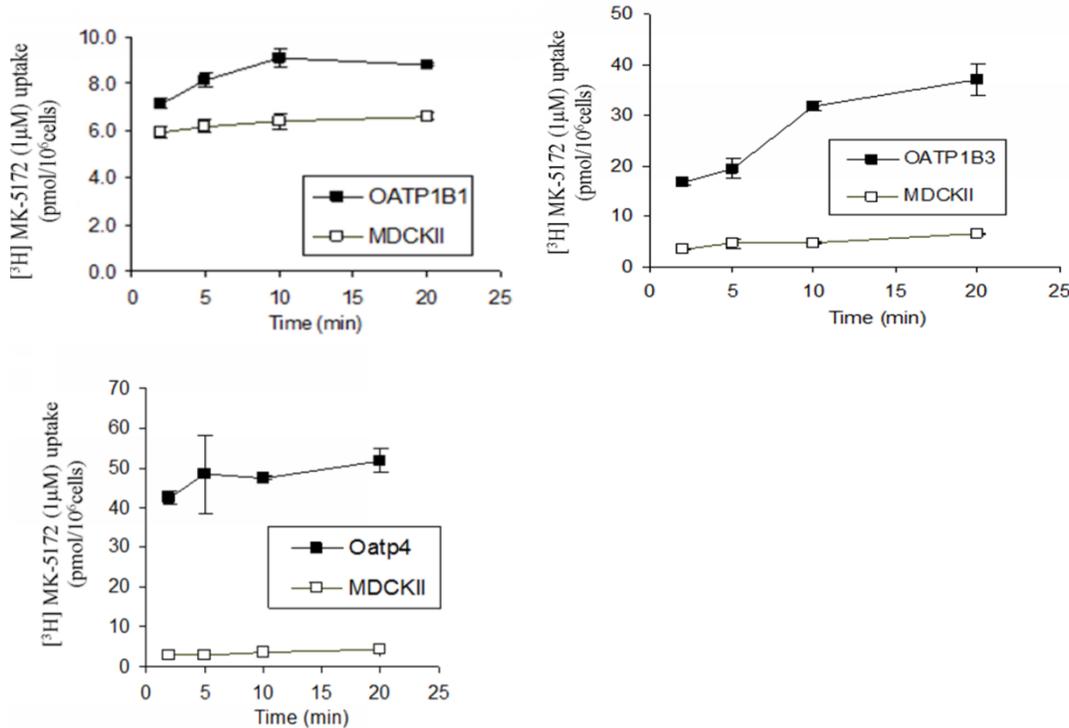
3. Recombinant cell line uptake studies (OATP1B1 and OATP1B3 uptake)

Methods

MDCKII cells were stably transfected with OATP1B1, OATP1B3, or rat Oatp4. Cells were dislodged with trypsin EDTA and resuspended in HBSS with 10 mM HEPES, pH 7.4. Cells were then suspended in 96-deep well plates at a density of 0.6×10^6 cells/well. Uptake was initiated by the addition of [^3H]MK-5172 (final concentration 1 μM) dissolved in HBSS containing 0.5% BSA or the positive control substrates [^3H]E217 β G (final concentration 1 μM ; dissolved in HBSS) for OATP1B1 and Oatp4, and [^3H]cholecystinin octapeptide (CCK8) (final concentration 4 nM; dissolved in HBSS) for OATP1B3. Uptake was stopped by the addition of ice cold PBS containing 0.1% BSA, followed by immediate centrifugation at 1800g at 4°C. The cell pellets were then washed in triplicate with PBS. Cell pellets were re-suspended in 50% acetonitrile, scintillation fluid was added (b)(4), and radioactivity was measured using liquid scintillation counting.

Results

Uptake of MK-5172 into OATP1B1 or OATP1B3 in transfected MDCKII cells



Conclusion

MK-5172 is a substrate of human OATP1B1, human OATP1B3, and rat Oatp4 (Oat1b2) in vitro.

4. Recombinant cell line inhibition studies (OATP1B1 and OATP1B3 uptake)

Methods

MDCKII cells were stably transfected with OATP1B1 or OATP1B3. Uptake was initiated by the addition of 0.1 μM [^3H]pitavastatin or 0.1 μM [^3H]BSP containing various concentrations of MK-5172 dissolved in HBSS buffer with 10 mM HEPES (pH 7.4). Cells were incubated at 37°C. Uptake was stopped by the addition of ice cold PBS containing 0.1% BSA, followed by immediate centrifugation at 1800g at 4°C. The cell pellets were then washed and re-suspended in 50% acetonitrile, scintillation fluid was added (b)(4), and radioactivity was measured using liquid scintillation counting. OATP1B1-mediated pitavastatin uptake or OATP1B3-mediated BSP uptake was calculated by subtracting pitavastatin or BSP uptake rate in MDCKII-OATP1B1 or MDCKII-OATP1B3 cells from that of MDCKII cells.

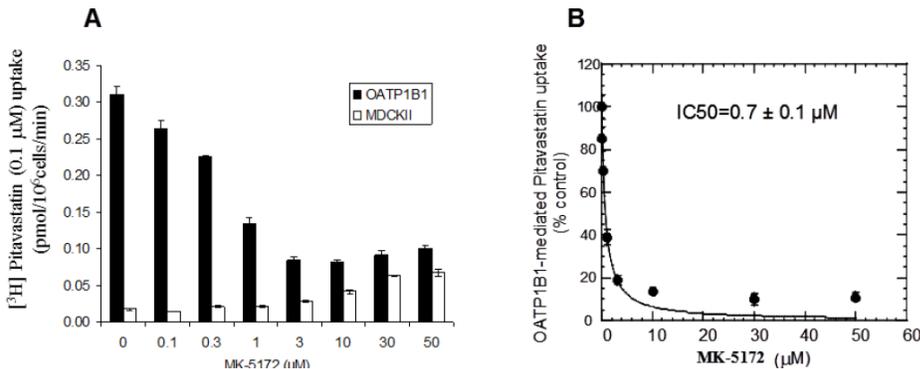
Percent control was calculated according to the following equation:

$$\% \text{ Control} = (R_I / R_0) \times 100$$

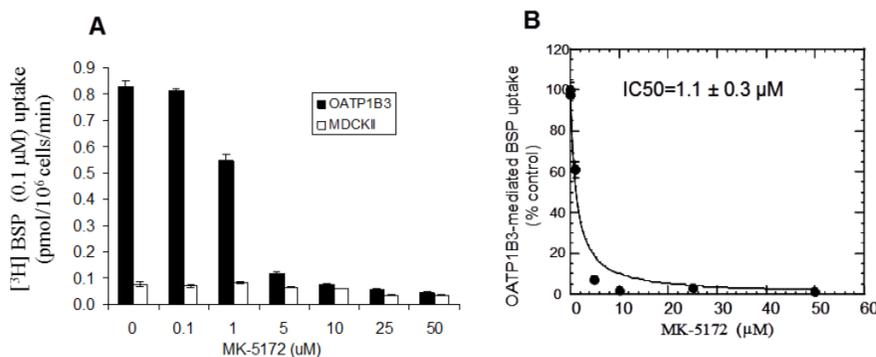
where R_I represents the uptake rate measured in the presence of various concentrations of inhibitor; R_0 represents the uptake rate in the absence of inhibitor.

Results

1. Inhibitory effects of MK-5172 on OATP1B1-mediated pitavastatin uptake



2. Inhibitory effects of MK-5172 on OATP1B3-mediated BSP uptake



Conclusion

MK5172 inhibited OATP1B1-mediated pitavastatin uptake with an IC_{50} value of $0.7 \pm 0.1 \mu M$

MK-5172 inhibited OATP1B3-mediated BSP uptake with an IC_{50} value of $1.1 \pm 0.3 \mu M$

5. Plasma protein binding

Methods

Protein binding of MK-5172 was evaluated by equilibrium dialysis. [3H]MK-5172 at final concentrations of 0.1, 1, or 10 μM was added to rat, dog, or human plasma. Equilibrium dialysis was performed using a Harvard Apparatus 96-well Equilibrium Dialyzer™ plate with a molecular weight cut-off of 10k Daltons. To one side of the dialysis plate, Dulbecco's phosphate-buffered saline (b) (4) was added. To the other side of the dialysis plate, an aliquot of plasma containing [3H]MK-5172 was added. The equilibrium dialysis plate was then equilibrated overnight at 37°C. The amount of [3H]MK-5172 was determined in the dialyzed samples, buffer, and non-dialyzed samples by adding an aliquot to liquid scintillation cocktail (b) (4) for analysis by liquid scintillation counting. The fraction unbound of MK-5172 in plasma was determined by dividing the dpm in the buffer by the dpm in the dialyzed plasma samples.

Results

In vitro plasma protein binding of MK-5172

Species	Fraction Unbound (Free)			
	0.1 μM	1 μM	10 μM	Average
Rat	0.016 \pm 0.001	0.016 \pm 0.002	0.018 \pm 0.002	0.016 \pm 0.002
Dog	0.008 \pm 0.001	0.009 \pm 0.001	0.009 \pm 0.000	0.009 \pm 0.001
Human	0.012 \pm 0.003	0.013 \pm 0.000	0.012 \pm 0.001	0.012 \pm 0.001

Data represent mean \pm SD (n=3).

Conclusion

MK-5172 is highly plasma protein bound with an average free fraction of 0.016, 0.009, and 0.012 in rat, dog, and human, respectively. Plasma protein binding was independent of MK-5172 concentrations from 1 to 10 μM .

6. Blood-to-Plasma partitioning

Methods

Fresh whole blood from rat, dog, and human was incubated with 0.1, 1, or 10 μM final concentration of [3H]MK-5172 to evaluate the blood-to-plasma partitioning. As a surrogate for whole blood values, the radioactive counts of [3H]MK-5172 were determined in plasma at 30 minutes following incubation at 37°C. To obtain actual plasma values, an aliquot of whole blood was pipetted into a culture tube and [3H]MK-5172 was added. Samples were incubated at 37°C. After 30 minutes, aliquots were transferred to centrifuge tubes. Samples were centrifuged at 13,000 rpm for 10 minutes to separate the plasma from the blood cells. Aliquots of plasma were transferred to LSC vials containing 15 mL scintillant (b) (4)

(b) (4) for analysis by liquid scintillation counting. The blood to plasma ratio was calculated by dividing the surrogate whole blood values by the actual plasma values.

Results

In vitro Whole blood to plasma concentration ratios for MK-5172

Species	Whole Blood/Plasma Ratio			
	0.1 μ M	1 μ M	10 μ M	Average
Rat	0.60 \pm 0.03	0.62 \pm 0.04	0.62 \pm 0.03	0.61 \pm 0.03
Dog	0.46 \pm 0.03	0.46 \pm 0.01	0.49 \pm 0.03	0.47 \pm 0.03
Human	0.68 \pm 0.02	0.69 \pm 0.07	0.63 \pm 0.04	0.67 \pm 0.04

Data represent mean \pm SD (n=3).

Conclusion

MK-5172 did not preferentially partition into red blood cells, with an average blood-to-plasma partition ratio of 0.61, 0.47, and 0.67 in rat, dog, and human, respectively. The blood-to-plasma ratio of MK-5172 was concentration independent from 0.1 to 10 μ M.

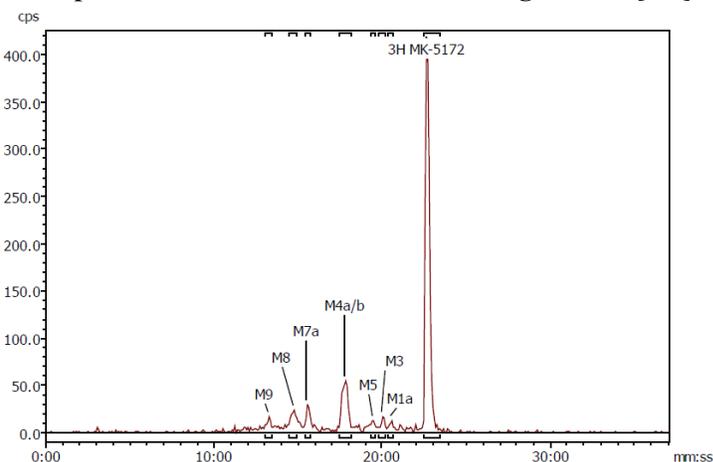
7. In Vitro Metabolism in hepatocytes

Methods

Hepatocytes were prepared from cryopreserved human tissue using standard methodology. Cells (2 million cells/mL) were suspended in HBSS with 10 mM HEPES and were incubated with 10 μ M [3 H]MK-5172 for 0 or 4 hours. Incubations were quenched with an equal volume of acetonitrile, vortexed, and centrifuged at 3,800 rpm for 10 minutes. An aliquot of the supernatant was removed and added to an equal volume of water for analysis by the LC-MS/MS and radiometric methods.

Results

Representative HPLC-Radiochromatograms of [3 H]MK-5172 Incubations with Hepatocytes



Conclusion: MK-5172 was minimally metabolized human hepatocytes. Eight minor metabolites (M1a, M3, M4a, M4b, M5, M7a, M8, and M9) were observed.

8. Pre-incubation dependent inhibition of human liver microsomal cytochrome P450 isoforms

Methods

Pooled human liver microsomes were preincubated at 37°C with 0.78, 1.56, 3.13, 6.25, 12.5, 25, and 50 µM of MK-5172 in 100 mM potassium phosphate buffer (pH 7.4) in an NADPH-generating system for a duration ranging from 5 to 30 min. The incubation mixtures were diluted 10-fold with the same buffer containing 250 µM testosterone and an NADPH-generating system. The incubation was continued for an additional 10 minutes to monitor the extent of testosterone 6β-hydroxylation. The first order rate constants (k_{obs}) for inactivation at the various concentrations were calculated from the negative slope of the lines by linear regression analysis of the natural logarithm of the remaining activity as a function of time

Results

Pre-Incubation Dependent Inhibition of CYP3A4 by MK-5172

Concentration of MK-5172 (µM)	K_{obs} (min ⁻¹)
0	0.0004
0.78	0.003
1.56	0.006
3.13	0.007
6.25	0.006
12.5	0.003
25	0.007
50	0.007

Conclusion

MK-5172 demonstrated weak pre-incubation dependent inhibition of CYP3A4. Due to the low k_{obs} values, no K_i or k_{inact} values could be calculated.

9. Induction of CYP3A4 and CYP1A2 in Human Hepatocytes

Methods

Commercially available cryopreserved human hepatocytes prepared from livers of two individual donors (b) (4) and fresh plated human hepatocytes prepared from the liver of one donor (b) (4) were used. Fresh and cryopreserved hepatocytes were treated for 48 hours with vehicle control (0.1% (v/v) DMSO), MK-5172 (0.1-20 µM), or the positive control inducers rifampicin (10 µM) and omeprazole (50 µM). At the end of the 48 hour incubation, CYP3A4 and CYP1A2 enzyme changes were evaluated using testosterone 6β-hydroxylation and phenacetin O-deethylation, respectively, measured by LC-MS/MS detection. Total RNA was isolated for quantitative PCR analysis of CYP3A4 and CYP1A2 mRNA expression. Changes in the measured responses following treatment with test compounds were reported as fold change (response to test compound relative to vehicle control) and as percent positive control.

Results

Evaluation of MK-5172 as a CYP3A4 Inducer in Human Hepatocytes

Lot #Hu0965

Treatment	Dose (µM)	CYP3A4 RNA		Testosterone 6β-Hydroxylase Activity	
		Fold ^a	% of PC ^b	Fold ^a	% of PC ^b
Rifampicin	10	8387.1	100.0	17.8	100.0
MK-5172	0.1	1.9	0.0	0.9	NR
	0.5	0.7	0.0	0.7	NR
	1	1.4	0.0	0.6	NR
	5	12.1	0.3	0.3	NR
	10	50.2	0.6	0.4	NR
	20	30.2	0.3	0.3	NR

Lot #KQG

Treatment	Dose (µM)	CYP3A4 RNA		Testosterone 6β-Hydroxylase Activity	
		Fold ^a	% of PC ^b	Fold ^a	% of PC ^b
Rifampicin	10	106.2	100.0	14.2	100.0
MK-5172	0.1	0.4	NR	1.1	0.9
	0.5	0.2	NR	1.0	NR
	1	0.3	NR	0.8	NR
	5	0.8	NR	0.6	NR
	10	1.4	0.3	0.5	NR
	20	1.8	0.7	0.4	NR

Lot #SCT

Treatment	Dose (µM)	CYP3A4 RNA		Testosterone 6β-Hydroxylase Activity	
		Fold ^a	% of PC ^b	Fold ^a	% of PC ^b
Rifampicin	10	10.3	100.0	5.5	100.0
MK-5172	0.1	1.0	0.2	0.6	NR
	0.5	0.8	NR	0.5	NR
	1	0.8	NR	0.4	NR
	5	1.0	0.5	0.4	NR
	10	1.4	3.9	0.3	NR
	20	2.0	10.2	0.2	NR

^a Fold denotes the change of treatment relative to the vehicle control.

^b % PC denotes the percent induction relative to the positive control inducer Rifampicin at 10 µM corrected for the vehicle control.

NR = denotes not determined because value is less than vehicle control.

Evaluation of MK-5172 as a CYP1A2 Inducer in Human Hepatocytes

Lot #Hu0965

Treatment	Dose (µM)	CYP1A2 RNA		Phenacetin O-Deethylation Activity	
		Fold ^a	% of PC ^b	Fold ^a	% of PC ^b
Omeprazole	50	58.9	100.0	20.0	100.0
MK-5172	0.1	0.7	NR	1.2	1.1
	0.5	0.5	NR	0.9	NR
	1	0.5	NR	1.1	0.6
	5	0.3	NR	0.7	NR
	10	0.2	NR	0.7	NR
	20	0.0	NR	0.5	NR

Lot #KQG

Treatment	Dose (µM)	CYP1A2 RNA		Phenacetin O-Deethylation Activity	
		Fold ^a	% of PC ^b	Fold ^a	% of PC ^b
Omeprazole	50	64.6	100.0	17.6	100.0
MK-5172	0.1	0.8	NR	0.9	NR
	0.5	0.5	NR	0.6	NR
	1	0.5	NR	0.7	NR
	5	0.4	NR	0.8	NR
	10	0.3	NR	0.6	NR
	20	0.2	NR	0.6	NR

Lot #SCT

Treatment	Dose (µM)	CYP1A2 RNA		Phenacetin O-Deethylation Activity	
		Fold ^a	% of PC ^b	Fold ^a	% of PC ^b
Omeprazole	50	30.5	100.0	13.5	100.0
MK-5172	0.1	1.3	0.9	1.0	0.2
	0.5	0.9	1.0	1.0	NR
	1	0.7	0.0	0.9	NR
	5	1.3	NR	0.8	NR
	10	0.6	NR	0.7	NR
	20	0.7	NR	0.5	NR

^a Fold denotes the change of treatment relative to the vehicle control.

^b % PC denotes the percent induction relative to the positive control inducer Omeprazole at 50 µM corrected for the vehicle control.

NR = denotes not determined because value is less than vehicle control.

Conclusion: MK-5172 did not induce CYP3A4 or CYP1A2 in human hepatocytes at concentrations up to 20 µM.

Study Title: P-glycoprotein-(P-gp) and BCRP-Mediated Transport of MK-8742, and Inhibitory Effect of MK-8742 on BCRP-Mediated Transport (PK004. 03Y5VM)

1. Bidirectional transport across MDCKII monolayers (P-gp or BCRP-mediated transport)

Methods

MDCKII, MDCK-MDR1, and MDCKII-BCRP cell lines were cultured in 96-well transwell culture plates. [3H]MK-8742 (final concentration 0.5 or 1 μM) was prepared in HBSS with 0.1% BSA, 10 mM HEPES, pH 7.4. Substrate solution (150 μL) was added to either the apical (A) or the basolateral (B) compartment of the culture plate, and buffer (150 μL; HBSS with 0.1% BSA, 10 mM HEPES, pH 7.4) was added to the compartment opposite to that containing the compound. At 3 hr, 50 μL of sample was removed from both sides and 200 μL of scintillation fluid (Scintisafe Econo 2; Fisher Chemicals, NJ) was added. Radioactivity was determined by liquid scintillation counting in a MicroBeta Wallac Trilux scintillation counter (Perkin Elmer, Boston, MA). [3H]Verapamil (1 μM) and [3H]Prazosin (5 μM) was used as the positive control for the assessment of P-gp or BCRP-mediated transport, respectively. The P_{app} was calculated by the following formula for samples taken at t=3 hr:

$$P_{app} = \frac{\Delta C \cdot V}{C_0 \cdot A \cdot \Delta t}$$

(b) (4)

Where: Volume of Receptor Chamber is 0.15 mL; Area of membrane is 0.11 cm²; the initial concentration is the sum of the concentration measured in the donor plus concentration measured in receiver compartments at t=3 h; Δ in concentration is concentration in the receiver compartment at 3 hr; and Δ in Time is the incubation time (3 x 60 x 60 = 10800 s). P_{app} was expressed as 10⁻⁶ cm/s.

The P_{app} reported in results are the average of the P_{app} for transport from A to B and P_{app} for transport from B to A at t = 3 hr.

$$B-A/A-B \text{ ratio} = \frac{P_{app} \text{ from B to A}}{P_{app} \text{ from A to B}}$$

(b) (4)

The B-A/A-B ratio was calculated by dividing the P_{app} from B to A by the P_{app} from A to B at t = 3 hr:

$$B-A/A-B \text{ ratio} = \frac{P_{app} \text{ from B to A}}{P_{app} \text{ from A to B}}$$

(b) (4)

Results

Bi-Directional Transport of MK-8742 across MDCKII and MDCKIIMDR1 Cell Monolayers

Compound	Human MDCK-MDR1 B-A/A-B Ratio	Control MDCKII B-A/A-B Ratio	Control MDCKII P _{app} (CM*E-6/SEC)
1 μM Verapamil	4.6	0.9	28.3
0.5 μM MK-8742	19.4	5.1	1.2
1 μM MK-8742	21.0	4.7	0.8

Bi-Directional Transport of MK-8742 Across MDCKII and MDCKIIBCRP Cell Monolayers

Compound	Human MDCK-BCRP B-A/A-B Ratio	Control MDCKII B-A/A-B Ratio	Control MDCKII P _{app} (CM ² E-6/SEC)
5 μM Prazosin	2.8	0.7	22.0
5 μM Prazosin+2 μM Ko143	1.2	1.2	23.1
0.5 μM MK-8742	12.6	8.1	1.6
0.5 μM MK-8742+0.5 μM PSC 833	2.3	1.9	0.7
0.5 μM MK-8742+2 μM Ko143	4.9	1.7	0.7

Conclusion

MK-8742 is a substrate of P-gp in vitro. The passive permeability of MK-8742 was low (P_{app}=0.8–1.2 x 10⁻⁶ cm/sec). No BCRP-mediated transport of MK-8742 was detected in MDCKII-BCRP cell monolayers. Although no BCRP-mediated transport of MK-8742 was detected in MDCKII-BCRP cell monolayers, it cannot be excluded that, due to its low P_{app}, MK-8742 was a BCRP substrate

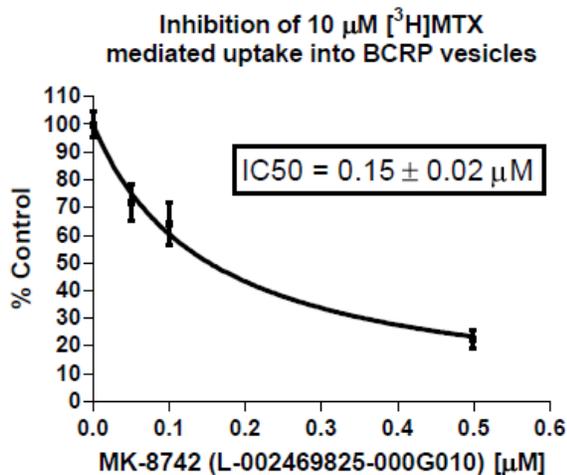
2. Inhibition of BCRP in membrane vesicles

Methods

The inhibitory effect of MK-8742 on ATP-dependent [³H]methotrexate uptake was conducted in membrane vesicles isolated from Sf9 cells containing human BCRP. Briefly, 20 μL of [³H]MTX, with or without various concentrations of MK-8742 or 8 μM Ko143 (prototypic BCRP inhibitor), dissolved in transport buffer was added to 10 μL (2.5 mg protein/mL) of BCRP vesicles and pre-incubated for 5 minutes at 37°C. Uptake was initiated by the addition of 20 μL ATP regenerating reagent or AMP reagent, followed by incubation at 37°C for the indicated time. Uptake was stopped by the addition of 200 μL ice-cold stop buffer, followed by transfer of the reaction mixture to pre-wetted 96-well glass fiber type B filter plate (1.0 μm) ^{(b) (4)} and application of vacuum. Filters containing the membrane vesicles were washed with 200 μL ice-cold stop buffer, six times. The filter plate was dried and 50 μL scintillation fluid (^{(b) (4)}) was added to each sample. Radioactivity was determined by liquid scintillation counting in a MicroBeta Wallac Trilux Scintillation Counter (Perkin Elmer, Boston, MA). ATP-dependent [³H]MTX uptake in BCRP containing vesicles was calculated by subtracting the uptake in the absence of ATP from that in the presence and data were then normalized to % control, where uptake in the absence of MK-8742 was 100%

Results

MK-8742 Inhibition of BCRP-Mediated [³H]Methotrexate Uptake (%Control)



Conclusion

MK-8742 inhibited the BCRP-mediated uptake of methotrexate in a dose-dependent manner with an IC_{50} of $0.15 \pm 0.02 \mu\text{M}$. MK-8742 may be a clinically relevant BCRP inhibitor.

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Study Title: Bi-directional transport of MK-5172 (L-002214070) in MDCKII-BCRP cells (PK006, 03DV8S).

Methods

MDCKII-BCRP cell lines were cultured in 96-well transwell culture plates. MK-5172 (final concentration 1 μM) was prepared in HBSS with 10 mM HEPES. Substrate solution (150 μL) was added to either the apical (A) or the basolateral (B) compartment of the culture plate, and buffer (150 μL) was added to the compartment opposite to that containing the compound. At 3 hr, 50 μL of sample was taken out from both sides and 200 μL of scintillation fluid ^{(b) (4)} was added. Radioactivity measurement and calculation for BA/AB ratio and Papp were the same as study PK004 (BCRP-mediated MK-8742 transport).

Results

Bi-directional transport of MK-5172 across MDCKII and MDCKII-BCRP cell monolayers

Compound	Papp BA/ Papp AB Ratio		Papp x 10 ⁻⁶ (cm/s) MDCKII
	MDCKII	Human-BCRP	
MK-5172 1 μM	3.7	8.5	11.6
MK-5172 1 μM + 1 μM KO143	1.9	3.7	8.0
Prazosin 5 μM	1.0	5.4	22.5
Prazosin 5 μM + 1 μM KO143	0.7	0.8	16.5

Conclusions

It appears that MK-5172 is a substrate of BCRP. However, due to endogenous transport in the MDCKII cells, definitive conclusions cannot be made. The passive permeability of MK-5172 in MDCKII cells was moderate (Papp 11.6×10^{-6} cm/s).

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Study Title: MK-5172 (L-002214070-001Z016) Inhibition of BSEP and MRP2 (PK007, 03Y34C)

Methods

The inhibitory effect of MK-5172 on ATP-dependent uptake of [³H] taurocholic acid (1 μM) by BSEP and ATP-dependent uptake of [¹⁴C] EA-SG (1 μM) by MRP2 were conducted in Sf9 membrane vesicles containing BSEP or MRP2, respectively. 10 μL BSEP or MRP2 containing membrane vesicles (2 mg protein/mL) were added to a 96-well plate at 20 μg/well. Then of [³H] taurocholic acid (final concentration of 1 μM) or [¹⁴C] EA-SG (final concentration of 1 μM) containing various concentrations of MK-5172, atorvastatin (final concentration of 100 μM), or BSP (final concentration of 100 μM) were dissolved in transport buffer and added into the wells containing vesicles. The mixtures of vesicle, substrate and inhibitors were preincubated for 5 minutes. Uptake was initiated by the addition of 20 μL of ATP regenerating reagent or 20 μL transport buffer, followed by incubation at 37 °C for 5 minutes. Uptake was stopped by the addition of 200 μL ice-cold stop buffer followed by transfer of the reaction mixture to pre-wetted 96-well glass fiber type B filter plate (1.0 μm) (Millipore, Billerica, MA), and application of vacuum. Filters containing the membrane vesicles were washed with 200 μL icecold stop buffer, five times. The filter plate was dried at 37 °C and 25 μL scintillation fluid (b) (4), (b) (4) was added to each sample. Radioactivity was determined by liquid scintillation counting in a MicroBeta Wallac Trilux Scintillation Counter (Perkin Elmer, Boston, MA).

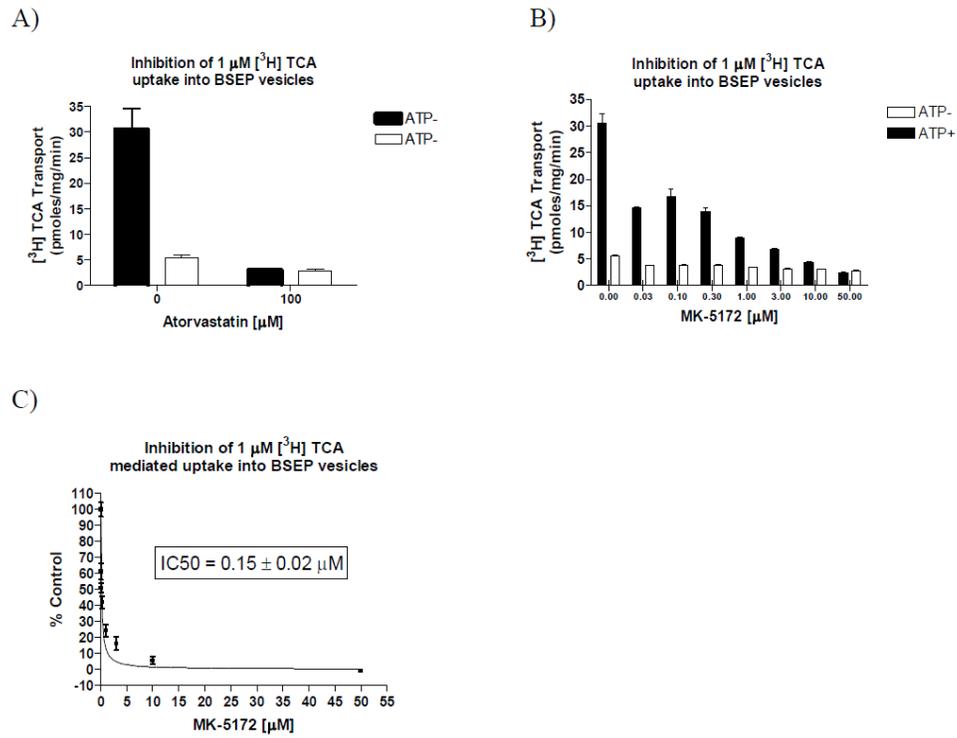
ATP-dependent uptake was calculated by subtracting the uptake in the absence of ATP from that in the presence. Percent control was calculated as follows

(b) (4)

where R_1 represents ATP-dependent uptake measured in the presence of various concentrations of inhibitor; R_0 represents the uptake in the absence of inhibitor.

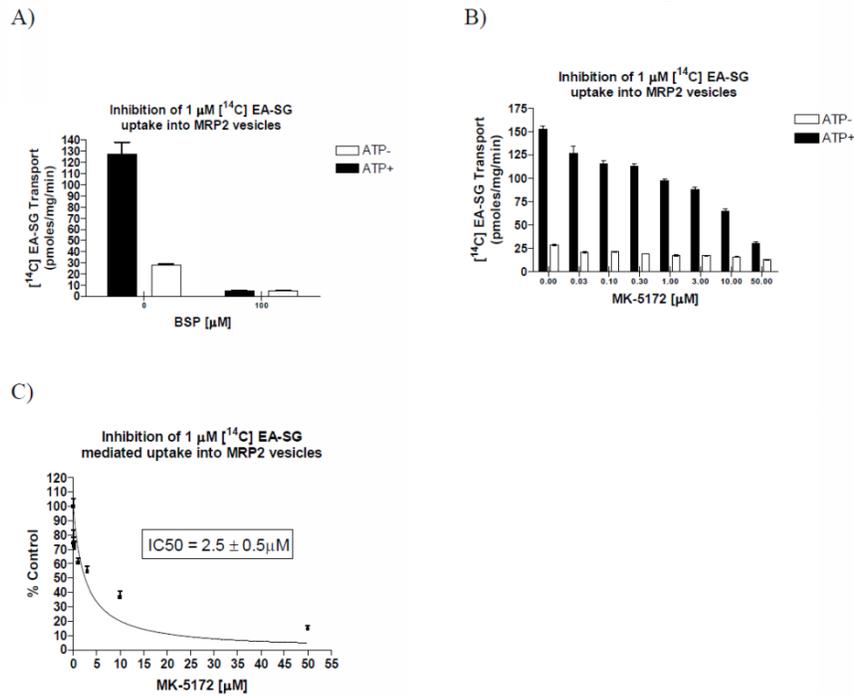
Results

The inhibitory effect of MK-5172 on the BSEP-mediated uptake of 1 μM [^3H] TCA



All data are mean \pm S.E. (n=6, except for 0.03 and 50 μM n=3).

The inhibitory effect of MK-5172 on the MRP-2-mediated uptake of 1 μM [^{14}C] EA-SG



Conclusion

MK-5172 inhibited ATP-dependent uptake of [³H] taurocholic acid mediated by human BSEP with an IC₅₀ value of 0.15 ± 0.02 μM, and inhibited ATP-dependent uptake of [¹⁴C] EA-SG (1 μM) mediated by human MRP2 with an IC₅₀ value of 2.5 ± 0.5 μM.

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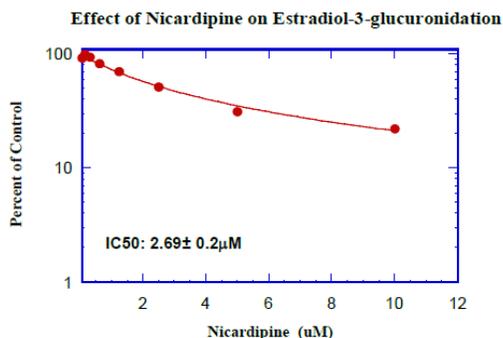
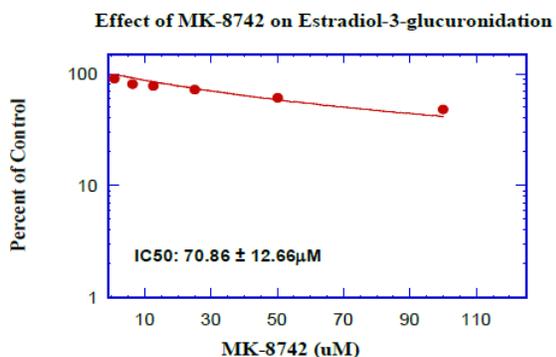
Study Title: Effect of MK-8742 on UGT1A1-mediated estradiol 3-glucuronidation in human liver microsomes (PK009, 03MBKP)

Methods:

Pooled human liver microsomes (0.5 mg/mL) were incubated at 37°C for 20 min in a 0.2 mL volume reaction mixture containing 20 μM of estradiol and 0.78 to 100 μM of MK-8742 in 81 mM HEPES buffer (pH 7.0) with 9 mM MgCl₂, 5 mM UDPGA, and 25 μg/mL alamethicin. Nicardipine was used as positive control inhibitor. The reactions were terminated by adding 0.2 mL of ice-cold methanol containing labetolol as the internal standard. The samples were spun in a centrifuge at 4,000 rpm for 30 min at 4°C. An aliquot of supernatant (200 μL) was mixed with 100 μL water containing 0.05% formic acid. The resultant samples were analyzed for estradiol 3-glucuronide contents using a PE Sciex API 4000 triple quadrupole mass spectrometer.

Results

Effect of MK-8742 on UGT1A1-Mediated Estradiol 3-Glucuronidation in Human Liver Microsomes



Conclusion

MK-8742 inhibited UGT1A1 mediated estradiol 3-glucuronidation with an IC₅₀ value of 70.9 μM. Considering plasma concentrations of MK-8742 following the administration of clinical doses (50 mg, C_{max} 0.14 μM), this is unlikely clinically relevant.

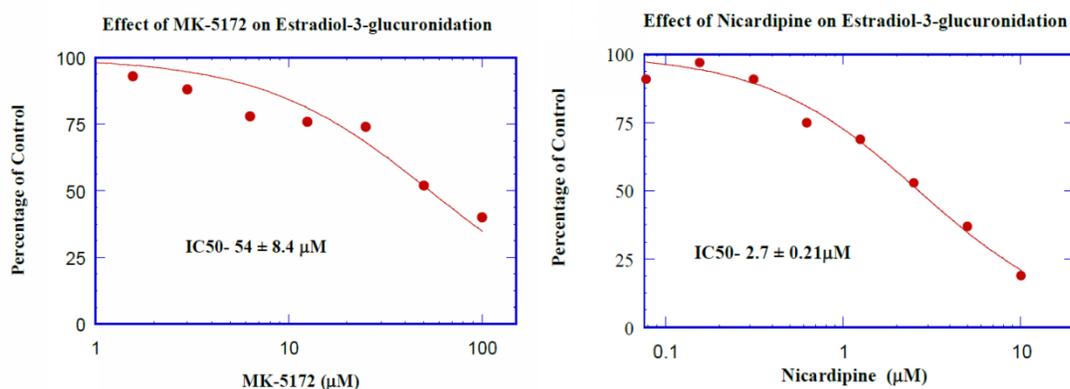
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Study Title: Effect of MK-5172 on UGT1A1-Mediated Estradiol 3- Glucuronidation in Human Liver Microsomes (03Y9RJ; PK008)

Methods: Pooled human liver microsomes (0.5 mg/mL) was incubated with 20 μ M estradiol a substrate and up to 100 μ M of MK-5172 in 81 mM HEPES buffer (pH 7.0) with 9 mM $MgCl_2$, 5 mM UDPGA, and 25 μ g/mL alamethicin. Assays were conducted as previously described in PK009 (effects of MK-8742 on UGT1A1)

Results

Effect of MK-5172 on UGT1A1-Mediated Estradiol 3-Glucuronidation in Human Liver Microsomes



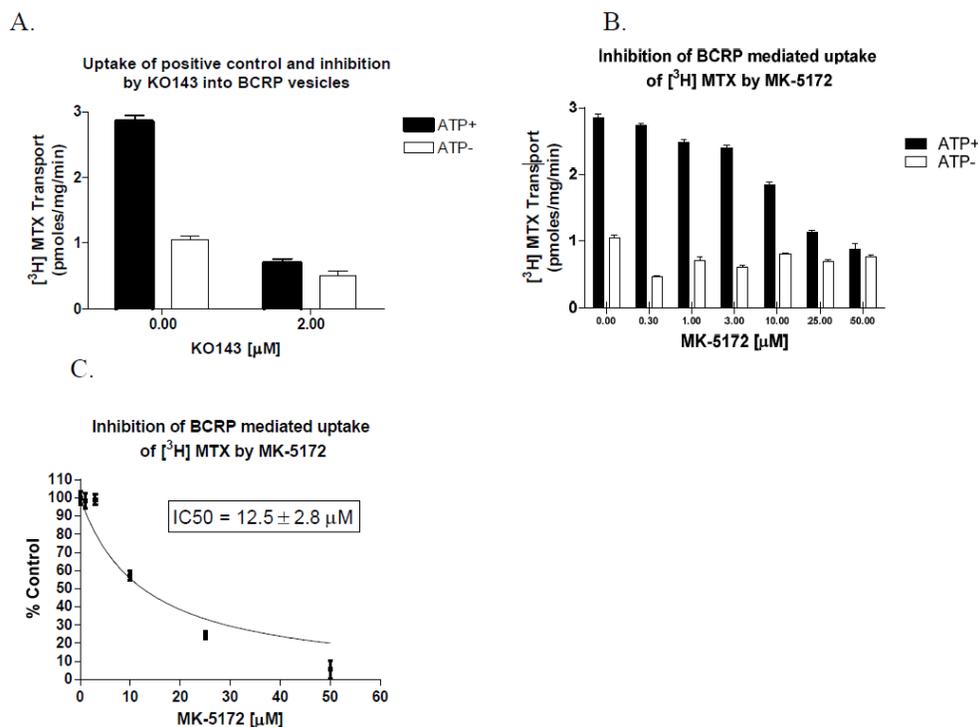
Conclusion: MK-5172 did not inhibit estradiol 3-glucuronidation in human liver microsomes at clinically relevant concentrations ($IC_{50} = 54 \pm 8.4 \mu M$).

Study Title: MK-5172 inhibition of BCRP (PK010, 34Y34H)

Methods: The inhibitory effect of MK-5172 on ATP-dependent [3H]-MTX uptake was conducted in membrane vesicles isolated from Sf9 cells containing human BCRP (b) (4), (b) (4). Briefly, 20 μ L of [3H]-MTX were incubated with or without various concentrations of MK-5172 or 100 μ M KO143 (prototypic BCRP inhibitor). The experimental conditions and methods were the same with those in PK004 (MK-8742 inhibition of BCRP).

Results

Inhibition of BCRP in Membrane Vesicles



Conclusion

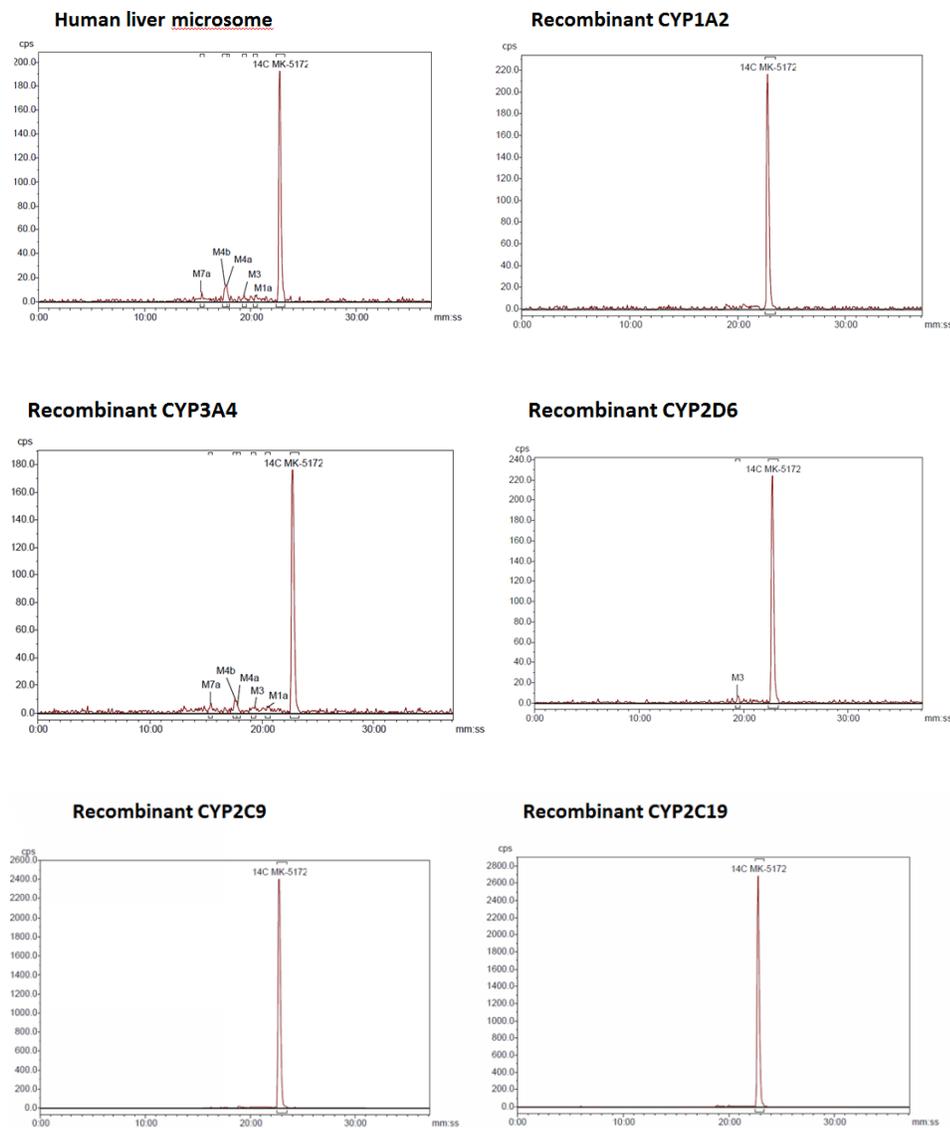
MK-5172 inhibited BCRP-mediated [³H]-Methotrexate (MTX) uptake with an IC₅₀ of 12.5 ± 2.8 μM in vesicle containing BCRP. MK-5172 may be a clinically relevant BCRP inhibitor considering maximum theoretical concentration of MK-5172 in the gut (~ 500 μM).

Study Title: Metabolism of MK-5172 with Recombinant CYP450s (PK011, 044RQK)

Methods: Human liver microsomes ((b) (4) : lot 38289) and rCYPs (1A2 (lot 21667), 3A4 (lot 27001), 2C9 (lot 11293), 2C19 (lot 10141), and 2D6 (lot 16088)) were obtained from (b) (4). Incubations were conducted at 10 and 100 μM final concentration [¹⁴C]MK-5172, 1 mg/mL liver microsomal fraction or 50 pmol/mL rCYP in 100 mM phosphate buffer (pH 7.4). Incubations were initiated by the addition of 1 mM NADPH and were incubated for 60 minutes at 37°C in a shaking water bath. Incubations were quenched with an equal volume of acetonitrile, vortexed, and centrifuged at 3,800 rpm for 10 minutes. An aliquot of the supernatant was removed for analysis by the LC-MS/MS and radiometric methods.

Results

Representative HPLC-Radiochromatograms of [¹⁴C]MK-5172 Incubations with Human Liver Microsomes (HLM) or Recombinant Cytochrome P450s



Conclusion

CYP3A4 is the predominant CYP enzyme responsible for the metabolism of MK-5172.

Study Title: Evaluation of MK-5172 as reversible inhibitors of eight cytochrome P450 activities in pooled human liver microsomes (PK013, 042TXL)

Methods

The reactions were initiated upon addition of 96 μL of a freshly prepared NADPH-generating system to the reaction mixture containing 0.25 m/mL microsome, MK-5172, and one of the isoform-specific probe substrates. The reactions were carried out in a water bath at 37 $^{\circ}\text{C}$, and were allowed to proceed for 3 to 20 minutes. Reactions were terminated with the addition of 200 μL of methanol for the CYP2D6-D and CYP3A4-M assays, or with 50 μL of 50% acetonitrile/ 2.5% formic acid/ 0.1% methanol (v/v, in water) for all other assays. Termination solutions were fortified with stable-label internal standards. The quenched reaction mixtures were vortexed thoroughly and centrifuged for 10 minutes at 3500 rpm. Samples (185 μL) of the supernatants were transferred to clean 96-well plates and analyzed (5 to 20 μL) by LC/MS/MS.

CYP isoform-specific substrates and reaction time

Assay	Substrate	Substrate conc (μM)	Reaction time (min)
CYP1A2	Phenacetin	100	10
CYP2B6	Bupropion	180	10
CYP2C8	Amodiaquine	4	3
CYP2C9	Diclofenac	10	10
CYP2C19	S-mephenytoin	30	20
CYP2D6	Dextromethorphan	10	20
CYP3A4	Midazolam	3	3
CYP3A4	Testosterone	50	10

Results

Effect MK-5172 on Cytochrome P450 Activities in Pooled Human Liver Microsomes

CYP	Reaction	Absolute IC_{50} (μM) ^a , Relative IC_{50} (μM) ^b		
		Control Inhibitor	MK-3118	MK-5172
1A2	Phenacetin O-Deethylation	0.0083, 0.0066 \pm 0.00039 (MK-3118) 0.0066, 0.0052 \pm 0.00016 (MK-5172) (α -Naphthoflavone)	>100, >100 (22 \pm 1.3%) ^c	>100, >100 (21 \pm 9.2%)
2B6	Bupropion Hydroxylation	0.72, 0.67 \pm 0.048 (Ticlopidine)	26, 25 \pm 1.6	66, 66 \pm 2.1
2C8	Amodiaquine N-Deethylation	0.15, 0.16 \pm 0.0095 (Montelukast)	1.5, 1.5 \pm 0.088	6.1, 6.0 \pm 0.31
2C9	Diclofenac 4'-Hydroxylation	0.82, 0.81 \pm 0.045 (Sulfaphenazole)	60, 60 \pm 2.5	>100, >100 (48 \pm 3.5%)
2C19	S-Mephenytoin 4'-Hydroxylation	0.20, 0.20 \pm 0.0039 (Benzylirvanol)	>100, >100 (32 \pm 0.74%)	>100, >100 (46 \pm 0.45%)
2D6	Dextromethorphan O-Demethylation	0.091, 0.084 \pm 0.0062 (Quinidine)	41, 42 \pm 0.91	>100, >100 (49 \pm 0.63%)
3A4	Midazolam 1'-Hydroxylation	0.029, 0.027 \pm 0.0014 (Ketoconazole)	7.2, 6.8 \pm 0.19	73, 65 \pm 3.3
3A4	Testosterone 6 β -Hydroxylation	0.028, 0.028 \pm 0.0013 (Ketoconazole)	15, 15 \pm 0.44	>100, >100 (20 \pm 7.3%)

^a The absolute IC_{50} is defined as the inhibitor concentration at 50% of the mean control activity (i.e. x when $y=50\%$).

^b The relative IC_{50} is defined as the inhibitor concentration at the midpoint of the calculated maximum and minimum. By definition, the minimum for the 3 parameter logistic equation is zero. The relative IC_{50} is represented as the mean \pm asymptotic standard error.

^c Values in parentheses represent the percent inhibition (mean \pm standard deviation) observed at 100 μM .

See Materials and Methods section for details on substrate concentrations, incubation conditions and analytical conditions.

Conclusion: *MK-5172 inhibited CYP2C8, CYP2B6, and CYP3A4 with IC₅₀ values of 6.1 ± 0.31, 66 ± 2.1, and 73 μM ± 3.3 in vitro using human liver microsomal assay.*

Study title: Evaluation of induction potential of CYP2B6 by L002214070 (MK-5172) in cryopreserved human hepatocytes (PK014, 03Z52M)

Methods: Hepatocytes from three donors (lot number 246, 285, 295, (b) (4)) were thawed, plated in collagen I coated 24-well plates, and cultured. Following the adaptation period, the hepatocytes were then treated for approximately 48 hours with vehicle controls (0.1% DMSO) and media, MK-5172, and the positive control inducer phenobarbital (1000 μM). At the end of the 48 hour incubation period, whole cell-based CYP2B6 enzyme changes were evaluated using bupropion hydroxylation. Total RNA was isolated for quantitative PCR analysis of CYP2B6 mRNA expression

Results

The Effect of L-002214070 on CYP2B6 mRNA and Enzyme Activity in Cryopreserved Human Hepatocytes

Treatment	[μM]	Lot 246				Lot 285				Lot 295			
		hCYP2B6 mRNA		Bupropion hydroxylation		hCYP2B6 mRNA		Bupropion hydroxylation		hCYP2B6 mRNA		Bupropion hydroxylation	
		Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b
PB	1000	17.8	100.0	12.2	100.0	7.3	100.0	8.7	100.0	10.2	100.0	9.7	100.0
L-002214070	0.1	0.8	nr	1.3	4.2	0.9	nr	0.8	nr	0.7	nr	1.0	nr
	0.5	0.7	nr	1.0	0.6	0.9	nr	0.8	nr	1.0	0.3	0.9	nr
	1	0.9	nr	1.0	nr	1.1	1.1	0.8	nr	0.6	nr	0.7	nr
	5	0.7	nr	0.8	nr	1.2	2.8	0.9	nr	0.8	nr	0.7	nr
	10	0.8	nr	0.6	nr	2.0	15.2	0.8	nr	1.2	2.2	0.6	nr
	20	1.1	0.7	0.4	nr	0.9	nr	0.5	nr	0.7	nr	0.4	nr

^a Fold – represents the mean fold change of treated samples (test article) compared to DMSO vehicle control samples (n=3) or the mean fold change of positive control compared to PBS vehicle control samples (n=3).

^b % PC – represents the percent of induction relative to positive control phenobarbital (1000 μM) corrected for vehicle control.

nr – not reported since response was less than vehicle control

Conclusion: *MK-5172 did not induce CYP2B6 at concentrations up to 20 μM in human hepatocytes.*

Study Title: Transporter phenotyping of MK-8742 using transiently transfected HEK293 cells (PK015, 03Y4Z0)

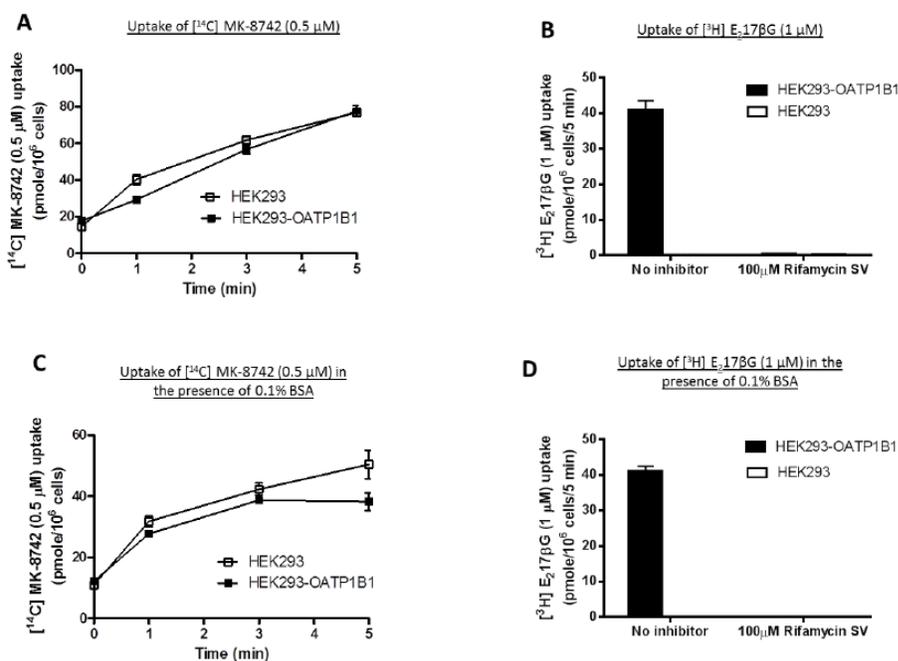
Methods

The uptake of the MK-8742 into HEK293 cells and HEK293 cells transiently transfected with OATP1B1 or OATP1B3 in the absence or presence of 0.1% BSA were measured. Cells were dislodged with trypsin EDTA (b) (4) and re-suspended in HBSS with 10 mM HEPES, in the absence or presence of 0.1% BSA, pH 7.4. Cells were then suspended in 96-glass-coated deep well plates at a density of 0.2 x

10⁶cells/well. Uptake was initiated by the addition of 125 μ L of the radiolabeled MK-8742 or positive control substrate [³H]estradiol-17 β -glucuronide (E₂17 β G, 1 μ M) for OATP1B1 or positive control substrate [³H]cholecystinin octapeptide (CCK8, 5 nM) for OATP1B3, with and without rifamycin SV (100 μ M), a known OATP inhibitor. Cells were then incubated at 37°C in a temperature controlled shaker and uptake was stopped by the addition of ice cold PBS with or without 0.1% BSA, immediate centrifugation for 1 minute at 3000 rpm at 4°C followed by washing of the cell pellets with PBS. Cell pellets were lysed in 20 μ L 20% acetonitrile and 200 μ L scintillation fluid was added (b) (4). Radioactivity was determined by liquid scintillation counting in a MicroBeta Wallac Trilux scintillation counter.

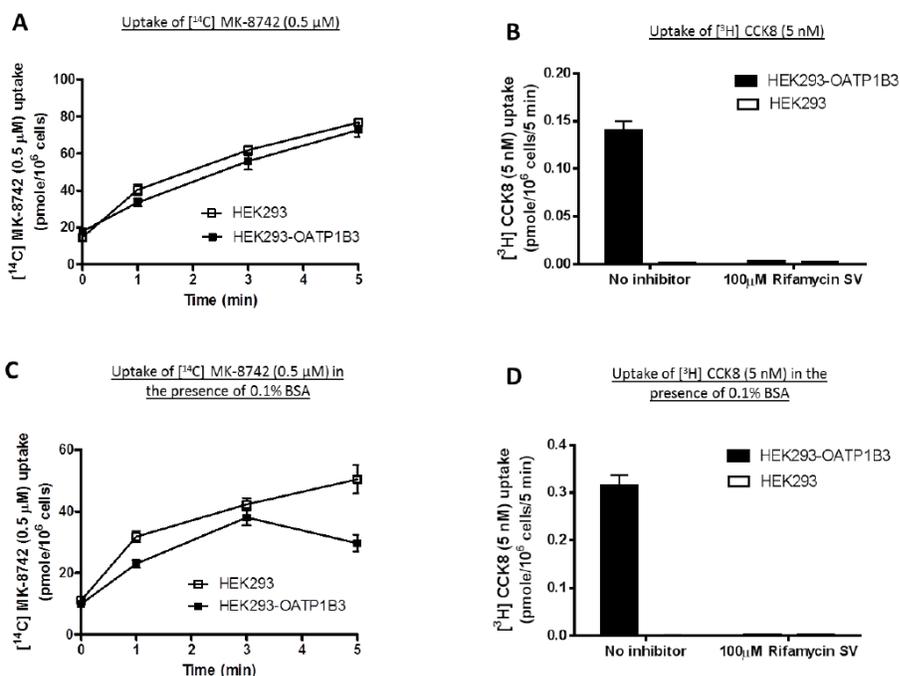
Results

OATP1B1-mediated MK-8742 uptake



A, C) Time course of 0.5 μ M [¹⁴C]MK-8742 uptake into HEK293 and HEK293-OATP1B1 cells in the absence (A) or presence (C) of 0.1% BSA. B, D) Positive control; uptake of 1 μ M [³H]E₂17 β G into HEK293 and HEK293-OATP1B1 cells in the absence (B) or presence (D) of 0.1% BSA at 5 minutes. All data are mean \pm S.E.M.

OATP1B3-mediated MK-8742 uptake



Conclusion

MK-8742 does not appear to be a substrate of OATP1B1 or OATP1B3. Definitive conclusions cannot be made due to high background transport in HEK293 cells (passive transport).

Study Title: Evaluation of MK-8742 as a reversible inhibitor of eight cytochrome P450 activities in pooled human liver microsomes (PK020, 03Y5BR)

Methods: The reaction mixtures (200 μL final volume) contained MK-8742, one of the probe substrates, 100 mM potassium phosphate buffer (pH 7.4) and 0.25 mg microsomal protein/mL. The reactions were initiated upon the addition of a freshly prepared NADPH-generating system. Reactions were terminated with the addition of 200 μL of methanol or acetonitrile. Termination solutions were fortified with stable-label internal standards. The quenched reaction mixtures were vortexed thoroughly and centrifuged for 20 minutes at 4000 rpm. Samples of the supernatants were transferred to clean 96-well plates (mixed with HPLC water) and analyzed (10 μL) by LC/MS/MS.

CYP isoform-specific substrates and reaction time

Assay	Substrate	Substrate Concentration (μM)	Reaction Time (min)	Supernatants dilution ratio (v/v, in water)
CYP1A2-P	Phenacetin	100	10	1:3 (API4000)
CYP2B6-B	Bupropion	180	10	1:10 (API4000)
CYP2C8-A	Amodiaquine	4	3	1:9 (API4000)
CYP2C9-D	Diclofenac	10	10	1:7 (API4000)
CYP2C19-M	(S)-Mephenytoin	30	20	1:1 (API4000)
CYP2D6-D	Dextromethorphan	10	20	1:9 (API4000)
CYP3A4-M	Midazolam	3	3	1:3 (API4000)
CYP3A4-T	Testosterone	50	10	1:3 (API4000)

Results

Effect of MK-8742 (L-002469825-000G003) on Cytochrome P450 activities

CYP	Reaction	Absolute IC_{50} (μM) ^a	
		Control Inhibitor	L-002469825-000G003
1A2	Phenacetin O-Deethylation	0.014 α -Naphthoflavone	>100 (-1.6 \pm 1.2%) ^b
2B6	Bupropion Hydroxylation	0.37 Ticlopidine	>100 (13 \pm 3.5%)
2C8	Amodiaquine N-Deethylation	0.18 Montelukast	>100 (14 \pm 1.2%)
2C9	Diclofenac 4'-Hydroxylation	0.80 Sulfaphenazole	>100 (19 \pm 3.9%)
2C19	(S)-Mephenytoin 4'-Hydroxylation	0.23 Benzylirivanol	>100 (12 \pm 1.1%)
2D6	Dextromethorphan O-Demethylation	0.15 Quinidine	>100 (8.5 \pm 1.3%)
3A4	Midazolam 1'-Hydroxylation	0.025 Ketoconazole	>100 (26 \pm 0.89%)
3A4	Testosterone 6 β -Hydroxylation	0.032 Ketoconazole	>100 (13 \pm 3.6%)

^a The absolute IC_{50} is defined as the inhibitor concentration that yields 50% of the mean control activity.

^b The values in parentheses represent the percent inhibition (mean \pm standard deviation) observed at 100 μM .

Conclusion: MK-8742 did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (IC_{50} values > 100 μM) in vitro.

Study Title: Evaluation of induction potential of cytochrome P450 isoforms by MK-8742 in cryopreserved human hepatocytes (PK020, 03Y5BR).

Methods: Hepatocytes from three donors (lot number 246, 295, 295, (b) (4)) were thawed, plated in collagen I coated 24-well plates. Following the adaptation period, the hepatocytes were then treated for 48 hours with vehicle controls 0.1% (v/v) DMSO and media, MK-8742, or the positive control inducers rifampicin (10 μ M), phenobarbital (1000 μ M) or omeprazole (50 μ M). At the end of the 48 hour incubation period, CYP3A4, CYP2B6 and CYP1A2 enzyme changes were evaluated using testosterone 6 β -hydroxylation, bupropion hydroxylation and phenacetin *O*-deethylation, respectively, measured by LC-MS/MS detection. Total RNA was isolated for quantitative PCR analysis of CYP3A4, CYP2B6 and CYP1A2 mRNA expression.

Results

The Effect of MK-8742 (L-002469825) on CYP3A4 mRNA and Enzyme Activity in Human Hepatocytes

Treatment	[μ M]	Lot 246				Lot 285				Lot 295			
		hCYP3A4 mRNA		Testosterone 6 β -hydroxylation		hCYP3A4 mRNA		Testosterone 6 β -hydroxylation		hCYP3A4 mRNA		Testosterone 6 β -hydroxylation	
		Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b
RIF	10	9.2	100.0	6.0	100.0	44.4	100.0	7.5	100.0	9.0	100.0	4.2	100.0
L-002469825	0.1	0.2	nr	0.6	nr	2.2	2.8	1.3	4.9	0.6	nr	1.3	10.2
	0.5	0.4	nr	0.6	nr	3.0	4.7	1.0	nr	0.6	nr	1.2	7.4
	1	0.4	nr	0.5	nr	4.2	7.4	0.9	nr	1.1	1.3	1.1	3.6
	5	0.4	nr	0.6	nr	4.4	7.8	0.9	nr	1.1	0.7	0.9	nr
	10	0.7	nr	0.5	nr	4.3	7.6	0.9	nr	1.7	8.3	1.1	2.2
	20	1.1	1.4	0.6	nr	5.1	9.4	0.9	nr	1.4	5.4	1.0	nr

^a Fold – represents the mean fold change of treated samples compared to DMSO vehicle control samples (n=3).

^b % PC – represents the percent of induction relative to positive control rifampicin (10 μ M) corrected for vehicle control.

nr- not reported since response was less than vehicle control

The Effect of MK-8742 (L-002469825) on CYP2B6 mRNA and Enzyme Activity in Human Hepatocytes

Treatment	[μ M]	Lot 246				Lot 285				Lot 295			
		hCYP2B6 mRNA		Bupropion hydroxylation		hCYP2B6 mRNA		Bupropion hydroxylation		hCYP2B6 mRNA		Bupropion hydroxylation	
		Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b
PB	1000	11.0	100.0	13.9	100.0	6.9	100.0	6.5	100.0	8.1	100.0	8.6	100.0
L-002469825	0.1	0.3	nr	0.8	nr	1.6	10.0	1.1*	4.6	0.4	nr	0.9	nr
	0.5	0.5	nr	0.9	nr	1.8	13.8	0.9	nr	0.4	nr	1.0	0.2
	1	0.4	nr	1.3	4.7	1.5	8.5	0.7	nr	0.6	nr	1.2	4.6
	5	0.4	nr	1.3	3.6	1.8	14.5	0.8	nr	0.5	nr	1.4	9.4
	10	0.8	nr	1.1	1.6	1.6	9.8	0.9*	nr	1.1*	1.2	1.6	14.0
	20	1.3	2.7	1.6	7.6	2.1	18.0	1.9	26.7	0.7	nr	1.8	17.8

^a Fold – represents the mean fold change of treated samples (test articles) compared to DMSO vehicle control samples (n=3) or the mean fold change of positive control compared to PBS vehicle control samples (n=3) except for * where n=2 due to an outlier.

^b % PC – represents the percent of induction relative to positive control phenobarbital (1000 μ M) corrected for vehicle control.

The Effect of L-002469825 on CYP1A2 mRNA and Enzyme Activity in Human Hepatocytes

Treatment	[μM]	Lot 246				Lot 285				Lot 295			
		hCYP1A2 mRNA		Phenacetin O-deethylation		hCYP1A2 mRNA		Phenacetin O-deethylation		hCYP1A2 mRNA		Phenacetin O-deethylation	
		Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b	Fold ^a	% of PC ^b
OM	50	41.4	100.0	12.4	100.0	39.5	100.0	9.8	100.0	25.4	100.0	18.3	100.0
L-002469825	0.1	0.4	nr	1.0	nr	1.1	0.3	1.8*	9.5	0.8	nr	1.2	1.4
	0.5	0.7	nr	1.0	0.4	1.2	0.5	1.5	5.1	0.5	nr	1.3	1.9
	1	0.6	nr	1.0	0.4	1.3	0.8	1.3	3.9	1.0	0.2	1.5	2.7
	5	0.6	nr	1.2	2.1	1.6	1.5	1.8	8.9	0.8	nr	1.9	5.0
	10	0.8	nr	1.4	3.1	1.7	1.7	2.3	14.6	1.4	1.7	1.7	4.2
	20	1.3	0.7	1.8	6.8	1.8	2.2	2.3	15.0	1.2	0.7	2.4	8.2

^a Fold – represents the mean fold change of treated samples compared to DMSO vehicle control samples (n=3) except for * where n=2 due to an outlier.

^b % PC – represents the percent of induction relative to positive control omeprazole (50 μM) corrected for vehicle control.

Conclusion: MK-8742 (up to 20 μM) did not induce CYP1A2, CYP2B6, and CYP3A4 in vitro using human hepatocytes.

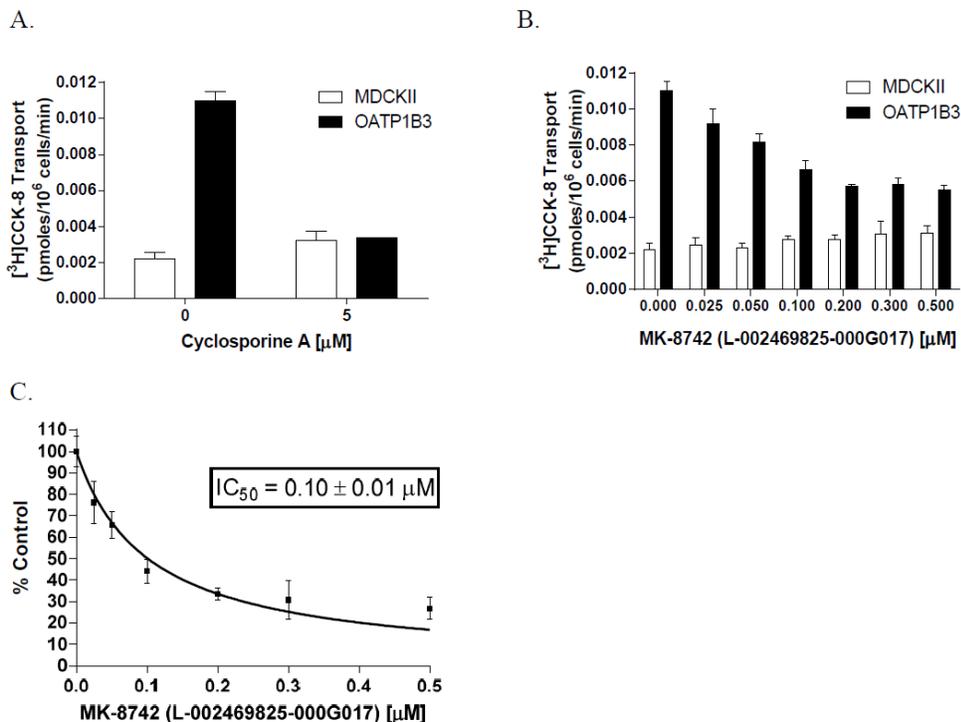
Study Title: Inhibitory effect of MK-8742 on OATP1B3-mediated transport (PK021, 03YS0W)

Methods

The inhibitory effect of MK-8742 on OATP1B3-mediated [³H]CCK-8 uptake was conducted in MDCKII cells with stable transfection of OATP1B3 (MDCKII-OATP1B3). Cells were dislodged with trypsin EDTA (b) (4) and re-suspended in HBSS with 10 mM HEPES, pH 7.4. Cells were then suspended in 96-deep well plates at a density of 0.4 x 10⁶ cells/well in 247.5 μL of HBSS. Uptake was initiated by the addition of 2.5 μL of [³H]CCK-8 containing various concentrations of the MK-8742 or CsA, a prototypical OATP1B inhibitor. Cells were then incubated for 5 minutes at 37°C in a temperature controlled shaker, and uptake was stopped by the addition of ice-cold phosphate buffered saline (PBS), immediate centrifugation for 2 minutes at 3000 rpm at 4°C. Cell pellets were dissolved in 20 μL 20% acetonitrile and 200 μL scintillation fluid was added (b) (4). Radioactivity was determined by liquid scintillation counting in a MicroBeta Wallac Trilux Scintillation Counter (Perkin Elmer, Boston MA). OATP1B3-mediated CCK-8 uptake was calculated by subtracting the uptake of CCK-8 into MDCKII cells from that observed in MDCKII-OATP1B3 cells and data were normalized to % control, where uptake in the absence of test compound was 100%

Results

The Inhibitory Effect of MK-8742 on the Uptake of 5 nM [³H]CCK-8 in MDCKII-OATP1B3 and MDCKII Cells



Conclusion

MK-8742 inhibited the OATP1B3-mediated uptake of CCK-8 in a concentration-dependent manner with an estimated IC_{50} of $0.10 \pm 0.01 \mu\text{M}$. MK-8742 may be a clinically relevant inhibitor of OATP1B3.

Study Title: Interactions of MK-8742 and benchmarking compounds with the human multidrug resistance protein MDR1 P-gp (PK022, 03YZ27)

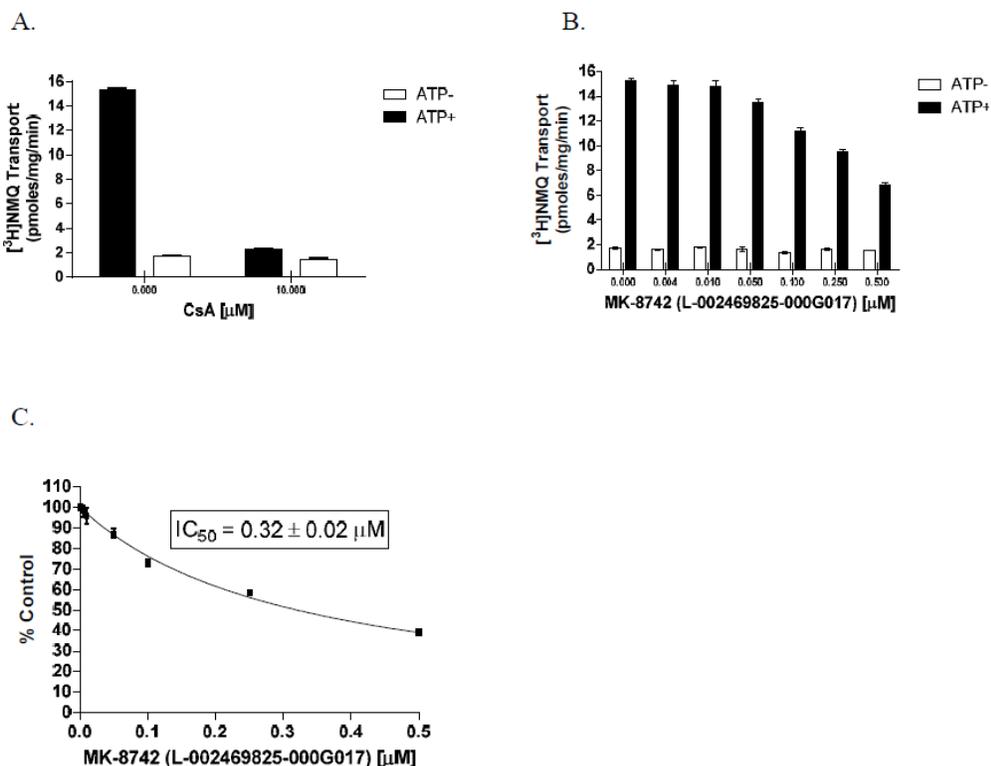
Methods

The inhibitory effect of MK-8742 on ATP-dependent [³H]N-methylquinidine (NMQ, 0.1 μM) uptake was conducted in membrane vesicles isolated from baculovirus infected *Spodoptera frugiperda* cells containing human MDR1 P-gp (ABCB1). Briefly, 19 μL of [³H]NMQ containing transport buffer was added to 10 μL (2 mg/mL in transport buffer) of MDR1 P-gp vesicles. One microliter of various concentrations of MK-8742 or Cyclosporine A (CsA) (prototypic MDR1 P-gp inhibitor) was added to each well and pre-incubated for 5 minutes at 37 °C. Uptake was initiated by the addition of 20 μL ATP regenerating reagent or AMP reagent and 12.8 U/mL creatine phosphokinase in transport buffer, followed by incubation at 37 °C for 5 minutes. Uptake was stopped by the addition of 200 μL ice-cold

stop buffer, followed by transfer of the reaction mixture to a pre-wetted 96-well glass fiber type B filter plate (1.0 μm) (b) (4), and application of vacuum. Filters containing the membrane vesicles were washed with 200 μL ice-cold stop buffer, six times. The filter plate was dried at room temperature and 100 μL scintillation fluid (b) (4) was added to each sample. Radioactivity was determined by liquid scintillation counting in a MicroBeta Wallac Trilux Scintillation Counter (Perkin Elmer, Boston, MA). ATP-dependent MDR1 P-gp mediated [^3H]NMQ uptake was calculated by subtracting the uptake of [^3H]NMQ in the absence of ATP from that in its presence and data were then normalized to % control, where uptake in the absence of test compound was 100%.

Results

The Inhibitory Effect of MK-8742 on the Uptake of [^3H]NMQ (0.1 μM) in MDR1 P-gp Containing Membrane Vesicles



Conclusions

MK-8742 inhibited [^3H]NMQ uptake in membrane vesicles containing MDR1 P-gp with an estimated IC_{50} of $0.32 \pm 0.02 \mu\text{M}$. MK-8742 may be a clinically relevant inhibitor of P-gp.

Study Title: In vitro evaluation of MK-8742/5172 off-target activities (CES1, CES2, CatA; PD012)

Methods

1. Carboxylesterases 1/2 Inhibition Studies

MK-5172 and MK-8742 inhibitory potencies for CES were determined *in vitro* using the recombinant human CES1 and CES2 proteins with C-terminal 10-His tag. CES1/2 mediated hydrolysis of 4-NPA (substrate) results in the formation of 4-nitrophenol, which can be monitored at 405 nm absorbance in real-time kinetic mode. For the CES1 inhibition studies, the final enzyme and substrate (4-NPA) concentrations were 2 nM and 2 mM ($4xK_m$), respectively. The CES2 inhibition studies were performed with 0.5 nM enzyme and 2 mM 4-NPA ($2xK_m$). Reactions without compounds or enzymes were, respectively, the high and low controls. Reactions were initiated by the addition of the substrate/buffer mix to the plate. The quadruplicated dose dependent percent inhibition data were fit by nonlinear regression in the software application GraphPad Prism to obtain the IC_{50} values. The studies were repeated on a separate day for an N = 2 experiment.

2. Cathepsin A Inhibition Studies

MK-5172 and MK-8742 inhibitory potencies for CatA were determined *in vitro* using the recombinant human CatA protein with C-terminal 10-His tag. A LC-TOF/MS-based enzymatic assay was developed to monitor CatA-mediated hydrolysis of NS5B prodrug (MK-2248). Briefly, CatA was preactivated using recombinant Cathepsin L (CatL) (b) (4) in a reaction mixture containing 50 $\mu\text{g/mL}$ CatA and 5 $\mu\text{g/mL}$ CatL at 37 °C for 30 minutes. The activated enzyme was subsequently preincubated with MK-5172 and MK-8742 for 30 minutes prior to the addition of 150 μM MK-2248 substrate to initiate the reaction. The hydrolysis reactions were performed for 15 minutes. The reactions were quenched with DMSO/acetonitrile and spun for 2000 rpm for 5 minutes. Samples were analyzed quantitatively by LC/TOF Mass Spectrometer. The triplicated dose-dependent percent inhibition data were fit by nonlinear regression in the software application GraphPad Prism to obtain the IC_{50} values. The studies were repeated on a separate day for an N = 2 experiment.

Results

Inhibitory Activities of MK-5172 and MK-8742 on Carboxylesterase 1 and Carboxylesterase 2

	Inhibitory Potency IC_{50} (μM)	
	CES1	CES2
MK-5172	157	105
MK-8742	>50	>50

Inhibitory activities of MK-5172 and MK-8742 on Cathepsin A

	Inhibitory Potency IC₅₀ (μM)
	Cat A
MK-5172	>200
MK-8742	>50

Conclusion: MK-5172 and MK-8742 did not inhibit CES1, CES2, and CatA in vitro (IC₅₀ > 50 μM).

5. PHARMACOMETRIC REVIEW

1. SUMMARY OF FINDINGS

The population pharmacokinetic (PPK) model developed by the Applicant is capable of characterizing the pharmacokinetics of grazoprevir (GZR) based on dataset consisting of eight Phase 1 studies (5172-001, 004, 009, 014, 040, 042, 069 and 8742-008), nine Phase 2 studies (5172-003, 035, 038, 039, 047, 048, 058, 059 and 074) and four Phase 3 studies (5172-052, 060, 061 and 068).

The structural model that best described the pharmacokinetics of GZR was a 2-compartment model with first order elimination, oral absorption described by two parallel first order pathways (a pathway with a food-dependent absorption rate that, in HCV patients, is faster compared to the second pathway, and a secondary pathway with a slower absorption rate, particularly for doses less than or equal to 100 mg). The factors that increased GZR exposure included Asian race, Hispanic ethnicity, female gender, compensated cirrhosis, low body weight, and increased age.

The PPK model developed by Applicant is able to describe the pharmacokinetics of Elbasvir (EBR) by pooling data from six Phase 1 (i.e., 8742-001, 002, 003, 004, 008 and 7009-050) and ten Phase 2 and 3 studies (i.e., 5172-035, 047, 048, 052, 058, 059, 060, 061, 068 and 074).

The structural model was a 2-compartment model with lagged first order absorption. AUC_{0-24h} is 47% higher in women relative to men. Other intrinsic covariates (i.e., race, ethnicity, age, EGFR, body weight, health status and prior treatment status) had smaller effects on AUC_{0-24h} than female gender.

The exposure-response analysis for efficacy used data from the full analysis set (FAS) population of seven Phase 2/3 studies in which GZR and EBR were co-administered, with and without RBV, for nominal treatment durations of 8, 12, 16, and 18 weeks (P035, P047, P048, P052, P060, P061, and P068; including only patients infected with HCV GT1, 4, or 6; excluding the deferred treatment arms). EBR AUC_{0-24h} was associated with SVR12 ($p=0.003$) in the final model, while GZR AUC_{0-24h} was not associated with SVR12 ($p>0.2$). Treatment duration, baseline HCV RNA and baseline NS5A resistance (No/Yes) were identified as significant covariates of the exposure-response relationship. In general, SVR12 rates were lower for short treatment durations (e.g., 8 weeks), higher baseline log₁₀ HCV RNA, and in patients who had baseline resistance to NS5A inhibitors.

The relationship between GZR plasma PK exposures and increase in ALT/AST post-nadir 4 weeks into treatment (i.e., Late ALT/AST Elevation Events) was assessed using data from thirteen Phase 2/3 studies (P003, P035, P038, P039, P047AB, P048, P052, P058 Part 1, P059A, P060, P061, P068 and P074, excluding the deferred treatment, 4- and 6- week treatment, and boceprevir treatment arms). The results demonstrate that the risk of Late ALT/AST Elevation Events is correlated with GZR exposures ($p<0.001$).

1.1 Recommendations

The Division of Pharmacometrics (Office of Clinical Pharmacology) has reviewed this application and agrees with the Applicant's conclusion from the population PK analysis that no dose adjustments are necessary for the fixed dose combination based on age, body weight, sex, race, or renal function in adult patients. Hepatic impairment increases GZR exposure, thus the fixed dose combination is not recommended in patients with moderate hepatic impairment (C-P B) and should be contraindicated in patients with severe hepatic impairment (C-P C). The exposure-response relationship for efficacy and safety support the proposed dose of 100 mg GZR and 50 mg EBR fixed dose combination administered once daily in adult patients with normal hepatic function or mild hepatic impairment (C-P A).

2 RESULTS OF APPLICANT'S ANALYSIS

The pharmacometric analyses in this review cover the Applicant's population PK analyses for GZR and EBR, and exposure-response analysis for efficacy and safety.

2.1 Population PK analysis for GZR

2.1.1 Objectives

1. To develop a population PK model to characterize GZR plasma concentration-time profiles in healthy volunteers and HCV infected patients following oral administration of a wide range of GZR doses;
2. To explore the effects of select covariates on pertinent GZR PK parameters to derive a final predictive model.
3. To generate empirical Bayes estimates of PK summary measures ($C_{min,ss}$, $C_{max,ss}$ and AUC_{0-24h}) for individual patients in the Phase 2/3 studies for exposure-response analyses;

2.1.2 Trials included in the population PK model

The population PK model was developed using data from eight Phase 1 studies (5172-001, 5172-004, 5172-009, 5172-014, 5172-040, 5172-042, 5172-069 and 8742-008), nine Phase 2 studies (5172-003, 5172-035, 5172-038, 5172-039, 5172-047, 5172-048, 5172-058, 5172-059 and 5172-074) and four Phase 3 studies (5172-052, 5172-060, 5172-061 and 5172-068). Data from the deferred treatment arms of 052 and 060 were not included in the analysis, and only data from Part 1 of 058 and Part A of 059 were included.

The population PK analysis was conducted by several steps. Step 1 developed the base model using richly sampled plasma concentration-time data from seven Phase 1 studies (001, 008, 009, 014, 040, 042 and 069) which did not involve any studies with HCV-infected patients. Step 2 involved the dataset from Step 1 plus the addition of one Phase 1 study involving HCV-infected patients (004) and five Phase 2 studies (003, 035, 038, 039 and 047). Step 3 updated the base model with the creation of the final dataset by the addition of datasets from four Phase 2 studies (048, 058, 059 and 074) and four Phase 3 studies (052, 060, 061 and 068). The final dataset from Step 3 was used to develop a working full model in Step 4.

2.1.3 Base model

The final base model was a two compartment open model with first order elimination. Oral absorption was described by two parallel first order pathways: 1) a pathway handling the majority of absorption that has a food-dependent absorption rate that, for HCV-infected patients, is faster compared to the other pathway, and 2) a secondary pathway with an absorption rate that is slower than the majority pathway, especially for lower doses (doses less than or equal to 100 mg). The Step 3 final base model structure was similar to the model used in Steps 1 and 2 and is shown in Figure 1. Parameter estimates along with standard errors for the Step 3 final base PK model are provided in Table 1.

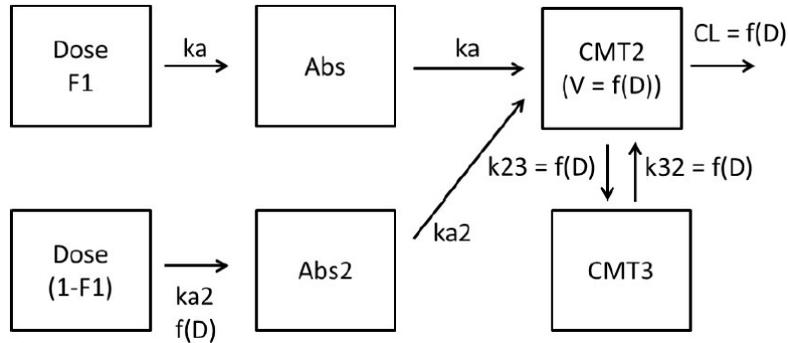


Figure 1 Step 3 base model structure diagram

Source: Applicant's GZR population PK report, Page 74, Figure 8.

Table 1 Parameter estimates for the base model

Parameter	θ	Estimate	SE	95%CI
CL/F (L/hr)	1	30.6	2.05	(26.582 - 34.618)
V/F (L) for healthy	2	105	12	(81.48 - 128.52)
ka (hr ⁻¹) for fasted, healthy	3	0.724	0.0332	(0.659 - 0.789)
k23 (hr ⁻¹) for healthy	4	0.0361	0.0043	(0.028 - 0.045)
k32 (hr ⁻¹)	5	0.0259	0.00178	(0.022 - 0.029)
Proportional Error	6	0.507	0.00574	(0.496 - 0.518)
F1 Split	8	0.96	0.00473	(0.951 - 0.969)
Dose on V/F ^a	9	-0.69	0.0687	(-0.825 - -0.555)
Dose on k23 ^a	10	-1.49	0.0862	(-1.659 - -1.321)
Dose on k32 ^a	11	-0.542	0.0601	(-0.66 - -0.424)
Dose on CL/F ^a	12	-0.557	0.0481	(-0.651 - -0.463)
ka2 (hr ⁻¹) for Dose≤100	13	0.0906	0.00836	(0.074 - 0.107)
ka2 (hr ⁻¹) for Dose>100	15	0.132	0.0129	(0.107 - 0.157)
AMP ^c	16	0.077	0.0161	(0.045 - 0.109)
PEAK ^c	17	12	FIXED	
PERD ^c	18	24	FIXED	
Fed on V/F ^b	19	-0.0685	0.0346	(-0.136 - -0.001)
ka (hr ⁻¹) for fed	20	2.29	0.565	(1.183 - 3.397)
V/F (L) for HCV	21	143	12.7	(118.108 - 167.892)
ka (hr ⁻¹) for fasted & HCV	22	1.47	0.0789	(1.315 - 1.625)
k23 (hr ⁻¹) for HCV	23	0.0111	0.00121	(0.009 - 0.013)
ka (hr ⁻¹) for fed & HCV	24	1.57	0.188	(1.202 - 1.938)
	IIV			
CL/F	1	0.229	0.0157	(0.1982 - 0.2598)
V/F	2	0.771	0.028	(0.7161 - 0.8259)

Source: Applicant's GZR population PK report, Page 73, Table 22.

2.1.4 Covariate model development

The working full model was developed using a stepwise addition/removal process where covariate effects were initially added to the PK parameters CL/F, V/F and k23. If a continuous or categorical covariate effect resulted in a <0.2 parameter point estimate, the covariate was removed from the model. The covariates with >0.2 parameter point estimate were left in the model and the process was repeated until all the covariates were tested. Table 2 lists all the covariates that were tested in building the working full model.

Table 2 List of Covariate Effects Tested and Included in the Working Full model

Parameter	Covariates Tested and Included (marked with a **) in the Working Full Model
CL/F	dose*, age*, sex*, Black race*, Asian race*, other race*, Hispanic*, body weight*, eGFR, GT1a*, GT1b*, GT3*, GT4*, GT6, prior treatment with Peg-IFN and RBV, prior treatment with DAA, HEPFUN2*, HEPFUN3*, HEPFUN4*, coinfecting with HIV, coadministered with MK-8742, coadministered with RBV, coadministered with peg-IFN*, dialysis
V/F	HCV-infected patients*, dose*, age*, sex*, Black race*, Asian race*, other race*, Hispanic, body weight*, eGFR, GT1a, GT1b, GT3, GT4, GT6*, prior treatment with Peg-IFN and RBV, prior treatment with DAA*, HEPFUN2*, HEPFUN3*, HEPFUN4*, coinfecting with HIV*, coadministered with MK-8742, coadministered with RBV, coadministered with peg-IFN*, dialysis
k23	HCV-infected patients*, HEPFUN4, dose*, age*, sex, Black race, Asian race*, other race, Hispanic*, body weight*, eGFR, GT1a, GT1b, GT3, GT4, GT6, prior treatment with Peg-IFN and RBV, prior treatment with DAA*, coinfecting with HIV, coadministered with MK-8742*, coadministered with RBV*, coadministered peg-IFN*, dialysis*
k32	dose*, diurnal effect
ka	food* food & HCV-infected patients*
F1	food

* Covariate effects included in the Step 4 working full model

Source: Applicant's GZR population PK report, Page 81, Table 25.

2.1.5 Final population PK model

The working full model structure was similar to the model used in Step 3 and is shown in Figure 1. Parameter estimates along with standard errors for the Step 4 working full model are provided in Table 3. Overall, the parameters of the model, including the covariate effects, are estimated with good precision.

Table 3 GZR Parameter Estimates for the Step 4 Working Full Model

Parameter	θ	Estimate	SE	95%CI	Parameter	θ	Estimate	SE	95%CI
CL/F (L/hr)	1	48.9	3.48	(42.079 - 55.721)	PEGN on CL/F ^b	47	-0.432	0.029	(-0.489 - -0.375)
V/F (L) for healthy	2	142	16.4	(109.856 - 174.144)	Age on V/F ^a	49	-0.605	0.0931	(-0.787 - -0.423)
ka (hr ⁻¹) for fasted, healthy	3	0.697	0.0376	(0.623 - 0.771)	Sex on V/F ^b	50	-0.363	0.0289	(-0.42 - -0.306)
k23 (hr ⁻¹) for healthy	4	0.0584	0.00811	(0.043 - 0.074)	Black race on V/F ^b	51	0.272	0.0826	(0.11 - 0.434)
k32 (hr ⁻¹)	5	0.0367	0.00102	(0.035 - 0.039)	Asian race on V/F ^b	52	-0.383	0.0549	(-0.491 - -0.275)
Proportional error	6	0.51	0.00558	(0.499 - 0.521)	Other race on V/F ^b	53	0.427	0.174	(0.086 - 0.768)
F1 Split	8	0.632	0.0598	(0.515 - 0.749)	WT on V/F ^a	55	0.7	0.137	(0.431 - 0.969)
Dose on V/F ^a	9	-0.534	0.103	(-0.736 - -0.332)	Genotype 6 on V/F ^b	61	-0.0603	0.134	(-0.323 - 0.202)
Dose on k23 ^a	10	-1.37	0.118	(-1.601 - -1.139)	PRTR3 on V/F ^b	63	-0.147	0.147	(-0.435 - 0.141)
Dose on k32 ^a	11	-0.205	0.0446	(-0.292 - -0.118)	HFUN2 on V/F ^b	64	-0.218	0.0493	(-0.315 - -0.121)
Dose on CL/F ^a	12	-0.567	0.0504	(-0.666 - -0.468)	HFUN3 on V/F ^b	65	-0.411	0.03	(-0.441 - -0.352)
ka2 (hr ⁻¹) for Dose≤100	13	0.282	0.0446	(0.195 - 0.369)	V/F (L/hr) for HFUN4	66	21.2	4.37	(12.635 - 29.765)
ka2 (hr ⁻¹) for Dose>100	15	0.798	0.0439	(0.712 - 0.884)	HIVCOINF on V/F ^b	67	0.157	0.0565	(0.046 - 0.268)
AMP ^c	16	0	FIXED		PEGN on V/F ^b	70	-0.215	0.0692	(-0.351 - -0.079)
PEAK ^c	17	12	FIXED		Age on k23 ^a	72	-0.271	0.133	(-0.532 - -0.01)
PERD ^c	18	24	FIXED		Asian race on k23 ^b	75	-0.204	0.101	(-0.402 - -0.006)
Fed on V/F ^b	19	-0.0486	0.0379	(-0.123 - 0.026)	Hispanic on k23 ^b	77	-0.303	0.0826	(-0.465 - -0.141)
ka (hr ⁻¹) for fed	20	2.35	0.32	(1.723 - 2.977)	WT on k23 ^a	78	0.505	0.199	(0.115 - 0.895)
V/F (L) for HCV	21	142	13.1	(116.324 - 167.676)	PRTR3 on k23 ^b	86	0.227	0.286	(-0.334 - 0.788)
ka (hr ⁻¹) for fasted & HCV	22	1.4	0.075	(1.253 - 1.547)	MK8742 on k23 ^b	91	-0.159	0.0558	(-0.268 - -0.05)
k23 (hr ⁻¹) for HCV	23	0.0277	0.00333	(0.021 - 0.034)	RBV on k23 ^b	92	-0.00126	0.0497	(-0.099 - 0.096)
ka (hr ⁻¹) for fed & HCV	24	1.52	0.159	(1.208 - 1.832)	PEG on k23 ^b	93	-0.514	0.0821	(-0.675 - -0.353)
Age on CL/F ^a	26	-0.704	0.0572	(-0.816 - -0.592)	Dialysis on k23 ^b	94	0.376	0.163	(0.057 - 0.695)
Sex on CL/F ^b	27	-0.236	0.0247	(-0.284 - -0.188)	IIV				
Black race on CL/F ^b	28	0.15	0.052	(0.048 - 0.252)	CL/F	1	0.177	0.0145	(0.1486 - 0.2054)
Asian race on CL/F ^b	29	-0.339	0.0344	(-0.406 - -0.272)	V/F	2	0.473	0.0214	(0.4311 - 0.5149)
Other race on CL/F ^b	30	0.294	0.106	(0.086 - 0.502)	FIXED: Indicates that the parameter value was fixed in the NONMEM control stream				
Hispanic on CL/F ^b	31	-0.173	0.0514	(-0.274 - -0.072)	^a Continuous covariate effect represented as $\theta_{TV,ij} = \theta_{REF} \left(\frac{x_{ij}}{x_{REF}} \right)^{\theta_x}$ Eq. 5				
WT on CL/F ^a	32	0.372	0.0832	(0.209 - 0.535)	^b Categorical covariate effect represented as $\theta_{(TV,ij)} = \theta_{REF} \cdot (1 + \theta_x \cdot x_{ij})$ Eq. 6				
Genotype 1a on CL/F ^b	34	-0.212	0.0364	(-0.283 - -0.141)	^c Diurnal Effect represented as SHIFT=(COS(2*3.14*((TSLDA-PEAK)/PERD)))				
Genotype 1b on CL/F ^b	35	-0.209	0.0376	(-0.283 - -0.135)	k32=k32*(1+AMP*SHIFT) Eq. 8				
genotype 3 on CL/F ^b	36	-0.204	0.05	(-0.302 - -0.106)					
genotype 4 on CL/F ^b	37	-0.242	0.0523	(-0.345 - -0.139)					
HFUN2 on CL/F ^b	41	-0.197	0.0372	(-0.27 - -0.124)					
HFUN3 on CL/F ^b	42	-0.394	0.0225	(-0.438 - -0.35)					
CL/F(L/hr) for HFUN4	43	11.2	1.79	(7.692 - 14.708)					

Source: Applicant's GZR population PK report, Page 82, Table 26.

Table 4 shows the typical values of GZR CL/F from the Step 4 working full model, using a 100 mg dose (the clinical dose) and for various populations relevant to those treated in the Phase 2/3 studies. The results suggest that moderate hepatic insufficiency (HCV-infected, with cirrhosis, Child-Pugh B) leads to the largest increase in all three summary PK measures, with an approximately 4-fold increase in AUC relative to non-cirrhotic HCV-infected patients. Other factors that led to increased AUC of GZR (all by less than 2-fold) include Asian race, Hispanic ethnicity, female gender, compensated cirrhosis (Child-Pugh A), low body weight and increased age. Combinations of these factors (e.g., low body weight Asian female) may lead to larger than 2-fold increases in AUC of GZR, but less than a 5-fold increase.

Table 4 GZR CL/F Typical Values and Covariate Effects for Representative Subjects

PK Parameters and Baseline Covariates		Baseline Covariate Value	Estimate	Change from Typical (%)	Inter-individual Variability (%)
Typical CL/F, L/hr (100 mg dose, Trt Naive, White Non-Hispanic Male, HCV GT1a, 50 years old, Weight = 75 kg, eGFR=95 mL/min/1.73 m ²)			85	--	42.1
Dose	25 mg		186	119	--
	400 mg		39	-54	--
Hepatic Function	Non-cirrhotic, Metavir F3		68	-20	--
	Compensated Cirrhosis (CP-A)		51	-39	--
	Cirrhosis, CP-B		19	-77	--
HCV GT	GT6		107	27	--
Age	5 th Percentile	30 years	121	43	--
	95 th Percentile	67 years	69	-19	--
Weight	5 th Percentile	53 kg	74	-12	--
	95 th Percentile	107 kg	97	14	--
Sex	Female		65	-24	--
Race	Black		97	15	--
	Asian		56	-34	--
	Other		109	29	--
Ethnicity	Hispanic		69	-17	--
Use of Peg-IFN			48	-43	--

Source: Applicant's GZR population PK report, Page 101, Table 31.

2.1.6 Model assessment

The predictive performance of the working full model was evaluated using posterior predictive check (PPC). The 90% prediction intervals (i.e. 5th and 95th percentiles of all 1000 simulated datasets binned according to time) were overlaid on the individual observed data. The individual observed data were largely contained within the 90% prediction interval indicating that the working full PK model could simulate concentration-time data that was consistent with the observed data. The representative result of the PPC (100 mg QD dose of GZR) is provided in Figure 2 for Studies 035.

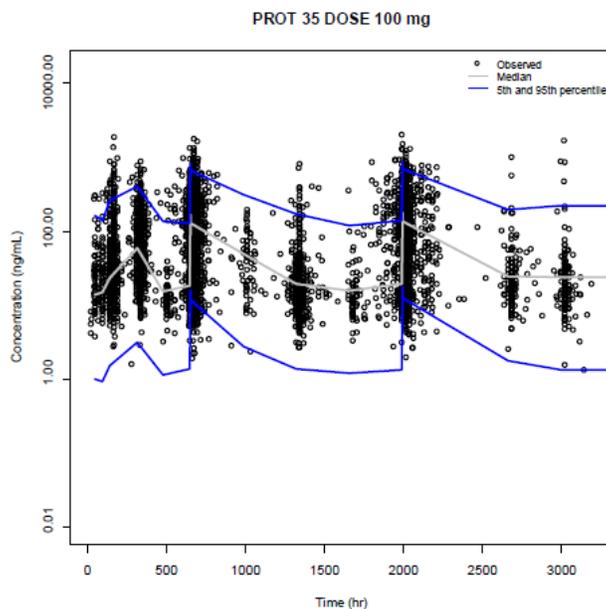


Figure 2 Results of Model Evaluation (PPC): Predicted Median (solid grey line) and 90% Prediction Intervals (solid blue lines) and Observed Plasma GZR Concentration versus Time Profiles for Study 035.

Source: Applicant's GZR population PK report, Page 85, Figure 11.

2.1.7 Simulation results using the working full PK model

The simulations predicted the steady state geometric mean (GM) and 90% CI of minimum drug concentration ($C_{min,ss}$), maximum drug concentration ($C_{max,ss}$) and area under the plasma concentration-time profile for one dosing interval (AUC_{0-24h}) where the drug is administered 100 mg QD in a population of HCV-infected, non-cirrhotic, non-CKD, non-Japanese patients. The GM (90%CI) for steady state $C_{min,ss}$, $C_{max,ss}$ and AUC_{0-24h} were 23.4 (23.2, 25.9) nM, 215.1 (209.3, 229.5) nM and 1857.3 (1826.5, 1993.3) nM·h, respectively.

Reviewer's comment: Based on reviewer's independent analysis, the GM (90%) for steady state $C_{min,ss}$, $C_{max,ss}$ and AUC_{0-24h} were 21.2 (20.4, 21.9) nM, 199.0 (193.0, 205.1) nM and 1691.3 (1640.7, 1743.5) nM·h, respectively, for 1175 HCV-infected, non-cirrhotic, non-CKD, non-Asian patients who receiving 100 mg QD dosing of GZR. The results are a little lower than the Applicant's value, because all Asians have been excluded from the dataset compared (only Japanese patients were excluded in Applicant's analysis). Overall, the simulated exposures by Applicant are acceptable. The sample size in these covariate subgroups is large enough (>20 subjects) for assessing the impact of the noted covariates on exposure and the precision of population PK parameters appears to be reasonable to derive the predicted exposures.

2.1.8 Applicant's conclusion

GZR population PK was well described by a 2-compartment model with first order elimination, oral absorption described by two parallel first order pathways (a pathway with a food-dependent absorption

rate that, in HCV patients, is faster compared to the second pathway, and a secondary pathway with a slower absorption rate, particularly for doses less than or equal to 100 mg). Nonlinearity of GZR disposition was included in the model as dose-dependent clearance (CL/F), volume of distribution (V/F), and rate constants for distribution between the central and peripheral compartments (k_{23} and k_{32}).

AUC₀₋₂₄ exposure was increased in HCV-infected patients with cirrhosis and Child-Pugh B hepatic insufficiency by approximately 4-fold compared to non-cirrhotic patients. Use of the 100 mg dose is not recommended in Child-Pugh B patients.

Other factors that increased GZR exposure included Asian race, Hispanic ethnicity, female gender, compensated cirrhosis (Child-Pugh A), low body weight, and increased age. Each of these intrinsic factor effects was estimated to lead to less than a 2-fold increase in GZR AUC (with combinations estimated to lead to less than a 5-fold increase), and none of the covariates listed above are considered clinically important.

Reviewer's comment: The reviewer has assessed the Applicant's population PK analysis for GZR. The goodness-of-fit plots indicate that the model reasonably describes the data. In addition, the reviewer agrees that no clinically significant impact of age, sex, body weight, race, renal function was identified from the available data. Hepatic impairment results in increased GZR exposure, and the use of the 100 mg dose is not recommended in Child-Pugh B patients due to a 4-fold increase in exposure (predicted based on the population PK model; 5-fold increase observed in the dedicated study). Based upon Table 4, GZR AUC is estimated to be 20% higher in subject >65-year-old, 30% higher in females, 15% higher in 53-kg subject, 50% higher in Asians, and 70% higher in non-HCV-infected subjects with mild hepatic impairment (Child-Pugh A) compared to reference population (patients are treatment naïve, white, non-Hispanic, male, HCV GT1a, 50-year-old, 75-kg-weight, and eGFR of 95 mL/min/1.73 m²). The results are consistent with GZR/EBR label proposed by Applicant except with respect to labeling for elderly patients. In that situation, the Applicant was comparing the elderly exposures (67-year-olds) with younger patients (reference 30-year-old).

Based on the population PK results, GZR AUC was unchanged in dialysis-dependent subjects and 40% higher in non-dialysis-dependent subjects with severe renal impairment compared to GZR AUC in subjects without renal impairment. The results for non-dialysis-dependent subjects with severe renal impairment is similar to that provided by the Applicant from their dedicated renal impairment study, but much lower for dialysis-dependent subjects with severe renal impairment compared to the dedicated study's results (10% and 40% for dialysis-dependent and non-dialysis-dependent, respectively).

2.2 Population PK analysis for EBR

2.2.1 Objectives

1. Develop population PK models to adequately describe EBR PK in healthy subjects and HCV-infected patients
2. Explore the effects of select covariates on pertinent PK parameters to derive final predictive models for EBR.

3. Generate empirical Bayes' estimates of steady state EBR plasma PK summary measures (C_{min} , C_{max} and AUC_{0-24h}) for patients in Phase 2/3 studies

2.2.2 Trials included in the population PK model

The population PK model was developed from pooled analyses of six Phase 1 (8742-001, 8742-002, 8742-003, 8742-004, 8742-008, and 5172-035) and ten Phase 2 and 3 studies (5172-047, 5172-048, 7009-050, 5172-052, 5172-058, 5172-059, 5172-060, 5172-061, 5172-068, and 5172-074).

The population PK analysis was conducted by several steps. The Step-1 base structural model was developed based upon the Step-1 dataset including EBR plasma concentration data from the Phase 1 studies and 5172-035A. Afterwards, the Step-1 base model was updated based on the Step-2 dataset which included additional data from 5172-035B and 5172-047 to obtain the Step-2 base model. Finally, the Step-3 base model update was performed by refitting the Step-2 base model to the final dataset.

2.2.3 Base model

The base model consisted of a 2-compartment disposition model with lagged first order absorption. Parameter estimates for the Step-3 base model are provided in Table 5.

Table 5 EBR Population PK Parameter Estimates

Parameter	Estimate ± SE			Parameter	Estimate ± SE		
	Base	Full	Final		Base	Full	Final
Ka (1/hr)	0.679 ± 0.0318	0.751 ± 0.0359	0.750 ± 0.0352	Strong CYP/Pgp inhibitors on F1	NA	-0.107 ± 0.218	NA
V2/F (L)	440 ± 13	414 ± 19.6	415 ± 19.1	Moderate CYP/Pgp inhibitors on F1	NA	-0.0307 ± 0.0833	NA
CL/F (L/hr)	25.3 ± 0.27	30.1 ± 0.424	30.2 ± 0.424	Methadone on F1	NA	-0.306 ± 0.108	NA
V3/F (L)	253 ± 13.2	264 ± 12.6	264 ± 12.2	Strong CYP/Pgp inhibitors on CL/F	NA	-0.148 ± 0.166	NA
Q/F (L/hr)	23.8 ± 2.26	22.5 ± 2.02	22.5 ± 1.96	Moderate CYP/Pgp inhibitors on CL/F	NA	-0.204 ± 0.0627	-0.185 ± 0.038
F1 for formulations other than 100 mg potency capsules	1 fixed	1 fixed	1 fixed	Methadone on CL/F	NA	-0.45 ± 0.0861	-0.252 ± 0.0449
F1 for 100 mg potency capsule	0.298 ± 0.00859	0.302 ± 0.00863	0.302 ± 0.00864	ω^2_{F1}	0.447 ± 0.0395	0.461 ± 0.0417	0.462 ± 0.0418
ALAG1 (hr)	0.464 ± 0.000745	0.464 ± 0.000718	0.464 ± 0.000719	$\omega^2_{V2/F}$	0.0611 ± 0.00937	0.0687 ± 0.00832	0.0693 ± 0.00833
Age on Ka	NA	0.454 ± 0.0977	0.461 ± 0.0976	$\omega^2_{CL/F}$	0.0381 ± 0.00421	0.0179 ± 0.00338	0.018 ± 0.00339
WT on V2/F	NA	0.419 ± 0.0641	0.42 ± 0.064	$\omega^2_{Q/F}$	0.0838 ± 0.0321	0.087 ± 0.0337	0.0869 ± 0.0336
Female on V2/F	NA	-0.351 ± 0.0351	-0.354 ± 0.035	ω^2_{F1}	0.158 ± 0.00749	0.125 ± 0.00626	0.125 ± 0.00628
HCV on V2/F	NA	0.25 ± 0.0417	0.256 ± 0.0414	RV	0.352 ± 0.00221	0.351 ± 0.00221	0.351 ± 0.0022
Age on CL/F	NA	-0.17 ± 0.0255	-0.171 ± 0.0255	OFV	-10897.129	-11735.268	-11725.769
EGFR on CL/F	NA	0.0905 ± 0.0125	0.0902 ± 0.0125				
Female on CL/F	NA	-0.38 ± 0.0175	-0.382 ± 0.0174				
Black on CL/F	NA	-0.0833 ± 0.0204	-0.0839 ± 0.0204				
Asian on CL/F	NA	-0.138 ± 0.0218	-0.138 ± 0.0218				
Hispanic on CL/F	NA	-0.0923 ± 0.0209	-0.0926 ± 0.0209				
Treatment experienced with IFN on CL/F	NA	-0.054 ± 0.015	-0.0534 ± 0.0151				
RBV on CL/F	NA	0.0921 ± 0.0143	0.092 ± 0.0143				

Source: Applicant's EBR population PK report, Page 55, Table 17.

2.2.4 Covariate model development

After the identification of the Step-3 base model, a two-stage approach was employed for the development of PK covariate models based on the final dataset. The Stage-1 covariate models including Stage-1 full and final models were developed using covariates that were assumed to be recorded with high accuracy. The Stage-1 final covariate model was then expanded to include concomitant medications (other than RBV which was included in the Stage-1 covariate model development since it was a study treatment by design) for the Stage-2 full and final model development. The two-stage strategy was adopted to reduce the chances of spurious covariate effects in the final model, which may be caused by potentially spurious correlations between the less accurately measured concomitant medications and the other more accurately collected covariates.

The Stage-1 full model was fitted by simultaneously including all the covariates specified in Table 6 into the Step-3 base PK model.

Table 6 Covariates Evaluated in Stage-1 Full Model Development

Parameter	Covariates in the Stage-1 full model
k_a	Age
F	HIV co-infection, formulation (100 mg potency capsule vs other solid dosage forms) ^a , concomitant ribavirin (RBV)
CL/F	Age, sex, race, ethnicity, body weight (BW), estimated glomerular filtration rate (EGFR), dialysis, health status (healthy subjects vs. HCV-infected patients), HCV genotype (GT 1a, GT 1b, GT 3, GT 4, GT 6 and others), cirrhosis ^b , Child-Pugh (CP) classification (HCV-infected non CP-B, CP-B, and healthy (non CP-B)) ^b , HIV co-infection, treatment status (treatment naïve, treatment experienced with direct acting antiviral (DAA) therapy, experienced with pegylated interferon (Peg-IFN) and RBV based therapy), concomitant RBV
V2/F	Age, sex, race, BW, ethnicity, health status (healthy subjects vs. HCV-infected patients)

a: formulation was included as a structural covariate on F and retained throughout covariate model development.
b: In the actual modeling, cirrhosis and CP classification were combined to form a new categorical variable for liver function, which had three possible categories, i.e., non-cirrhotic (non-CP-B), cirrhotic and not CP-B, cirrhotic and CP-B.

Source: Applicant's EBR population PK report, Page 19, Table 1.

The Stage-1 final parsimonious covariate model chosen by multiple rounds of forward inclusion and backward elimination procedures contained 12 covariate parameters, including age on K_a , body weight, gender and health status on on V2/F, age, EGFR, gender, race (black and Asian races), ethnicity (Hispanic), treatment status (treatment experienced with Peg-IFN/RBV) and RBV coadministration on CL/F.

The Stage-1 final covariate model was expanded to a Stage-2 full covariate model by simultaneously including all the concomitant medications listed in Table 7.

Table 7 Covariates Included in Stage-2 Full Model

PK Parameter	Covariates included in the Stage-2 full model
F	Strong CYP/Pgp inhibitors, moderate CYP/Pgp inhibitors, methadone
CL/F	Strong CYP/Pgp inhibitors, moderate CYP/Pgp inhibitors, methadone

Source: Applicant's EBR population PK report, Page 20, Table 2.

Relative to the Stage-1 final covariate model, the Stage-2 final covariate model contained 2 additional covariate parameters accounting for moderate CYP/Pgp inhibitors and methadone on CL/F, respectively.

2.2.5 Final population PK model

The parameter estimates for the Stage-2 full and final covariate models based on the final dataset are presented in Table 5. The final model included a number of categorical and continuous covariates on select PK parameters including age on Ka; body weight, gender and health status on V2/F; and age, EGFR, gender, race (black and Asian races), ethnicity (Hispanic), treatment status (treatment experienced with Peg-IFN/RBV), RBV coadministration, moderate CYP/Pgp inhibitors coadministration and methadone coadministration on CL/F. The impact of these covariate effects on the population PK parameter values, along with the corresponding percent change relative to the parameter estimates at their respective reference levels are summarized in Table 8.

Table 8 Key EBR Population PK Parameter (CL/F) Values and Covariate Effects in the Stage-2 Final Covariate Model

PK Parameters and Baseline Covariates		Baseline Covariate Value	Estimate	Change from Typical (%)	Inter-individual Variability (%)
Typical CL/F, L/hr (Trt Naive, White Non-Hispanic Male, eGFR=95 mL/min/1.73 m ²)			30.2	--	13.4
Age	5 th Percentile	32 years	33.1	9.7	--
	95 th Percentile	68 years	29.1	-3.6	--
eGFR	Severe RI	17 mL/min/1.73 m ²	25.9	-14.4	--
	Moderate RI	45 mL/min/1.73 m ²	28.2	-6.5	--
	Mild RI	75 mL/min/1.73 m ²	29.6	-2.1	--
Sex	Female		20.6	-31.8	--
Race	Black		27.8	-8.0	--
	Asian		26.3	-12.9	--
Ethnicity	Hispanic		27.5	-8.8	--
Prior Treatment	Treatment Experienced with Peg-IFN/RBV		28.6	-5.2	--
Use of RBV			33.1	9.6	--
Use of Moderate CYP/Pgp Inhibitors			25.1	-16.9	--
Use of Methadone			23.5	-22.3	--

Source: Applicant's EBR population PK report, Page 73, Table 25.

Most notably, AUC_{0-24h} exposure was increased in women relative to men by 47%. Other intrinsic covariates (i.e., race, ethnicity, age, EGFR, body weight, health status and prior treatment status) had smaller effects on AUC_{0-24hr} than female gender.

2.2.6 Model assessment

The PPC procedure was used to evaluate the predicative performance of the Stage-2 final covariate model. To illustrate model predictions under different covariate conditions, representative PPC plots for the 50 mg dose stratified by health status and PK sampling day are provided in Figure 3, overlaying observed geometric means with their corresponding 90% prediction intervals (PI) from the PPC procedure.

These PPC plots suggested that the observed geometric means were generally contained within their corresponding 90% PI. For HCV patients, the final covariate model slightly over-predicted the observed GM (Figure3). However, note that the PPC evaluation was performed without accounting for parameter uncertainty. Thus, the 90% PIs are likely to be too narrow as a result of the large number of HCV patients included in some of these plots and would likely contain the observed GM if parameter uncertainty was taken into account. Overall, results from the PPC procedure confirmed that the Stage-2 final covariate model adequately predicts the central tendency in the observed data.

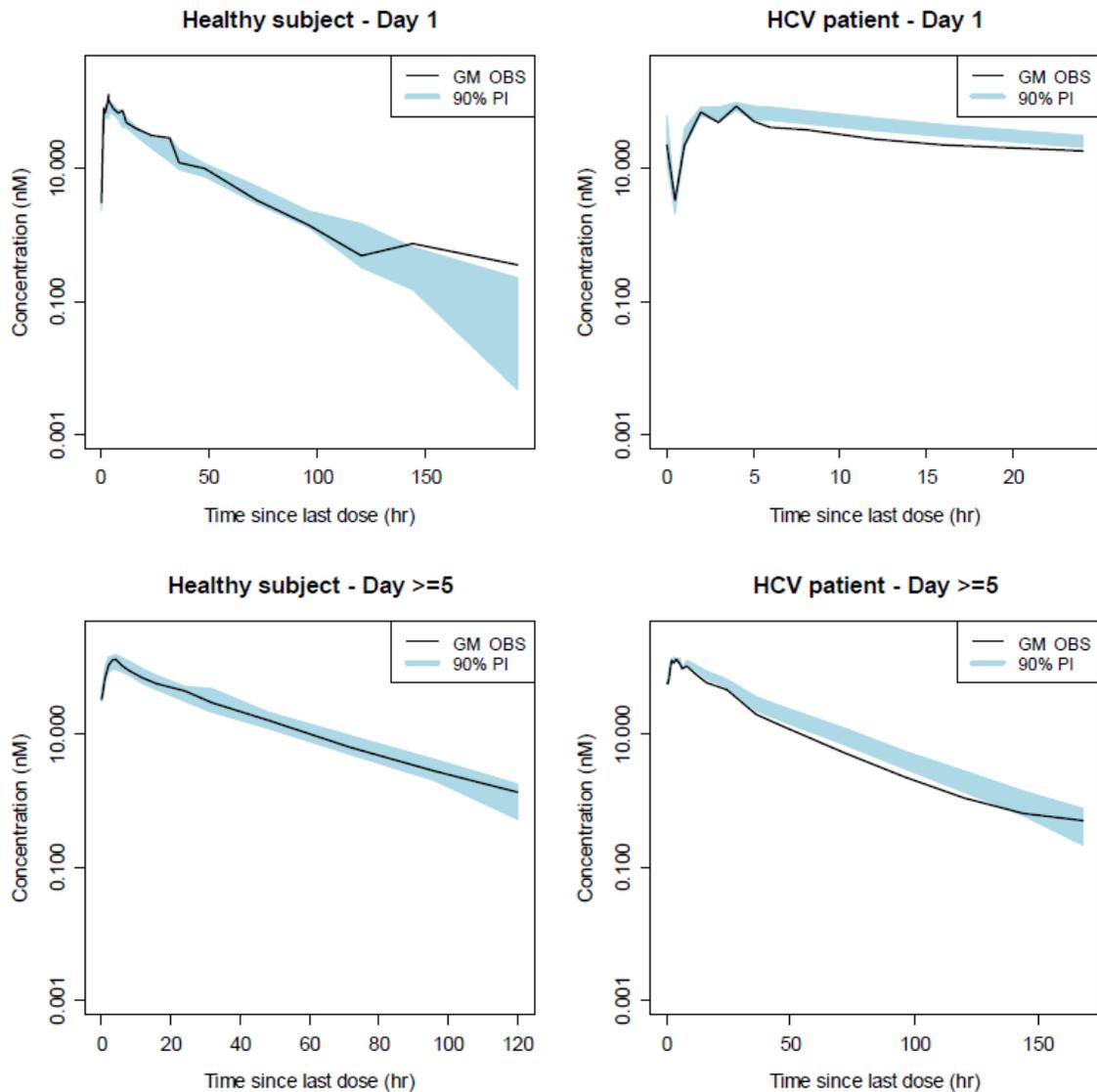


Figure 3 PPC Results Stratified by Health Status and PK Sampling Day

Source: Applicant's EBR population PK report, Page 54, Figure 8.

2.2.7 Simulation results using the working full PK model

Geometric means and 90% CI for steady state C_{min} , C_{max} and AUC_{0-24h} for the non-cirrhotic, non-CKD HCV patient population are summarized in Table 9. Note that unlike the simulations performed for typical individual subjects with specified covariate values, these geometric means reflect EBR exposures that could be expected in a typical HCV patient population averaging over the distribution of the observed covariates in this population.

Table 9 Geometric means and 90% CI of steady state C_{min} , C_{max} and AUC_{0-24h} in a non-cirrhotic non-CKD HCV patient population

PK measure	Steady state C _{min} (nM)	Steady state C _{max} (nM)	Steady state AUC _{0-24hr} (nM·hr)
GM (90% CI)	54.9 (53.6-56.2)	137.3 (133.4-139.6)	2181.3 (2128.8 – 2222.8)

Source: Applicant's EBR population PK report, Page 59, Table 18.

Reviewer's comment: Based on reviewer's independent analysis, the GM (90%) for steady state C_{min,ss}, C_{max,ss} and AUC_{0-24h} were 54.1 (52.9, 55.3) nM, 141.4 (138.8, 144.0) nM and 2204.9 (2162.6, 2248.1) nM·h, respectively, for 1071 HCV-infected, non-cirrhotic, non-CKD, non-Asian patients who receiving 50 mg QD dosing of EBR. The results are comparable to Applicant's values, although all Asians have been excluded from the dataset whereas only Japanese patients were excluded in Applicant's analysis. Overall, the simulated exposures by Applicant are acceptable. The sample size in these covariate subgroups is large enough (>20 subjects) for assessing the impact of the noted covariates on exposure and the precision of population PK parameters appears to be reasonable to derive the predicted exposures.

2.2.8 Applicant's conclusion

EBR population PK was well described by a 2-compartment model with lagged first order absorption. EBR exhibited linear PK following administration of 1 and 10 mg potency (b) (4) 50 mg potency tablets and FDC tablets for GZR/EBR (100 mg/50 mg) up to a 100 mg dose.

AUC_{0-24h} was increased in women relative to men by 47%. This magnitude of increase was not expected to be clinically relevant. Other intrinsic covariates (i.e., race, ethnicity, age, EGFR, body weight, health status and prior treatment status) had smaller effects on AUC_{0-24h} than female gender. None were considered clinically relevant.

Extrinsic covariates including coadministration of moderate CYP/Pgp inhibitors, methadone and RBV were associated with differences in AUC_{0-24h} of less than 30%. These changes were not considered clinically relevant.

Subpopulations of female patients and Asian, female patients resulted in approximately 45% and 69% increases in AUC_{0-24h} relative to male and white male reference subpopulations, respectively. All other subpopulations evaluated led to < 30% changes in AUC_{0-24h}. These changes were not considered clinically relevant.

Reviewer's comment: The reviewer has assessed the Applicant's population PK analysis for EBR. The goodness-of-fit plots indicate that the model reasonably describes the data. As no clinical relevant difference for PK would be expected based on age, sex, body weight, race, renal function, hepatic function, dose adjustment is not necessary for EBR.

Based on Table 8, EBR AUC is estimated to be 5% higher in subject>65%-year-old, 50% higher in females, and 15% higher in Asians compared to reference population, in which patient are considered as treatment naïve, white, non-Hispanic, male, and eGFR of 95 mL/min/1.73 m². The results are consistent

Based on the population PK result, EBR AUC was 28% higher in dialysis-dependent subjects and 52% higher in non-dialysis-dependent subjects with severe renal impairment compared to EBR AUC in subjects without severe renal impairment, the results are similar to those from Applicant's analysis (25% and 46% for dialysis-dependent and non-dialysis-dependent, respectively)

2.3 Exposure-response analyses for efficacy

2.3.1 Objectives

1. Characterize the exposure-response relationship for GZR/EBR and SVR12.
2. Provide information to support characterization of the therapeutic window for GZR/EBR by defining a clinically relevant change in exposure (lower bound for clinical significance).

2.3.2 Trials included in the exposure-response analyses

Table 10, Table 11, and Table 12 contain a brief overview of the Phase 2 and 3 studies for GZR and EBR included in this analysis.

Table 10 Studies of GZR with HCV Medicines Other Than EBR

Trial	GT	N	Population	Regimens Evaluated
P038	1	87	TN non-cirrhotic	GZR 25 mg, 50 mg, or 100 mg QD with PR x 12 weeks
P039	1	26	TN non-cirrhotic	GZR 100 mg QD with RBV x 12 or 24 weeks (based on TW4 responses) GZR 100 mg QD with RBV x 24 weeks
†Only data from the GZR treatment arms were included in the analysis.				

Source: Applicant's exposure-response analysis for efficacy report, Page 12, Table 1.

Table 11 Phase 2 Studies of GZR + EBR

Trial	GT	N	Population	Regimens Evaluated
P035A	1	65	TN non-cirrhotic	GZR 100 mg + EBR 20 mg + RBV x 12 weeks GZR 100 mg + EBR 50 mg ± RBV x 12 weeks
P035B	1	217	TN ± cirrhosis	GZR 100 mg + EBR 50 mg ± RBV x 8-18 weeks
	1	130	Prior null responder ± cirrhosis	GZR 100 mg + EBR 50 mg ± RBV x 12-18 weeks
	1	59	HIV co-infected TN non-cirrhotic	GZR 100 mg + EBR 50 mg ± RBV x 12 weeks
P035C	1b	61	TN non-cirrhotic	GZR 100 mg + EBR 50 mg ± RBV x 8 weeks
P047AB	1,4, 6	34	TN non-cirrhotic	GZR 100 mg + EBR 50 mg ± RBV x 12 weeks
P048	1	79	Prior direct-acting antiviral agents (DAA) failures ± cirrhosis	GZR/EBR 100 mg/50 mg + RBV x 12 weeks

Source: Applicant's exposure-response analysis for efficacy report, Page 12, Table 2.

Table 12 Phase 3 Trials of GZR + EBR

Trial	GT	N	Population	Regimens Evaluated
P052 [†]	1	122	CKD Stages 4-5, including dialysis ± cirrhosis	GZR/EBR 100 mg/50 mg x12 weeks - immediate treatment
P060 [†]	1, 4, 6	316	TN ± cirrhosis	GZR/EBR 100 mg/50 mg x12 weeks - immediate treatment
P061	1, 4, 6	218	HIV co-infected (TN, non-cirrhotic and cirrhotic)	GZR/EBR 100 mg/50 mg x12 weeks
P068	1, 4, 6	420	Treatment-experienced ± cirrhosis	GZR/EBR 100 mg/50 mg ± RBV x12 weeks GZR/EBR 100 mg/50 mg ± RBV x16 weeks

[†]Only data from the immediate treatment arms were included in the analysis.

Source: Applicant's exposure-response analysis for efficacy report, Page 13, Table 3.

The scatter plots of SVR12 vs GZR/EBR AUC_{0-24h} are presented in Figure 4.

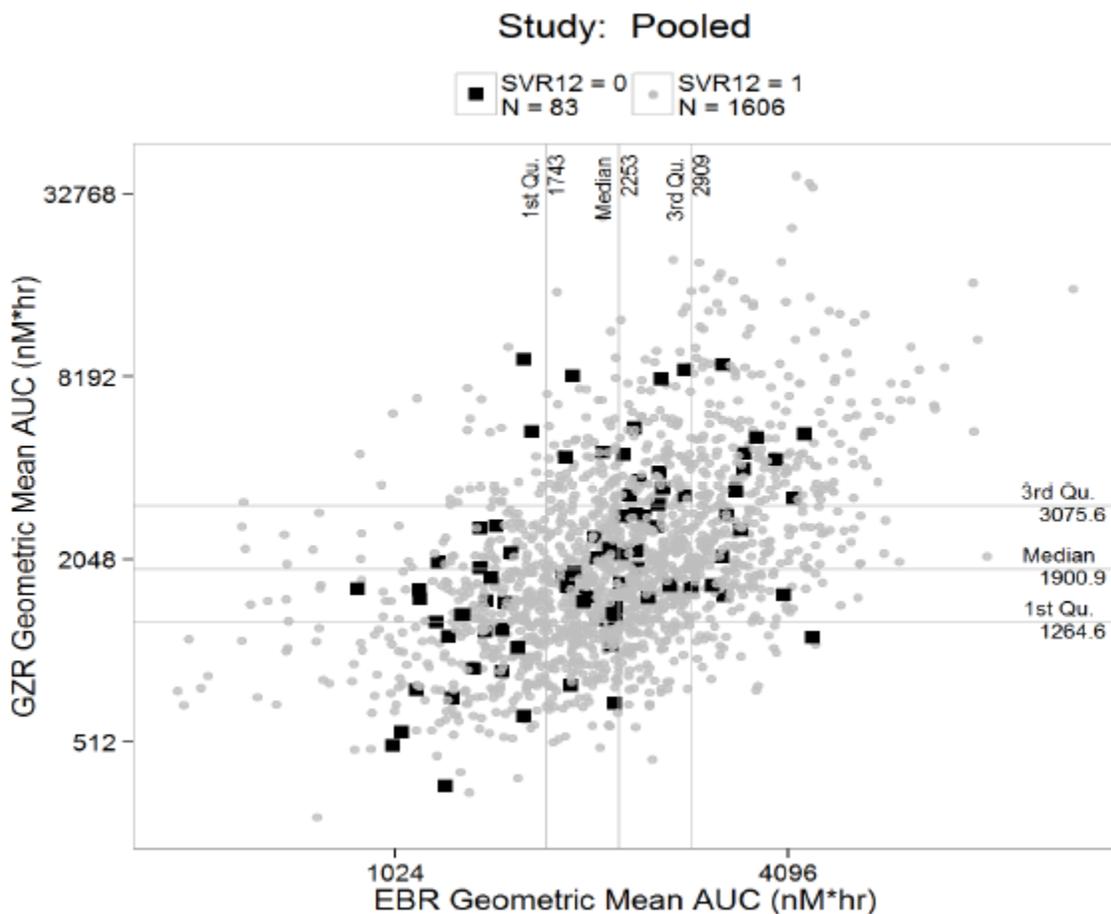


Figure 4 Scatter Plot of SVR12 vs GZR/EBR Steady State PK Parameters

Source: Applicant's exposure-response analysis for efficacy report, Page 26, Figure 3.

2.3.3 Base model

Table 13 summarizes the BIC values of base structural models, where lower BIC values indicate improved fit. Based on the BIC values, the linear logistic model with log (PK) as the predictor (log refers to natural log transformation throughout this document) was chosen as the best base structural model for AUC_{0-24h}.

Table 13 Base Structural Model Selection Results

GZR/EBR PK Parameter	Base Structural Model	BIC
AUC _{0-24hr}	Linear logistic on PK	693.4
	Linear logistic on log(PK)	685.2
	E _{max} logistic	700.8

Source: Applicant's exposure-response analysis for efficacy report, Page 33, Table 10.

2.3.4 Final model

Covariates of baseline NS5A resistance (No/Yes), gender, HCV genotype, co-administration with ribavirin (Yes/No), CKD, prior treatment history, GZR treatment duration, and baseline HCV RNA were found to be the potential covariates influencing the PK/SVR12 relationship. GZR treatment duration, baseline HCV RNA and baseline NS5A resistance (No/Yes) were retained in the final model based on the backward elimination procedure. The final models are in the following format for both PK parameters:

(b) (4)

where EBRPK and GZRPK refers to EBR and GZR steady state GZR AUC_{0-24h}, NS5A refers to baseline NS5A resistance, log₁₀HCV RNA refers to baseline log₁₀ HCV RNA, Duration refers to GZR treatment duration. The parameter estimates are displayed in Table 14.

Table 14 EBR/GZR Exposure-SVR12 Logistic Regression Model Effect Estimate

PK parameter	Model Parameter	Parameter Estimate	Standard Error	P-value	95% CI
AUC ₀₋₂₄	Intercept	1.248	2.930	0.6701	(-4.494, 6.991)
	EBR ln(AUC ₀₋₂₄)	1.034	0.352	0.0033	(0.344, 1.724)
	GZR ln(AUC ₀₋₂₄)	-0.280	0.224	0.2105	(-0.718, 0.158)
	Treatment Duration of GZR	0.037	0.009	0.0001	(0.019, 0.055)
	Baseline Log ₁₀ HCV RNA	-1.168	0.267	0.0000	(-1.691, -0.645)
	Baseline NS5A resistance(No)	1.294	0.142	0.0000	(1.016, 1.572)

Source: Applicant's exposure-response analysis for efficacy report, Page 35, Table 12.

In the final model, EBR AUC was a significant predictor (p=0.0033) indicating increasing probability of SVR with increasing EBR AUC. In that model, GZR AUC was not significant (p=0.2105). Figure 5 shows the predicted SVR12 probabilities with 95% confidence limits versus GZR/EBR AUC0-24h on log scale by

baseline NS5A resistance. The SVR12 predicted probability curve in Figure 5 is calculated by fixing at 50 mg EBR or 100 mg GZR AUC_{0-24h} geometric mean, mean baseline Log₁₀ HCV RNA and at 12 week treatment duration. In patients without baseline NS5A resistance, the SVR rate is predicted to be high across the AUC range in the dataset, with a slight fall at exposure associated with the lowest decile of exposure at 50 mg EBR. Overall, the SVR response curve is shifted lower across the EBR exposure range for patients with baseline NS5A resistance and exposure-response is more evident for these patients. The exposure-response curves for GZR have a slope trend towards lower SVR12 at higher AUC, but with wide uncertainty that encompasses a flat relationship, consistent with the non-significant findings for GZR AUC.

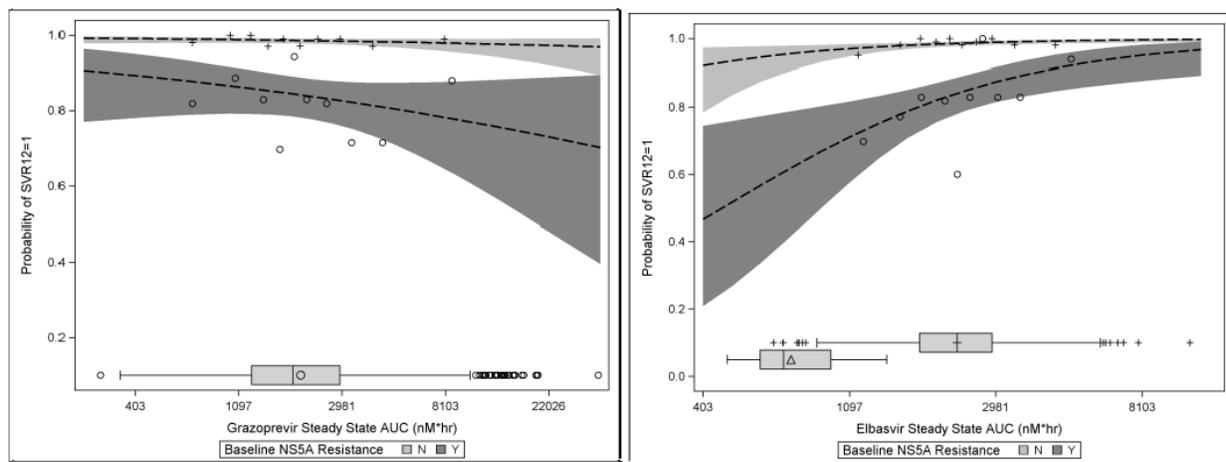


Figure 5 Predicted SVR12 versus GZR (left) and EBR (right) AUC_{0-24h} based on Observations from Phase 2 and Phase 3 Studies.

Cross and circles denote subjects without and with baseline NS5A resistance, respectively. Boxplots at the bottom of each figure depict exposures for 100 mg GZR (left) and 20 mg (triangle, right) and 50 mg (cross, right) EBR

Source: Applicant's exposure-response analysis for efficacy report, Page 36, Figure 6.

2.3.5 Model prediction

Table 15, Table 16, and Table 17 present the predicted SVR12 occurrence probability for treatment durations of 8 weeks, 12 weeks, and 16 weeks, respectively. Patients with baseline NS5A resistance have lower SVR12 occurrence probability compared to patients without NS5A resistance. In addition, the SVR12 occurrence probability increases with increasing treatment duration.

Table 15 SVR12 Occurrence Predicted Probability -Treatment Duration 8 weeks

PK parameter	% of GM EBR PK at 50 mg [†]	% of GM GZR PK at 100 mg [†]	Baseline NS5A resistance	Predicted SVR12 probability from Final Model (95% CI)
AUC	100	100	N	0.961 (0.927, 0.980)
		50	N	0.968 (0.936, 0.984)
		40	N	0.970 (0.937, 0.986)
	50	100	N	0.924 (0.852, 0.962)
		50	N	0.936 (0.880, 0.967)
		40	N	0.940 (0.885, 0.970)
AUC	100	100	Y	0.651 (0.488, 0.784)
		50	Y	0.693 (0.521, 0.825)
		40	Y	0.707 (0.526, 0.840)
	50	100	Y	0.476 (0.294, 0.665)
		50	Y	0.525 (0.343, 0.700)
		40	Y	0.540 (0.353, 0.717)

Source: Applicant's exposure-response analysis for efficacy report, Page 38, Table 13.

Table 16 SVR12 Occurrence Predicted Probability -Treatment Duration 12 weeks

PK parameter	% of GM EBR PK at 50 mg [†]	% of GM GZR PK at 100 mg [†]	Baseline NS5A resistance	Predicted SVR12 probability from Final Model (95% CI)
AUC	100	100	N	0.986 (0.978, 0.991)
		50	N	0.988 (0.980, 0.993)
		40	N	0.989 (0.980, 0.994)
	50	100	N	0.972 (0.951, 0.984)
		50	N	0.976 (0.960, 0.986)
		40	N	0.978 (0.961, 0.987)
AUC	100	100	Y	0.840 (0.781, 0.886)
		50	Y	0.865 (0.791, 0.915)
		40	Y	0.872 (0.790, 0.925)
	50	100	Y	0.720 (0.592, 0.820)
		50	Y	0.757 (0.641, 0.845)
		40	Y	0.769 (0.648, 0.857)

Source: Applicant's exposure-response analysis for efficacy report, Page 39, Table 14.

Table 17 SVR12 Occurrence Predicted Probability -Treatment Duration 16 weeks

PK parameter	% of GM EBR PK at 50 mg [†]	% of GM GZR PK at 100 mg [‡]	Baseline NS5A resistance	Predicted SVR12 probability from Final Model (95% CI)
AUC	100	100	N	0.995 (0.990, 0.998)
		50	N	0.996 (0.991, 0.998)
		40	N	0.996 (0.991, 0.998)
	50	100	N	0.990 (0.977, 0.995)
		50	N	0.992 (0.981, 0.996)
		40	N	0.992 (0.982, 0.996)
AUC	100	100	Y	0.937 (0.888, 0.965)
		50	Y	0.947 (0.896, 0.974)
		40	Y	0.950 (0.897, 0.977)
	50	100	Y	0.879 (0.772, 0.939)
		50	Y	0.898 (0.803, 0.950)
		40	Y	0.904 (0.808, 0.954)

Source: Applicant's exposure-response analysis for efficacy report, Page 40, Table 15.

Results from final model indicate that reducing the exposures associated with 100 mg GZR by 60% results in generally small decreases in SVR12. Reducing the exposures associated with 50 mg EBR by 50% also results in generally small decreases in SVR12, though subjects treated for shorter durations (less than 12 weeks) and with baseline resistance to NS5A inhibitors may be more sensitive to reductions in EBR exposure.

2.3.6 Applicant's conclusion

In a dataset predominantly composed of data from 100 mg GZR and 50 mg EBR, EBR exposure is better correlated with SVR12 compared to GZR exposure.

Other important factors in determining SVR12 include baseline resistance to NS5A inhibitors, baseline HCV RNA, and treatment duration. In general, SVR12 rates were lower for short treatment durations (e.g., 8 weeks), higher baseline log₁₀ HCV RNA, and in patients who had baseline resistance to NS5A inhibitors.

Exposures associated with the combination of 100 mg QD GZR and 50 mg QD EBR are generally on the maximal response plateau of the exposure-response curve.

Reducing the exposures associated with 100 mg GZR by 60% results in generally small decreases in SVR12.

Reviewer's comment: An exposure-response relationship for efficacy was observed for EBR. Treatment duration, baseline log₁₀ HCV RNA and baseline resistance to NS5A inhibitors had significant impacts on response rate. For the clinical dose of EBR 50 mg, SVR12 was uniformly high in patients who do not have baseline NS5A resistance and approximately 80% in patients who do have baseline NS5A resistance without regard to the degree of resistance, which supports the proposed dose of 50 mg in the fixed dose combination. No exposure-response relationship for efficacy was observed for GZR, consistent with

results of a phase 2 study showing that GZR 100 mg reaches the plateau for efficacy. The reviewer has verified the Applicant's analyses.

2.4 Exposure-response analyses for safety

2.4.1 Objectives

1. Characterize the exposure-response relationship for GZR effects based on liver enzyme tests (Late ALT/AST Elevation Events).
2. Provide information to support characterization of the therapeutic window for GZR by defining a clinically relevant change in exposure (upper bound for clinical significance).

2.4.2 Trials included in the exposure-response analyses

Table 18, Table 19 and Table 20 contain a brief overview of the 13 Phase 2 and 3 studies/arms included in this analysis.

Table 18 Phase 2 Studies of GZR with HCV Medicines Other Than EBR

Trial	GT	N	Population	Regimens Evaluated
P003 [†]	1	266	Treatment-naïve (TN) non-cirrhotic	GZR 100, 200, 400, 800 mg QD with PR x 12 weeks, followed by 12 or 36 weeks of PR (based on TW4 responses)
P003-6	1	36	TN cirrhotic	GZR 100 mg QD with PR x 12 weeks, followed by 12 or 36 weeks of PR (based on TW4 responses)
P038	1	87	TN non-cirrhotic	GZR 25 mg, 50 mg, or 100 mg QD with PR x 12 weeks
P039	1	26	TN non-cirrhotic	GZR 100 mg QD with RBV x 12 or 24 weeks (based on TW4 responses) GZR 100 mg QD with RBV x 24 weeks
P047B	2	30	TN non-cirrhotic	GZR 100 mg + RBV x 12 weeks

[†]Only data from the GZR treatment arms were included in the analysis.

Source: Applicant's exposure-response analysis for safety report, Page 12, Table 1.

Table 19 Phase 2 Studies of GZR + EBR

Trial	GT	N	Population	Regimens Evaluated
P035A	1	65	TN non-cirrhotic	GZR 100 mg + EBR 20 mg + RBV x 12 weeks GZR 100 mg + EBR 50 mg ± RBV x 12 weeks
P035B	1	217	TN ± cirrhosis	GZR 100 mg + EBR 50 mg ± RBV x 8-18 weeks
	1	130	Prior null responder ± cirrhosis	GZR 100 mg + EBR 50 mg ± RBV x 12-18 weeks
	1	59	HIV co-infected TN non-cirrhotic	GZR 100 mg + EBR 50 mg ± RBV x 12 weeks
P035C	1b	61	TN non-cirrhotic	GZR 100 mg + EBR 50 mg ± RBV x 8 weeks
P035D	3	41	TN non-cirrhotic	GZR 100 mg + EBR 50 mg + RBV x 12-18 weeks
P047AB	2,4,5,6	68	TN non-cirrhotic	GZR 100 mg + EBR 50 mg ± RBV x 12 weeks
P048	1	79	Prior direct-acting antiviral agents (DAA) failures ± cirrhosis	GZR 100 mg + EBR 50 mg + RBV x 12 weeks
P058 Part 1 [†]	1	62	Non-cirrhotic Japanese	GZR 50 mg + EBR 50 mg x 12 weeks GZR 100 mg + EBR 50 mg x 12 weeks
P059A	1	40	Child-Pugh B (CP-B) cirrhotic; Non-cirrhotic	GZR 50 mg + EBR 50 mg x 12 weeks GZR 100 mg + EBR 50 mg x 12 weeks
P074 [‡]	1,3	62	TN ± cirrhosis	GZR 100 mg + EBR 50 mg + sofosbuvir x 8-12 weeks

[†]Only data from Part 1 were included in the analysis.
[‡]Data from the 4- and 6- week treatment arms were excluded from the analysis.

Source: Applicant's exposure-response analysis for safety report, Page 13, Table 2.

Table 20 Phase 3 Studies of GZR + EBR

Trial	GT	N	Population	Regimens Evaluated
P052 [†]	1	122	CKD Stages 4-5, including dialysis ± cirrhosis	GZR/EBR 100 mg/50 mg x12 weeks - immediate treatment
P060 [†]	1, 4, 6	316	TN ± cirrhosis	GZR/EBR 100 mg/50 mg x12 weeks - immediate treatment
P061	1, 4, 6	218	HIV co-infected, TN, ± cirrhosis	GZR/EBR 100 mg/50 mg x12 weeks
P068	1, 4, 6	420	Treatment-experienced ± cirrhosis	GZR/EBR 100 mg/50 mg ± RBV x12 weeks GZR/EBR 100 mg/50 mg ± RBV x16 weeks

[†]Only data from the immediate treatment arms were included in the analysis.

Source: Applicant's exposure-response analysis for safety report, Page 13, Table 3.

2.4.3 Base model

Table 21 summarizes the BIC values of base structural models. Based on the BIC values, the linear logistic regression model with log (PK) as the predictor was chosen as the best base model structure for all three GZR PK parameters.

Table 21 Base Structural Model Selection Results

GZR PK Parameter	Base Structural Model	BIC
AUC0-24	Linear logistic on PK	239.3
	Linear logistic on log (PK)	221.3
	E _{max} logistic	230.6

Source: Applicant’s exposure-response analysis for safety report, Page 37, Table 11.

2.4.4 Final model

Initially, age, gender, GZR treatment duration, baseline eGFR, HIV co-infection and Metavir fibrosis score were found to be the potential covariates influencing the PK/Late ALT/AST Elevation Events relationship. After backward elimination procedure, no covariate was retained in the final model based on the backward elimination procedure at the pre-specified alpha=0.001 level, indicating that none of these covariates significantly affect the risk of Late ALT/AST Elevation Events (at alpha=0.001 level) after accounting for GZR PK parameter values. Therefore, the final models were in the following format for all three PK parameters:

(b) (4)

where PK refers to steady state GZR AUC0-24, C_{max} or C₂.

The parameter estimates are available in Table 22. Figure 6 plot the predicted Late ALT/AST Elevation Event probabilities with 95% confidence limits versus GZR AUC_{0-24h} on log scale.

Table 22 Parameter Estimates of the Logistic Regression Models

GZR PK Parameter Based Model	Model Parameter	Parameter Estimate	95% CI	p-value
AUC0-24	b0 – Intercept	-11.993	(-14.256, -9.729)	<.0001
	b1 - Coefficient for log(AUC)	0.883	(0.644, 1.122)	<.0001

Source: Applicant’s exposure-response analysis for safety report, Page 41, Table 14.

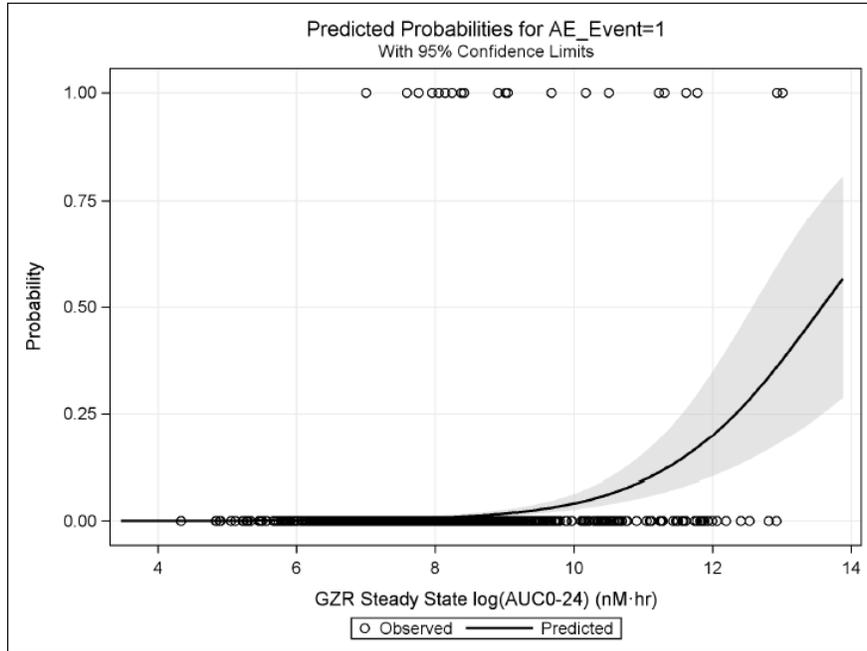


Figure 6 GZR Exposure – Safety Logistic Regression Plot: Late ALT/AST Elevation Event Probability versus Individual GZR Steady State AUC_{0-24}

Source: Applicant’s exposure-response analysis for safety report, Page 42, Figure 5.

2.4.5 Model prediction

Figure 7 display the plots of the estimated population Late ALT/AST Elevation Event rate versus fold change over GZR exposures at the 100 mg dose in the reference population (non-cirrhotic, non-severe CKD and non-Asian HCV-infected patients), together with the observed event rates at various doses, for AUC_{0-24h} . The results suggest that a 5-fold increase in GZR exposures relative to the reference population at 100 mg corresponds to a predicted population Late ALT/AST Elevation Event rate of ~2%, for AUC_{0-24h} . In addition, there is a predicted population Late ALT/AST Elevation Event rate of 5% when the population geometric means (GMs) of GZR AUC_{0-24h} reaches ~ 23743 nM·h. These geometric mean exposures represent GZR exposure margins of ~13 to 14 fold above geometric mean exposures observed with 100 mg GZR in the reference population.

At the 100 mg dose, two populations were identified. One is the reference population and the second, identified as “100 mg other” group, refers to patients with selected baseline characteristics (e.g. cirrhotic, or severe CKD, or Asian subjects) that are anticipated to have higher GZR exposure relative to the reference population. In general, the predicted event rates are consistent with the observed rates.

The observed and predicted event rates of Late ALT/AST Elevation Events in selected subpopulations at a 100 mg GZR dose are summarized in Table 23. The subpopulations are patients with intrinsic factors that are expected to be associated with increased GZR exposures, i.e., Hispanic, or Asian, or female, or elderly, or low body weight patients, or patients with severe CKD, or cirrhosis. Patients with a

combination of the two intrinsic factors that are associated with highest GZR PK increase were also evaluated (Asian, cirrhotic, non CP -B patients). The predicted event rates are in general consistent with the observed rates, with predicted rate higher than the observed rates in some subpopulations and lower in some others, but in all cases the predicted incident rate was < 2%.

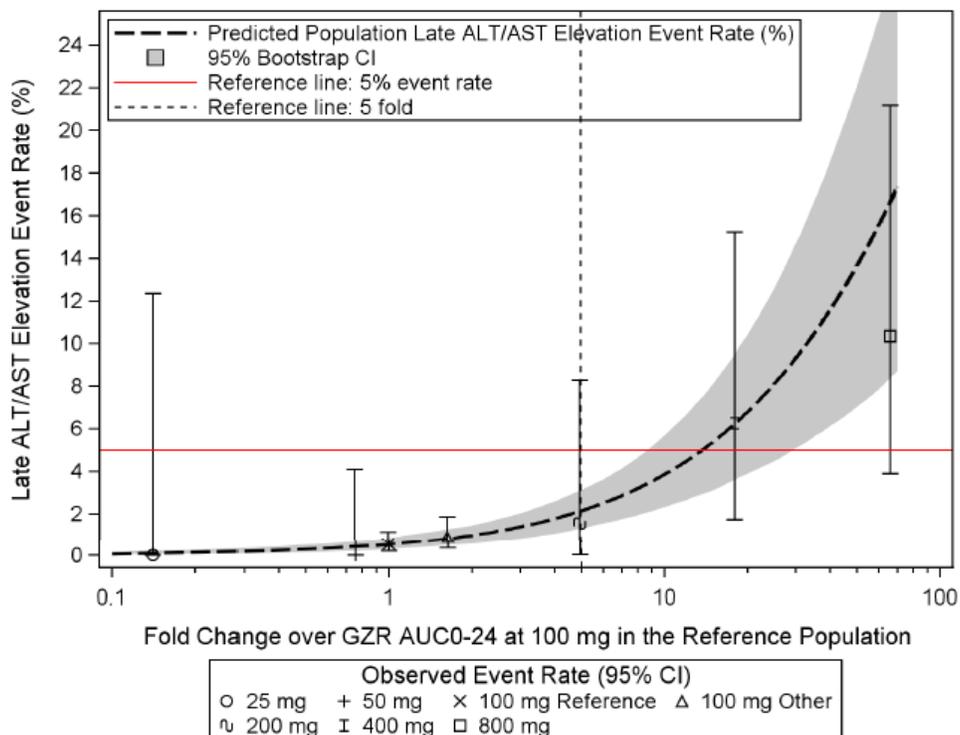


Figure 7 Predicted Late ALT/AST Elevation Event Rate versus Fold Change over GZR AUC₀₋₂₄ at steady state

A Fold-Change of 1 Reflects Exposures for GZR 100 mg QD in the Reference Population. This reference population included non-cirrhotic, non-severe CKD, non-Asian HCV-infected patients in the 100 mg dosing arms of the Phase 2/3 studies/arms included in this analysis.

Source: Applicant’s exposure-response analysis for safety report, Page 47, Figure 8.

Table 23 Observed and Predicted Population Late ALT/AST Elevation Event Rate at GZR 100 mg in Selected Subpopulations – AUC₀₋₂₄ Based Results

Population [†]	GZR AUC Values in Patients with PK Data			Observed Event Rate in Patients with Safety Data			Predicted Rate (%; 95% CI)
	N (PK) [‡]	GM AUC ₀₋₂₄ (nM·hr)	GMR [§]	N (Event)	N (Safety) [¶]	Rate (%; 95% CI)	
Hispanic or Latino	117	1820	1.06	0	113	0.0 (0.0, 3.2)	0.6 (0.3, 0.9)
Low body weight (Weight ≤ 53 kg)	53	1899	1.10	0	53	0.0 (0.0, 6.7)	0.6 (0.3, 0.9)
Female	505	2018	1.17	6	502	1.2 (0.4, 2.6)	0.6 (0.3, 0.9)
Severe CKD	104	2404	1.40	0	108	0.0 (0.0, 3.4)	0.7 (0.4, 1.1)
Elderly (Age ≥ 65 years)	100	2454	1.43	2	99	2.0 (0.2, 7.1)	0.7 (0.4, 1.1)
Asian	130	2499	1.45	3	130	2.3 (0.5, 6.6)	0.7 (0.4, 1.1)
Cirrhotic, non-CP-B	486	2980	1.73	3	480	0.6 (0.1, 1.8)	0.9 (0.5, 1.3)
Asian, cirrhotic, non-CP-B	38	3439	2.00	1	38	2.6 (0.1, 13.8)	1.0 (0.5, 1.5)

Source: Applicant's exposure-response analysis for safety report, Page 53, Figure 20.

2.4.6 Applicant's conclusion

Steady state AUC_{0-24h} was well-correlated with Late ALT/AST Elevation Events,

The predicted rate of Late ALT/AST Elevation Events in the reference population (noncirrhotic, non-severe CKD, non-Asian HCV-infected patients) at a 100 mg GZR dose is approximately 0.5%, which is consistent with the observed rate.

The predicted rate of Late ALT/AST Elevation Events in other examined subpopulations that have higher GZR exposures relative to the reference population (e.g., female subjects, elderly subjects, subjects who are both Asian and cirrhotic) at a 100 mg GZR dose is < 2%.

The predicted rate of Late ALT/AST Elevation Events associated with a 5-fold increase in GZR steady state AUC_{0-24h} relative to the reference population at a 100 mg GZR dose is ~ 2%.

Reviewer's comment: The exposure-response relationship for safety was only identified for GZR. No additional covariate was identified as predictors of Late ALT/AST Elevation. Based on reviewer's independent analysis, 100 mg GZR was predicted to result in 0.5% (90% PI: [0.2%, 1.1%]) event rate of Late ALT/AST Elevation and 200 mg GZR was predicted to result in 1.5% (90% PI: [1.0%, 3.7%]) event rate (Figure 8). The results are consistent with those of Applicant's analyses. However, due to the wide range of exposure, the safety event rate for the patients receiving 200 mg dosing of GZR could be even higher than 3%. Thus, the result of exposure-safety analysis supports the dose of 100 mg for GZR that provides a clinical acceptable safety margin for late ALT/AST elevation. Overall, the exposure-response relationship between exposure and late ALT/AST elevation was well described by the logistic model. The prediction is comparable to observation. The exposure-safety analysis appears to be reasonable from pharmacometrics perspective.

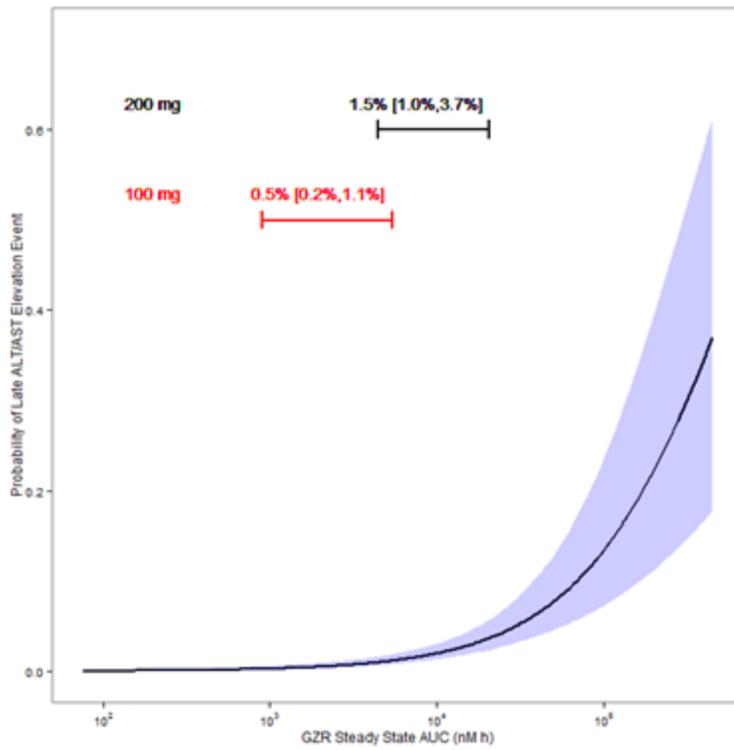


Figure 8 Predicted Late ALT/AST Elevation Event Rate versus GZR steady state AUC based on data from Applicant’s exposure-safety analysis

Source: Reviewer’s independent analysis

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/s/

SU-YOUNG CHOI
10/27/2015

STANLEY AU
10/27/2015

Reviewer for 5172-046, 8742-013, 5172-030, 8742-010, 8742-021, 8742-023, and 5172-070 trials:
concur with these reviews.

LUNING ZHUANG
10/27/2015

JEFFRY FLORIAN
10/27/2015

SHIRLEY K SEO
10/28/2015