




Pharmacokinetic Interactions between the Hepatitis C Virus Inhibitors Elbasvir and Grazoprevir and HIV Protease Inhibitors Ritonavir, Atazanavir, Lopinavir, and Darunavir in Healthy Volunteers

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ABSTRACT The combination of the hepatitis C virus (HCV) nonstructural protein 5A (NS5A) inhibitor elbasvir and the NS3/4A protease inhibitor grazoprevir is a potent, once-daily therapy indicated for the treatment of chronic HCV infection in individuals coinfecting with human immunodeficiency virus (HIV). We explored the pharmacokinetic interactions of elbasvir and grazoprevir with ritonavir and ritonavir-boosted HIV protease inhibitors in three phase 1 trials. Drug-drug interaction trials with healthy participants were conducted to evaluate the effect of ritonavir on the pharmacokinetics of grazoprevir ($n = 10$) and the potential two-way pharmacokinetic interactions of elbasvir ($n = 30$) or grazoprevir ($n = 39$) when coadministered with ritonavir-boosted atazanavir, lopinavir, or darunavir. Coadministration of ritonavir with grazoprevir increased grazoprevir exposure; the geometric mean ratio (GMR) for grazoprevir plus ritonavir versus grazoprevir alone area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) was 1.91 (90% confidence interval [CI]; 1.31 to 2.79). Grazoprevir exposure was markedly increased with coadministration of atazanavir-ritonavir, lopinavir-ritonavir, and darunavir-ritonavir, with GMRs for grazoprevir AUC_{0-24} of 10.58 (90% CI, 7.78 to 14.39), 12.86 (90% CI, 10.25 to 16.13), and 7.50 (90% CI, 5.92 to 9.51), respectively. Elbasvir exposure was increased with coadministration of atazanavir-ritonavir, lopinavir-ritonavir, and darunavir-ritonavir, with GMRs for elbasvir AUC_{0-24} of 4.76 (90% CI, 4.07 to 5.56), 3.71 (90% CI, 3.05 to 4.53), and 1.66 (90% CI, 1.35 to 2.05), respectively. Grazoprevir and elbasvir had little effect on atazanavir, lopinavir, and darunavir pharmacokinetics. Coadministration of elbasvir-grazoprevir with atazanavir-ritonavir, lopinavir-ritonavir, or darunavir-ritonavir is contraindicated, owing to an increase in grazoprevir exposure. Therefore, HIV treatment regimens without HIV protease inhibitors should be considered for HCV/HIV-coinfecting individuals who are being treated with elbasvir-grazoprevir.

KEYWORDS virology, elbasvir, grazoprevir, ritonavir, atazanavir, lopinavir, darunavir

Globally, 2.3 million people infected with human immunodeficiency virus (HIV) also are infected with hepatitis C virus (HCV) (1). Chronic HCV infection is a major cause of morbidity and death in individuals coinfecting with HIV and HCV (2). HCV/HIV-coinfecting people are at 2-fold greater risk for cirrhosis and 6-fold greater risk for

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decompensated liver disease than are people with HIV infection who are not coinfecting with HCV (3). These risks are even higher among coinfecting individuals with low CD4 T lymphocyte cell counts (4). People with HCV/HIV coinfection may have more rapid progression to AIDS and AIDS-related death (5). Therefore, treatment of HCV infection in the HIV-infected population represents an important unmet medical need.

Elbasvir (EBR) is a small-molecule inhibitor of HCV nonstructural protein 5A (NS5A), and grazoprevir (GZR) is a reversible, noncovalent, competitive inhibitor of the HCV NS3/4A protease (6, 7). The fixed-dose combination of EBR and GZR is indicated for the treatment of chronic HCV genotype 1 or 4 infection (8, 9), and it displayed high efficacy in people with chronic HCV infection in phase 3 clinical trials (10–13). In particular, EBR/GZR administered for 12 weeks achieved sustained HCV virologic response rates of 96% in a phase 3 trial of people with HCV genotype 1, 4, or 6 infection and HIV coinfection (14). Following oral administration, EBR has a time to maximum concentration (T_{\max}) of ~ 3 h, with a mean half-life ($t_{1/2}$) of ~ 24 h (8, 9). EBR elimination is mediated by both cytochrome P450 3A (CYP3A) metabolism and excretion of the parent compound (8, 9). Elimination of EBR into urine is negligible. EBR is a substrate of CYP3A and P-glycoprotein (P-gp), is an inhibitor of intestinal breast cancer resistance protein (BCRP), and minimally inhibits intestinal P-gp. EBR does not inhibit CYP3A (8, 9). Following oral administration, GZR has a T_{\max} of ~ 2 h and undergoes rapid uptake into the liver via organic-anion-transporting polypeptide 1B (OATP1B) (8, 9). The mean $t_{1/2}$ of GZR is ~ 31 h (8, 9). GZR is eliminated predominantly into feces as the parent compound and as CYP3A oxidative metabolites. In addition to OATP1B and CYP3A, GZR is a substrate of P-gp, a weak CYP3A inhibitor, and a BCRP inhibitor (8, 9, 15). Based on their $t_{1/2}$ values, EBR and GZR are expected to reach state steady state within 7 days following once-daily administration.

Several recommended antiretroviral treatment regimens for HIV infection include boosted protease inhibitors, such as atazanavir (ATV), darunavir (DRV), and lopinavir (LPV). One booster agent with which these HIV protease inhibitors are often coadministered is ritonavir (RTV) (100 mg), which inhibits CYP3A metabolism and intestinal P-gp transport, thereby increasing the exposure of the HIV protease inhibitors, which are predominantly cleared via CYP3A metabolism (4). Based on *in vitro* data and the associated *R* values, RTV is not predicted to be an inhibitor of OATP1B at the 100-mg twice-daily dose. In contrast, data suggest that ATV, DRV, and LPV, when not coadministered with RTV, inhibit OATP1B. Therefore, the HIV protease inhibitor-RTV combination regimens have the potential to inhibit CYP3A, P-gp, and OATP1B (16, 17).

Because treatment of HCV/HIV coinfection represents an important unmet medical need and because the overlapping and inhibitory metabolic pathways of CYP3A, P-gp, and OATP1B for elbasvir-grazoprevir (EBR/GZR) and HIV protease inhibitors suggest the potential for drug interactions, the effects of multiple doses of RTV, atazanavir-ritonavir (ATV/RTV), lopinavir-ritonavir (LPV/RTV), and darunavir-ritonavir (DRV/RTV) on GZR and EBR pharmacokinetics (PK) were evaluated in three separate open-label trials, one trial assessing the effect of RTV on GZR PK (trial 1; Merck trial no. MK-5172-PN006 [EudraCT identification no. 2011-001242-15]) and two trials assessing the potential two-way PK interactions of GZR (trial 2; Merck trial no. MK-5172-PN029) or EBR (trial 3; Merck trial no. MK-8742 PN017) when coadministered with the RTV-boosted HIV protease inhibitors (ATV, LPV, or DRV).

(Portions of these data were presented at the 64th Annual Meeting of the American Association for the Study of Liver Diseases, Washington, DC, 1 to 5 November 2013 [18], and at the 2014 Conference on Retroviruses and Opportunistic Infections, Boston, MA, 3 to 6 March 2014 [19].)

RESULTS

Trial populations. In trial 1, 10 healthy male participants were enrolled and all participants completed the trial per protocol. In trial 2, 39 participants were enrolled (13 per each arm) and 35 completed the trial. Two participants discontinued in the ATV arm, 1 who discontinued secondary to an adverse event (AE) and 1 who was lost to

TABLE 1 Participant characteristics

Characteristic	GZR + RTV (n = 10)	GZR + ATV/RTV (n = 13)	GZR + LPV/RTV (n = 13)	GZR + DRV/RTV (n = 13)	EBR + ATV/RTV (n = 10)	EBR + LPV/RTV (n = 10)	EBR + DRV/RTV (n = 10)
Sex (no. [%])							
Male	10 (100)	9 (69)	7 (54)	9 (69)	6 (60)	6 (60)	6 (60)
Female	0	4 (31)	6 (46)	4 (31)	4 (40)	4 (40)	4 (40)
Race (no. [%])							
White	10 (100)	11 (84)	10 (100)	12 (92)	8 (80)	9 (90)	9 (90)
Black	0	1 (8)	0	1 (8)	2 (20)	1 (10)	0
Asian	0	1 (8)	0	0	0		1 (10)
Ethnicity (no. [%])							
Hispanic/Latino	0	10 (77)	13 (100)	12 (92)	2 (20)	1 (10)	1 (10)
Non-Hispanic/non-Latino	10 (100)	3 (23)	0	1 (8)	8 (80)	8 (80)	8 (80)
Unknown	0	0	0	0	0	1 (10)	1 (10)
Age (mean [range]) (yr)	30.7 (24–44)	40 (25–49)	37 (19–47)	44 (28–55)	31 (20–48)	35 (21– 52)	34 (23–49)
Weight (mean [range]) (kg)	78.9 (71.0–94.2)	75.0 (53.4–96.9)	72.2 (51.7–85.5)	74.8 (54.0–92.3)	75.4 (58.6–90.9)	78.5 (58.8–109.7)	78.8 (53.9–101.9)
Body mass index (mean [range]) (kg/m ²)	25.1 (22.4– 29.9)	25.8 (24.4– 29.5)	27.3 (24.2– 29.7)	26.6 (22.4–29.8)	24.5 (19.0–30.5)	26.0 (21.6–30.5)	26.2 (20.0–31.9)

follow-up monitoring. Two participants discontinued in the DRV arm, 1 secondary to an AE and 1 because of a trial violation. In trial 3, 30 participants were enrolled (10 per arm) and 23 completed the trial per protocol. Three participants discontinued due to AEs (1 from each arm), 2 were lost to follow-up monitoring (1 each in the ATV arm and the DRV arm), 1 was withdrawn by the investigator (ATV arm), and 1 withdrew consent (DRV arm). Participant characteristics for each trial are summarized in Table 1.

Pharmacokinetics. (i) Trial 1 (GZR/RTV). Coadministration of RTV with GZR increased the single-dose GZR area under the concentration-time curve from 0 to infinity ($AUC_{0-\infty}$) and the plasma concentration at 24 h (C_{24}) by approximately 2-fold (Table 2 and Fig. 1). The median T_{max} of GZR was unaffected by coadministration of GZR with RTV (Table 2).

(ii) Trial 2 (GZR/HIV protease inhibitor/RTV). GZR exposure was increased when GZR was coadministered with each of the three HIV protease inhibitor-RTV combinations, with GZR area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) exposures being 8 to 13 times higher than when GZR was administered alone (Table 3 and Fig. 2). The median T_{max} of GZR administered alone was generally comparable to that observed when GZR was coadministered with RTV-boosted HIV protease inhibitors.

GZR administered at 200 mg once daily increased ATV exposure (AUC_{0-24}), maximum observed plasma concentration [C_{max}], and C_{24}) by 12% to 43% following coadministration of ATV/RTV once daily and GZR once daily (Table 4 and Fig. 3). LPV and DRV exposures were similar following coadministration of either RTV-boosted HIV protease

TABLE 2 Comparison of GZR plasma PK following the administration of a single oral dose of 200 mg GZR with or without the coadministration of multiple, twice-daily, oral doses of 100 mg RTV for 15 days to healthy adult participants (trial 1)

PK parameter	GZR ^a (GM [95% CI]) (n = 10)	GZR + RTV ^b (GM [95% CI]) (n = 10)	GZR + RTV vs GZR (GMR [90% CI])	rMSE ^c
$AUC_{0-\infty}$ ($\mu\text{M} \times \text{h}$) ^d	1.50 (2.03–2.19)	3.05 (2.09–4.44)	2.03 (1.60–2.56)	0.286
C_{max} (μM) ^d	0.202 (0.115–0.355)	0.232 (0.132–0.407)	1.15 (0.60–2.18)	0.782
C_{24} (nM) ^d	10.7 (7.15–15.8)	20.0 (13.4–29.8)	1.88 (1.65–2.14)	0.157
T_{max} (h) ^e	4.0 (1.0–6.0)	4.0 (1.5–6.0)		

^aA single oral dose of 200 mg GZR.

^bDoses of 100 mg RTV twice daily on days 1 to 21 coadministered with a single oral dose of 200 mg GZR on day 15.

^cThe square root of mean squared error (rMSE) (residual error) from the linear mixed-effect model times 100% approximates the within-subject percent coefficient of variation (CV) on the raw scale.

^dBack-transformed least-squares mean (ratio) and CI from a linear mixed-effects model with natural-log-transformed values.

^eMedian and range are reported for T_{max} .

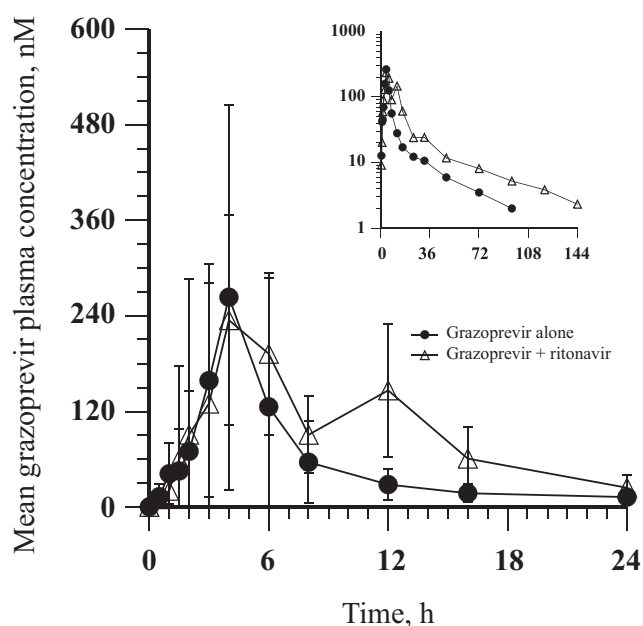


FIG 1 GZR arithmetic mean \pm SD plasma concentration-time profiles following administration of a single oral dose of 200 mg GZR with and without the coadministration of multiple, twice-daily, oral doses of 100 mg RTV for 15 days to healthy adult participants ($n = 10$) (inset, semilog scale).

inhibitor with GZR, compared with administration of LPV/RTV alone or DRV/RTV alone (Table 4 and Fig. 3). The median T_{max} of the boosted HIV protease inhibitors administered alone was generally comparable to that observed when these agents were coadministered with GZR.

TABLE 3 Comparisons of GZR plasma PK following coadministration of 200 mg GZR once daily and 300 mg ATV/100 mg RTV once daily, 400 mg LPV/100 mg RTV twice daily, or 600 mg DRV/100 mg RTV twice daily for 7 days versus administration of 200 mg GZR once daily for 7 days to healthy adult participants (trial 2)

PK parameter	GM (95% CI)	GM (95% CI)	GMR (90% CI)	Pseudo-within-subject CV (%) ^a
GZR/ATV/RTV ^b	GZR ($n = 12$)	GZR + ATV/RTV ($n = 11$) ^c	GZR + ATV/RTV vs GZR	
AUC ₀₋₂₄ ($\mu\text{M} \times \text{h}$) ^d	3.38 (2.26–5.05)	35.7 (26.1–49.0)	10.58 (7.78–14.39)	40.5
C_{max} (μM) ^d	0.952 (0.573–1.58)	5.94 (4.48–7.87)	6.24 (4.42–8.81)	46.1
C_{24} (nM) ^d	14.7 (10.7–20.2)	171 (104–280)	11.64 (7.96–17.02)	48.9
T_{max} (h) ^e	2.50 (2.00–5.00)	3.00 (2.00–4.00)		
GZR/LPV/RTV ^f	GZR ($n = 13$)	GZR + LPV/RTV ($n = 13$)	GZR + LPV/RTV vs GZR	
AUC ₀₋₂₄ ($\mu\text{M} \times \text{h}$) ^d	3.63 (2.37–5.56)	46.7 (30.1–72.5)	12.86 (10.25–16.13)	32.4
C_{max} (μM) ^d	0.954 (0.568–1.60)	6.97 (5.30–9.16)	7.31 (5.65–9.45)	36.8
C_{24} (nM) ^d	15.1 (11.7–19.5)	327 (149–721)	21.70 (12.99–36.25)	73.4
T_{max} (h) ^e	3.00 (1.00–6.03)	3.02 (2.00–6.01)		
GZR/DRV/RTV ^g	GZR ($n = 13$)	GZR + DRV/RTV ($n = 11$) ^h	GZR + DRV/RTV vs GZR	
AUC ₀₋₂₄ ($\mu\text{M} \times \text{h}$) ^d	3.31 (2.25–4.86)	24.8 (18.7–32.9)	7.50 (5.92–9.51)	32.2
C_{max} (μM) ^d	0.824 (0.502–1.35)	4.34 (3.27–5.75)	5.27 (4.04–6.86)	36.8
C_{24} (nM) ^d	15.7 (12.2–20.1)	126 (91.0–175)	8.05 (6.33–10.24)	30.9
T_{max} (h) ^e	3.02 (1.00–5.03)	4.00 (2.00–5.03)		

^aPseudo-within-subject percent coefficient of variation (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 two treatments and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

^bGZR plasma PK following GZR administration alone and coadministration with ATV/RTV.

^cOne participant was discontinued by the investigator on day 3 of period 1, and one participant was discontinued by the investigator on day 13 of period 2.

^dBack-transformed least-squares mean (ratio) and CI from a linear mixed-effects model with natural-log-transformed values.

^eMedian and range are reported for T_{max} .

^fGZR plasma PK following GZR administration alone and coadministration with LPV/RTV.

^gGZR plasma PK following GZR administration alone and coadministration with DRV/RTV.

^hOne participant discontinued on day 6 of period 3, and one participant discontinued on day 1 of period 2.

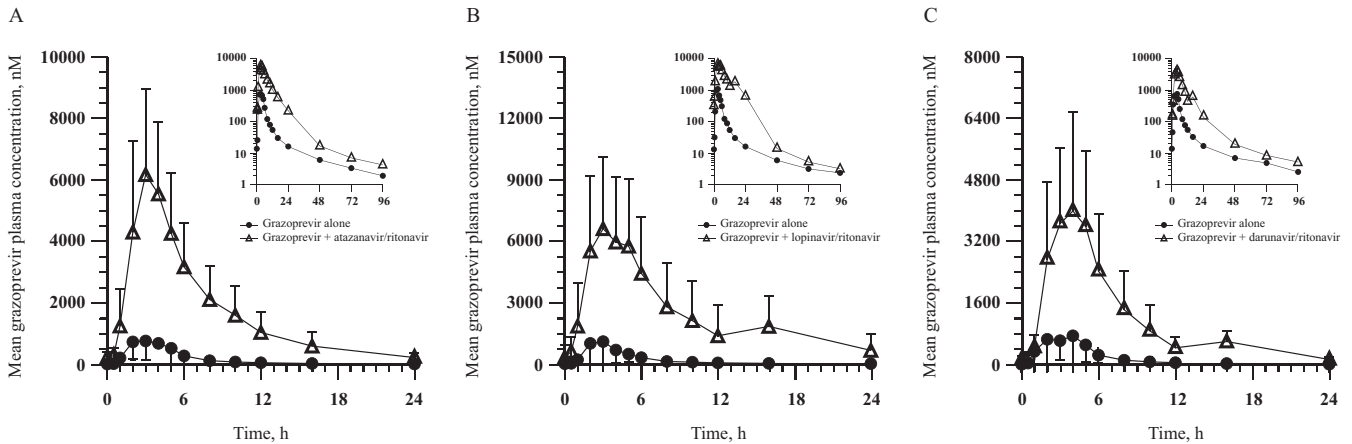


FIG 2 GZR arithmetic mean \pm SD plasma concentration-time profiles following administration of 200 mg GZR once daily alone for 7 days and coadministration with 300 mg ATV/100 mg RTV once daily for 7 days (GZR alone, $n = 12$; in combination with ATV/RTV, $n = 11$) (A), 400 mg LPV/100 mg RTV twice daily for 7 days (both arms, $n = 13$) (B), or 600 mg DRV/100 mg RTV twice daily for 7 days (GZR alone, $n = 13$; in combination with DRV/RTV, $n = 11$) (C) to healthy adult participants (insets, semilog scale).

(iii) Trial 3 (EBR/HIV protease inhibitor/RTV). EBR exposure was increased with coadministration of the three HIV protease inhibitor-RTV combinations, with EBR AUC_{0-24} exposures being 2- to 5-fold greater than when EBR was administered alone (Table 5 and Fig. 4). The median T_{max} of EBR was unaffected by the coadministration of EBR with HIV protease inhibitors and RTV.

Coadministration of EBR with RTV-boosted ATV, LPV, or DRV generally did not meaningfully affect the ATV, LPV, and DRV PK (Table 6 and Fig. 5). The median T_{max} values for ATV, LPV, and DRV were unaffected by coadministration with EBR.

TABLE 4 Comparison of ATV, LPV, and DRV plasma PK following coadministration of 200 mg GZR once daily and 300 mg ATV/100 mg RTV once daily, 400 mg LPV/100 mg RTV twice daily, or 600 mg DRV/100 mg RTV twice daily for 7 days versus administration of the boosted HIV protease inhibitor for 14 days to healthy adult participants (trial 2)

PK parameter	GM (95% CI)	GM (95% CI)	GMR (90% CI)	Pseudo-within-subject CV (%) ^a
ATV PK parameters with GZR/ATV/RTV^b				
AUC_{0-24} (ng \times h/ml) ^e	ATV/RTV ($n = 11$) ^c 42,400 (32,300–55,600)	GZR + ATV/RTV ($n = 11$) ^d 60,600 (45,800–80,300)	GZR + ATV/RTV vs ATV/RTV 1.43 (1.30–1.57)	12.0
C_{max} (ng/ml) ^e	4,560 (3,650–5,680)	5,100 (4,330–6,000)	1.12 (1.01–1.24)	13.2
C_{24} (ng/ml) ^e	798 (544–1,170)	983 (670–1,400)	1.23 (1.13–1.34)	11.3
T_{max} (h) ^f	4.00 (2.00–5.00)	3.00 (3.00–4.02)		
LPV PK parameters with GZR/LPV/RTV^g				
AUC_{0-12} (ng \times h/ml) ^e	LPV/RTV ($n = 13$) 103,000 (81,600–131,000)	GZR + LPV/RTV ($n = 13$) 10,700 (93,800–121,000)	GZR + LPV/RTV vs LPV/RTV 1.03 (0.92–1.16)	16.4
C_{max} (ng/ml) ^e	12,600 (10,500–15,100)	12,300 (11,200–13,400)	0.97 (0.88–1.08)	14.6
C_{12} (ng/ml) ^e	5,220 (3,520–7,740)	5,040 (3,680–6,910)	0.97 (0.81–1.15)	25.2
T_{max} (h) ^f	4.00 (2.00–5.05)	4.01 (2.00–10.03)		
DRV PK parameters with GZR/DRV/RTV^h				
AUC_{0-12} (ng \times h/ml) ^e	DRV/RTV ($n = 12$) 68,900 (59,700–79,500)	GZR + DRV/RTV ($n = 11$) ⁱ 76,400 (67,700–86,300)	GZR + DRV/RTV vs DRV/RTV 1.11 (0.99–1.24)	15.0
C_{max} (ng/ml) ^e	8,660 (7,990–9,610)	9,480 (8,430–10,700)	1.10 (0.96–1.25)	17.1
C_{12} (ng/ml) ^e	3,680 (2,950–4,600)	3,690 (2,980–4,580)	1.00 (0.85–1.18)	21.5
T_{max} (h) ^f	4.02 (2.02–5.00)	3.01 (1.99–6.00)		

^aPseudo-within-subject percent CV = $100 \times \sqrt{(\sigma^2_A + \sigma^2_B - 2\sigma_{AB})/2}$, where σ^2_A and σ^2_B are the estimated variances on the log scale for the two treatments and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

^bATV plasma PK following ATV/RTV administration alone and coadministration with GZR.

^cOne participant was discontinued by the investigator on day 3 of period 1.

^dOne participant was discontinued by the investigator on day 13 of period 2.

^eBack-transformed least-squares mean and CI from a linear mixed-effects model with natural-log-transformed values.

^fMedian and range are reported for T_{max} .

^gLPV plasma PK following LPV/RTV administration alone and coadministration with GZR.

^hDRV plasma PK following DRV/RTV administration alone and coadministration with GZR.

ⁱOne participant discontinued on day 6 of period 3, and one participant discontinued on day 1 of period 2.

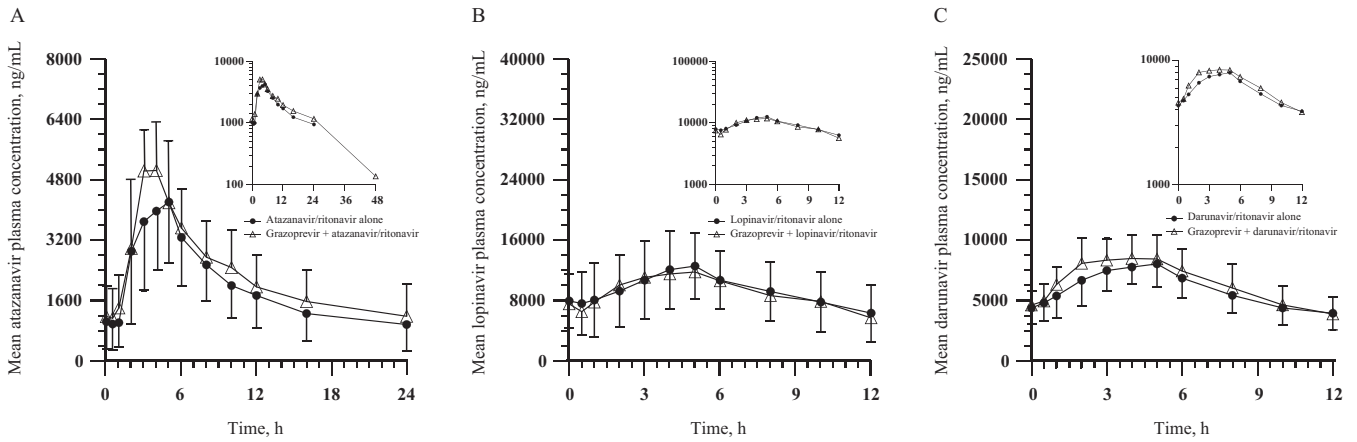


FIG 3 ATV, LPV, and DRV arithmetic mean \pm SD plasma concentration-time profiles following administration of boosted HIV protease inhibitor alone for 14 days and coadministration with 200 mg GZR once daily for 7 days to healthy adult participants: 300 mg ATV/100 mg RTV once daily (both arms, $n = 11$) (A), 400 mg LPV/100 mg RTV twice daily (both arms, $n = 13$) (B), or 600 mg DRV/100 mg RTV twice daily (DRV/RTV alone, $n = 12$; in combination with GZR, $n = 11$) (C) (insets, semilog scale).

Safety. In trial 1, 8 of 10 participants reported 41 postdose AEs (see Table S1 in the supplemental material); of those, 34 were considered drug related (4 following GZR alone, 14 following RTV alone, and 16 following GZR plus RTV). Two participants reported 3 severe AEs (abdominal pain and diarrhea in 1 participant and syncope in 1 participant), which were considered drug related by the investigator. The remaining AEs were mild to moderate in intensity and generally resolved at the completion of the trial. The most common drug-related AEs (≥ 2 occurrences) were headache, fatigue, abdominal discomfort, diarrhea, and nausea. No serious AEs, discontinuations due to AEs, or deaths occurred.

TABLE 5 Comparisons of EBR plasma PK following coadministration of 50 mg EBR once daily and 300 mg ATV/100 mg RTV once daily, 400 mg LPV/100 mg RTV twice daily, or 600 mg DRV/100 mg RTV twice daily for 7 days versus administration of (200 mg) GZR once daily for 7 days to healthy adult participants (trial 3)

PK parameter	GM (95% CI)	GM (95% CI)	GMR (90% CI)	Pseudo-within-subject CV (%) ^a
EBR/ATV/RTV ^b	EBR ($n = 10$)	EBR + ATV/RTV ($n = 8$) ^c	EBR + ATV/RTV vs EBR	
AUC ₀₋₂₄ ($\mu\text{M} \times \text{h}$) ^d	1.42 (1.04–1.96)	6.77 (5.18–8.85)	4.76 (4.07–5.56)	16.9
C _{max} (nM) ^d	97.5 (68.9–138)	405 (317–516)	4.15 (3.46–4.97)	20.5
C ₂₄ (nM) ^d	37.9 (27.3–52.6)	245 (181–330)	6.45 (5.51–7.54)	16.6
T _{max} (h) ^e	4.09 (3.00–6.04)	4.01 (3.01–8.01)		
EBR/LPV/RTV ^f	EBR ($n = 10$)	EBR + LPV/RTV ($n = 9$) ^g	EBR + LPV/RTV vs EBR	
AUC ₀₋₂₄ ($\mu\text{M} \times \text{h}$) ^d	1.43 (1.11–1.83)	5.29 (3.86–7.26)	3.71 (3.05–4.53)	22.4
C _{max} (nM) ^d	109 (86.7–137)	313 (225–434)	2.87 (2.29–3.58)	25.3
C ₂₄ (nM) ^d	40.6 (30.1–54.7)	186 (136–254)	4.58 (3.72–5.64)	23.7
T _{max} (h) ^e	5.00 (4.00–8.00)	5.00 (4.00–6.00)		
EBR/DRV/RTV ^h	EBR ($n = 10$)	EBR + DRV/RTV ($n = 8$) ⁱ	EBR + DRV/RTV vs EBR	
AUC ₀₋₂₄ ($\mu\text{M} \times \text{h}$) ^d	1.40 (0.972–2.00)	2.32 (1.71–3.15)	1.66 (1.35–2.05)	22.4
C _{max} (nM) ^d	96.4 (65.5–142)	161 (114–228)	1.67 (1.36–2.05)	22.1
C ₂₄ (nM) ^d	38.4 (24.9–59.2)	70.0 (47.8–102)	1.82 (1.39–2.39)	28.9
T _{max} (h) ^e	4.50 (2.00–6.00)	4.00 (2.01–5.00)		

^aPseudo-within-subject percent 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 two treatments and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

^bEBR plasma PK following EBR administration alone and coadministration with ATV/RTV.

^cOne participant was discontinued by the investigator on day 13 of period 2, and one participant was discontinued by the investigator on day 7 of period 2.

^dBack-transformed least-squares mean (ratio) and CI from a linear mixed-effects model with natural-log-transformed values.

^eMedian and range are reported for T_{max}.

^fEBR plasma PK following EBR administration alone and coadministration with LPV/RTV.

^gOne participant withdrew from the study on day 4 of period 2 (during the administration of LPV).

^hEBR plasma PK following EBR administration alone and coadministration with DRV/RTV.

ⁱOne participant was discontinued from the study on day 11 of period 2, and one participant was discontinued from the study on day 13 of period 2.

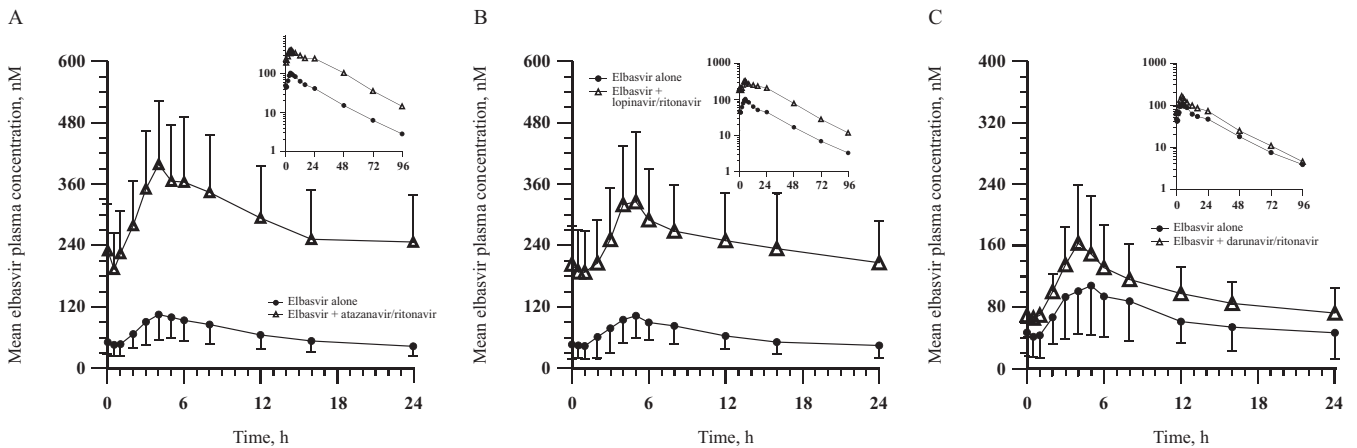


FIG 4 EBR arithmetic mean ± SD plasma concentration-time profiles following administration of 50 mg EBR once daily alone for 7 days and coadministration with 300 mg ATV/100 mg RTV once daily for 7 days (EBR alone, *n* = 10; in combination with ATV/RTV, *n* = 8) (A), 400 mg LPV/100 mg RTV twice daily for 7 days (EBR alone, *n* = 10; in combination with LPV/RTV, *n* = 9) (B), or 600 mg DRV/100 mg RTV twice daily for 7 days (EBR alone, *n* = 10; in combination with DRV/RTV, *n* = 8) (C) to healthy adult participants (insets, semilog scale).

In trial 2, 25 of 36 participants reported 74 AEs (Table S2), of which 55 were considered to be related to trial drug(s); 12 were considered to be related to GZR alone, 3 were related to GZR/ATV/RTV, 14 were related to ATV/RTV alone, 7 were related to GZR/LPV/RTV, 11 were related to LPV/RTV alone, 3 were related to GZR/DRV/RTV, and 5 were related to DRV/RTV alone. The most common drug-related AEs were headache and nausea. Most AEs were mild in intensity. No serious AEs or deaths occurred. Two participants discontinued treatment because of AEs; 1 participant discontinued treatment because of a drug-related maculopapular rash while receiving ATV/RTV alone, and 1 participant discontinued treatment because of an increased alanine aminotransferase

TABLE 6 Comparison of ATV, LPV, and DRV plasma PK following coadministration of 50 mg EBR once daily and 300 mg ATV/100 mg RTV once daily, 400 mg LPV/100 mg RTV twice daily, or 600 mg DRV/100 mg RTV twice daily for 7 days versus administration of the boosted HIV protease inhibitor for 14 days to healthy adult participants (trial 3)

PK parameter	GM (95% CI)	GM (95% CI)	GMR (90% CI)	Pseudo-within-subject CV (%) ^a
ATV PK parameters with EBR/ATV/RTV^b				
AUC ₀₋₂₄ (ng × h/ml) ^d	ATV/RTV, (<i>n</i> = 8) ^c 57,800 (46,000–72,500)	EBR + ATV/RTV (<i>n</i> = 8) ^c 61,700 (47,500–80,000)	EBR + ATV/RTV vs ATV/RTV 1.07 (0.98–1.17)	9.4
C _{max} (ng/ml) ^d	5,740 (4,720–6,970)	5,840 (4,790–7,100)	1.02 (0.96–1.08)	6.3
C ₂₄ (ng/ml) ^d	1,230 (803–1,880)	1,410 (899–2,220)	1.15 (1.02–1.19)	12.4
T _{max} (h) ^e	3.00 (2.00–5.00)	3.5 (2.00–5.00)		
LPV PK parameters with EBR/LPV/RTV^f				
AUC ₀₋₁₂ (ng × h/ml) ^d	LPV/RTV (<i>n</i> = 9) ^g 101,000 (83,300–121,000)	EBR + LPV/RTV (<i>n</i> = 9) ^g 103,000 (84,000–126,000)	EBR + LPV/RTV vs LPV/RTV 1.02 (0.93–1.13)	11.4
C _{max} (ng/ml) ^d	11,600 (9,880–13,600)	11,800 (10,200–13,800)	1.02 (0.92–1.13)	11.4
C ₁₂ (ng/ml) ^d	5,780 (4,210–7,930)	6,170 (4,490–8,480)	1.07 (0.97–1.18)	10.9
T _{max} (h) ^e	4.00 (3.00–6.00)	4.01 (3.00–8.00)		
DRV PK parameter with EBR/DRV/RTV^h				
AUC ₀₋₁₂ (ng × h/ml) ^d	DRV/RTV (<i>n</i> = 8) ⁱ 54,000 (48,700–60,000)	EBR + DRV/RTV (<i>n</i> = 8) ⁱ 51,400 (42,800–61,900)	EBR + DRV/RTV vs DRV/RTV 0.95 (0.86–1.06)	10.9
C _{max} (ng/ml) ^d	7,190 (6,650–7,900)	6,800 (5,720–8,090)	0.95 (0.85–1.05)	10.8
C ₁₂ (ng/ml) ^d	2,870 (2,230–3,700)	2,700 (2,030–3,600)	0.94 (0.85–1.05)	11.4
T _{max} (h) ^e	3.00 (2.00–5.00)	3.5 (2.00–5.00)		

^aPseudo-within-subject percent CV = 100 × sqrt((σ²_A + σ²_B - 2σ_{AB})/2), where σ²_A and σ²_B are the estimated variances on the log scale for the two treatments and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

^bATV plasma PK following ATV/RTV administration alone and coadministration with EBR.

^cOne participant was discontinued by the investigator on day 13 of period 2, and one participant was discontinued by the investigator on day 7 of period 2.

^dBack-transformed least-squares mean and CI from a linear mixed-effects model with natural-log-transformed values.

^eMedian and range are reported for T_{max}.

^fLPV plasma PK following LPV/RTV administration alone and coadministration with EBR.

^gOne participant withdrew from the study on day 4 of period 2 (during the administration of LPV).

^hDRV plasma PK following DRV/RTV administration alone and coadministration with EBR.

ⁱOne participant was discontinued from the study on day 11 of period 2, and one participant was discontinued from the study on day 13 of period 2.

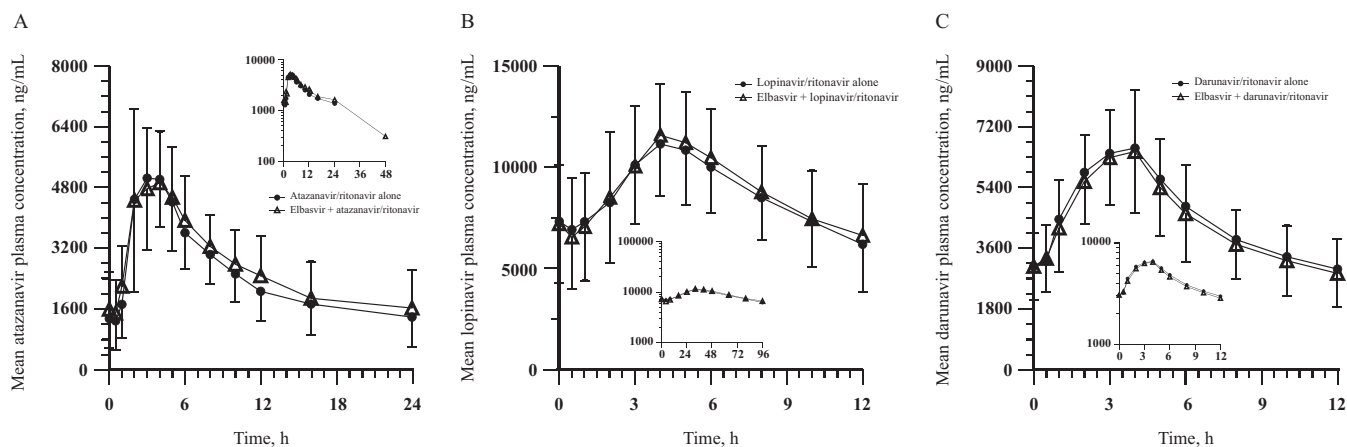


FIG 5 ATZ, LPV, and DRV arithmetic mean \pm SD plasma concentration-time profiles following administration of boosted HIV protease inhibitor alone for 14 days and coadministration with 50 mg EBR once daily for 7 days to healthy adult participants. (A) 300 mg ATZ/100 mg RTV once daily (both arms, $n = 8$). (B) 400 mg LPV/100 mg RTV twice daily (both arms, $n = 9$). (C) 600 mg DRV/100 mg RTV twice daily (both arms, $n = 8$) (insets, semilog scale).

(ALT) level while receiving GZR alone, which was considered by the investigator to be unrelated to the trial drug.

In trial 3, 20 of 30 participants reported 100 AEs (Table S3), of which 61 were considered to be related to trial drug(s); 2 were considered to be related to EBR alone, 3 were related to ATZ/RTV alone, 47 were related to LPV/RTV alone, and 9 were related to DRV/RTV alone. The most common drug-related AEs were diarrhea, abdominal pain, rash, and pruritus. All AEs were mild in intensity. No serious AEs or deaths occurred. Five participants discontinued treatment because of AEs, 2 while receiving ATZ/RTV (1 with a maculopapular rash and 1 a bilirubin level increase), 1 with multiple gastrointestinal AEs while receiving LPV/RTV, and 2 with mild papular/macropapular rashes while receiving DRV/RTV. The 3 cases of rash were each considered drug related, and the participant with gastrointestinal AEs withdrew from the trial. The participant with an elevated bilirubin level was discontinued from the trial by the investigator.

DISCUSSION

The combination of EBR and GZR has proved to be a potent direct-acting antiviral regimen for people with chronic HCV genotype 1 and 4 infections, in both clinical trials (10–14, 20–23) and real-world experience (24). Data from the present trials inform the use of EBR/GZR in HCV/HIV-coinfected people who are treated with HIV protease inhibitors. In the current trials, GZR was administered at a dose of 200 mg/day because it has \sim 2-fold greater exposure in HCV-infected people than in healthy people at steady state. Therefore, the 200-mg dose in healthy participants was selected to match the exposure achieved when administering a 100-mg dose, which is the approved dose for the treatment of HCV infection (8, 9). In trial 3, EBR was administered at a dose of 50 mg/day, since this is the indicated dose for HCV-infected individuals (8, 9) and EBR PK are similar for HCV-infected and healthy people. RTV-boosted ATZ, LPV, or DRV was administered at the clinically indicated doses.

The GZR/RTV interaction trial (trial 1) was designed as a one-way interaction trial investigating the effect of RTV on GZR, because it was not anticipated that GZR would perpetrate interactions with RTV based on the known metabolic and transporter properties of the two drugs. In the GZR/RTV trial, the coadministration of multiple, twice-daily, oral doses of 100 mg RTV with a single oral dose of 200 mg GZR increased the $AUC_{0-\infty}$ of GZR 2-fold, while the C_{max} was relatively unchanged. This increase is likely attributable to CYP3A/P-gp inhibition by RTV (4), since a similar increase was observed for GZR when it was administered in combination with the strong CYP3A4/P-gp inhibitor ketoconazole (8, 9). This magnitude of increase is not considered clinically relevant for GZR, but it is also noted that twice-daily administration of 100 mg of RTV is not a clinically relevant dose when RTV

is administered alone with other HIV protease inhibitors (25). The potential for higher doses of RTV to inhibit OATP1B (16) and thereby further increase GZR exposure cannot be excluded and has not been evaluated clinically.

In the trials of RTV-boosted ATV, LPV, or DRV administered in combination with GZR, the potential for drug interactions was assessed after repeated GZR administration, owing to the nonlinear and time-dependent PK of GZR (8, 9). GZR was expected to have reached steady state after 7 days of dosing, based on the $t_{1/2}$ of 30 h. The trials of RTV-boosted ATV, LPV, or DRV administered with EBR were also designed as multiple-dose trials in order to parallel the trial design for the trials of RTV-boosted ATV, LPV, or DRV combined with GZR. Steady-state PK of ATV, LPV, and DRV were not meaningfully altered by the coadministration of GZR or EBR. The lack of an effect of EBR or GZR on ATV, LPV, and DRV PK profiles is consistent with the known major elimination mechanism involving CYP3A for HIV protease inhibitors (4) and the weak inhibitory potency of GZR toward CYP3A. In contrast, GZR and EBR exposures increased with coadministration of HIV protease inhibitors, with AUC_{0-24} geometric mean ratios (GMRs) ranging from 7.5- to 13-fold for GZR and from 2- to 5-fold for EBR. GZR is a substrate of CYP3A/P-gp and OATP1B (8, 9). The increase in the exposure of GZR when it is coadministered with ATV/RTV, LPV/RTV, and DRV/RTV cannot be explained solely on the basis of CYP3A/P-gp-mediated interactions, since the effects of ATV/RTV, LPV/RTV, and DRV/RTV on GZR were substantially larger than that of RTV alone. Because, based on *in vitro* and clinical data, GZR is also a known OATP1B substrate (8, 9), the greater magnitude of GZR exposure when RTV is used in combination with ATV, LPV, or DRV might be due to OATP1B inhibition. *In vitro* and clinical data suggest that the HIV protease inhibitors have the potential to inhibit OATP1B (4). Additionally, based on *in vitro* data and the calculated K_i values at the clinically relevant doses, the rank order of OATP1B1 inhibition potential of the HIV protease inhibitors at the clinically relevant doses is as follows: LPV > ATV > DRV (16). This rank order is consistent with the trend observed with the magnitude of the effect on GZR exposures in the clinical trials. Furthermore, the magnitude of the increase in GZR exposure with RTV-boosted HIV protease inhibitors is greater than that with RTV alone (CYP3A/P-gp inhibition) and is comparable to that with intravenous rifampin (primarily OATP1B inhibition) alone (8, 9, 26) and with cyclosporine alone (8, 9). These results suggest that OATP1B inhibition is an important component of the interaction between RTV-boosted HIV protease inhibitors and GZR, that GZR is a sensitive OATP1B substrate, and that the pathway of OATP1B-mediated hepatic uptake of GZR is a probable rate-limiting step in GZR disposition, compared with CYP3A-mediated metabolism (27). Nevertheless, CYP3A inhibition may also contribute, as ATV, LPV, and DRV are also strong CYP3A inhibitors.

Increased GZR exposure is associated with late ALT/aspartate aminotransferase (AST) elevation events (8, 9, 28), which are defined as increases in ALT and/or AST levels of >5-fold above the upper limits of normal after treatment week 4 in a person with at least 1 ALT and/or AST value in the normal range between treatment week 2 and treatment week 4. These events were initially observed in a phase 2 dose-ranging trial of GZR in combination with pegylated interferon and ribavirin for the treatment of HCV genotype 1 and 3 infection in participants who received high doses of GZR (up to 800 mg/day) (29). PK/pharmacodynamic analyses indicated that an 8- to 13-fold increase in GZR exposure may considerably increase the risk of transaminase elevations and could consequently lead to further liver injury in individuals with already impaired liver function. Therefore, the concomitant use of RTV-boosted HIV protease inhibitors was excluded in phase 2 and 3 trials, and the coadministration of EBR/GZR with HIV protease inhibitors is contraindicated, owing to the potential for increased risk of late transaminase elevations due to high GZR exposure (8, 9).

The increase in EBR exposure when EBR is coadministered with RTV-boosted HIV protease inhibitors is likely due in part to CYP3A inhibition. The effect of RTV alone on EBR PK was not evaluated, but it is expected that RTV would increase EBR exposure by about 2-fold, based on clinical data on drug-drug interactions with ketoconazole (a strong CYP3A/P-gp inhibitor) (8, 9). The minor increase in EBR exposure is not consid-

ered clinically relevant, based on the EBR exposure distribution among participants in the phase 3 trials, which demonstrated favorable efficacy and safety profiles.

ATV alone, saquinavir/RTV, and tipranavir/RTV were not directly assessed in a clinical drug-drug interaction trial with GZR and/or EBR, but they are known inhibitors of CYP3A (4) and several drug transporters (30). In addition, *in vitro* data and the associated *R* values calculated at the clinically relevant doses suggest that ATV alone, saquinavir, and tipranavir would likely demonstrate clinically relevant OATP1B inhibition (4, 16). Based on the similarity of enzyme/transporter inhibition profiles to those of the RTV-boosted protease inhibitors included in this clinical trial, it is predicted that ATV alone, saquinavir/RTV, and tipranavir/RTV would also considerably increase GZR concentrations. Therefore, the concomitant use of HIV protease inhibitors, including ATV, saquinavir/RTV, and tipranavir/RTV, is contraindicated in individuals taking GZR/EBR (8, 9). Cobicistat is an inhibitor of CYP3A, CYP2D6, P-gp, and OATP1B (4, 31). Cobicistat is metabolized by CYP3A and, to a minor extent, by CYP2D6 (31). A drug-drug interaction trial with EBR/GZR and elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine demonstrated a >5-fold increase in GZR exposure, which can be attributed to a combination of the inhibition of CYP3A and OATP1B by cobicistat (31, 32). Based on these data and findings described in the current publication, it is predicted that HIV protease inhibitors boosted by cobicistat would result in considerably higher GZR exposures. For this reason, many HIV protease inhibitors boosted with cobicistat are contraindicated or not recommended for use with EBR/GZR (8, 9).

Alternative HIV medications such as nucleoside reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitor rilpivirine, or the integrase inhibitors dolutegravir and raltegravir can be coadministered with EBR/GZR without dose adjustment (4, 8, 9, 33). In a phase 3 trial of EBR/GZR in 218 participants coinfecting with HIV and HCV genotype 1, 4, or 6, sustained virologic responses 12 weeks after the end of treatment were achieved by 210 participants (96%) (14). Approximately 52% and 27% of the participants in that study were receiving raltegravir and dolutegravir, respectively. The drug-drug interaction potential for bicitgravir and EBR/GZR has not been evaluated clinically.

While coadministration of either GZR or EBR with HIV protease inhibitors boosted with RTV did not have an appreciable effect on the PK of ATV, LPV, or DRV, significant increases in GZR exposure were observed and are attributable to CYP3A and OATP1B inhibition. HCV protease inhibitors are substrates of CYP3A and OATP1B, and HIV protease inhibitors are inhibitors of these pathways; therefore, the drug-drug interactions between these two classes of HCV and HIV therapies, as described here, have been observed with many of the currently available HCV protease inhibitors, such as simeprevir, paritaprevir, glecaprevir, and voxilaprevir (34–38). Because increased GZR exposure is associated with late ALT/AST elevation events, coadministration of the EBR/GZR fixed-dose combination with ATV, LPV, or DRV is contraindicated, and HIV antiretroviral therapy regimens that do not include HIV protease inhibitors should be considered for HCV/HIV-coinfecting individuals treated with EBR/GZR.

MATERIALS AND METHODS

Ethics approval and consent. The protocols and informed consent forms were reviewed and approved by the Medical Ethics Review Committee of University Hospitals Leuven (Leuven, Belgium) (trial 1) and Chesapeake Research Review Inc. (Columbia, MD) (trials 2 and 3). All participants provided written informed consent. The trials were performed under the Declaration of Helsinki, ICH good clinical practice guidelines, and the code of conduct for clinical trials of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Kenilworth, NJ).

Participants. All three trials enrolled healthy male or female adult participants, 18 to 45 years of age (trial 1) or 18 to 55 years of age (trials 2 and 3). All participants were required to have normal body mass index and no clinically significant abnormalities in laboratory profiles, vital signs, or electrocardiograms. Individuals with a history or presence of significant illness were excluded from the trials. People who had a positive urine screen for drugs or who had used inhibitors of CYP or P-gp/OATP or inducers of CYP within 14 and 28 days of the first dose, respectively, were also excluded.

Trial design. Trial 1 (GZR/RTV) was a two-period, fixed-sequence trial. In period 1, all participants received a single oral dose of GZR (200 mg) on day 1, followed by an 8-day washout. In period 2, participants received 100 mg RTV twice daily for 21 days. On day 15, participants received the morning RTV dose with a single oral dose of 200 mg GZR. Participants fasted from all food and drink (except water)

for 8 h prior to receiving GZR. In period 2, RTV was taken with food except on the morning of day 15, when RTV was coadministered with GZR. Blood samples were collected in vials with K₂EDTA before the dose and up to 96 h after the day 1 dose and up to 168 h after the day 15 dose for GZR PK analyses. Immediately after collection, the samples were centrifuged at 1,000 to 1,300 relative centrifugal force (RCF) ($\times g$) at 4°C to 10°C for 10 min, the resulting plasma was transferred to cryotubes, and samples were stored at -20°C until analysis.

Trials 2 and 3 both were open-label, fixed-sequence, three-period trials, one with GZR (trial 2; GZR/HIV protease inhibitors/RTV) and the other with EBR (trial 3; EBR/HIV protease inhibitors/RTV). In period 1 of trial 2, all participants received 200 mg GZR once daily for 7 days, followed by a 7-day washout. In period 2, participants received 300 mg ATV/100 mg RTV once daily, 400 mg LPV/100 mg RTV twice daily, or 600 mg DRV/100 mg RTV twice daily for 14 days, with no subsequent washout. In period 3, participants received the same combination of RTV-boosted HIV protease inhibitors as administered in period 2 in combination with 200 mg GZR once daily for 7 days. A moderate-fat breakfast was administered prior to all doses. A similar treatment regimen was followed for the EBR trial (trial 3), with 50 mg EBR once daily for 7 days administered in periods 1 and 3. In trials 2 and 3, blood samples were collected before the dose and up to 96 h after the day 7 dose of period 1 and period 3 for GZR and EBR. Blood samples for the determination of plasma concentrations of LPV and DRV were collected before the dose and up to 24 h after the dose on day 14 of period 2 and on day 7 of period 3. Blood samples for ATV were collected before the dose and up to 24 h after the dose on day 14 of period 2 and up to 96 h after the dose on day 7 of period 3. Blood samples for GZR and EBR analyses were collected in K₂EDTA-containing tubes, and samples for HIV protease inhibitor analyses were collected in K₂EDTA-containing tubes (trial 2) or K₃EDTA-containing tubes (trial 3). Immediately after collection, the samples were centrifuged at 1,000 to 1,300 RCF ($\times g$) (for EBR and GZR) or 650 to 1,450 RCF ($\times g$) (for HIV protease inhibitors) at 4°C to 10°C for 10 to 15 min. The resulting plasma was transferred to cryotubes, and samples were stored at -20°C until analysis.

Pharmacokinetic evaluations. (i) Analytical assessments. Plasma samples for GZR were analyzed using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, with a lower limit of quantification of 1.3 nM (1.0 ng/ml) (range, 1.3 to 1,300 nM [1.0 to 1,000.0 ng/ml]), by PPD Laboratories (Richmond, VA). Plasma samples for EBR were analyzed using a validated high-performance liquid chromatography (HPLC)-MS/MS method, with a lower limit of quantification of 0.283 nM (0.25 ng/ml) (range, 0.283 to 566 nM [0.25 to 500.0 ng/ml]), by Merck Research Laboratories (Oss, The Netherlands). Plasma ATV, LPV, and DRV concentrations were determined using validated methods employing either protein precipitation or LC-MS/MS, by PPD Laboratories. The lower limits of quantification for ATV, LPV, and DRV were all 10.0 ng/ml. The analytical ranges of quantitation for all assays were 10.0 to 10,000 ng/ml.

(ii) Pharmacokinetic methods. PK parameters of interest (as appropriate for each analyte) were the following: $AUC_{0-\infty}$, AUC_{0-24} , C_{max} , plasma concentration at 12 h (C_{12}), C_{24} and T_{max} , C_{max} , C_{24} and C_{12} values were determined directly from the observed plasma concentration-time data. AUC values were calculated using noncompartmental analysis with the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. C_{24} and C_{12} values were determined using SAS (version 9.1); all other PK parameters were calculated using Phoenix WinNonlin software (version 6.3).

Safety. In all three trials, safety was assessed by AE monitoring, physical examinations, monitoring of vital signs, electrocardiograms, and laboratory safety assessments.

Statistical analysis and sample sizes. Individual AUC values were natural log transformed and evaluated with a linear mixed-effects model with a fixed effect for treatment. The covariance structure for the repeated observations was assumed to be compound symmetry (trial 1) or unstructured (trials 2 and 3). The Kenward-Roger method was used to calculate the denominator degrees of freedom for the fixed effects. A two-sided 90% confidence interval (CI) for the true mean difference (coadministration minus administration alone) in ln AUC was obtained from the model. These confidence limits were then exponentiated to obtain a CI for the true geometric mean (GM) AUC ratio (coadministration/administration alone). C_{max} and C_{24} (or C_{12} for LPV and DRV) for GZR, EBR, and the HIV protease inhibitor were analyzed in a similar fashion.

With a sample size of 10 participants in trial 1, the half-width of the 90% CI for the GZR $AUC_{0-\infty}$ GMR on the natural log scale would be 0.22 assuming a within-participant standard deviation (SD) of 0.27 on the natural log scale. With a sample size of 10 participants in trial 2, the half-width of the 90% CI for the GMR on the natural log scale would be 0.21 assuming a within-participant SD of 0.26 on the natural log scale (GZR AUC_{0-24}), 0.15 assuming a within-participant SD of 0.18 on the natural log scale (ATV AUC_{0-24}), 0.11 assuming a within-participant SD of 0.14 on the natural log scale (LPV area under the concentration-time curve from 0 to 12 h [AUC_{0-12}]), and 0.16 assuming a within-participant SD of 0.19 on the natural log scale (DRV AUC_{0-12}). With a sample size of 8 participants in trial 3, the half-width of the 90% CI for the GMR on the natural log scale would be 0.11 assuming a within-participant SD of 0.12 on the natural log scale (EBR AUC_{0-24}), 0.15 assuming a within-participant SD of 0.18 on the natural log scale (ATV AUC_{0-24}), 0.11 assuming a within-participant SD of 0.14 on the natural log scale (LPV AUC_{0-12}), and 0.16 assuming a within-participant SD of 0.19 on the natural log scale (DRV AUC_{0-12}).

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at <https://doi.org/10.1128/AAC.02142-18>.

SUPPLEMENTAL FILE 1, PDF file, 0.3 MB.

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