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ARTICLE

No Pharmacokinetic Interactions Between Elbasvir or Grazoprevir and Buprenorphine/Naloxone in Healthy Participants and Participants Receiving Stable Opioid Agonist Therapy

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The aims of these phase I trials were to evaluate the pharmacokinetic interaction between elbasvir (EBR) or grazoprevir (GZR) and buprenorphine/naloxone (BUP/NAL). Trial 1 was a single-dose trial in healthy participants. Trial 2 was a multiple-dose trial in participants on BUP/NAL maintenance therapy. Coadministration of EBR or GZR with BUP/NAL had minimal effect on the pharmacokinetics of BUP/NAL, EBR, and GZR. The geometric mean ratios (GMRs (90% CI)) for BUP, norbuprenorphine, and NAL $AUC_{0-\infty}$ were 0.98 (0.89–1.08), 0.97 (0.86–1.09), and 0.88 (0.78–1.00) in the presence/absence of EBR; 0.98 (0.81–1.19), 1.13 (0.97–1.32), and 1.10 (0.82–1.47) in the presence/absence of GZR. The GMRs (90% CI) for EBR and GZR $AUC_{0-\infty}$ in the absence/presence of BUP/NAL were 1.22 (0.98–1.52) and 0.86 (0.63–1.18). In conclusion, no dose adjustment for BUP/NAL, EBR, or GZR is required for patients with HCV infection receiving EBR/GZR and BUP/NAL maintenance therapy.
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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
✔ HCV infection is common among people who are on opioid maintenance therapy.

WHAT QUESTION DID THIS STUDY ADDRESS?
✔ This study evaluated potential drug–drug interactions between the opioid substitution therapy BUP/NAL 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, BUP, or NAL in this study.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
✔ EBR/GZR dose adjustments are therefore not required in people also receiving BUP/NAL maintenance therapy. The EBR/GZR fixed-dose combination is a treatment option for HCV-infected people receiving opioid substitution 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 often receive opioid substitution therapy, such as the mixed partial agonist opioid-receptor modulator buprenorphine (BUP), which is commonly administered with the opioid antagonist naloxone (NAL).

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 studies 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,[10–12] and those with HIV coinfection[13] or stage 4/5 chronic kidney disease.[14] The EBR/GZR fixed-dose combination is administered once daily, without regard to food intake.

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Buprenorphine undergoes oxidative metabolism to form the reportedly active metabolite norbuprenorphine (NorBUP) via cytochrome P450 3A (CYP3A), whereas NAL elimination involves oxidative metabolism via glucuronidation and reductive metabolism.[15–17] It has not been unequivocally established whether BUP and NAL are P-glycoprotein (P-gp) substrates, and it is unknown whether BUP and NAL are breast cancer resistance protein (BCRP) substrates.[18] Both BUP and NorBUP are inhibitors of CYP2D6, and BUP additionally inhibits CYP3A.[19] Naloxone is not a P-gp inhibitor, and it is unknown whether BUP inhibits P-gp or whether BUP or NAL inhibits organic anion transporting polypeptide (OATP)1B1/3.[18] Both EBR and GZR are substrates of CYP3A/P-gp, and GZR is a substrate for OATP1B1/3. 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, BUP, and NAL, coadministration of EBR/GZR with BUP/NAL 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 disposition pathways and enzyme inhibition profiles, such as CYP3A. 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) studies were conducted to assess the PK effects of EBR or GZR coadministered with BUP and NAL. PK interactions between EBR and BUP/NAL were assessed in healthy participants, whereas the interaction between GZR and BUP/NAL was assessed in participants who were receiving stable opioid 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.

EBR and BUP/NAL drug interaction trial (Trial 1; MK-8742 P021)

Clinical conduct

This was a phase I, open-label, three-period, fixed-sequence trial in healthy male and female participants who were 19–55 years of age, with a body mass index (BMI) 18–32 kg/m^2 (**Figure S1**). Participants were required to be medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, and electrocardiograms (ECGs). Participants with a history or presence of clinically significant medical or psychiatric diseases, or with any condition that might confound the results of the study, were excluded.

On day 1 of Period 1, all participants received a single dose of the sublingual fixed-dose combination of BUP 8 mg/NAL 2 mg, followed by a washout period of 15 days. In Period 2, all participants received a single oral dose of EBR 50 mg, followed by a washout period of 13 days. In Period 3, all participants received a single oral dose of EBR 50 mg, followed within 5 minutes by a single dose of the sublingual fixed-dose combination of BUP 8 mg/NAL 2 mg. To block the major adverse effects of BUP, healthy participants received naltrexone (NTX) blockade with a single 50-mg NTX dose on day −1 of Periods 1 and 3, ~14 hours before each BUP/NAL dose and repeated approximately every 12 hours thereafter (hour −2 of day 1 pre-BUP/NAL dosing and hour 10 on day 1 post-BUP/NAL dosing), for a total of three NTX doses in each period. All study treatments were administered under fasted conditions to eliminate the potential confounding effect of food.

Analytical methods

Bioanalytical methods for the determination of plasma EBR, BUP, NorBUP, and NAL are described in the **Supplementary Information**.

PK and safety assessments

Blood samples for determination of EBR, BUP, NorBUP, and NAL PKs were collected predose and at specified timepoints over 96 hours (in Periods 2 and 3 for EBR) or 144 hours (in Periods 1 and 3 for BUP/NorBUP/NAL). Estimates of the following PK parameters were determined: $AUC_{0-\infty}$ (area under the concentration–time curve from time 0 postdose to infinity) and $T_{½}$ (apparent terminal half-life) using noncompartmental analysis, and C_{max} (maximum concentration), C_{24} (concentration at 24 hours postdose), and T_{max} (time to C_{max}) directly from 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

Values of exposure parameters ($AUC_{0-\infty}$, 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 measures within each participant. The Kenward–Roger's method was used to calculate the appropriate degrees of freedom for the fixed effects. 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. The back-transformed summary results are reported for each parameter as the geometric LSMs (GMs) and corresponding 95% CIs, as well as the GM ratios (GMRs, coadministered drugs/single-administered drug) and corresponding 90% CIs.

With a sample size of 14 participants, the half-widths of the 90% CI of GMR on the log scale would be 0.27 assuming a within-participant standard deviation (SD) of 0.40 on the natural log scale (NAL AUC; EBR AUC), 0.17 assuming a within-participant SD of 0.26 on the natural log scale (BUP

AUC), and 0.14 assuming a within-participant SD of 0.21 on the natural log scale (NorBUP AUC).

GZR and BUP/NAL drug interaction trial (Trial 2; MK-5172 P030)

Clinical conduct

This was a phase I, open-label, fixed-sequence, multiple-dose trial in participants on stable oral BUP/NAL maintenance therapy (**Figure S1**). Participants were 18–55 years of age with a BMI of 18–36 kg/m^2. All participants were required to be in good health based on medical history, physical examination, vital signs, and laboratory safety tests. Participants with clinically significant disease as described for Trial 1 were excluded. Prior to enrolling in this study, participants were part of an opioid maintenance program, receiving BUP/NAL therapy (8/2 mg once daily (q.d.) to 24/6 mg q.d.) for opioid use disorder for at least 2 months with stable dosing for at least the previous 14 days. Participants who were on a BUP maintenance program were eligible to participate but were required to switch to BUP/NAL $\geq$2 weeks before day 1. On day 1 of this study, participants received a sublingual dose of BUP/NAL after an overnight fast. On days 2–11, participants received oral GZR 200 mg q.d. followed by a maintenance dose of BUP/NAL after an overnight fast. Participants received either sublingual film or sublingual tablet formulation of BUP/NAL as long as the same formulation was used throughout the study. All study treatments were administered under fasted conditions to eliminate the potential confounding effect of food.

Analytical methods

Bioanalytical methods for the determination of plasma GZR, BUP, NorBUP, and NAL are described in the **Supplementary Materials**.

PK and safety assessments

Blood samples for determination of GZR, BUP, NorBUP, and unconjugated NAL PKs were collected predose and at specified timepoints over 24 hours on days 1 and 11. Estimates of the following PK parameters were determined: $AUC_{0\text{-}24}$ and $T_{½}$ by noncompartmental analysis and C_{max} and T_{max} directly from observed concentration–time data. Safety was assessed by monitoring AEs, physical examination findings, vital signs, ECGs, pulse oximetry, and laboratory safety assessments.

Statistical analysis and power

Dose-normalized exposure parameters for BUP, NorBUP, and NAL ($AUC_{0\text{-}24}$ and C_{max}) were natural log-transformed and analyzed as described for the EBR and BUP/NAL drug interaction trial (Trial 1). To provide an estimate of the effect of BUP/NAL coadministration on GZR PKs, GZR exposures following coadministration with BUP/NAL 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 the reference comparator group. A total of 107 non-HCV-infected participants from a historical database were pooled and used for comparison of 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. Grazoprevir $AUC_{0\text{-}24}$, C_{max}, and C_{24} following BUP/NAL coadministration in Trial 2 and administration alone in the historical database were log-transformed and analyzed with a linear fixed-effect model containing a fixed-effect term for treatment and covariates of race (white/Asian, black, other), ethnicity (Hispanic or Latino, non-Hispanic or non-Latino), age, sex, and body weight. Grazoprevir exposure data from the treatment of GZR + methadone were also included in the model (i.e., a total of three treatments in the model) and the results are reported separately (Feng *et al.*, submitted to *Clinical and Translational Science,* December 2017). 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 12 participants, the half-widths of the 90% CI of GMR on the log scale would be 0.29 assuming a within-participant SD of 0.40 on the natural log scale (NAL AUC), 0.19 assuming a within-participant SD of 0.26 on the natural log scale (BUP AUC), and 0.15 assuming a within-participant SD of 0.21 on the natural log scale (NorBUP AUC). For the comparison of GZR AUC using pooled historical data, with sample sizes of 106 and 12 for the two groups and assuming a between-participant SD of 0.60 on the natural log scale, the half-width of the 90% CI of GMR on the log scale would be 0.31.

RESULTS

Trial populations

In the EBR and BUP/NAL drug interaction trial (Trial 1), 16 healthy participants were enrolled; of those, 13 completed treatment and three discontinued due to an AE of vomiting. Of the three participants who discontinued, one discontinued on day 1 of Period 1 (BUP/NAL alone) due to vomiting within 3 hours of dosing (last sample was 2 hours postdose); therefore, complete PK profiles for EBR, BUP, NorBUP, and unconjugated NAL were not obtained for this participant with any treatment. Two other participants were discontinued on day 1 of Period 3 (EBR + BUP/NAL) due to vomiting within 8 hours of dosing (last blood samples were 2 hours postdose, and predose in Period 3). Therefore, EBR, BUP, norBUP, and unconjugated NAL PKs could not be determined following EBR + BUP/NAL for these participants.

In the GZR and BUP/NAL drug interaction trial (Trial 2), 12 participants receiving ongoing BUP/NAL treatment were enrolled and completed treatment. Of the 12 participants enrolled in Trial 2, six were taking BUP/NAL 8/2 mg, one was taking 12/3 mg, three were taking 16/4 mg, and two were taking 24/6 mg. A total of 107 non-HCV-infected participants from a historical database were included as the reference in the statistical analysis to assess the effect of BUP/NAL coadministration on GZR PKs; one participant 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 controls are provided in **Table 1**.

Table 1 Participant characteristics

	EBR BUP/NAL DDI trial ($n = 16$)	GZR BUP/NAL DDI trial ($n = 12$)	Historical data: GZR ($n = 107$[a])
Sex, no. (%)			
Male	9 (56.2)	9 (75.0)	71 (66.4)
Female	7 (43.8)	3 (25.0)	36 (33.6)
Age, years, mean (range)	29 (23–44)	30 (22–47)	37 (18–64)
Height, m, mean (range)	1.73 (1.60–1.86)	1.73 (1.57–1.85)	1.71 (1.49–1.90)
Weight, kg, mean (range)	82.9 (66.8–102.2)	76.8 (56.0–100.2)	77.3 (52.3–111.0)
BMI, kg/m^2, mean (range)	27.8 (23.1–31.6)	26.0 (20.3–35.3)	26.3 (19.3–35.0)
Race, no. (%)			
White	10 (100.0)	12 (100.0)	89 (83.2)
Black/African American	0 (0)	0 (0)	9 (8.4)
Asian	0 (0)	0 (0)	2 (1.9)
Other	0 (0)	0 (0)	6 (5.6)
Unknown[a]	0 (0)	0 (0)	1 (0.9)
Ethnicity, no. (%)			
Hispanic or Latino	0 (0)	2 (16.7)	22 (20.6)
Not Hispanic or Latino	16 (100)	10 (83.3)	85 (79.4)

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

Effect of EBR or GZR coadministration on BUP, NorBUP, and NAL PKs

In healthy participants, coadministration of EBR with BUP/NAL had no meaningful effect on the concentration–time profiles of BUP, its active metabolite NorBUP, or NAL (**Figure 1**). Statistical comparisons showed no notable changes in the PKs of BUP or NorBUP when BUP/NAL was coadministered with EBR. GMRs for $AUC_{0-\infty}$, C_{max}, and C_{24} (BUP/NAL coadministered with EBR relative to BUP/NAL alone) ranged from 0.94–0.98 for BUP and 0.97–1.10 for NorBUP, with narrow CIs (**Table 2**). The GMRs for NAL $AUC_{0-\infty}$ and C_{max} (BUP/NAL coadministered with EBR relative to BUP/NAL alone) were 0.88 and 0.85, respectively, with 90% CIs containing 1. T_{max} and apparent $T_{½}$ for BUP, NorBUP, and NAL were similar for the two treatments.

In participants on stable BUP/NAL opioid agonist therapy, coadministration of GZR with BUP/NAL had no meaningful effect on the concentration–time profiles of BUP, NorBUP, or NAL (**Figure 2**). Statistical comparisons for BUP showed that the GMRs for dose-normalized AUC_{0-24} and C_{max} (BUP/NAL coadministered with GZR relative to BUP/NAL alone) were 0.98 and 0.90, respectively, with 90% CIs containing 1 (**Table 3**). Statistical comparisons for NorBUP and NAL showed that the GMRs for dose-normalized $AUC_{0-\infty}$ (BUP/NAL coadministered with GZR relative to BUP/NAL alone) were 1.13 and 1.10, respectively, with 90% CIs containing 1. The dose-normalized C_{max} GMRs (BUP/NAL coadministered with GZR relative to BUP/NAL alone) were 1.10 and 1.00, respectively, with 90% CIs containing 1 (**Table 3**).

Effect of BUP/NAL coadministration on EBR or GZR PKs

In healthy participants, coadministration of BUP/NAL with EBR had no meaningful effect on the concentration–time profile of EBR (**Figure 1**). EBR GMRs for $AUC_{0-\infty}$, C_{max}, and C_{24} (EBR coadministered with BUP/NAL relative to EBR alone) ranged from 1.13–1.22, with 90% CIs containing 1. The observed EBR median T_{max} was ~1 hour later when administered alone than when coadministered with BUP/NAL (4.00 vs. 3.01 hours) (**Table 4**). The EBR GM apparent terminal $T_{½}$ was similar in the absence and presence of BUP/NAL (18.46 hours vs. 18.60 hours).

To assess the effect of BUP/NAL coadministration on GZR PKs, GZR exposures (AUC_{0-24}, C_{max}, and C_{24}) from participants who were on stable maintenance BUP/NAL opioid agonist therapy were compared with those following multiple administration of GZR 200 mg alone in a historical database. GMRs for GZR AUC_{0-24}, C_{max}, and C_{24} (GZR coadministered with BUP/NAL relative to GZR alone) ranged from 0.80–0.97 (**Table 5**) with the associated 90% CIs containing 1. In addition, coadministration did not appear to have an effect on the range of GZR T_{max}.

Safety and tolerability in the clinical drug interaction studies

Coadministration of EBR or GZR with BUP/NAL was generally well tolerated in healthy participants. In the EBR and BUP/NAL drug interaction trial (Trial 1), three participants discontinued due to AEs of drug-related vomiting. Thirteen participants reported a total of 78 AEs, of which 73 were considered drug-related (three AEs were related to NTX ($n = 3$), 4 to EBR ($n = 3$), 28 to EBR, BUP/NAL, and NTX ($n = 7$), and 38 to BUP/NAL and NTX ($n = 11$)). All AEs were mild or moderate in intensity and resolved by the end of the trial. There were no serious AEs, clinically meaningful laboratory AEs, AEs of special interest, or deaths reported. The most frequent drug-related AEs were nausea (63%), dizziness (38%), vomiting (31%), and headache and somnolence (25% each), all of which were reported during periods when BUP/NAL was administered and are known side effects of these drugs.[17]

In the GZR and BUP/NAL drug interaction trial (Trial 2), there were no serious AEs, treatment discontinuations, or deaths during the trial. Seven participants receiving stable

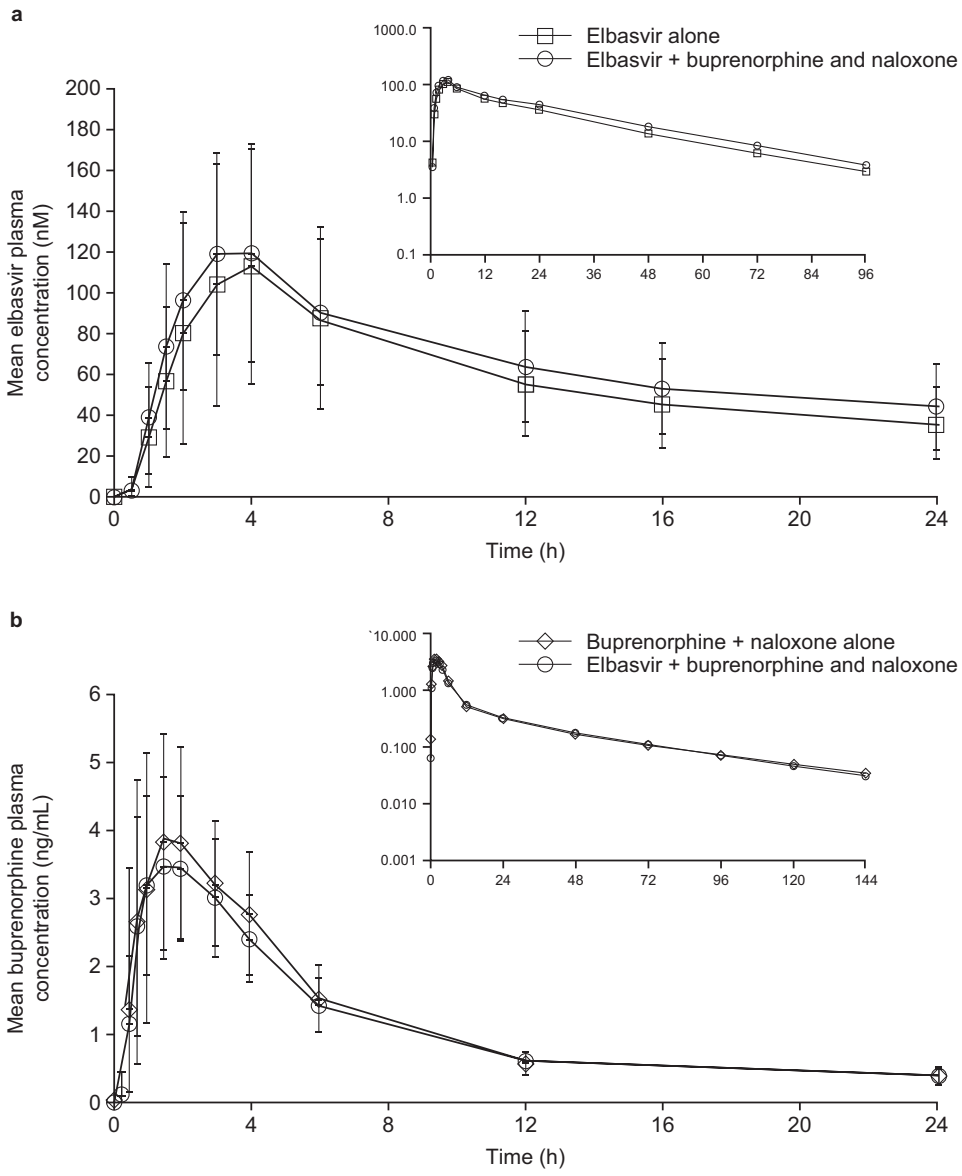

Figure 1 Arithmetic mean (standard deviation) plasma concentration–time profiles of (**a**) elbasvir, (**b**) buprenorphine, (**c**) norbuprenorphine, and (**d**) naloxone following the administration of a single oral dose of elbasvir 50 mg with and without a single sublingual dose of buprenorphine/naloxone 8/2 mg in healthy participants ($N = 16$).

BUP/NAL opioid agonist therapy reported a total of 13 AEs, of which two were considered drug-related. The two drug-related AEs were dry mouth and constipation, both in participants receiving GZR with BUP/NAL. All AEs were mild to moderate in intensity and resolved by trial completion. The most frequent AE was headache, noted in two participants (one receiving BUP/NAL and one receiving GZR with BUP/NAL). There were no clinically meaningful changes in laboratory values, vital signs, or ECGs noted in either study.

DISCUSSION

Data from the present trials demonstrate that in healthy participants or non-HCV-infected participants on stable BUP/NAL maintenance therapy, coadministration of EBR or GZR with BUP/NAL had a minimal effect on the PKs of BUP and NAL. The stable plasma concentrations of BUP and NAL suggest that coadministration with EBR or GZR is unlikely to lead to opioid intoxication or withdrawal. Similarly, coadministration of BUP/NAL with EBR in healthy participants and GZR in non-HCV-infected participants on stable BUP/NAL maintenance therapy also did not meaningfully impact the PKs of EBR or GZR, suggesting that the safety and efficacy profiles of EBR or GZR would not be affected if coadministered with BUP/NAL. The results from these DDI studies supported the inclusion of HCV-infected participants who were on opioid agonist therapy in phase III clinical studies that investigated the safety and efficacy of EBR/GZR for the treatment of individuals with HCV infection.

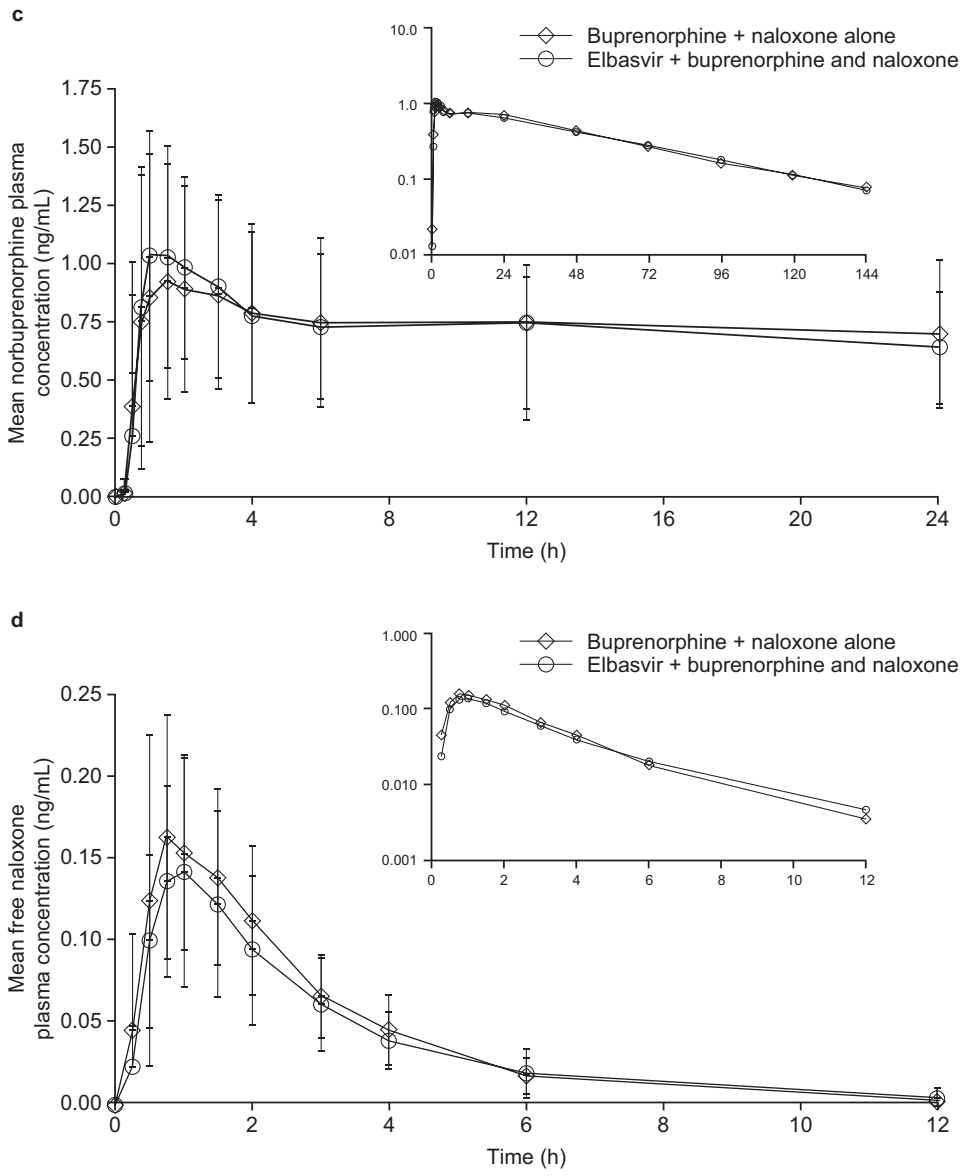

Figure 1 *Continued.*

Although the two DDI studies reported here were conducted as separate studies using single-entity formulations of EBR or GZR, the conclusion from these studies is expected to be applicable to the clinical setting of coadministering BUP/NAL with the fixed-dose combination of EBR/GZR, because i) it has been demonstrated that EBR and GZR coadministration have no meaningful effect on the PK of either EBR or GZR (AUC GMRs (90% CIs) for EBR and GZR were 1.01 (0.83–1.24) and 0.90 (0.63–1.28) for the comparisons EBR + GZR/EBR alone and GZR + EBR/GZR alone, respectively),[4,5] and ii) the lack of clinically meaningful interactions noted with EBR and GZR separately provides support that the combination is unlikely to produce clinically meaningful effects on BUP/NAL exposures. In addition, participants in these studies received either sublingual film or sublingual tablet formulations of BUP/NAL as long as the same formulation was used throughout the study. Since the results were summarized based on the effects in each individual participant, the potential difference in the PK profiles for each formulation is not expected to affect the DDI assessment and interpretation.

The potential for drug interaction between EBR and BUP/NAL was assessed in a single-dose design in healthy volunteers. Elbasvir was administered at a dose of 50 mg/day in the present study, the approved dose for individuals with HCV infection. Since *in vitro* data have shown that EBR does not induce drug-metabolizing enzymes or transporters,[4,5] and neither BUP nor NAL is reported to induce enzymes or transporters involved in the disposition of EBR, it is not necessary to assess the potential for drug interaction due to induction using a multiple-dose study design. In addition, since EBR exhibits linear PKs and the BUP and NAL PKs are

Table 2 Summary statistics of buprenorphine, norbuprenorphine, and naloxone plasma pharmacokinetics following administration of a single oral dose of elbasvir 50 mg with and without a single sublingual dose of buprenorphine 8 mg / naloxone 2 mg in healthy participants

	BUP/NAL alone			BUP/NAL + EBR			BUP/NAL + EBR/ BUP/NAL alone		Pseudo within-participant %CV[b]
Pharmacokinetic parameter	***n*[a]**	**GM**	**95% CI**	***n*[a]**	**GM**	**95% CI**	**GMR**	**90% CI**	
BUP									
$AUC_{0-\infty}$[c,d], ng·hr/mL	14	38.4	30.5–48.4	13	37.6	31.4–45.2	0.98	0.89–1.08	13.1
C_{max}[c], ng/mL	15	3.79	3.05–4.72	13	3.57	2.85–4.48	0.94	0.82–1.08	19.7
T_{max}[e], hr	15	1.51	0.75, 3.00	13	1.49	0.73, 2.99			
Apparent terminal $T_{½}$[d,f], hr	14	37.39	32.53	13	39.59	36.24			
NorBUP									
$AUC_{0-\infty}$[c,d], ng·hr/mL	14	49.4	38.9–62.6	13	47.7	37.1–61.4	0.97	0.86–1.09	17.5
C_{max}[c], ng/mL	15	0.992	0.751–1.31	13	1.09	0.823–1.44	1.10	0.98–1.23	16.5
T_{max}[e], hr	15	1.51	0.50, 12.01	13	1.01	0.49, 11.98			
Apparent terminal $T_{½}$[d,f], hr	14	38.81	33.64	13	33.92	33.27			
NAL									
$AUC_{0-\infty}$[c,d], ng·hr/mL	14	0.47	0.37–0.598	13	0.416	0.316–0.549	0.88	0.78–1.00	17.9
C_{max}[c], ng/mL	15	0.165	0.133–0.203	13	0.139	0.103–0.188	0.85	0.66–1.09	36.3
T_{max}[e], hr	15	0.75	0.50, 1.51	13	0.98	0.49, 1.01			
Apparent terminal $T_{½}$[d,f], hr	14	1.93	51.48	13	2.08	48.71			

BUP/NAL alone: a single sublingual dose of BUP 8 mg / NAL 2 mg (with naltrexone (NTX) blockage administered as NTX HCl 50 mg every 12 hours starting 14 hours prior to the BUP/NAL dose, for a total of three NTX doses).
BUP/NAL + EBR: a single oral dose of EBR 50 mg coadministered with a single sublingual dose of BUP 8 mg / NAL 2 mg (with NTX blockage administered as NTX HCl 50 mg every 12 hours starting 14 hours prior to the BUP/NAL dose, for a total of three NTX doses).
$AUC_{0-\infty}$, area under the concentration–time curve from time 0 to extrapolated to infinity; BUP, buprenorphine; CI, confidence interval; C_{max}, maximum concentration; EBR, elbasvir; GM, geometric mean; GMR, geometric mean ratio; NAL, naloxone; NorBUP, norbuprenorphine; T_{max}, time to C_{max}.
[a]One participant was discontinued on day 1 of Period 1 (BUP/NAL alone) due to vomiting within 3 hours of dosing, and two participants were discontinued on day 1 of Period 3 (EBR+ BUP/NAL) due to vomiting within 8 hours of dosing.
[b]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.
[c]Back-transformed least-squares mean and CI from the linear mixed-effects model performed on natural log-transformed values
[d]The terminal elimination phase could not be characterized for one participant following BUP/NAL alone; therefore, $AUC_{0-\infty}$ and apparent terminal $T_{½}$ could not be calculated for this participant.
[e]Median (minimum, maximum) reported for T_{max}.
[f]GM and geometric CV reported for apparent terminal $T_{½}$.

dose-proportional,[20,21] the results and interpretation from the single-dose study can be extended to repeated administration. The NAL AUC and C_{max} were slightly decreased, with GMRs of ~0.8 in this single-dose study, and it is possible that the magnitude of the effect could theoretically increase with multiple dosing of EBR if there is underlying enzyme or transporter induction that was not predictable from *in vitro* studies. However, EBR has not been observed to have any induction potential in the numerous DDI studies that have been conducted in the clinical development program.[4,5] Furthermore, the favorable safety and efficacy data from the phase III C-EDGE CO-STAR trial in HCV-infected participants who were receiving opioid agonist therapy support no clinically meaningful interaction between BUP/NAL and EBR.[22] Given that a single-dose study design was adequate to interrogate the DDI potential between BUP/NAL and EBR, it was possible to conduct this short study with NTX blockade to minimize the major adverse effects of BUP in healthy volunteers. The administration of NTX in the BUP/NAL and EBR study is not expected to affect the PKs of EBR, GZR, BUP, and NAL,[23] since NTX is not an inhibitor or inducer of drug-metabolizing enzymes.

In contrast, the potential for BUP/NAL and GZR interaction was assessed after multiple doses of BUP/NAL and GZR administration to fully assess the victim potential of GZR due to the nonlinear and time-dependent PKs of GZR.[4,5] Since it is considered unethical to administer long-term daily BUP/NAL in healthy volunteers given the 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. In this study, GZR 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 people with HCV infection. For the DDI assessment between EBR and BUP/NAL, no dose adjustment was necessary, as all participants received the same dose of BUP/NAL. In contrast, in the GZR and BUP/NAL DDI study, comparisons of BUP and NAL 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 BUP and NAL PKs (both AUC and C_{max}) are reported to be dose-proportional within the dose range used.[20,21]

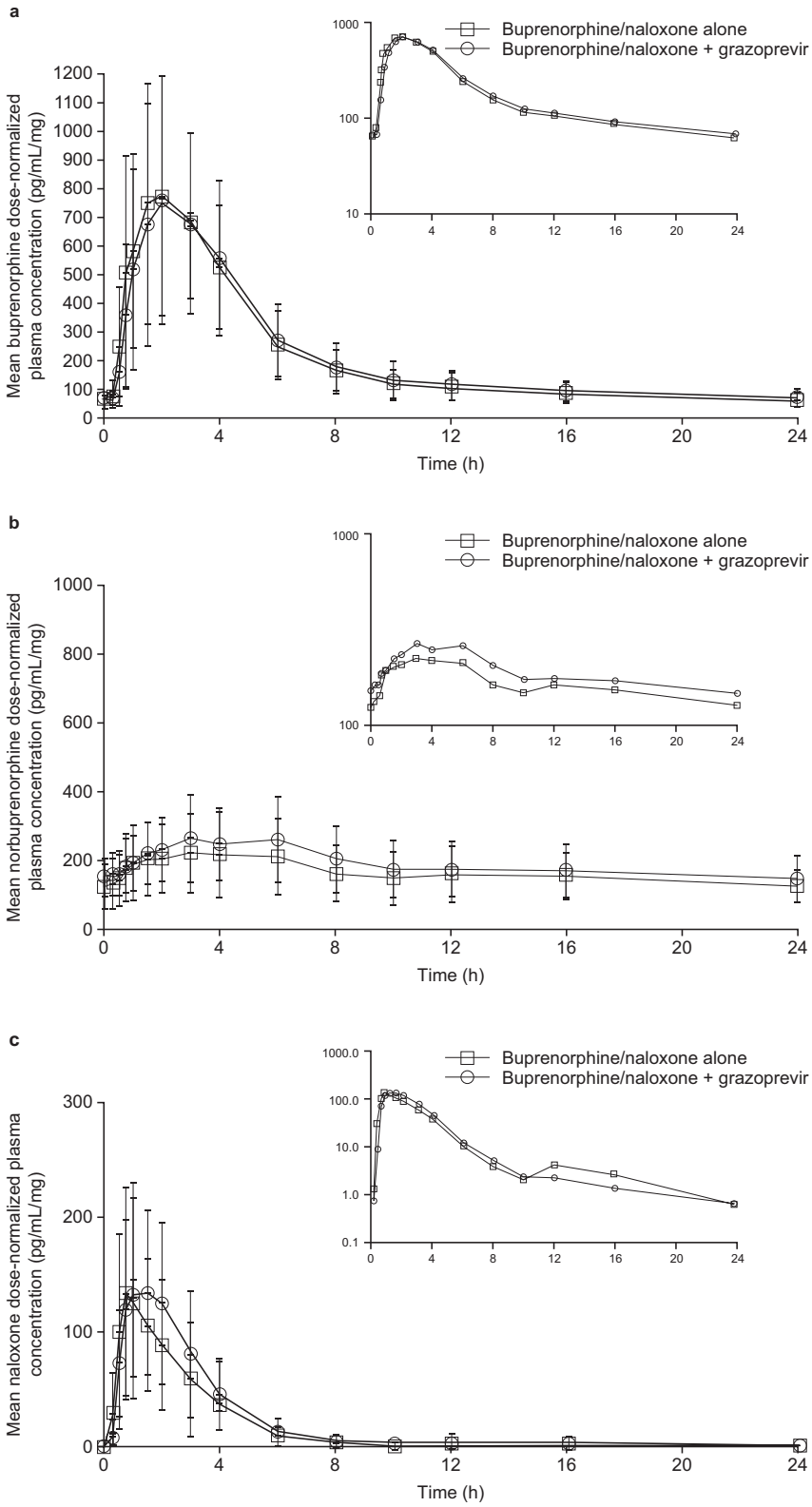

Figure 2 Arithmetic mean (standard deviation) dose-normalized plasma concentration–time profiles of (**a**) buprenorphine, (**b**) norbuprenorphine, and (**c**) naloxone following multiple oral doses of grazoprevir 200 mg once daily with and without coadministration of stable maintenance doses of buprenorphine/naloxone 8/2 mg to 24/6 mg once daily in adult participants receiving stable buprenorphine/naloxone substitution therapy ($N = 12$).

Table 3 Summary statistics of buprenorphine, norbuprenorphine, and naloxone plasma pharmacokinetics following stable maintenance doses of buprenorphine/naloxone 8/2 mg to 24/6 mg once daily with or without coadministration of multiple doses of grazoprevir 200 mg once daily for 10 days in adult participants receiving stable buprenorphine/naloxone substitution therapy

	BUP/NAL alone			BUP/NAL + GZR			BUP/NAL + GZR/ BUP/NAL alone		Pseudo within-participant %CV[a]
Pharmacokinetic parameter	***n***	**GM**	**95% CI**	***n***	**GM**	**95% CI**	**GMR**	**90% CI**	
BUP									
$AUC_{0-\infty}/D$[b], ng·hr/mL/mg	12	4.65	3.64–5.95	12	4.57	3.35–6.23	0.98	0.81–1.19	26.4
C_{max}/D[b], ng/mL/mg	12	0.802	0.628–1.02	12	0.722	0.509–1.02	0.90	0.76–1.07	23.4
T_{max}[c], hr	12	1.99	1.00, 3.00	12	2.01	1.00, 4.00			
Apparent terminal $T_{½}$[d,e], hr	10	10.71	73.09	11	13.43	30.71			
NorBUP									
$AUC_{0-\infty}/D$[b], ng·hr/mL/mg	12	3.53	2.55–4.90	12	3.99	2.76–5.76	1.13	0.97–1.32	20.9
C_{max}/D[b], ng/mL/mg	12	0.223	0.153–0.324	12	0.246	0.167–0.36	1.10	0.97–1.25	17.2
T_{max}[c], hr	12	3.00	1.00, 12.00	12	3.00	1.50, 6.00			
Apparent terminal $T_{½}$[d,f], hr	5	16.13	26.12	8	33.87	49.98			
NAL									
$AUC_{0-\infty}/D$[b], ng·hr/mL/mg	12	0.352	0.257–0.482	12	0.387	0.256–0.584	1.10	0.82–1.47	39.6
C_{max}/D[b], ng/mL/mg	12	0.149	0.113–0.196	12	0.149	0.110–0.204	1.00	0.80–1.27	31.7
T_{max}[c], hr	12	0.75	0.50, 3.00	12	1.24	0.50, 2.02			
Apparent terminal $T_{½}$[d,g], hr	10	3.33	92.14	12	5.20	107.25			

BUP/NAL alone: BUP 8 mg / NAL 2 mg to 24/6 mg on day 1.
BUP/NAL + GZR: coadministration of BUP 8 mg / NAL 2 mg to 24/6 mg once daily with GZR 200 mg once daily on days 2–11.
$AUC_{0-\infty}$, area under the concentration–time curve from time 0 extrapolated to infinity; BUP, buprenorphine; CI, confidence interval; C_{max}, maximum concentration; D, dose normalized; GM, geometric mean; GMR, geometric mean ratio; GZR, grazoprevir; NAL, naloxone; NorBUP, norbuprenorphine; 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}.
[d]GM and geometric CV reported for apparent terminal $T_{½}$.
[e]No apparent terminal $T_{½}$ could be calculated for two participants following administration of BUP/NAL alone and for one participant following coadministration of BUP/NAL with GZR, due to the lack of data in the terminal phase.
[f]No apparent terminal $T_{½}$ could be calculated for seven participants following administration of BUP/NAL alone and for four participants following coadministration of BUP/NAL with GZR, due to the lack of data in the terminal phase.
[g]No apparent terminal $T_{½}$ could be calculated for two participants following administration of BUP/NAL alone due to the lack of data in the terminal phase.

Since participants in the BUP/NAL and GZR drug interactions study were already receiving stable maintenance BUP/NAL therapy and BUP/NAL dosing could not be interrupted in this study population without substantial risk of inducing withdrawal symptoms and their psychological sequelae, it was not feasible to assess the effect of BUP/NAL coadministration on GZR PKs in the same participants using a crossover study design. Therefore, in order to provide an estimate of the effect of BUP/NAL coadministration on GZR PKs, GZR exposures when coadministered with BUP/NAL were compared with pooled GZR exposures in non-HCV-infected healthy participants in a historical database. All historical controls were selected based on the following criteria that were chosen to match the conditions of the DDI study: i) PK data were from non-HCV-infected participants; ii) PK data were measured after multiple-dose administration of GZR 200 mg alone; and iii) the study treatment was administered under fasted conditions. As such, the pooled data set represented a general non-HCV-infected population that can be compared with the study populations in the GZR BUP/NAL DDI study. Although the validity of pooling the historical data for the GZR comparison was supported by the similar demographics between the participants in the GZR BUP/NAL DDI study and the historical cohort as well as additional analyses suggesting that the interstudy variation in the historical cohort is minimal, there may be potential limitations in the GZR comparison since the historical cohort was not matched to participants in the GZR BUP/NAL study. A GZR population PK model has been developed with the primary goal of characterizing GZR PK in HCV-infected individuals. The model was developed based on PK data from a limited number of non-HCV participants and PK data from several studies in a large number of HCV-infected participants. As such, the GZR population PK model was not suited to assess the effect of BUP/NAL coadministration on GZR exposure in non-HCV-infected participants as described in the studies in this article. Instead, the GZR PK comparison in non-HCV-infected participants was 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 PK that are derived from population PK analyses.[4,24]

Despite the limitations of the study designs and the two-step approach of noncompartmental analysis for the estimation of GZR PK in non-HCV-infected populations followed by statistical analysis PK comparisons, the lack of

Table 4 Statistical comparison and summary statistics of elbasvir plasma pharmacokinetics following administration of a single oral dose of elbasvir 50 mg with and without a single sublingual dose of buprenorphine/naloxone 8/2 mg in healthy participants

EBR pharmacokinetic parameter	EBR alone			BUP/NAL + EBR			BUP/NAL + EBR/EBR alone		Pseudo within-participant %CV[b]
	n[a]	GM	95% CI	*n*[a]	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$[c], μM·hr	15	2.08	1.54–2.83	13	2.55	1.94–3.35	1.22	0.98–1.52	32.1
C_{max}[c], μM	15	0.103	0.076–0.139	13	0.116	0.091–0.149	1.13	0.87–1.46	38.3
C_{24}[c], nM	15	32.5	24.50–43.1	13	39.7	30.20–52.1	1.22	0.99–1.51	30.9
T_{max}[d], hr	15	4.00	2.00, 6.00	13	3.01	2.00, 6.05			
Apparent terminal $T_{½}$[e], hr	10	18.46	17.34	3	18.60	18.92			

EBR alone: a single oral dose of EBR 50 mg.
BUP/NAL + EBR: a single oral dose of EBR 50 mg coadministered with a single sublingual dose of BUP 8 mg / NAL 2 mg (with naltrexone (NTX) blockage administered as NTX HCl 50 mg every 12 hours starting 14 hours prior to the BUP/NAL dose, for a total of three NTX doses).
$AUC_{0-\infty}$, area under the concentration–time curve from time 0 extrapolated to infinity; BUP, buprenorphine; 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; NAL, naloxone; T_{max}, time to C_{max}.
[a]Two participants were discontinued from the trial by the investigator on day 1 of Period 3 (EBR+ BUP/NAL) due to vomiting within 8 hours of dosing, and one participant was discontinued by the investigator on day 1 of Period 1 (BUP/NAL alone) due to vomiting within 3 hours of dosing.
[b]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.
[c]Back-transformed least-squares mean and CI from the linear mixed-effects model performed on natural log-transformed values.
[d]Median (minimum, maximum) reported for T_{max}.
[e]GM and geometric CV reported for apparent terminal $T_{½}$.

Table 5 Statistical comparison of grazoprevir pharmacokinetic parameter values following multiple-dose administration of grazoprevir 200 mg alone once daily (historical cohort) and coadministration of grazoprevir 200 mg and buprenorphine/naloxone in non-HCV-infected participants

GZR pharmacokinetic parameter	GZR alone			BUP/NAL + GZR			BUP/NAL + GZR/GZR alone		rMSE[b]
	n[a]	GM	95% CI	*n*	GM	95% CI	GMR	90% CI	
AUC_{0-24}[c], μM·hr	106	2.47	2.20–2.77	12	2.13	1.49–3.03	0.86	0.63–1.18	0.600
C_{max}[c], μM	106	0.583	0.508–0.681	12	0.473	0.302–0.739	0.80	0.54–1.20	0.757
C_{24}[c], nM	106	13.9	12.8–15.2	12	13.5	10.5–17.5	0.97	0.77–1.22	0.436
T_{max}[d], hr	107	3.00	1.00, 6.00	12	4.00	2.00, 6.00			

AUC_{0-24}, area under the concentration–time curve from time 0–24 hours postdose; BUP, buprenorphine; 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; NAL, naloxone.
[a]Race of one participant was unknown. This participant was excluded from the model-based analysis for the comparison of GZR pharmacokinetics with and without BUP/NAL coadministration.
[b]rMSE: square root of mean squared error (residual error) from the analysis of covariance model. rMSE*100% approximates the between-participant %CV on the raw scale.
[c]Back-transformed least-squares mean and CI from the linear fixed-effects model performed on natural log-transformed values.
[d]Median (minimum, maximum) reported for T_{max}.

clinically meaningful DDIs observed in these studies is supported 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.[22] In this study, HCV-infected participants received either an immediate EBR 50 mg / GZR 100 mg fixed-dose combination q.d. 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.[22] 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. These results demonstrate that antiviral activity and the safety profile are maintained in HCV-infected participants receiving EBR/GZR and opioid agonist therapy with BUP or BUP/NAL and that the coadministration of EBR/GZR with BUP or BUP/NAL is well tolerated in this population.[22]

Taken together, the findings of these studies demonstrate that no dose adjustment is required for people with HCV infection receiving the EBR/GZR fixed-dose combination in combination with stable BUP/NAL opioid agonist therapy and that the fixed-dose combination of EBR/GZR is a safe and effective treatment option for people with HCV infection who are receiving opioid agonist therapy.

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Conflict of Interest. H.-P.F., Z.G., L.C., F.L., D.P., P.V., A.B., C.R., P.J., J.G. D.W., R.V., M.M. J.R.B., M.I., and W.W.Y. are current or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ. W.L.M. is an employee of Alexion Pharmaceuticals Inc., but was a Merck employee at the time this study was conducted. I.F. is an employee of Abide Therapeutics, Inc., but was a Merck employee at the time this study was conducted. L.W. is a consultant for Acobra, Egalet, Elysium, Kempharm, Pain Therapeutics, Pfizer, Shionogi, and Teva; is an advisor for Daiichi Sankyo, Egalet, Inspirion, and Teva; and has received travel expenses from Alcobra, Daiichi Sankyo, Depomed, Egalet, Elysium, Inspirion, Insys, Kempharm, Pfizer, and Teva.

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