Pharmacokinetic Interactions Between the HCV Inhibitors Elbasvir and Grazoprevir and HIV Protease Inhibitors Ritonavir, Atazanavir, Lopinavir, or Darunavir in Healthy Participants

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Running head: PK DDI between EBR/GZR and HIV PI

ABSTRACT

The combination of the hepatitis C virus (HCV) NS5A inhibitor elbasvir and NS3/4A protease inhibitor grazoprevir is a potent, once-daily therapy indicated for the treatment of chronic HCV infection in individuals coinfected with human immunodeficiency virus-1 (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 in healthy participants were conducted to evaluate the effect of ritonavir on the pharmacokinetics of grazoprevir (N = 10) and the potential 2-way pharmacokinetic interaction 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: geometric mean ratio (GMR) for grazoprevir + 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 (7.78 to 14.39), 12.86 (10.25 to 16.13), and 7.50 (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 (4.07 to 5.56), 3.71 (3.05 to 4.53), and 1.66 (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. As such, HIV treatment regimens without HIV protease inhibitors should be considered in HCV/HIV-coinfected individuals who are treated with elbasvir/grazoprevir.

KEYWORDS

elbasvir, grazoprevir, ritonavir, atazanavir, lopinavir, darunavir

INTRODUCTION

Globally, 2.3 million people infected with human immunodeficiency virus (HIV) also are infected with the hepatitis C virus (HCV) (1). Chronic HCV infection is a major cause of morbidity and mortality in individuals coinfected with HIV and HCV (2). HCV/HIV-coinfected people are at a 2-fold greater risk for cirrhosis and a 6-fold greater risk for decompensated liver disease than are people with HIV infection who are not coinfected with HCV (3). These risks are even higher among coinfected 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). Treatment of HCV infection in the HIV-infected population therefore represents an important unmet medical need.

Elbasvir (EBR) is a small molecule inhibitor of hepatitis C virus (HCV) non-structural (NS) protein 5A, and grazoprevir (GZR) is a reversible, noncovalent, competitive inhibitor of the HCV NS3/4A protease (6, 7). The fixed-dose combination of EBR/GZR is indicated for the treatment of chronic HCV genotype 1 or 4 infection (8, 9) and 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 reaches time to maximal concentration (T_{max}) at ~3 hours, with a mean half-life ($t_{1/2}$) of ~24 hours (8, 9). Elbasvir elimination is mediated by both cytochrome P450 (CYP) 3A metabolism and excretion of the parent compound (8, 9). Elimination of EBR into urine is negligible. Elbasvir is a substrate of CYP3A and P-glycoprotein (P-gp), 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 reaches T_{max} at ~2 hours and

71 undergoes rapid uptake into the liver via organic anion transporting polypeptide 1B (OATP1B)
72 (8, 9). The mean $t_{1/2}$ of GZR is ~31 hours (8, 9). Grazoprevir is eliminated predominantly into
73 feces as the parent compound and as CYP3A oxidative metabolites. In addition to OATP1B and
74 CYP3A, GZR is a substrate of P-gp, a weak CYP3A inhibitor, and a BCRP inhibitor (8, 9, 15).
75 Based on the $t_{1/2}$, EBR and GZR are expected to reach state steady state within 7 days following
76 once-daily administration.

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

87 Because treatment of HCV/HIV coinfection represents an important unmet medical need,
88 and as the overlapping and inhibitory metabolic pathways of CYP3A, P-gp, and OATP1B
89 between EBR/GZR and HIV protease inhibitors suggest potential for drug interactions, the effect
90 of multiple doses of RTV, ATV/RTV, LPV/RTV, and DRV/RTV on GZR and EBR
91 pharmacokinetics was evaluated in 3 separate open-label trials: 1 trial assessing the effect of
92 RTV on the pharmacokinetics of GZR (Trial 1; Merck trial number MK-5172-PN006; EudraCT

ID, 2011-001242-15) and 2 trials assessing the potential 2-way pharmacokinetic (PK) interaction of GZR (Trial 2; MK-5172-PN029) or EBR (Trial 3; MK-8742 PN017) when coadministered with the RTV-boosted HIV protease inhibitors, ATV, LPV, or DRV.

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 were discontinued in the ATV arm, 1 secondary to an AE and 1 who was lost to follow-up. Two participants were 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 (1 each in the ATV arm and 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

Trial 1: GZR/RTV

Coadministration of RTV with GZR increased single-dose GZR $AUC_{0-\infty}$ and C_{24} by approximately 2-fold (**Table 2** and **Figure 1**). Median T_{max} of GZR was unaffected by coadministration of GZR with RTV (**Table 2**).

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Trial 2: GZR/HIV protease inhibitor/RTV

GZR exposure was increased when GZR was coadministered with each of the 3 HIV protease inhibitor/RTV combinations, with GZR AUC_{0-24} exposures 8 to 13 times higher than when GZR was administered alone (**Table 3** and **Figure 2**). Median T_{max} of GZR administered alone was generally comparable to that when GZR was coadministered with RTV-boosted HIV protease inhibitors.

GZR 200 mg once daily increased ATV exposure (AUC_{0-24}, C_{max}, and C_{24}) by 12% to 43% following coadministration of ATV/RTV once daily and GZR once daily (**Table 4** and **Figure 3**). LPV and DRV exposures were similar following coadministration of either RTV-boosted HIV protease inhibitor with GZR compared with administration of LPV/RTV alone or DRV/RTV alone (**Table 4 and Figure 3**). Median T_{max} of the boosted HIV protease inhibitors administered alone was generally comparable to that when these agents were coadministered with GZR.

Trial 3: EBR/HIV protease inhibitor/RTV

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

Coadministration of EBR with RTV-boosted ATV, LPV, or DRV generally did not meaningfully affect the pharmacokinetics of ATV, LPV, and DRV (**Table 6** and **Figure 5**). Median T_{max} of ATV, LPV, or DRV were unaffected by coadministration with EBR.

Safety

In Trial 1, 8 of 10 participants reported 41 postdose AEs (**Table S1**); of these, 34 were considered drug related (4 following GZR alone, 14 following RTV alone, and 16 following GZR + RTV). Two participants reported 3 severe AEs (abdominal pain and diarrhea in 1 participant and syncope in a second participant) that 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.

In Trial 2, 25 of 36 participants reported 74 AEs (**Table S2**), of which 55 were considered related to trial drug(s): 12 were considered 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. The majority of AEs were mild in intensity. No serious AEs or deaths occurred. Two participants discontinued treatment because of AEs, 1 participant discontinued because of a drug-related maculo-papular rash while receiving ATV/RTV alone, and 1 participant discontinued treatment owing to an

increased 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 related to trial drug(s): 2 were considered related to EBR alone, 3 were related to ATV/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 were mild in intensity. No serious AEs or deaths occurred. Five participants discontinued treatment because of AEs, 2 while receiving ATV/RTV (1 each of maculopapular rash and bilirubin increase), 1 owing to multiple gastrointestinal AEs while receiving LPV/RTV, and 2 owing to mild papular/macropapular rashes in participants 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, 18-21) and real-world experience (22). 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 a ~2-fold higher exposure in HCV-infected people compared with healthy people at steady state. The 200-mg dose in healthy

participants was therefore 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 is similar between HCV-infected and healthy people. Ritonavir-boosted ATV, 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 both 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 C_{max} was relatively unchanged. This increase is likely attributed to CYP3A/P-gp inhibition by RTV (4), since a similar increase was observed for GZR when administered in combination with the strong CYP3A4/P-gp inhibitor ketoconazole (8, 9). This magnitude of increase is not considered clinically relevant for GZR, yet 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 (23). 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 pharmacokinetics of GZR (8, 9). Grazoprevir was expected to have reached steady state after 7 days of dosing based on the half-life 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 with the trials of RTV-boosted ATV, LPV, or DRV combined with GZR. Steady-state pharmacokinetics 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 of 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 $AUC_{0\text{-}24}$ 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 coadministered with ATV/RTV, LPV/RTV, and DRV/RTV cannot be explained based solely on CYP3A/P-gp-mediated interactions, since the effect of ATV/RTV, LPV/RTV, and DRV/RTV on GZR was 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, LRV, or DRV might be due to OATP1B inhibition. In vitro and clinical data suggest that the HIV protease inhibitors have a 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 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 of GZR exposure with RTV-boosted HIV protease inhibitors is greater than with RTV alone (CYP3A/P-gp inhibition) and is comparable to that with intravenous rifampin (primarily OATP1B-inhibition) alone (8, 9, 24) and with cyclosporine alone (8, 9). These results suggest that OATP1B inhibition is an important component in the interaction between RTV-boosted HIV protease inhibitors and GZR, that GZR

is a sensitive OATP1B substrate, and the pathway of OATP1B-mediated hepatic uptake of GZR is a probable rate-limiting step in GZR disposition as compared to CYP3A-mediated metabolism (25). 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, 26), which are defined as an increase in ALT and/or AST levels of >5-fold above upper limits of normal after treatment week 4 in a person with at least 1 value of ALT and/or AST 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 genotypes 1 and 3 infection in participants who received high doses of GZR (up to 800 mg/day) (27). Pharmacokinetic/pharmacodynamic analyses indicated that an 8- to 13-fold increase of 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. The concomitant use of RTV-boosted HIV protease inhibitors was therefore 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 from 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 pharmacokinetics was not evaluated, but it is expected that RTV will increase EBR exposure by about 2-fold based on clinical drug–drug interaction data with ketoconazole (a strong CYP3A/P-gp inhibitor) (8, 9). The minor increase in EBR exposure is not considered clinically relevant,

based on the EBR exposure distribution in participants in the phase 3 trials that demonstrated favorable efficacy and safety profiles.

Atazanavir 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 inhibitors (4) and several drug transporters (28). In addition, in vitro data and the associated R-values calculated at the clinically relevant doses suggest that ATV alone, saquinavir, and tipranavir will 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 will also considerably increase GZR concentrations. As such, 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, 29). Cobicistat is metabolized by CYP3A and, to a minor extent, by CYP2D6 (29). 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 (29, 30). Based on these data and findings described in the current publication, it is predicted that HIV protease inhibitors boosted by cobicistat will 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).

Alternate 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, 31). In a phase 3 trial of EBR/GZR in 218 participants coinfected with HIV and HCV genotype 1, 4, or 6, sustained virologic response 12 weeks after the end of treatment was achieved by 210 (96%) of participants (14, 32). Approximately 52% and 27% of the participants in this study were on raltegravir and dolutegravir, respectively. The drug–drug interaction potential for bictegravir 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 pharmacokinetics of ATV, LPV, or DRV, significant increases in GZR exposure were observed that 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, and therefore the drug–drug interactions between these 2 classes of HCV and HIV therapies as described in this manuscript have been observed with many of the currently available HCV protease inhibitors, such as simeprevir, paritaprevir, glecaprevir, and voxilaprevir (33-37). Because increased GZR exposure is associated with late ALT/AST elevation events, the 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 in HCV/HIV-coinfected individuals treated with EBR/GZR.

METHODS

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, Maryland (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 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, Code of Conduct for Clinical Trials.

Participants

All 3 trials enrolled healthy male or female adult participants aged 18 to 45 years (Trial 1) or aged 18 to 55 years (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 with a positive urine screen for drugs or who used inhibitors of CYP or P-gp/OATP or inducers of CYP, within 14 and 28 days of first dose, respectively, were also excluded.

Trial Design

Trial 1 (GZR/RTV) was a 2-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 wash-out. In period 2, participants received RTV 100 mg twice daily for 21 days. On day 15, participants received the morning RTV dose with a single oral dose of GZR 200 mg. Participants fasted from all food and drink (except water) for 8 hours 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 K_2EDTA predose and up to 96 hours post–day 1 dose and up to 168 hours post–day 15 dose for GZR pharmacokinetics. Immediately after collection, the samples were centrifuged between 1,000 and 1,300 RCF (× g) at 4°C to 10°C for 10 minutes, 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, 3-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 GZR 200 mg once daily for 7 days, followed by a 7-day washout. In period 2, participants received ATV 300 mg/RTV 100 mg once daily, LPV 400 mg/RTV 100 mg twice daily, or DRV 600 mg/RTV 100 mg twice daily for 14 days with no subsequent washout. In period 3, participants received the same combination of RTV-boosted HIV protease inhibitor as administered in period 2 in combination with GZR 200 mg 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 predose and up to 96 hours post–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 predose and up to 24 hours postdose on day 14 of period 2 and on day 7 of period 3. Blood samples for ATV were collected predose and up to 24 hours postdose on day 14 of period 2 and up to 96 hours post–day 7 dose of period 3. Blood samples for GZR and EBR analyses were collected in K_2EDTA tubes and samples for HIV protease inhibitor analyses were collected in K_2EDTA tubes (Trial 2) or K_3EDTA tubes (Trial 3). Immediately after collection, the samples were centrifuged between 1,000 and 1,300 RCF (× g) (for EBR and GZR) or between 650 and1450

RCF (× g) (for HIV protease inhibitors) at 4°C to 10°C for 10 to 15 minutes. The resulting plasma was transferred to cryotubes and samples were stored at –20°C until analysis.

Pharmacokinetic Evaluations

Analytical Assessments

GZR

Plasma samples for GZR were analyzed using a validated liquid chromatography with 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 1300 nM, or 1.0 to 1000.0 ng/ml) by PPD Laboratories, Richmond, VA.

EBR

Plasma samples for EBR were analyzed using a validated HPLC-MS/MS method, with a lower limit of quantification of 0.283 nM (0.25 ng/ml) (range, 0.283 to 566 nM, or 0.25 to 500.0 ng/ml) by Merck Research Laboratories, Oss, The Netherlands.

ATV/LPV/DRV

Plasma ATV, LPV, and DRV concentrations were determined using validated methods employing either protein precipitation or LC-MS/MS by PPD Laboratories, Richmond, VA. The

LLOQs for ATZ, 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.

Pharmacokinetic Methods

Pharmacokinetic (PK) parameters of interest (as appropriate for each analyte) were the following: area under the concentration versus time curve from 0 to infinity ($AUC_{0-\infty}$), area under the concentration-time curve from 0 to 24 h (AUC_{0-24}), maximum observed plasma concentration (C_{max}), plasma concentration at 12 hours (C_{12}), plasma concentration at 24 hours (C_{24}), and T_{max}.

C_{max}, C_{24}, and C_{12} values were directly determined from the observed plasma concentration-time data. AUC was calculated using the noncompartmental analysis with the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. C_{24} and C_{12} were obtained using SAS (Version 9.1); all other PK parameters were calculated using the software Phoenix® WinNonlin® (version 6.3).

Safety

In all 3 trials, safety was assessed by monitoring adverse events (AEs), physical examinations, 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 2-sided 90% confidence interval for the true mean difference (coadministration – administration alone) in ln-AUC was obtained from the model. These confidence limits were then exponentiated to obtain a confidence interval for the true geometric mean AUC ratio (coadministration / administration alone). C_{max} and C_{24} (or C_{12} for LPV and DRV) of 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% confidence interval 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% confidence interval 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 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% confidence interval 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}).

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H-PF contributed to the analysis of the data, interpretation of the results, drafting the manuscript, and reviewing/revising the manuscript.

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AAC

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421 KD contributed to the analysis of the data and reviewing/revising the manuscript.
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423 WDH contributed to the study design and reviewing/revising the manuscript.
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599

600

601 **Figure 1.** Grazoprevir arithmetic mean (±SD) plasma concentration-time profiles following
602 administration of a single oral dose of 200 mg grazoprevir with and without the coadministration
603 of multiple twice daily oral doses of 100 mg ritonavir for 15 days to healthy adult participants (*N*
604 = 10) (inset = semi-log scale).

605

606 **Figure 2.** Grazoprevir arithmetic mean (±SD) plasma concentration-time profiles following
607 administration of grazoprevir 200 mg once daily alone for 7 days and coadministration with (A)
608 300 mg atazanavir/100 mg ritonavir once daily for 7 days (grazoprevir alone, *N* = 12; in
609 combination with atazanavir/ritonavir, *N* = 11), (B) 400 mg lopinavir/100 mg ritonavir twice
610 daily for 7 days (*N* = 13, both arms), or (C) 600 mg darunavir/100 mg ritonavir twice daily for 7
611 days (grazoprevir alone, *N* = 13; in combination with darunavir/ritonavir, *N* = 11) to healthy
612 adult participants (insets = semi-log scale).

613

614 **Figure 3.** Atazanavir, lopinavir, and darunavir arithmetic mean (±SD) plasma concentration-time
615 profiles following administration of boosted HIV protease inhibitor alone for 14 days and
616 coadministration with grazoprevir 200 mg once daily for 7 days to healthy adult participants: (A)
617 300 mg atazanavir/100 mg ritonavir once daily (*N* = 11, both arms), (B) 400 mg lopinavir/100
618 mg ritonavir twice daily (*N* = 13, both arms), or (C) 600 mg darunavir/100 mg ritonavir twice
619 daily (darunavir/ritonavir alone, *N* = 12; in combination with grazoprevir, *N* = 11) (insets = semi-
620 log scale).

621

Figure 4. Elbasvir arithmetic mean (±SD) plasma concentration-time profiles following administration of elbasvir 50 mg once daily alone for 7 days and coadministration with (A) 300 mg atazanavir/100 mg ritonavir once daily for 7 days (elbasvir alone, *N* = 10; in combination with atazanavir/ritonavir, *N* = 8), (B) 400 mg lopinavir/100 mg ritonavir twice daily for 7 days (elbasvir alone, *N* = 10; in combination with lopinavir/ritonavir, *N* = 9), or (C) 600 mg darunavir/100 mg ritonavir twice daily for 7 days (elbasvir alone, *N* = 10; in combination with darunavir/ritonavir, *N* = 8) to healthy adult participants (insets = semi-log scale).

Figure 5. Atazanavir, lopinavir, and darunavir arithmetic mean (±SD) plasma concentration-time profiles following administration of boosted HIV protease inhibitor alone for 14 days and coadministration with elbasvir 50 mg once daily for 7 days to healthy adult participants: (A) 300 mg atazanavir/100 mg ritonavir once daily (*N* = 8, both arms), (B) 400 mg lopinavir/100 mg ritonavir twice daily (*N* = 9, both arms), or (C) 600 mg darunavir/100 mg ritonavir twice daily (*N* = 8, both arms) (insets = semi-log scale).

637 **Table 1.** Participant characteristics[a]

	GZR + RTV (*N* = 10)	**GZR +**			**EBR +**		
		ATV/RTV (*n* = 13)	**LPV/RTV (*n* = 13)**	**DRV/RTV (*n* = 13)**	**ATV/RTV (*n* = 10)**	**LPV/RTV (*n* = 10)**	**DRV/RTV (*n* = 10)**
Sex, *n* (%)							
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, *n* (%)							
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, *n* (%)							
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), years	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)

638 [a]Abbreviations: ATV, atazanavir; DRV, darunavir; EBR, elbasvir; GZR, grazoprevir; LPV, lopinavir; RTV, ritonavir.

639

640 **Table 2**. Comparison of grazoprevir plasma pharmacokinetics following the administration of a single oral dose of 200 mg
641 grazoprevir with or without the coadministration of multiple twice-daily oral doses of 100 mg ritonavir for 15 days to healthy adult
642 participants (Trial 1)[a]

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

643 [a]Abbreviations: AUC, area under the concentration versus time curve from 0 to infinity; C_{24}, plasma concentration at 24 hours; CI,
644 confidence interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; GM, geometric mean; GMR,
645 geometric mean ratio; GZR, grazoprevir; PK, pharmacokinetics; rMSE, square root of mean squared error (residual error) from the
646 linear mixed effect model; RTV, ritonavir; T_{max}, time to maximal concentration.
647 [b]A single oral dose of 200 mg grazoprevir.
648 [c]100 mg ritonavir twice daily on days 1 to 21 coadministered with a single oral dose of 200 mg grazoprevir on day 15.
649 [d]rMSE*100% approximates the within-subject % CV on the raw scale.

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

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

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655 **Table 3.** Comparisons of grazoprevir plasma pharmacokinetics following coadministration of grazoprevir 200 mg once daily and 300
656 mg atazanavir/100 mg ritonavir once daily, 400 mg lopinavir/100 mg ritonavir twice daily, or 600 mg darunavir/100 mg ritonavir
657 twice daily for 7 days vs administration of grazoprevir 200 mg once daily for 7 days to healthy adult participants (Trial 2)[a]

GZR/ATV/RTV[b]				
PK parameter	**GZR, GM (95% CI) (*N* = 12)**	**GZR + ATV/RTV, GM (95% CI) (*N* = 11)[c,d]**	**GZR + ATV/RTV vs GZR, GMR (90% CI)**	**Pseudo within-subject %CV[e]**
$AUC_{0\text{-}24}$, µM × h[f]	3.38 (2.26, 5.05)	35.7 (26.1, 49.0)	10.58 (7.78, 14.39)	40.5
C_{max}, µM[f]	0.952 (0.573, 1.58)	5.94 (4.48, 7.87)	6.24 (4.42, 8.81)	46.1
C_{24}, nM[f]	14.7 (10.7, 20.2)	171 (104, 280)	11.64 (7.96, 17.02)	48.9
T_{max}, h[g]	2.50 (2.00, 5.00)	3.00 (2.00, 4.00)		

GZR/LPV/RTV[h]				
PK parameter	**GZR GM (95% CI) (*N* = 13)**	**GZR + LPV/RTV, GM (95% CI) (*N* = 13)**	**GZR + LPV/RTV vs GZR, GMR (90% CI)**	**Pseudo within-subject %CV**[e]
$AUC_{0\text{-}24}$, µM × h[f]	3.63 (2.37, 5.56)	46.7 (30.1, 72.5)	12.86 (10.25, 16.13)	32.4
C_{max}, µM[f]	0.954 (0.568, 1.60)	6.97 (5.30, 9.16)	7.31 (5.65, 9.45)	36.8
C_{24}, nM[f]	15.1 (11.7, 19.5)	327 (149, 721)	21.70 (12.99, 36.25)	73.4
T_{max}, h[g]	3.00 (1.00, 6.03)	3.02 (2.00, 6.01)		
GZR/DRV/RTV[i]				

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PK parameter	**GZR, GM (95% CI) (*N* = 13)**	**GZR + DRV/RTV, GM (95% CI) (*N* = 11)[i,k]**	**GZR + DRV/RTV vs GZR, GMR (90% CI)**	**Pseudo within-subject %CV[e]**
$AUC_{0\text{-}24}$, µM × h[f]	3.31 (2.25, 4.86)	24.8 (18.7, 32.9)	7.50 (5.92, 9.51)	32.2
C_{max}, µM[f]	0.824 (0.502, 1.35)	4.34 (3.27, 5.75)	5.27 (4.04, 6.86)	36.8
C_{24}, nM[f]	15.7 (12.2, 20.1)	126 (91.0, 175)	8.05 (6.33, 10.24)	30.9
T_{max}, h[g]	3.02 (1.00, 5.03)	4.00 (2.00, 5.03)		

[a]Abbreviations: ATV, atazanavir; $AUC_{0\text{-}24}$, area under the concentration-time curve from 0 to 24 h; C_{24}, plasma concentration at 24 hours; CI, confidence interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; DRV, darunavir; GM, geometric mean; GMR, geometric mean ratio; GZR, grazoprevir; LPV, lopinavir; PK, pharmacokinetics; RTV, ritonavir; T_{max}, time to maximal concentration.

[b]GZR plasma pharmacokinetics following GZR administration alone and coadministration with ATV/RTV.

[c]One participant was discontinued by the investigator on day 3 of period 1.

[d]One participant was discontinued by the investigator on day 13 of period 2.

[e]Pseudo within-subject %CV = 100 × sqrt([σ^2_A + σ^2_B – 2 × σ_{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.

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

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

[h]GZR plasma pharmacokinetics following GZR administration alone and coadministration with LPV/ RTV.

[i]GZR plasma pharmacokinetics following GZR administration alone and coadministration with DRV/ RTV.

[j]One participant was discontinued on day 6 of period 3.

[k]One participant was discontinued on day 1 of period 2.

674 **Table 4.** Comparison of atazanavir, lopinavir, and darunavir plasma pharmacokinetics following coadministration of grazoprevir 200
675 mg once daily and 300 mg atazanavir/100 mg ritonavir once daily, 400 mg lopinavir/100 mg ritonavir twice daily, or 600 mg
676 darunavir/100 mg ritonavir twice daily for 7 days vs. administration of the boosted HIV protease inhibitor for 14 days to healthy adult
677 participants (Trial 2)[a]

GZR/ATV/RTV[b]				
ATV PK parameter	**ATV/RTV, GM (95% CI) (*N* = 11[c])**	**GZR+ATV/RTV, GM (95% CI) (*N* = 11[d])**	**GZR+ATV/RTV vs ATV/RTV, GMR (90% CI)**	**Pseudo within-subject %CV[e]**
$AUC_{0\text{-}24}$, ng × h/ml[f]	42,400 (32,300, 55,600)	60,600 (45,800, 80,300)	1.43 (1.30, 1.57)	12.0
C_{max}, ng/ml[f]	4560 (3650, 5680)	5100 (4330, 6000)	1.12 (1.01, 1.24)	13.2
C_{24}, ng/ml[f]	798 (544, 1170)	983 (670, 1400)	1.23 (1.13, 1.34)	11. 3
T_{max}, h[g]	4.00 (2.00, 5.00)	3.00 (3.00, 4.02)		
GZR/LPV/RTV[h]				
LPV PK parameter	**LPV/RTV, GM (95% CI)**	**GZR+LPV/RTV, GM (95% CI)**	**GZR+LPV/RTV vs LPV/RTV, GMR**	**Pseudo within-subject %CV[e]**

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	N = 13	**N = 13**	**(90% CI)**	
$AUC_{0\text{-}12}$, ng × h/ml[f]	103,000 (81,600, 131,000)	10,700 (93,800, 121,000)	1.03 (0.92, 1.16)	16.4
C_{max}, ng/ml[f]	12,600 (10,500, 15,100)	12,300 (11,200, 13,400)	0.97 (0.88, 1.08)	14.6
C_{12}, ng/ml[f]	5,220 (3,520, 7,740)	5,040 (3,680, 6,910)	0.97 (0.81, 1.15)	25.2
T_{max}, h[g]	4.00 (2.00, 5.05)	4.01 (2.00, 10.03)		
GZR/DRV/RTV[i]				
DRV PK parameter	**DRV/RTV, GM (95% CI) (*N* = 12)**	**GZR+DRV/RTV, GM (95% CI) (*N* = 11[j,k])**	**GZR+DRV/RTV vs DRV/RTV, GMR (90% CI)**	**Pseudo within-subject %CV[e]**
$AUC_{0\text{-}12}$, ng × h/ml[f]	68,900 (59,700, 79,500)	76,400 (67,700, 86,300)	1.11 (0.99, 1.24)	15.0
C_{max}, ng/ml[f]	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)		

[a]Abbreviations: ATV, atazanavir; AUC_{0-12}, area under the concentration-time curve from 0 to 12 h; AUC_{0-24}, area under the concentration-time curve from 0 to 24 h; C_{12}, plasma concentration at 12 hours; C_{24}, plasma concentration at 24 hours; CI, confidence interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; DRV, darunavir; GM, geometric mean; GMR, geometric mean ratio; GZR, grazoprevir; LPV, lopinavir; PK, pharmacokinetics; RTV, ritonavir; T_{max}, time to maximal concentration.

[b]ATV plasma pharmacokinetics following ATV/RTV administration alone and coadministration with GZR.

[c]One participant was discontinued by the investigator on day 3 of period 1.

[d]One participant was discontinued by the investigator on day 13 of period 2.

[e]Pseudo within-subject %CV = $100*\mathrm{Sqrt}((\sigma^2_A + \sigma^2_B - 2*\sigma_{AB})/2)$, 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.

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

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

[h]LPV plasma pharmacokinetics following LPV/RTV administration alone and coadministration with GZR.

[i]DRV plasma pharmacokinetics following DRV/RTV administration alone and coadministration with GZR.

692 [j]One participant was discontinued on day 6 of period 3.

693 [k]One participant was discontinued on day 1 of period 2.

694 **Table 5.** Comparisons of elbasvir plasma pharmacokinetics following coadministration of elbasvir 50 mg once daily and 300 mg
695 atazanavir/100 mg ritonavir once daily, 400 mg lopinavir/100 mg ritonavir twice daily, or 600 mg darunavir/100 mg ritonavir twice
696 daily for 7 days vs administration of grazoprevir 200 mg once daily for 7 days to healthy adult participants (Trial 3)[a]

EBR/ATV/RTV[b]				
PK parameter	**EBR, GM (95% CI) (*N* = 10)**	**EBR + ATV/RTV, GM (95% CI) (*N* = 8)**[c,d]	**EBR + ATV/RTV vs EBR, GMR (90% CI)**	**Pseudo within-subject %CV**[e]
$AUC_{0\text{-}24}$, µM × h[f]	1.42 (1.04, 1.96)	6.77 (5.18, 8.85)	4.76 (4.07, 5.56)	16.9
C_{max}, nM[f]	97.5 (68.9, 138)	405 (317, 516)	4.15 (3.46, 4.97)	20.5
C_{24}, nM[f]	37.9 (27.3, 52.6)	245 (181, 330)	6.45 (5.51, 7.54)	16.6
T_{max}, h[g]	4.09 (3.00, 6.04)	4.01 (3.01, 8.01)		
EBR/LPV/RTV[h]				

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PK parameter	**EBR, GM (95% CI) (*N* = 10)**	**EBR + LPV/RTV, GM (95% CI) (*N* = 9)[i]**	**EBR + LPV/RTV vs EBR, GMR (90% CI)**	**Pseudo within-subject %CV[e]**
$AUC_{0\text{-}24}$, µM × h[f]	1.43 (1.11, 1.83)	5.29 (3.86, 7.26)	3.71 (3.05, 4.53)	22.4
C_{max}, nM[f]	109 (86.7, 137)	313 (225, 434)	2.87 (2.29, 3.58)	25.3
C_{24}, nM[f]	40.6 (30.1, 54.7)	186 (136, 254)	4.58 (3.72, 5.64)	23.7
T_{max}, h[g]	5.00 (4.00, 8.00)	5.00 (4.00, 6.00)		
EBR/DRV/RTV[j]				
PK parameter	**EBR, GM (95% CI) (*N* = 10)**	**EBR + DRV/RTV, GM (95% CI) (*N* = 8)[k,l]**	**EBR + DRV/RTV vs EBR, GMR (90% CI)**	**Pseudo within-subject %CV[e]**
$AUC_{0\text{-}24}$, µM × h[f]	1.40 (0.972,	2.32 (1.71, 3.15)	1.66 (1.35, 2.05)	22.4

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	2.00)			
C_{max}, nM[f]	96.4 (65.5, 142)	161 (114, 228)	1.67 (1.36, 2.05)	22.1
C_{24}, nM[f]	38.4 (24.9, 59.2)	70.0 (47.8, 102)	1.82 (1.39, 2.39)	28.9
T_{max}, h[g]	4.50 (2.00, 6.00)	4.00 (2.01, 5.00)		

[a]Abbreviations: ATV, atazanavir; AUC_{0-24}, area under the concentration-time curve from 0 to 24 h; C_{24}, plasma concentration at 24 hours; CI, confidence interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; DRV, darunavir; EBR, elbasvir; GM, geometric mean; GMR, geometric mean ratio; LPV, lopinavir; PK, pharmacokinetics; RTV, ritonavir; T_{max}, time to maximal concentration.

[b]EBR plasma pharmacokinetics following EBR administration alone and coadministration with ATV/RTV.

[c]One participant was discontinued by the investigator on day 13 of period 2.

[d]One participant was discontinued by the investigator on day 7 of period 2.

[e]Pseudo within-subject %CV = $100 \times \text{sqrt}([\sigma^2_A + \sigma^2_B - 2 \times \sigma_{AB}]/2)$, 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.

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

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

[h]EBR plasma pharmacokinetics following EBR administration alone and coadministration with LPV/RTV.

[i]One participant withdrew from the study on day 4 of period 2 (during the administration of LPV portion of period 2).

[j]EBR plasma pharmacokinetics following EBR administration alone and coadministration with DRV/RTV.

[k]One participant was discontinued from the study on day 11 of period 2.

[l]One participant was discontinued from the study on day 13 of period 2.

714 **Table 6.** Comparison of atazanavir, lopinavir, and darunavir plasma pharmacokinetics following coadministration of elbasvir 50 mg
715 once daily and 300 mg atazanavir/100 mg ritonavir once daily, 400 mg lopinavir/100 mg ritonavir twice daily, or 600 mg
716 darunavir/100 mg ritonavir twice daily for 7 days vs administration of the boosted HIV protease inhibitor for 14 days to healthy adult
717 participants (Trial 3)[a]

EBR/ATV/RTV[b]				
ATV PK parameter	**ATV/RTV, GM (95% CI) (*N* = 8[c,d])**	**EBR + ATV/RTV, GM (95% CI) (*N* = 8[c,d])**	**EBR + ATV/RTV vs ATV/RTV, GMR (90% CI)**	**Pseudo within-subject %CV[e]**
$AUC_{0\text{-}24}$, ng × h/ml[f]	57,800 (46,000, 72,500)	61,700 (47,500, 80,000)	1.07 (0.98, 1.17)	9.4
C_{max}, ng/ml[f]	5,740 (4,720, 6,970)	5,840 (4,790, 7,100)	1.02 (0.96, 1.08)	6.3
C_{24}, ng/ml[f]	1,230 (803, 1,880)	1,410 (899, 2220)	1.15 (1.02, 1.19)	12.4
T_{max}, h[g]	3.00 (2.00, 5.00)	3.5 (2.00, 5.00)		
EBR/LPV/RTV[h]				

LPV PK parameter	**LPV/RTV, GM (95% CI) (*N* = 9[i])**	**EBR + LPV/RTV, GM (95% CI) (*N* = 9[i])**	**EBR + LPV/RTV vs LPV/RTV, GMR (90% CI)**	**Pseudo within-subject %CV[e]**
$AUC_{0\text{-}12}$, ng × h/ml[f]	101,000 (83,300, 121,000)	103,000 (84,000, 126,000)	1.02 (0.93, 1.13)	11.4
C_{max}, ng/ml[f]	11,600 (9880, 13,600)	11,800 (10,200, 13,800)	1.02 (0.92, 1.13)	11.4
C_{12}, ng/ml[f]	5,780 (4,210, 7,930)	6,170 (4,490, 8,480)	1.07 (0.97, 1.18)	10.9
T_{max}, h[g]	4.00 (3.00, 6.00)	4.01 (3.00, 8.00)		
EBR/DRV/RTV[j]				
DRV PK parameter	**DRV/RTV, GM (95% CI) (*N* = 8[k,l])**	**EBR + DRV/RTV, GM (95% CI) (*N* = 8[k,l])**	**EBR + DRV/RTV vs DRV/RTV, GMR (90% CI)**	**Pseudo within-subject %CV[e]**
$AUC_{0\text{-}12}$, ng × h/ml[f]	54,000 (48,700, 60,000)	51,400 (42,800, 61,900)	0.95 (0.86, 1.06)	10.9

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C_{max}, ng/ml[f]	7,190 (6,650, 7,900)	6,800 (5,720, ,8090)	0.95 (0.85, 1.05)	10.8
C_{12}, ng/ml[f]	2,870 (2,230, 3,700)	2,700 (2,030, 3,600)	0.94 (0.85, 1.05)	11.4
T_{max}, h[g]	3.00 (2.00, 5.00)	3.5 (2.00, 5.00)		

[a]Abbreviations: ATV, atazanavir; AUC_{0-12}, area under the concentration-time curve from 0 to 12 h; AUC_{0-24}, area under the concentration-time curve from 0 to 24 h; C_{12}, plasma concentration at 12 hours; C_{24}, plasma concentration at 24 hours; CI, confidence interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; DRV, darunavir; EBR, elbasvir; GM, geometric mean; GMR, geometric mean ratio; LPV, lopinavir; PK, pharmacokinetics; RTV, ritonavir; T_{max}, time to maximal concentration.

[b]ATV plasma pharmacokinetics following ATV/ RTV administration alone and coadministration with EBR.

[c]One participant was discontinued by the investigator on day 13 of period 2.

[d]One participant was discontinued by the investigator on day 7 of period 2.

[e]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.

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

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

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[h]LPV plasma pharmacokinetics following LPV/RTV administration alone and coadministration with EBR.

[i]One participant withdrew from the study on day 4 of period 2 (during the administration of LPV portion of period 2).

[j]DRV plasma pharmacokinetics following DRV/RTV administration alone and coadministration with EBR.

[k]One participant was discontinued from the study on day 11 of period 2.

[l]One participant was discontinued from the study on day 13 of period 2.

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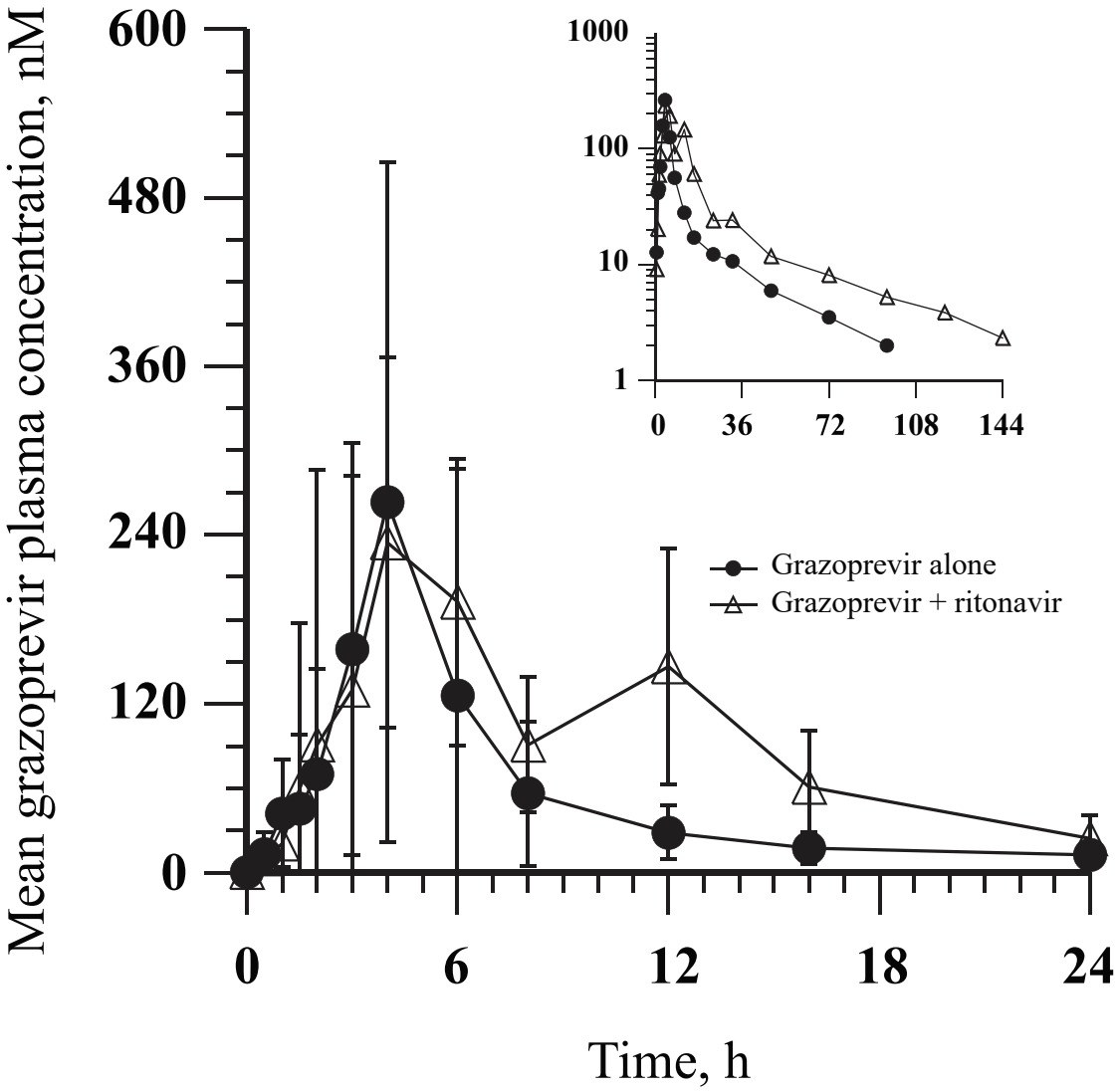

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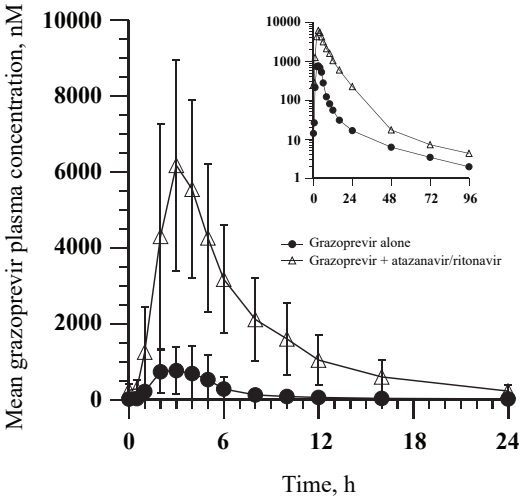

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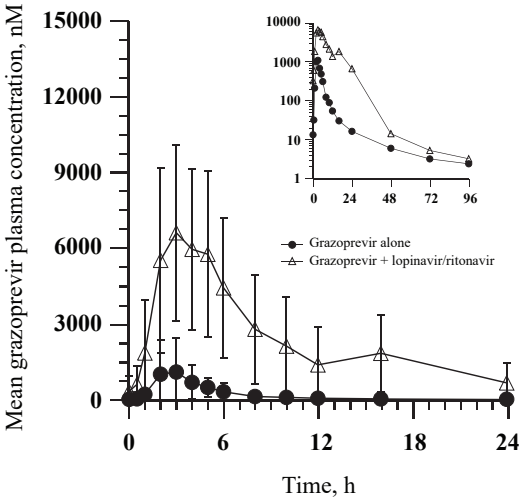

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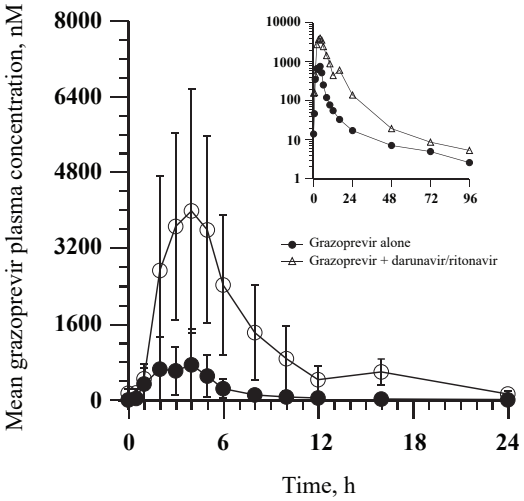

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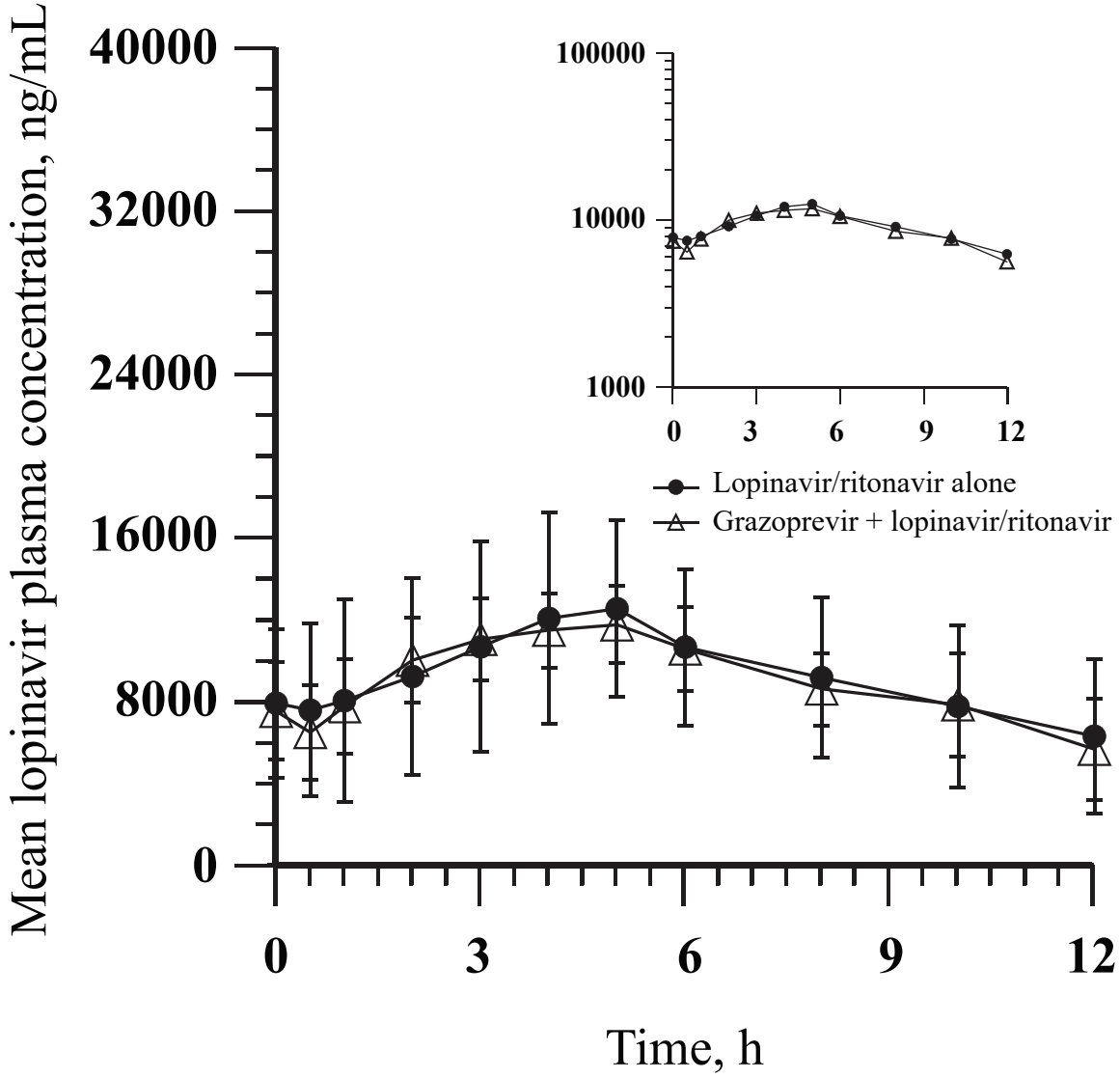

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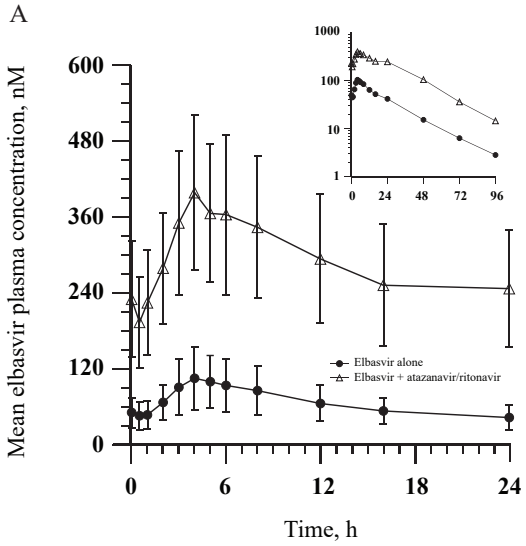

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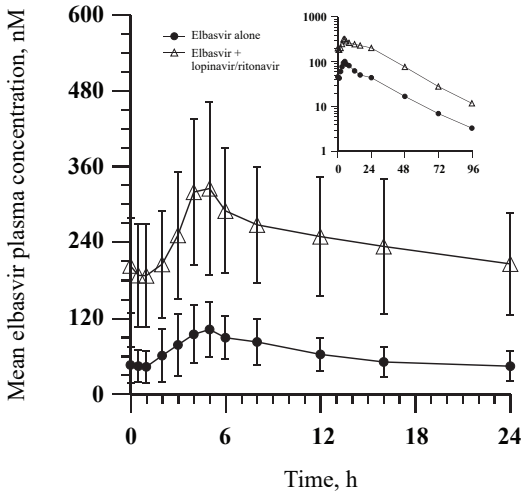

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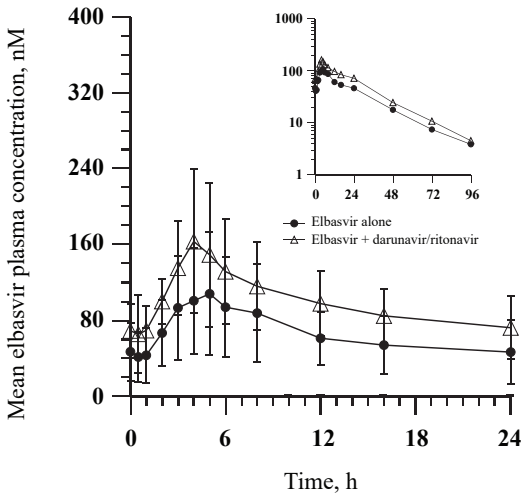

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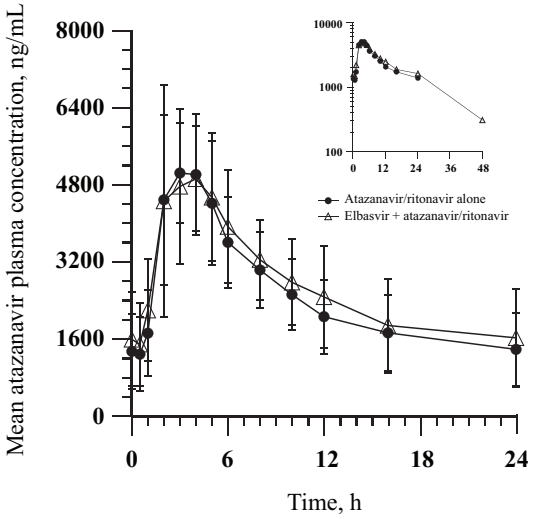

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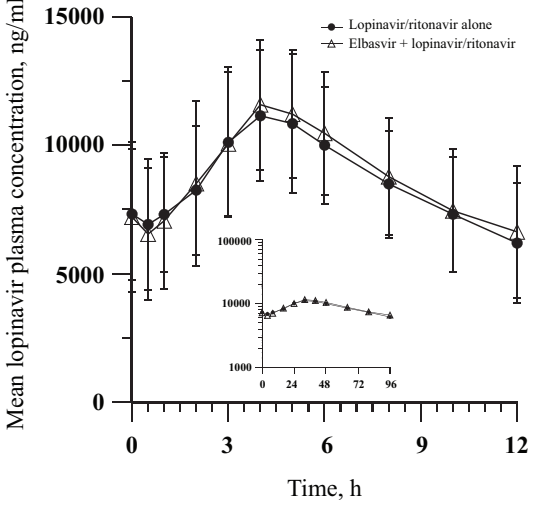

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