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ARTICLE

No Pharmacokinetic Interaction Between the Hepatitis C Virus Inhibitors Elbasvir/Grazoprevir and Famotidine or Pantoprazole

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Use of agents to suppress gastric acid secretion is common among patients with hepatitis C virus (HCV) infection. The aims of this open-label, three-period, fixed-sequence study were to evaluate the effect of famotidine and pantoprazole on the pharmacokinetics and safety of elbasvir/grazoprevir fixed-dose combination (FDC) in 16 healthy subjects. Elbasvir and grazoprevir each exhibited similar pharmacokinetics following single-dose administration of elbasvir/grazoprevir with or without famotidine or pantoprazole. Geometric mean ratios (GMRs) of grazoprevir AUC(0,∞), C_{max}, and C_{24} (elbasvir/grazoprevir + famotidine or elbasvir/grazoprevir + pantoprazole vs. elbasvir/grazoprevir) ranged from 0.89–1.17. Similarly, GMRs of elbasvir AUC(0,∞), C_{max}, and C_{24} (elbasvir/grazoprevir + famotidine or elbasvir/grazoprevir + pantoprazole vs. elbasvir/grazoprevir) ranged from 1.02–1.11. These results indicate that gastric acid-reducing agents do not modify the pharmacokinetics of elbasvir or grazoprevir in a clinically relevant manner and may be coadministered with elbasvir/grazoprevir in HCV-infected patients without restriction.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
✔ PPIs and histamine H2 receptor antagonists can attenuate the absorption, and, hence, affect the bioavailability, of certain treatments for HCV.

WHAT QUESTION DID THIS STUDY ADDRESS?
✔ To evaluate the effect of famotidine (an H2 receptor antagonist) and pantoprazole (a PPI) on the PK profile of EBR and GZR.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
✔ Gastric acid-reducing agents do not modify the PKs of EBR or GZR in a clinically relevant manner.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE
✔ The EBR/GZR FDC is a treatment option for HCV-infected patients receiving gastric-acid reducing agents who are restricted in terms of their other treatment choices.

Chronic hepatitis C virus (HCV) infection is a global public health challenge affecting up to 170 million people worldwide, with up to 4 million new infections annually.[1] People with chronic HCV infection are at risk of developing liver disease, including cirrhosis and liver cancer, and efficacious treatments to cure HCV infection are needed to reduce the burden of disease.

Major advances have been made in the treatment of chronic HCV infection, with several new drug classes now available that have largely replaced interferon-based treatments that were associated with limited efficacy and poor tolerability.[2] These agents directly interrupt the viral replication lifecycle, and as a result cause dramatic reductions in HCV replication and significant improvements in cure rates compared with interferon-based therapies. The fixed-dose combination (FDC) of elbasvir (EBR; MK-8742), a potent once-daily HCV NS5A protein inhibitor, and grazoprevir (GZR; MK-5172), a potent once-daily inhibitor of the HCV NS3/4A protease, is one such interferon-free treatment for chronic HCV infection. EBR/GZR is administered once daily without regard to food intake.[3–5] Phase III studies of EBR/GZR treatment in patients with HCV genotype 1 or 4 infection have consistently reported high rates of sustained virologic response in diverse populations of patients, including treatment-naive[6] and treatment-experienced[7,8] patients, those with human immunodeficiency virus coinfection,[9] and those with stage 4/5 chronic kidney disease.[10] The EBR/GZR FDC is approved for marketing by the US Food and Drug Administration,[11] and has also received approval from various health authorities around the world.[12,13]

Patients with HCV infection frequently present with multiple comorbidities requiring alternative therapies; therefore, a clear understanding of the drug-drug interaction profiles of these new agents is important. In particular, the use of agents to suppress gastric acid secretion is common among patients with HCV infection who often have concomitant

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erosive esophagitis and/or gastroesophageal reflux disease, which are especially common in patients with HCV-related liver cirrhosis. Medications that increase gastric pH, such as proton-pump inhibitors (PPIs) and histamine H2 receptor antagonists, can affect the bioavailability of concomitantly administered drugs with pH-dependent solubility.[14] EBR is a basic compound and GZR is an acidic compound, and both exhibit pH-dependent solubility. In particular, although EBR was formulated to reduce any effect of increasing pH on solubility, nevertheless it is important to evaluate the potential of PPIs or H2 receptor antagonists to alter its pharmacokinetics (PKs) in order to guide the use of EBR/GZR when coadministered with acid-reducing agents. The aims of the present study were to evaluate the effect of famotidine (FAM; a competitive H2 receptor antagonist) and pantoprazole (PAN; a PPI) on the PK profile of EBR and GZR, as well as evaluating the safety and tolerability of the EBR/GZR FDC in both the absence and presence of FAM or PAN.

METHODS AND MATERIALS

This was an open-label, three-period, fixed-sequence study (Merck Protocol No. MK-5172-072-00) conducted in accordance with the principles of Good Clinical Practice and approved by the Chesapeake Institutional Review Board (Columbia, MD). All subjects provided written, informed consent.

Subjects

Healthy male and female subjects between the ages of 19 and 55 years (inclusive), with a body mass index $\geq$19 to $\leq$32 kg/m^2 at screening, were enrolled. Key exclusion criteria were: history of clinically significant medical or psychiatric condition; infection with human immunodeficiency virus, hepatitis B virus or HCV; creatinine clearance $<$80 mL/min; history of alcoholism or drug abuse; use of substances known to be significant inducers of cytochrome P450 enzymes and/or P-glycoprotein during or 14 days prior to the study; history of hypersensitivity to study drugs, ingredients, or related compounds; pregnancy or lactation; or recent participation in another clinical trial.

Treatments

This was a three-period study with a minimum 10-day washout between each study period. On day 1 of period 1 and following an overnight fast, all subjects received a single oral dose of EBR 50 mg/GZR 100 mg FDC. In period 2, all subjects received FAM (single 20-mg oral tablet) $\sim$10 h (evening of day $-$1) and 2 h (morning of day 1) prior to receiving EBR/GZR FDC on day 1. EBR/GZR FDC was administered as a single oral dose following an overnight fast. In period 3, all subjects received PAN (single 40-mg oral tablet once daily) on days 1–5 (within $\pm$2 h of dosing time on day 1). On day 5, following an overnight fast, a single oral dose of EBR/GZR FDC was administered $\sim$2 h after PAN dosing. This study was conducted in fasted subjects to eliminate the potential confounding effect of food.

Assessments

Previous studies have shown that both GZR and EBR have a time to maximum drug concentration (t_{max}) of 2–4 h and an apparent terminal half-life ($t_{½}$) of $\sim$20 h. In this study, plasma samples for determination of EBR and GZR PKs were collected predose and at 0.5, 1, 1.5, 2, 3, 3.5, 4, 6, 12, 16, 24, 48, 72, and 96 h following administration of EBR/GZR FDC in each treatment period. Safety was assessed by monitoring of adverse events (AEs), physical examinations, vital signs, electrocardiograms, and laboratory safety tests.

Plasma EBR and GZR concentrations were determined using validated liquid chromatography with tandem mass spectrometry methods, with a lower limit of quantitation of 0.25 ng/mL for EBR and 1 ng/mL for GZR. Plasma EBR and GZR concentrations and actual sampling times were used to determine area under the curve (AUC) $(0,\infty)$, maximum drug concentration (C_{max}), 24-h drug concentration (C_{24}), t_{max}, and $t_{½}$ for EBR and GZR. C_{max} and t_{max} values were determined directly from the observed EBR and GZR plasma concentration-time data. AUC$(0,\infty)$ was calculated using the noncompartmental analysis with linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. The AUC$(0,\infty)$ for EBR and GZR were calculated as AUC(0,last) + $C_{est,last}/\lambda_z$, where $C_{est,last}$ is the estimated concentration at the time of the last quantifiable concentration. For each subject, λ_z was calculated by regression of the terminal log-linear portion of the plasma concentration time profile, and the apparent terminal $t_{½}$ was calculated as the quotient of the natural log of 2 and λ_z.

Statistics

The sample size of 16 was determined based on the evaluation that 14 completers would provide adequate precision estimate for the geometric mean ratios (GMRs), according to the within-subject variability of EBR and GZR PK parameters observed in previously conducted studies. A total of 16 subjects were enrolled to account for potential dropouts. Demographics and safety data are summarized using descriptive statistics. Individual values of exposure parameters (AUC$(0,\infty)$, C_{max}, and C_{24}) for EBR and GZR were natural log-transformed and analyzed with a linear mixed-effects model containing a fixed-effect term for treatment. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the three treatment measurements within each subject. The two-sided 90% confidence intervals (CIs) for differences in least-squares means were constructed on the natural log-scale for the two comparisons, EBR/GZR FDC + FAM or EBR/GZR FDC + PAN, vs. EBR/GZR FDC. These differences in least-squares means and CIs were exponentiated to obtain the estimated GMRs and associated 90% CIs. The least-squares means and corresponding 95% CIs were exponentiated to obtain estimates for the population geometric means and corresponding 95% CIs on the original scale by treatment. As this was an estimation study, no bounds were specified for the various treatment comparisons/evaluations of EBR/GZR.

Table 1 Subject characteristics

Characteristics	All patients ($N = 16$)
Sex, no. (%)	
Male	8 (50.0)
Female	8 (50.0)
Race, no. (%)	
White	15 (93.8)
Asian	1 (6.3)
Ethnicity, no. (%)	
Not Hispanic/Latino	15 (93.8)
Hispanic/Latino	1 (6.3)
Age, years, mean (range)	36 (19–55)
Height, cm, mean (range)	170.3 (154.0–183.0)
Weight, kg, mean (range)	76.4 (51.4–91.8)
BMI, kg/m^2, mean (range)	26.2 (21.0–31.1)

BMI, body mass index.

RESULTS

Subject demographics

A total of 16 subjects were enrolled in the present study (**Table 1**). This population was primarily white with equal numbers of male and female subjects. Height, weight, and body mass index were all within specified ranges. Twelve of 16 subjects completed the study per protocol. Two subjects were discontinued by the investigator due to nondrug-related AEs, one subject was discontinued due to a protocol violation, and one subject withdrew from the study.

All 16 subjects completed dosing with single-dose EBR/GZR on day 1 of period 1 and were included in the PK analysis of EBR and GZR in period 1. Fourteen subjects completed dosing in period 2, EBR/GZR + FAM, and were included in the PK analysis of EBR and GZR in period 2. Twelve subjects completed dosing in period 3, EBR/GZR + PAN, and were included in the PK analysis of EBR and GZR in period 3.

Safety and tolerability

All 16 subjects were included in the assessment of safety and tolerability. Six subjects (37.5%) reported a total of 25 AEs, the most common of which were headache and nausea ($n = 2$ each; 12.5% overall). AEs were mild to moderate in intensity and mostly resolved by study completion. Five AEs were considered to be related to study drugs: three were considered to be related to EBR/GZR (nausea, $n = 2$; headache, $n = 1$); one was considered to be related to PAN (nausea, $n = 1$), and one was considered to be related to EBR/GZR + FAM (headache, $n = 1$). There were no serious AEs or deaths, and no clinically meaningful changes in clinical laboratory values, vital signs, or electrocardiograms.

Pharmacokinetics of elbasvir and grazoprevir

GZR exhibited a similar PK profile following single-dose administration of EBR/GZR with or without the coadministration of FAM or PAN (**Figure 1a**). GMRs of GZR AUC(0,∞), C_{max}, and C_{24} for the two comparisons (EBR/GZR FDC + FAM or EBR/GZR FDC + PAN vs. EBR/GZR FDC) ranged from 0.89–1.17, indicating no clinically meaningful change in GZR PKs with or without coadministration of FAM or PAN (**Tables 2 and 3**). The median time to reach C_{max} (t_{max}) for GZR was 1.5–2.0 h with EBR/GZR, either alone or in the presence of FAM or PAN. Coadministration of either FAM or PAN with EBR/GZR FDC did not appear to affect the apparent $t_{½}$ of GZR to a meaningful extent.

The PK profile of EBR was similar when EBR/GZR was administered alone or in the presence of FAM or PAN (**Figure 1b**). The GMRs of EBR AUC(0,∞), C_{max}, and C_{24} for the two comparisons (EBR/GZR FDC + FAM or EBR/GZR FDC + PAN, vs. EBR/GZR FDC) ranged from 1.02–1.11 (**Tables 4 and 5**). The median t_{max} for EBR was 3.5 h in the absence or presence of FAM or PAN. Coadministration of either FAM or PAN with EBR/GZR FDC did not appear

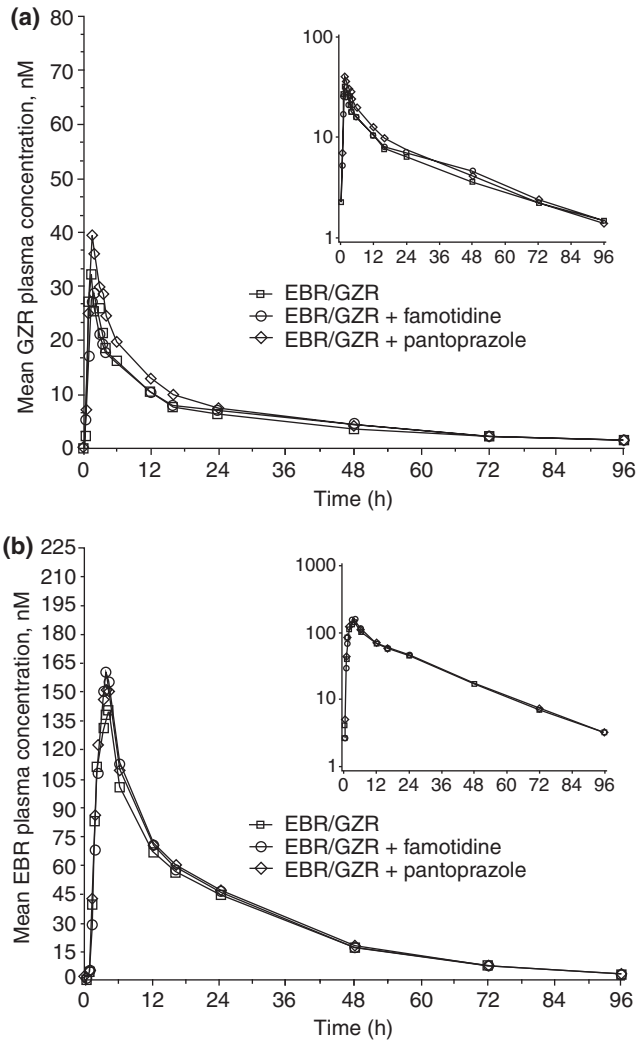

Figure 1 Arithmetic mean plasma concentration-time profiles of (**a**) grazoprevir (GZR) and (**b**) elbasvir (EBR) following administration of a single dose of EBR 50 mg/GZR 100 mg fixed-dose combination (FDC) with and without the coadministration of single-dose famotidine 20 mg or multiple doses of pantoprazole (PAN) 40 mg in healthy adult subjects ($n = 16$ for EBR/GZR FDC, $n = 14$ for EBR/GZR FDC + famotidine, and $n = 12$ for EBR/GZR FDC + PAN). Inset = semi-log scale.

Table 2 Statistical comparison and summary statistics of plasma pharmacokinetics of grazoprevir following administration of a single dose of elbasvir 50 mg/grazoprevir 100 mg fixed-dose combination with and without the coadministration of famotidine 20 mg in healthy adult subjects

	EBR/GZR FDC			EBR/GZR FDC + FAM			EBR/GZR FDC + FAM/EBR/GZR FDC		
GZR PK parameter	**No. of patients**	**GM**	**95% CI**	**No. of patients[a]**	**GM**	**95% CI**	**GMR**	**90% CI**	**Pseudo within-subject % CV[b]**
AUC (0,∞)[c] μM·h	16	0.573	0.465–0.707	14	0.633	0.545–0.735	1.10	0.95–1.28	23.1
C_{max}[c], μM	16	39.40	28.8–54.0	14	35.0	28.6–42.8	0.89	0.71–1.11	34.4
C_{24}[c], nM	16	6.00	4.86–7.40	14	6.72	5.50–8.21	1.12	0.97–1.30	22.5
t_{max}[d], h	16	1.50	1.0–12.0	14	2.00	1.00–4.00			
Apparent $t_{½}$[e], h	16	33.80	35.41	14	35.47	32.09			

AUC, area under the curve; CI, confidence interval; C_{24}, drug concentration at 24 h; C_{max}, maximum drug concentration; CV, coefficient of variation, EBR, elbasvir; FAM, famotidine; FDC, fixed-dose combination; GM, geometric mean; GMR, geometric mean ratio; GZR, grazoprevir; PK, pharmacokinetic; $t_{½}$, terminal half-life; t_{max}, time to reach C_{max}.
EBR/GZR FDC: single oral dose of EBR/GZR FDC (1 × EBR 50-mg/GZR 100-mg tablet FDC).
EBR/GZR FDC + FAM: single oral doses of FAM 20 mg (1 × 20-mg tablet) administered 10 h (day −1) and 2 h (day 1) prior to a single oral dose of EBR/GZR FDC (1 × EBR 50-mg/GZR 100-mg tablet FDC) on day 1.
[a]Two subjects discontinued on day −1 of period 2; therefore, these subjects had no data available for EBR/GZR FDC + FAM.
[b]Pseudo within-subject % CV = 100 × sqrt[(σA2 + σB2 -2σAB)/2], where σA2 and σB2 are the estimated variance on the log scale for the two treatments and σAB is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[c]Back-transformed least-squares GM (ratio) and CI from the linear mixed-effects model performed on natural log-transformed values.
[d]Median (min, max) reported for t_{max}.
[e]GM and geometric CV reported for apparent $t_{½}$.

Table 3 Statistical comparison and summary statistics of plasma pharmacokinetics of grazoprevir following administration of a single dose of elbasvir 50 mg/grazoprevir 100 mg fixed-dose combination with and without the coadministration of multiple doses of pantoprazole 40 mg in healthy adult subjects

	EBR/GZR FDC			EBR/GZR FDC + PAN			EBR/GZR FDC + PAN/EBR/GZR FDC		
GZR PK parameter	**No. of patients**	**GM**	**95% CI**	**No. of patients[a]**	**GM**	**95% CI**	**GMR**	**90% CI**	**Pseudo within-subject % CV[b]**
AUC (0,∞)[c], μM·h	16	0.573	0.465–0.707	12	0.640	0.534–0.767	1.12	0.96–1.30	21.9
C_{max}[c], μM	16	39.40	28.8–54.0	12	43.50	32.7–57.9	1.10	0.89–1.37	31.5
C_{24}[c], nM	16	6.00	4.86–7.40	12	7.02	5.83–8.45	1.17	1.02–1.34	19.6
t_{max}[d], h	16	1.50	1.0–12.0	12	1.50	1.00–4.00			
Apparent $t_{½}$[e], h	16	33.80	35.41	12	35.47	32.45			

AUC, area under the curve; CI, confidence interval; C_{24}, drug concentration at 24 h; C_{max}, maximum drug concentration; CV, coefficient of variation, EBR, elbasvir; FDC, fixed-dose combination; GM, geometric mean; GMR, geometric mean ratio; GZR, grazoprevir; PAN, pantoprazole; PK, pharmacokinetic; $t_{½}$, terminal half-life; t_{max}, time to reach C_{max}.
EBR/GZR FDC: single oral dose of EBR/GZR FDC (1 × EBR 50-mg/GZR 100-mg tablet FDC).
EBR/GZR FDC + PAN: multiple oral doses of PAN 40 mg (1 × 40-mg tablet) administered once daily on days 1 through 5 and a single oral dose of EBR/GZR FDC (1 × EBR 50-mg/GZR 100-mg tablet FDC) administered 2 h after PAN dosing on day 5.
[a]Two subjects discontinued on day −1 of period 2, one subject discontinued between periods 2 and 3, and one subject withdrew on day 1 of period 3; therefore, these subjects had no data available for EBR/GZR FDC + PAN.
[b]Pseudo within-subject % CV = 100 × sqrt[(σA2 + σB2 -2σAB)/2], where σA2 and σB2 are the estimated variance on the log scale for the two treatments and σAB is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[c]Back-transformed least-squares GM (ratio) and CI from the linear mixed-effects model performed on natural log-transformed values.
[d]Median (min, max) reported for t_{max}.
[e]GM and geometric CV reported for apparent $t_{½}$.

to affect the apparent terminal $t_{1/2}$ of EBR to a meaningful extent.

DISCUSSION

It is estimated that up to one-third of HCV-infected patients use PPIs and other acid-reducing agents.[15] Data from the present study show that the PKs of EBR and GZR, administered as a single dose of EBR/GZR FDC in healthy male and female subjects, are not meaningfully altered by coadministration with FAM or PAN. Furthermore, the administration of EBR/GZR FDC, in both the absence and presence of FAM or PAN, was generally well tolerated.

The FDC of EBR 50 mg/GZR 100 mg was selected for this study because it is the approved dose for treatment of chronic HCV infection.[11] The PK profiles of EBR and GZR were evaluated in healthy subjects in this study rather than in HCV-infected patients to eliminate potential confounding factors. The drug-drug interaction potential of EBR/GZR with H2 receptor antagonists and PPIs in healthy subjects is anticipated to be similar to that in HCV-infected patients based on the known PK properties of EBR and GZR in both these

Table 4 Statistical comparison and summary statistics of plasma pharmacokinetics of elbasvir following administration of a single dose of elbasvir 50 mg/grazoprevir 100 mg fixed-dose combination with and without the coadministration of famotidine 20 mg in healthy adult subjects

	EBR/GZR FDC			EBR/GZR FDC + FAM			EBR/GZR FDC + FAM/EBR/GZR FDC		
EBR PK parameter	**No. of patients**	**GM**	**95% CI**	**No. of patients[a]**	**GM**	**95% CI**	**GMR**	**90% CI**	**Pseudo within-subject % CV[b]**
AUC $(0,\infty)^c$, μM·h	16	2.75	2.38–3.19	14	2.88	2.44–3.41	1.05	0.92–1.18	18.6
$C_{max}{}^c$, μM	16	0.14	0.124–0.158	14	0.156	0.131–0.185	1.11	0.98–1.26	19.3
$C_{24}{}^c$, nM	16	42.60	37.00–49.00	14	43.90	37.10–51.90	1.03	0.91–1.17	19.2
$t_{max}{}^d$, h	16	3.50	3.00–4.00	14	3.50	3.00–4.00			
Apparent $t_{½}{}^e$, h	16	19.27	10.85	14	18.48	15.17			

AUC, area under the curve; CI, confidence interval; C_{24}, drug concentration at 24 h; C_{max}, maximum drug concentration; CV, coefficient of variation, EBR, elbasvir; FAM, famotidine; FDC, fixed-dose combination; GM, geometric mean; GMR, geometric mean ratio; GZR, grazoprevir; PK, pharmacokinetic; $t_{½}$, terminal half-life; t_{max}, time to reach C_{max}.

EBR/GZR FDC: single oral dose of EBR/GZR FDC (1 × EBR 50-mg/GZR 100-mg tablet FDC).

EBR/GZR FDC + FAM: single oral doses of FAM 20 mg (1 × 20-mg tablet) administered 10 h (day −1) and 2 h (day 1) prior to a single oral dose of EBR/GZR FDC (1 × EBR 50-mg/GZR 100-mg tablet FDC) on day 1.

[a]Two subjects discontinued on day −1 of period 2; therefore, these subjects had no data available for EBR/GZR FDC + FAM.

[b]Pseudo within-subject % CV = 100 × sqrt[(σA2 + σB2 -2σAB)/2], where σA2 and σB2 are the estimated variance on the log scale for the two treatments and σAB is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[c]Back-transformed least-squares GM (ratio) and CI from the linear mixed-effects model performed on natural log-transformed values.

[d]Median (min, max) reported for t_{max}.

[e]GM and geometric CV reported for apparent $t_{½}$.

Table 5 Statistical comparison and summary statistics of plasma pharmacokinetics of elbasvir following administration of a single dose of elbasvir 50 mg/grazoprevir 100 mg fixed-dose combination with and without the coadministration of multiple doses of pantoprazole 40 mg in healthy adult subjects

	EBR/GZR FDC			EBR/GZR FDC + PAN			EBR/GZR FDC + PAN/EBR/GZR FDC		
EBR PK parameter	**No. of patients**	**GM**	**95% CI**	**No. of patients[a]**	**GM**	**95% CI**	**GMR**	**90% CI**	**Pseudo within-subject % CV[b]**
AUC $(0,\infty)^c$, μM·h	16	2.75	2.38–3.19	12	2.88	2.42–3.42	1.05	0.93–1.18	16.5
$C_{max}{}^c$, μM	16	0.14	0.124–0.158	12	0.143	0.122–0.169	1.02	0.92–1.14	15.4
$C_{24}{}^c$, nM	16	42.60	37.00–49.00	12	44.00	37.30–52.00	1.03	0.92–1.17	16.8
$t_{max}{}^d$, h	16	3.50	3.00–4.00	12	3.50	3.00–4.00			
Apparent $t_{½}{}^e$, h	16	19.27	10.85	12	18.74	12.79			

AUC, area under the curve; CI, confidence interval; C_{24}, drug concentration at 24 h; C_{max}, maximum drug concentration; CV, coefficient of variation, EBR, elbasvir; FDC, fixed-dose combination; GM, geometric mean; GMR, geometric mean ratio; GZR, grazoprevir; PAN, pantoprazole; PK, pharmacokinetic; $t_{½}$, terminal half-life; t_{max}, time to reach C_{max}.

EBR/GZR FDC: single oral dose of EBR/GZR FDC (1 × EBR 50-mg/GZR 100-mg tablet FDC).

EBR/GZR FDC + PAN: multiple oral doses of PAN 40 mg (1 × 40-mg tablet) administered once daily on days 1 through 5 and a single oral dose of EBR/GZR FDC (1 × EBR 50-mg/GZR 100-mg tablet FDC) administered 2 h after PAN dosing on day 5.

[a]Two subjects discontinued on day −1 of period 2, one subject discontinued between periods 2 and 3, and one subject withdrew on day 1 of period 3; therefore, these subjects had no data available for EBR/GZR FDC + PAN.

[b]Pseudo within-subject % CV = 100 × sqrt[(σA2 + σB2 -2σAB)/2], where σA2 and σB2 are the estimated variance on the log scale for the two treatments and σAB is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[c]Back-transformed least-squares GM (ratio) and CI from the linear mixed-effects model performed on natural log-transformed values.

[d]Median (min, max) reported for t_{max}.

[e]GM and geometric CV reported for apparent $t_{1/2}$.

populations. The similarity in EBR and GZR absorption, distribution, metabolism, and elimination between these two populations justified the extrapolation of PK data from drug-drug interaction studies conducted in healthy subjects to patients with HCV.

FAM and PAN were selected as a prototypic H2 receptor antagonist and PPI, respectively, for this study. FAM is a competitive histamine H2 receptor antagonist that acts primarily by inhibiting gastric acid secretion. PAN, a PPI, is an antisecretory-substituted benzimidazole that suppresses H^+ ion formation by specific inhibition of the gastric enzyme system proton pump (H^+/K^+-ATPase) at the secretory surface of the gastric parietal cell. The doses of FAM (20 mg) and PAN (40 mg) used in this study were selected based on the recommended daily doses as stated in the prescribing information.[16,17] A FAM dosing regimen of 20 mg given in the evening and repeated the next day 2 h prior to EBR/GZR dosing is considered to generate the highest elevation in stomach pH and would, therefore, maximize any impact that an elevated pH may have on EBR/GZR absorption. Similarly,

5 days of dosing with PAN is anticipated to have elicited a maximal change on stomach pH and, thus, heighten any impact that an elevated pH would have on EBR/GZR absorption. Although higher doses of FAM (40 mg/day) are indicated for acute treatment of duodenal or benign gastric ulcers,[17] any effect on EBR/GZR absorption is not expected to be meaningful. In addition, other H2 receptor antagonists and PPIs that were not evaluated in this study are also not anticipated to impact EBR/GZR absorption. EBR and GZR are substrates of cytochrome P450 3A, and GZR is also a substrate of organic anion transporter proteins OATP1B1 and OATP1B3. EBR and GZR are not predicted to have drug-drug interactions with H2 receptor antagonists or PPIs based on metabolic or transporter interactions.

The solubility of both EBR and GZR are pH-dependent, and, therefore, changes in stomach pH have the potential to affect the gastric absorption of both compounds. The bioavailability of basic compounds, including certain NS5A inhibitors, may be particularly sensitive to elevated gastric pH. The solubilities of ledipasvir and velpatasvir, both NS5A inhibitors, decrease as stomach pH increases, and, thus, medications that raise stomach pH can lead to decreased absorption of these agents.[18,19] PPIs can attenuate ledipasvir and velpatasvir absorption. Coadministration of PPIs with velpatasvir is, therefore, not recommended, whereas doses of omeprazole are restricted to $\leq$20 mg when used in combination with ledipasvir.[18,19] Although EBR is a basic compound, it was formulated to reduce any effect of increasing pH on solubility and, therefore, bioavailability. Because of its acidic properties, GZR bioavailability is not expected to decrease under conditions of increasing gastric pH. Overall, the results of this study indicate that elevated gastric pH does not impact EBR or GZR absorption to a meaningful extent, and, thus, EBR/GZR FDC may be administered without restriction of the use of H2 receptor antagonists or PPIs. Importantly, a post hoc analysis of clinical trial data demonstrated that the efficacy of EBR/GZR was not impacted in patients receiving concomitant PPIs.[20]

In conclusion, these results indicate that gastric acid-reducing agents, such as H2 receptor antagonists and PPIs, do not modify the PKs of EBR or GZR in a clinically relevant manner and may be coadministered with EBR/GZR in HCV-infected patients without restriction.

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