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ARTICLE

No Pharmacokinetic Interactions Between Elbasvir or Grazoprevir and Methadone in Participants Receiving Maintenance Opioid Agonist Therapy

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We conducted two phase I trials to evaluate the pharmacokinetic interactions between elbasvir (EBR), grazoprevir (GZR), and methadone (MK-8742-P010 and MK-5172-P030) in non-hepatitis C virus (HCV)-infected participants on methadone maintenance therapy. Coadministration of EBR or GZR with methadone had no clinically meaningful effect on EBR, GZR, or methadone pharmacokinetics. The geometric mean ratios (GMRs) for R- and S-methadone $AUC_{0\text{-}24}$ were 1.03 (90% confidence interval (CI), 0.92–1.15) and 1.09 (90% CI, 0.94–1.26) in the presence/absence of EBR; and 1.09 (90% CI, 1.02–1.17) and 1.23 (90% CI, 1.12–1.35) in the presence/absence of GZR. The GMRs for EBR and GZR $AUC_{0\text{-}24}$ in participants receiving methadone relative to a healthy historical cohort not receiving methadone were 1.20 (90% CI, 0.94–1.53) and 1.03 (90% CI, 0.76–1.41), respectively. These results indicate that no dose adjustment is required for individuals with HCV infection receiving stable methadone therapy and the EBR/GZR fixed-dose regimen.
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STUDY HIGHLIGHTS

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
✔ HCV infection is common among people who inject drugs, including those receiving opioid maintenance therapy.

WHAT QUESTION DID THIS STUDY ADDRESS?
✔ This study evaluated potential drug–drug interactions between the opioid agonist methadone and the anti-HCV therapies EBR and GZR.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
✔ There were no clinically relevant changes in the pharmacokinetics of EBR, GZR, or methadone in this study.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
✔ EBR/GZR dose adjustments are therefore not required in people also receiving methadone. The EBR/GZR fixed-dose combination is a treatment option for HCV-infected people receiving methadone-based opioid agonist therapy.

Injection drug users are the largest group of persons infected with hepatitis C virus (HCV),[1] and the global emergence of injection drug use-related HCV epidemics is associated with an estimated HCV prevalence of 60–80%.[2,3] Many injection drug users are undergoing treatment for opioid addiction and as a consequence, HCV-infected people who are being treated for opioid addiction often receive opioid substitution therapy, such as the opioid agonist methadone. Methadone is a synthetic narcotic analgesic with multiple actions quantitatively similar to those of morphine that is widely used as an opiate substitute in North America.

Elbasvir (EBR), a potent inhibitor of the HCV NS5A protein, and grazoprevir (GZR), an HCV NS3/4A protease inhibitor, are components of a fixed-dose combination regimen that is approved in the United States, European Union, and several other regions for the treatment of chronic HCV genotype (GT)1 and 4 infection.[4,5] EBR and GZR have been shown to retain *in vitro* and *in vivo* activity against several clinically relevant resistant variants.[6–8] Phase III trials in participants with HCV GT1 or 4 infection have consistently reported rates of sustained virologic response ≥95% in diverse populations, including treatment-naive[9] and treatment-experienced participants[10,11] and those with HIV coinfection[12] or stage 4/5 chronic kidney disease.[13] The EBR/GZR fixed-dose combination is administered once daily, without regard to food intake.

Methadone is administered as a racemic mixture of two stereoisomers, R- and S-methadone, with the R-isomer accounting for most of the pharmacologic activity.[14] Based on *in vitro* data, methadone metabolism involves several cytochrome P450 (CYP) isozymes, including CYP3A4 and CYP2B6.[15,16] It is also a substrate and inhibitor of

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P-glycoprotein (P-gp), but it is unknown if it is a substrate of breast cancer resistance protein (BCRP) or an inhibitor of CYP3A or OATP1B1/3.[17] Both EBR and GZR are substrates of CYP3A and P-gp, and GZR is a substrate of the liver uptake transporter organic anion transporting polypeptide (OATP)1B1/3. Grazoprevir is a weak CYP3A inhibitor, and both EBR and GZR are inhibitors of BCRP; additionally, EBR has minimal inhibitory activity for intestinal P-gp.

Although the drug–drug interaction risk is relatively low based on known disposition pathways for EBR, GZR, and methadone, coadministration of EBR/GZR with methadone in HCV-infected people who are undergoing treatment for opioid addiction could theoretically result in pharmacokinetic (PK) drug interactions, since these drugs do share overlapping metabolic pathways and enzyme inhibition profiles, such as CYP3A and/or P-gp. In order to avoid unintentional opioid intoxication or withdrawal in the HCV-infected people who receive opioid substitution therapy and to inform the dosing recommendation for EBR/GZR in this population, two drug–drug interaction (DDI) trials were conducted to assess the PK effects of EBR or GZR coadministered with methadone in non-HCV-infected participants who were already receiving stable methadone maintenance therapy.

METHODS

These trials were conducted in accordance with the principles of Good Clinical Practice, and approved by the New England Institutional Review Board (Newton, MA). All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants provided written, informed consent. The studies were funded by Merck & Co., Kenilworth, NJ.

Clinical conduct

Both trials (trial 1, MK-8742-P010, and trial 2, MK-5172-P030) were phase I, open-label, fixed-sequence, multiple-dose trials in participants on stable oral methadone maintenance therapy (**Figure S1**). Participants were 18–55 years of age with a body mass index (BMI) of 19–32 kg/m^2 (Trial 1) or 18–36 kg/m^2 (Trial 2). All participants were required to be in good health based on medical history, physical examination, vital sign measurements, electrocardiograms (ECGs), and laboratory safety tests. Individuals with clinically significant endocrine, gastrointestinal, cardiovascular, hematologic, hepatic, immunologic, renal, respiratory, genitourinary, or major neurologic (including stroke and chronic seizures) abnormalities or diseases, or with a history of cancer, were excluded. Prior to enrolling in this study, participants were all part of an oral methadone maintenance program, receiving methadone therapy (20–150 mg once daily (q.d.)) for at least 2 months with stable dosing for at least 14 days immediately prior to the trial. On day 1, all participants received an oral maintenance dose of methadone after an overnight fast of at least 8 hours. On days 2–11, participants received oral EBR 50 mg q.d. (Trial 1) or oral GZR 200 mg q.d. (Trial 2) after an overnight fast, followed immediately by a maintenance dose of methadone. All study treatments were administered under fasted conditions to eliminate the potential confounding effect of food.

Analytical methods

Plasma EBR concentrations were determined using a validated bioanalytical method. The lower limit of quantitation (LLOQ) for EBR was 0.25 ng/mL (0.28 nM), with a calibration range of 0.25–500.00 ng/mL (0.28–567 nM). The analyte and stable-labeled internal standard were extracted from K_2-EDTA anticoagulated human plasma using liquid–liquid extraction (LLE). The extracted samples were injected into an Acquity (Waters, Milford, MA) UPLC chromatography system with an attached BEH Shield RP 18, 50 $\times$ 2.1 mm, 1.7 μm analytical column. The mobile phase for the separation was a combination of water/acetonitrile/ammonium acetate/EDTA, and the analytes were detected with tandem mass spectrometry (MS/MS) employing a turbo ionspray interface in the positive ion mode. The mass transitions monitored by multiple reaction monitoring (MRM) were m/z 882 $\rightarrow$ 708 and m/z 888 $\rightarrow$ 711 for the analyte and internal standard, respectively. The mean accuracy of interday quality controls (QCs) ranged from 102.9–105.1% of nominal for Trial 1. Interday QC precision was $\leq$5.5% for Study P010. EBR is stable in human plasma at –20°C for at least 21 months.

Plasma GZR concentrations were determined using a validated bioanalytical method. The LLOQ for GZR was 1.0 ng/mL (1.3 nM), with a calibration range of 1.00–1,000 ng/mL (1.3–1,300 nM). The analyte and stable-labeled internal standard were extracted from K_2-EDTA anticoagulated human plasma using LLE. The final extract was analyzed via high-performance liquid chromatography (HPLC) with a Discovery C18, 2.1 $\times$ 50 mm, 5 μm analytical column. The mobile phase was a combination of 0.1% formic acid in 0.1 mM EDTA / 0.1% formic acid in acetonitrile, and the analytes were detected with MS/MS employing a turbo ionspray interface in the positive ion mode. The mass transitions monitored by MRM were m/z 767.65 $\rightarrow$ 646.45 and m/z 773.60 $\rightarrow$ 652.50 for the analyte and internal standard, respectively. The mean accuracy of interday QCs ranged from 92.45–93.81% of nominal for Trial 2. Interday QC precision was $<$3.32% for Study P030. GZR is stable in human plasma at –20°C for at least 397 days.

(R)- and (S)-methadone concentrations were determined by PPD (Richmond, VA). The proprietary validated analytical method is based on supported liquid-phase extraction (SLE) of the enantiomers from human plasma containing K_3 EDTA. The analytes and stable-labeled internal standard (R, S)-methadone-d9 were assayed by HPLC with MS/MS detection. A calibration curve range of 5.0–1,000 ng/mL with a LLOQ of 5.0 ng/mL was used for both enantiomers in Trials 1 and 2. The assay met all regulatory acceptance criteria with the mean accuracy of study QCs $<$5.7% of nominal value for Trials 1 and 2. Assay precision ranged from 2.17–6.61% for Trial 2 and from 3.13–10.1% for Trial 1.

PK and safety assessments

Blood samples for determination of methadone plasma concentrations were collected predose and at specified timepoints over 24 hours on days 1 and 11 in both studies.

Blood samples for determination of EBR or GZR plasma concentrations were collected predose on day 11 and post-dose at specified timepoints over 72 hours. Estimates of the following PK parameters were determined: $AUC_{0\text{-}24}$ (area under the concentration time curve from time 0–24 hours postdose) and $T_{1/2}$ (apparent terminal half-life) using noncompartmental analysis, C_{max} (maximum concentration), C_{24} (plasma drug concentration at time 24 hours after dosing), and T_{max} (time to C_{max}) directly from observed concentration–time data. Safety was assessed by monitoring adverse events (AEs), physical examination, vital signs, ECGs, pulse oximetry, and laboratory safety assessments.

Statistical analysis and power

In both studies, dose-normalized values of R- and S-methadone exposure parameters ($AUC_{0\text{-}24}$, C_{max}, and $C_{24,}$) were natural log-transformed and analyzed with a linear mixed-effects model containing a fixed-effect term for treatment; an unstructured covariance matrix was assumed to allow for unequal treatment variances and to model the correlation between the two treatment measurements within each participant. The least-squares means (LSMs) and corresponding 95% confidence intervals (CIs) were calculated by treatment, and the difference in treatment LSMs and corresponding 90% CIs were estimated for each parameter. Kenward–Roger's method was used to calculate the appropriate degrees of freedom for the fixed effects. The back-transformed LSMs and LSM differences were reported for each parameter as the geometric LSMs (GMs) with corresponding 95% CIs, as well as the GM ratios (GMRs, EBR + methadone/methadone alone) with corresponding 90% CIs.

To provide an estimate of the effect of coadministration on EBR PKs, EBR exposures ($AUC_{0\text{-}24}$, C_{max}, and C_{24}, as appropriate) following administration of multiple 50-mg doses of EBR alone under fasted conditions in 56 non-HCV-infected participants in the historical database were pooled as a reference comparator group. Similarly, to provide an estimate of the effect of coadministration on GZR PKs, GZR exposures following coadministration with methadone were compared with pooled GZR exposures in non−HCV-infected healthy participants after multiple-dose administration of GZR 200 mg under fasted conditions in a historical database as a reference comparator group. A total of 107 non−HCV-infected participants from a historical database were pooled and used for comparison of GZR T_{max}; however, only 106 participants were included in the model-based AUC, C_{max}, and C_{24} analyses due to missing covariate information in one participant. Elbasvir and GZR exposures following methadone coadministration in the drug interaction clinical trials or following administration alone in the historical database were log-transformed and analyzed with a linear mixed-effect model (analysis of covariance model) containing a fixed-effect term for treatment and covariates of race (white/Asian/other or black), ethnicity (Hispanic or Latino, non-Hispanic or non-Latino), age, sex, and body weight. The LSMs obtained using observed margins as weights for categorical variables and corresponding 95% CIs were calculated by treatment for each PK parameter in the natural log scale. The differences in LSMs and corresponding 90% CIs were calculated for the comparisons between treatments. Exponentiating the LSMs (LSM differences) and the corresponding CIs yielded estimates for the GMs (GMRs) and corresponding CIs in the original scale.

With a sample size of 10 participants in the EBR study (Trial 1), the half-width of the 90% CI for the GMR on the log scale would be 0.18 assuming a within-participant standard deviation (SD) of 0.22 on the natural log scale (S-methadone AUC), and 0.14 assuming a within-participant SD of 0.17 on the natural log scale (R-methadone AUC). For the comparison of EBR AUC using pooled historical data, with sample sizes of 56 and 10 for the two groups and a between-participant SD of 0.41 on the natural log scale, the half-width of the 90% CI for the GMR on the log scale would be 0.24.

With a sample size of 12 participants in the GZR study (Trial 2), the half-width of the 90% CI for the GMR on the log scale would be 0.16 assuming a within-participant SD of 0.22 on the natural log scale (S-methadone AUC), and 0.12 assuming a within-participant SD of 0.17 on the natural log scale (R-methadone AUC). For the comparison of GZR AUC using pooled historical data, with sample sizes of 106 and 12 for the two groups and a between-participant SD of 0.60 on the natural log scale, the half-width of the 90% CI for the GMR on the log scale would be 0.31.

RESULTS

Trial populations

In the EBR methadone drug interaction trial (Trial 1), 10 participants were enrolled and completed treatment. In the GZR methadone drug interaction trial (Trial 2), 12 participants were enrolled and completed treatment. Actual methadone doses ranged from 20–120 mg q.d. among participants enrolled in Trial 1 and from 20–150 mg q.d. among participants enrolled in Trial 2. Participants treated with EBR or GZR monotherapy from a historical database were used as a reference population to assess the effect of methadone coadministration on EBR ($n = 56$) and GZR ($n = 107$) PKs; however, one participant receiving GZR was excluded in the model-based AUC, C_{max}, and C_{24} analyses due to missing covariate information. Demographic data for the trial populations and the historical control groups are summarized in **Table 1**.

Effect of EBR or GZR coadministration on methadone PKs

In non-HCV-infected participants on stable maintenance methadone therapy, coadministration of EBR or GZR had no meaningful effect on the concentration–time profiles of either R- or S-methadone (**Figures 1** and **2**). The observed median T_{max} of R- or S-methadone was not meaningfully affected by coadministration with EBR or GZR relative to administration of methadone alone, with median T_{max} values between 1.75 and 3.00 hours (**Tables 2** and **3**). There were no notable changes in the PKs of R- or S-methadone when coadministered with EBR, with the GMRs (EBR + methadone relative to methadone alone) for dose-normalized AUC and C_{max} ranging from 1.03–1.09, with narrow 90% CIs that included 1.0 (**Table 2**). GZR coadministration resulted in a small increase in the dose-normalized R-methadone AUC, with a GMR (90% CI) (GZR + methadone relative to methadone alone) of 1.09 (1.02–1.17). GZR coadministration

Table 1 Participant characteristics

	EBR methadone DDI trial ($n = 10$)	GZR methadone DDI trial ($n = 12$)	Historical data: EBR ($n = 56$)	Historical data: GZR ($n = 107$)[a]
Sex, no. (%)				
Male	6 (60.0)	9 (75.0)	44 (78.6)	71 (66.4)
Female	4 (40.0)	3 (25.0)	12 (21.4)	36 (33.6)
Age, years, mean (range)	31.9 (21–53)	32.8 (21–53)	36.6 (21–53)	37.1 (18–64)
Height, m, mean (range)	1.73 (1.55–1.94)	1.74 (1.55–1.93)	1.74 (1.58–1.95)	1.71 (1.49–1.90)
Weight, kg, mean (range)	79.7 (52.0–105.0)	81.6 (61.0–100.0)	79.9 (51.3–117.0)	77.3 (52.3–111.0)
BMI, kg/m^2, mean (range)	26.6 (18.7–31.5)	27.0 (18.2–31.2)	26.5 (19.5–31.7)	26.3 (19.3–35.0)
Ethnicity, no. (%)				
Hispanic or Latino	1 (10.0)	2 (16.7)	20 (35.7)	22 (20.6)
Not Hispanic or Latino	9 (90.0)	10 (83.3)	36 (64.3)	85 (79.4)
Race, no. (%)				
White	10 (100.0)	11 (91.7)	47 (83.9)	89 (83.2)
Black/African American	0 (0)	0 (0)	6 (10.7)	9 (8.4)
Asian	0 (0)	0 (0)	1 (1.8)	2 (1.9)
Other	0 (0)	1 (8.3)	2 (3.6)	6 (5.6)
Unknown	0 (0)	0 (0)	0 (0)	1 (0.9)[a]

BMI, body mass index; DDI, drug–drug interaction; EBR, elbasvir; GZR, grazoprevir.
[a]Race of one participant was unknown. The participant was excluded from the model-based analysis for the comparison of GZR AUC, C_{max}, and C_{24} with and without methadone coadministration ($n = 106$). A total of 107 non-HCV-infected participants from a historical database were pooled and used for comparison of GZR T_{max}.

resulted in no change in the dose-normalized R-methadone C_{max}. Grazoprevir coadministration increased S-methadone AUC and C_{max}, with GMRs (90% CI) (GZR + methadone relative to methadone alone) for dose-normalized of 1.23 (1.12–1.35) and 1.15 (1.07–1.25), respectively (**Table 3**).

Effect of methadone coadministration on EBR or GZR PKs

To assess the effect of methadone coadministration on EBR and GZR PKs, exposures ($AUC_{0\text{-}24}$, C_{max}, and C_{24}) from participants who were on stable maintenance methadone therapy were compared with historical data from participants receiving multiple doses of EBR 50 mg alone or GZR 200 mg alone. GMRs for EBR $AUC_{0\text{-}24}$, C_{max}, and C_{24} (EBR + methadone relative to EBR alone) ranged between 1.20 and 1.32, with the 90% CIs for AUC and C_{max} containing 1.0 (**Table 4**). GMRs for GZR $AUC_{0\text{-}24}$, C_{max}, and C_{24} (GZR + methadone relative to GZR alone) ranged between 0.89 and 1.03, with wide 90% CIs that included 1.0 (**Table 5**).

Safety and tolerability

Coadministration of EBR or GZR with methadone was generally well tolerated in these short-duration studies. In the EBR and methadone drug interaction trial (Trial 1), seven participants reported a total of 13 AEs, eight of which were considered related to study medication (upper abdominal pain, $n = 2$; nausea, vomiting, euphoric mood, anxiety, hyperhidrosis, and drug ineffective, $n = 1$ each). Many of these AEs are known side effects of methadone.[18] All drug-related AEs occurred following coadministration of EBR and methadone. There were no serious AEs, discontinuations, or deaths. Based on the Clinical Opioid Withdrawal Scale assessment, no participants showed any sign of opiate withdrawal.

In the GZR and methadone drug interaction trial (Trial 2), five participants reported a total of five AEs. No single AE was reported more than once and none were considered related to study medication. There were no serious AEs, treatment discontinuations, or deaths. For both trials, there were no clinically meaningful changes in laboratory values, vital signs, or ECG measurements.

DISCUSSION

Elbasvir/grazoprevir is an important therapy for the treatment of HCV infection. The assessment of the potential DDIs between opiate substitution therapy and EBR/GZR is important for dosing recommendations for HCV-infected people who are on treatment for drug addiction. Data from the present trials demonstrate that in non-HCV-infected participants on stable methadone maintenance therapy, coadministration with EBR or GZR had no meaningful significant effect on the PKs of R-methadone, while coadministration with GZR slightly increased the exposures of S-methadone. The mechanisms underlying the small increase in the exposures of S-methadone are unknown. However, as the R-isomer accounts for most of the pharmacologic activity of methadone, the stable plasma concentrations of R-methadone suggest that coadministration with EBR or GZR is unlikely to lead to opioid intoxication or withdrawal. Compared with exposures in the historical database,

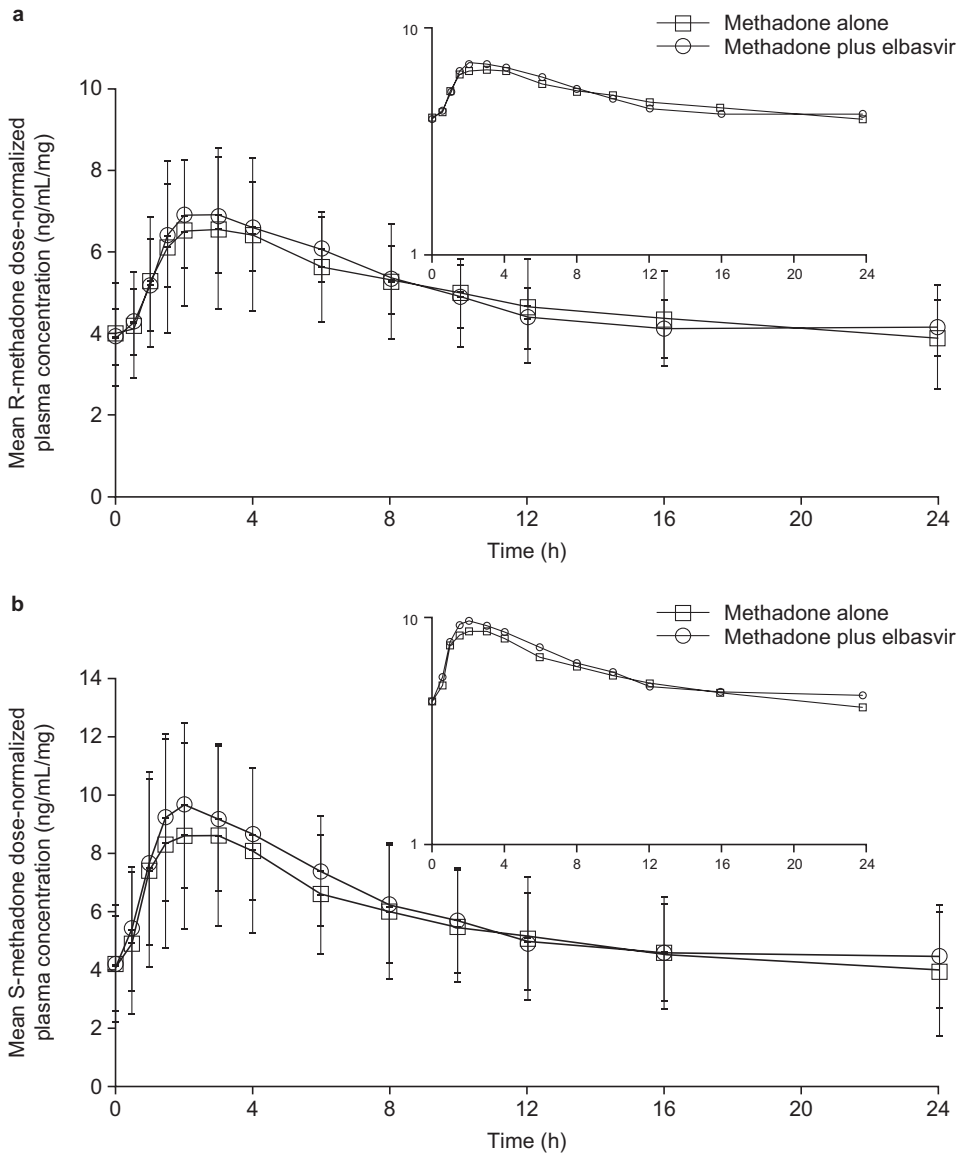

Figure 1 Arithmetic mean (standard deviation) plasma concentration–time profiles of (**a**) R- and (**b**) S-methadone following multiple oral doses of elbasvir 50 mg once daily with and without coadministration of stable maintenance doses of methadone in adult participants ($n = 10$) receiving stable methadone substitution therapy. Inset = semi-log plot.

coadministration of methadone with EBR or GZR in non-HCV-infected participants on stable methadone maintenance therapy did not have a meaningful effect on EBR or GZR exposures.

Although the two DDI studies reported here were conducted as separate studies using single-entity formulations of EBR or GZR, it has been demonstrated that EBR and GZR coadministration had no meaningful effect on the PK of either EBR or GZR.[4] Furthermore, if EBR and GZR were both mild perpetrators, it is possible in theory that the effect observed when both were coadministered would exceed the effect of each individual drug when administered alone. However, the lack of clinically meaningful interactions noted on methadone exposure coadministered with the single-entity formulations provides support that the combination is unlikely to produce clinically meaningful effects on methadone exposure. Therefore, the assessment of DDI potential with EBR or GZR alone with methadone is expected to be applicable to the clinical setting of coadministering methadone with the fixed-dose combination of EBR/GZR.

Grazoprevir was administered at a dose of 200 mg/day since it has an ~2-fold higher exposure in HCV-infected people compared with healthy people at steady state. The 200-mg dose in non-HCV-infected participants was therefore selected to match the exposure achieved when administering a 100-mg dose (the clinically approved dose) in HCV-infected people. Elbasvir was administered at a dose of 50 mg/day, since this is the approved dose in HCV-infected people. The potential for methadone and EBR or GZR interaction was assessed after multiple doses of EBR and GZR to fully assess the victim potential of GZR due to its nonlinear and time-dependent PKs.[4] Since it is considered unethical to

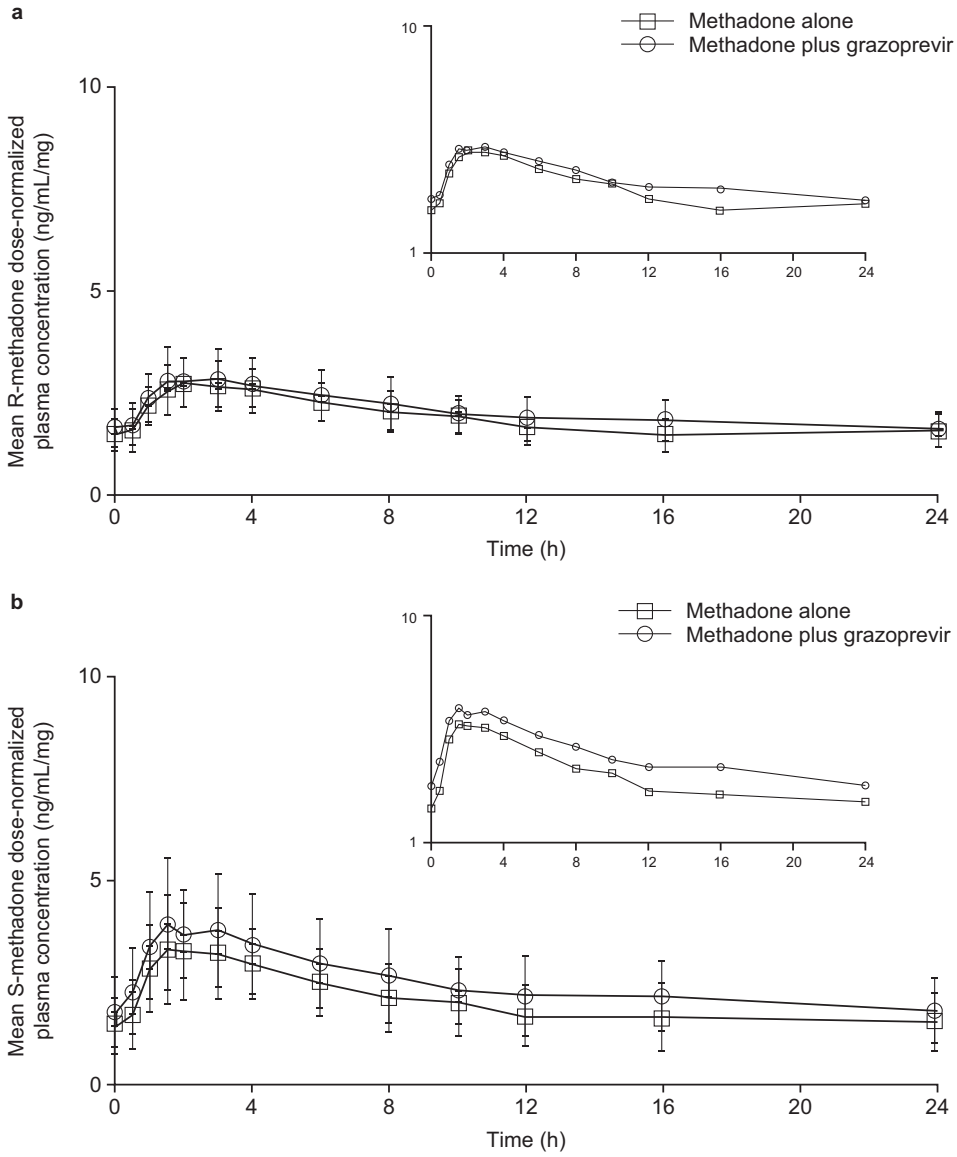

Figure 2 Arithmetic mean (standard deviation) plasma concentration–time profiles of (**a**) R- and (**b**) S-methadone following multiple oral doses of grazoprevir 200 mg once daily with and without coadministration of stable maintenance doses of methadone in adult participants ($n = 12$) receiving stable methadone substitution therapy. Inset = semi-log plot.

administer long-term daily methadone in healthy volunteers without a substantial risk of causing opioid addiction, this study was conducted in non-HCV-infected participants with established opioid dosing regimens who remained on their regimens throughout the study. Comparisons of methadone PKs were based on dose-normalized exposure parameters in non-HCV-infected participants who were on stable opioid maintenance therapy. This analysis is considered acceptable because methadone PKs (both AUC and C_{max}) are reported to be dose-proportional within the dose range used.[19]

Because participants in these studies were already receiving stable maintenance methadone therapy and dosing could not be interrupted without substantial risk of inducing withdrawal symptoms and their psychological sequelae, it was not feasible to assess the effect of methadone coadministration on EBR and GZR PKs in the same individuals using a crossover study design. Therefore, in order to provide an estimate of the effect of methadone on EBR and GZR PKs, EBR and GZR exposures when coadministered with methadone were compared with pooled EBR or GZR exposures in non-HCV-infected healthy participants in historical databases. All historical controls were selected based on the following criteria that were chosen to match the conditions of the DDI studies: i) PK data were from non-HCV-infected people; ii) PK data were measured after multiple-dose administration of either 50 mg EBR alone or 200 mg GZR alone; and iii) the study treatment was administered under fasted conditions. As such, the pooled data sets represented general non-HCV-infected populations that can be compared with the study populations in the DDI studies. Although the validity

Table 2 Summary statistics of R- and S-methadone plasma pharmacokinetics following stable maintenance doses of methadone 20–120 mg q.d. with or without the coadministration of multiple doses of elbasvir 50 mg q.d. for 10 days in adult participants receiving stable methadone substitution therapy

Pharmacokinetic parameter	Methadone alone			Methadone + EBR			Methadone + EBR/methadone alone		Pseudo within-participant %CV[a]
	n	GM	95% CI	*n*	GM	95% CI	GMR	90% CI	
R-methadone									
$AUC_{0\text{-}24}/D^b$, ng·hr/mL/mg	10	113	92.7–138	10	116	104–130	1.03	0.92–1.15	13.9
C_{max}/D^b, ng/mL/mg	10	6.73	5.44–8.33	10	7.19	6.35–8.14	1.07	0.95–1.20	14.1
C_{24}/D^b, ng/mL/mg	10	3.75	2.96–4.74	10	4.12	3.65–4.65	1.10	0.96–1.26	16.9
T_{max}[c], hr	10	3.00	1.50, 6.00	10	3.00	2.00, 6.00	–	—	—
S-methadone									
$AUC_{0\text{-}24}/D^b$, ng·hr/mL/mg	10	122	89.4–167	10	133	105–168	1.09	0.94–1.26	18.3
C_{max}/D^b, ng/mL/mg	10	8.61	6.39–11.6	10	9.42	7.59–11.7	1.09	0.95–1.25	16.7
C_{24}/D^b, ng/mL/mg	10	3.48	2.30–5.26	10	4.17	3.11–5.60	1.20	0.98–1.47	24.6
T_{max}[c], hr	10	2.51	1.50, 4.00	10	2.00	1.50, 4.00			

Methadone alone: methadone 20–120 mg on day 1.
Methadone + EBR: coadministration of methadone 20–120 mg q.d. with EBR 50 mg q.d. on days 2–11.
$AUC_{0\text{-}24}$, area under the concentration–time curve from time 0–24 hours postdose; C_{24}, plasma drug concentration at time 24 hours after dosing; CI, confidence interval; C_{max}, maximum concentration; D, dose-normalized; EBR, elbasvir; GM, geometric mean; GMR, geometric mean ratio; q.d., once daily; T_{max}, time to C_{max}.
[a]Pseudo within-participant %CV = $100 \times \text{sqrt}[(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2]$, where σ_A^2 and σ_B^2 are the estimated variance on the log scale for the two treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[b]Back-transformed least-squares mean and CI from the linear mixed-effects model performed on natural log-transformed values.
[c]Median (minimum, maximum) reported for T_{max}.

Table 3 Summary statistics of R- and S-methadone plasma pharmacokinetics following stable maintenance doses of methadone 20–150 mg q.d. with or without the coadministration of multiple doses of grazoprevir 200 mg q.d. for 10 days in adult participants receiving stable methadone substitution therapy

Pharmacokinetic parameter	Methadone alone			Methadone + GZR			Methadone + GZR/methadone alone		Pseudo within-participant %CV[a]
	n	GM	95% CI	*n*	GM	95% CI	GMR	90% CI	
R-methadone									
$AUC_{0\text{-}24}/D^b$, ng·hr/mL/mg	12	89.9	78.5–103	12	98.2	84.9–114	1.09	1.02–1.17	9.6
C_{max}/D^b, ng/mL/mg	12	5.79	5.10–6.58	12	5.98	5.13–6.97	1.03	0.96–1.11	10.3
T_{max}[c], hr	12	2.50	1.00, 4.02	12	2.00	1.50, 4.00			
S-methadone									
$AUC_{0\text{-}24}/D^b$, ng·hr/mL/mg	12	88.5	68.7–114	12	109.00	86–138	1.23	1.12–1.35	13.0
C_{max}/D^b, ng/mL/mg	12	6.67	5.37–8.29	12	7.69	6.12–9.67	1.15	1.07–1.25	10.6
T_{max}[c], hr	12	2.50	1.00, 15.93	12	1.75	1.00, 3.00			

Methadone alone: methadone 20 mg to 150 mg on day 1.
Methadone + GZR: coadministration of methadone 20–150 mg q.d. with GZR 200 mg q.d. on days 2–11.
$AUC_{0\text{-}24}$, area under the concentration–time curve from time 0–24 hours postdose; CI, confidence interval; C_{max}, maximum concentration; D, dose-normalized; GM, geometric mean; GMR, geometric mean ratio; GZR, grazoprevir; q.d., once daily; T_{max}, time to C_{max}.
[a]Pseudo within-participant %CV = $100 \times \text{sqrt}[(\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2]$, where σ_A^2 and σ_B^2 are the estimated variance on the log scale for the two treatments, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[b]Back-transformed least-squares mean and CI from the linear mixed-effects model performed on natural log-transformed values.
[c]Median (minimum, maximum) reported for T_{max}.

of pooling the historical data for the EBR and GZR comparisons were supported by the similar demographics between the participants in the DDI studies and the historical cohorts as well as additional analyses suggesting that the interstudy variation in the historical cohorts is minimal, there may be potential limitations in the EBR and GZR comparisons, since the historical cohorts were not matched to participants in the DDI studies. Population PK models for GZR and EBR have been developed with the primary goal of characterizing GZR and EBR PK in HCV-infected individuals. The models were developed based on PK data from a limited number of studies in non-HCV-infected participants and from several studies in a large number of HCV-infected participants. As such, these models were not suited to assess the magnitude of the effect of methadone coadministration on GZR and EBR exposures observed in the DDI studies in non-HCV-infected participants, as described in the studies in this article. Instead, the GZR and EBR PK comparisons in non-HCV-infected participants were treated using statistical mixed effects modeling considering various covariates as fixed effects in the statistical model. A large number of covariates, such as race, ethnicity, age, sex, and body weight, were included in the statistical model based on knowledge of the effects of these factors on GZR and EBR PK that are derived from population PK analyses. However, given that the point estimate for the effect of methadone on EBR AUC was 1.20, the EBR population PK model was used to evaluate whether methadone has a similar effect on EBR exposure in HCV-infected participants. In the phase III C-EDGE CO-STAR trial, the EBR

Table 4 Statistical comparison of EBR pharmacokinetic parameter values following multiple-dose q.d. administration of EBR 50 mg alone (historical cohort) or coadministration of EBR 50 mg and methadone in non-HCV-infected participants

EBR pharmacokinetic parameter	EBR alone			Methadone + EBR			Methadone + EBR/EBR alone		
	n	GM	95% CI	*n*	GM	95% CI	GMR	90% CI	rMSE[a]
$AUC_{0\text{-}24}$[b] (μM·hr)	56	1.99	1.78–2.22	10	2.38	1.82–3.12	1.20	0.94–1.53	0.406
C_{max}[b] (μM)	56	0.156	0.138–0.176	10	0.193	0.143–0.260	1.23	0.94–1.62	0.452
C_{24}[b] (nM)	56	48.3	43.3–53.8	10	63.5	48.7–82.9	1.32	1.03–1.68	0.401
T_{max}[c] (hr)	56	4.00	2.00, 5.02	10	3.99	2.00, 6.00			

$AUC_{0\text{-}24}$, area under the concentration–time curve from time 0 to 24 hours postdose; C_{24}, plasma drug concentration at time 24 hours after dosing; CI, confidence interval; C_{max}, maximum concentration; EBR, elbasvir; GM, geometric mean; GMR, geometric mean ratio; q.d., once daily; T_{max}, time to C_{max}.
[a]rMSE: square root of mean squared error (residual error) from the fixed effects model. rMSE*100% approximates the between-participant %CV on the raw scale.
[b]Back-transformed least-squares mean and CI from the fixed effects model performed on natural log-transformed values, with treatment as a fixed effect, and race, ethnicity, age, sex, and body weight as covariates.
[c]Median (minimum, maximum) reported for T_{max}.

Table 5 Statistical comparison of GZR pharmacokinetic parameter values following multiple-dose q.d. administration of GZR 200 mg alone (historical cohort) or coadministration of GZR 200 mg and methadone in non-HCV-infected participants

GZR pharmacokinetic parameter	GZR alone			Methadone + GZR			Methadone + GZR/GZR alone		
	n	GM	95% CI	*n*	GM	95% CI	GMR	90% CI	rMSE[a]
$AUC_{0\text{-}24}$[b] (μM·hr)	106	2.47	2.20–2.77	12	2.55	1.80–3.61	1.03	0.76–1.41	0.600
C_{max}[b] (μM)	106	0.588	0.508–0.681	12	0.525	0.338–0.814	0.89	0.60–1.32	0.757
C_{24}[b] (nM)	106	13.9	12.8–15.2	12	13.7	10.6–17.6	0.98	0.79–1.23	0.436
T_{max}[c] (hr)	107	3.00	1.00, 6.00	12	3.50	1.00, 6.00			

$AUC_{0\text{-}24}$, area under the concentration–time curve from time 0 to 24 hours postdose; C_{24}, plasma drug concentration at time 24 hours after dosing; CI, confidence interval; C_{max}, maximum concentration; GM, geometric mean; GMR, geometric mean ratio; GZR, grazoprevir; q.d. once daily; T_{max}, time to C_{max}.
[a]rMSE: square root of mean squared error (residual error) from the fixed effects model. rMSE*100% approximates the between-participant %CV on the raw scale.
[b]Back-transformed least-squares mean and CI from the fixed effects model performed on natural log-transformed values, with treatment as a fixed effect, and race, ethnicity, age, sex, and body weight as covariates.
[c]Median (minimum, maximum) reported for T_{max}.

AUC in HCV-infected participants who received methadone was estimated using the developed EBR population PK model and compared with that in HCV-infected participants in other phase III studies. The results showed an increase in EBR AUC, with a point estimate of ~1.28,[20] which is consistent with the results from the statistical analysis in non-HCV-infected participants observed in the studies described in this article.

Despite the limitations of the study designs and the two-step approach of noncompartmental analysis for the estimation of EBR and GZR PK in non-HCV-infected populations followed by statistical analysis PK comparisons, the results from these studies informed the inclusion of HCV-infected participants who were on opioid agonist therapy in the phase III clinical studies that investigated the safety and efficacy of EBR/GZR for the treatment of HCV infection. The lack of clinically meaningful DDIs observed in the studies described here are confirmed by the favorable safety and efficacy profiles in the phase III, placebo-controlled C-EDGE CO-STAR trial in treatment-naive participants with HCV GT1, 4, or 6 infection receiving opioid agonist therapy.[21] In that study, participants received either an immediate EBR/GZR fixed-dose combination once daily for 12 weeks or placebo for 12 weeks followed by deferred treatment with EBR/GZR. Overall, EBR/GZR demonstrated high efficacy, with 91.5% of participants in the immediate-treatment group achieving sustained virologic response at follow-up week 12. There were similar safety profiles in the active treatment group and the placebo treatment group, and there was excellent treatment adherence despite a high rate of ongoing drug use.[21] These results demonstrate that antiviral activity and safety profile are maintained in HCV-infected participants receiving EBR/GZR and opioid agonist therapy with methadone, and that coadministration of EBR/GZR with methadone is well tolerated in this population[21].

Taken together, the findings of these trials demonstrate that no dose adjustment is required for people with HCV infection receiving the EBR/GZR fixed-dose combination with stable methadone opiate agonist therapy. Data from these trials, supported by the C-EDGE COSTAR trial data, suggest that the fixed-dose combination of EBR/GZR is a safe and effective treatment option for people with HCV infection receiving opioid agonist therapy.

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