Assessment of Drug-Drug Interactions between Daclatasvir and Methadone or Buprenorphine-Naloxone

T. Garimella, a R. Wang, a W.-L. Luo, a P. Wastall, a H. Kandoussi, a M. DeMicco, b R. D. Bruce, c C. Hwang, a R. Bertz, a M. Bifano a

Hepatitis C virus (HCV) infection is common among people who inject drugs, including those managed with maintenance opioids. Pharmacokinetic interactions between opioids and emerging oral HCV antivirals merit evaluation. Daclatasvir is a potent pan-genotypic inhibitor of the HCV NS5A replication complex recently approved for HCV treatment in Europe and Japan in combination with other antivirals. The effect of steady-state daclatasvir (60 mg daily) on stable plasma exposure to oral opioids was assessed in non-HCV-infected subjects receiving methadone (40 to 120 mg; n = 14) or buprenorphine plus naloxone (8 to 24 mg plus 2 to 6 mg; n = 11). No relevant interaction was inferred if the 90% confidence interval (CI) of the geometric mean ratio (GMR) of opioid area under the plasma concentration-time curve over the dosing interval (AUCτ) or maximum concentration in plasma (Cmax) with versus without daclatasvir was within literature-derived ranges of 0.7 to 1.43 (R- and S-methadone) or 0.5 to 2.0 (buprenorphine and norbuprenorphine). Dose-normalized AUCτ for R-methadone (GMR, 1.08; 90% CI, 0.94 to 1.24), S-methadone (1.13; 0.99 to 1.30), and buprenorphine (GMR, 1.37; 90% CI, 1.24 to 1.52) were within the no-effect range. The norbuprenorphine AUCτ was slightly elevated in the primary analysis (GMR, 1.62; 90% CI, 1.30 to 2.02) but within the no-effect range in a supplementary analysis of all evaluable subjects. Dose-normalized Cmax for both methadone enantiomers, buprenorphine and norbuprenorphine, were within the no-effect range. Standardized assessments of opioid pharmacodynamics were unchanged throughout daclatasvir administration with methadone or buprenorphine. Daclatasvir pharmacokinetics were similar to historical data. Co-administration of daclatasvir and opioids was generally well tolerated. In conclusion, these data suggest that daclatasvir can be administered with buprenorphine or methadone without dose adjustments.

Ttreatment of chronic hepatitis C virus (HCV) infection has recently seen a shift away from older interferon- and ribavirin-based therapies toward all-oral combinations of newer directly acting antivirals that offer significantly greater rates of sustained virologic response, better tolerability, and shorter treatment durations (1–6). HCV infection is endemic among people who inject drugs (PWID); 67% of the global PWID population was estimated to be infected as of 2010, which represents ~10 million HCV-infected drug users—more than 3 times the number of PWID estimated to be infected with human immunodeficiency virus (HIV) (7). Estimates of country-specific HCV prevalence among PWID range widely, from 10% to almost 100% depending on the location (7). Among the 3 countries (China, Russia, and the United States) with the largest amounts of drug injection, ~70% of PWID are estimated to be chronically HCV infected (7). Emerging epidemics of injection drug use are also seeing a dramatic HCV prevalence rate, as observed among PWID in Tanzania (8).

The oral opioid analgesics methadone [MET; (RS)-6-((dimethylamino)-4,4-diphenylethano-3-one] and buprenorphine [BUP; (2S)-2-[(5R,6R,7R,14S)-9α-cyclopropylmethyl-4,5-eoxy-6,14-ethano-3-hydroxy-6-methoxymorphinan-7-yl]-3,3-dimethylbutan-2-ol] are evidence-based treatments for opioid dependence and are a staple in the management of this addiction (9–11). MET is a chiral compound normally administered as an RS racemic mixture of which most or all opioid activity resides with R-MET (12, 13). For maintenance treatment, BUP is usually coformulated with the opioid receptor antagonist naloxone (NLX) to discourage parenteral abuse. Individual MET and BUP-NLX dosing requires clinical titration to ensure a stable balance between symptoms of opioid withdrawal and overdose.

All patients living with chronic HCV infection will benefit from effective oral treatment with combinations of directly acting antivirals, but such regimens may prove particularly valuable for treating heroin-dependent drug users under medical management with BUP or MET, as their high tolerability and dosing simplicity are likely to encourage adherence, while the lack of a parenteral component may make them more acceptable to former and recovering users of injection drugs.

As has long been established in similar therapeutic paradigms, such as HIV management, multidrug therapeutic regimens present a risk of clinically significant pharmacokinetic (PK) interactions, both between the components of the regimen itself and with medications for concomitant comorbidities. Both MET and BUP are extensively metabolized by the cytochrome P450 (CYP) system, and drug interactions with maintenance opioids are of concern, given the threat to stable management posed by changes in exposure that could lead to symptoms of withdrawal or toxicity.

Address correspondence to T. Garimella, tushar.garimella@bms.com.

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MET primarily undergoes N-demethylation by CYP3A4 and CYP2B6, with minor contributions from other isozymes, to the inactive metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). Both the R- and S-enantiomers of MET are substrates for CYP3A4, while S-MET is preferentially metabolized by CYP2B6 (14–16). BUP is primarily N-dealkylated to the active metabolite norbuprenorphine (norBUP) by CYP3A4, with minor contributions from CYP2C8 and CYP2C9 (17, 18), and both the parent and metabolite are glucuronidated by several UDP-glucuronosyltransferase (UGT) isozymes (19, 20).

Daclatasvir (DCV) is a potent pan-genotypic directly acting antiviral inhibitor of the HCV NS5A replication complex (21) that was recently approved for treatment of HCV genotype 1 in Japan in combination with the NS3/4A protease inhibitor asunaprevir. DCV has also been recently approved in Europe for the treatment of HCV genotypes 1 to 4 in combination with other HCV antiviral agents. It has been studied at a standard dosage of 60 mg once daily in a number of different therapeutic regimens, including all-oral directly acting antiviral combinations with asunaprevir (5), in a number of different therapeutic regimens, including all-oral directly acting antiviral combinations with asunaprevir (5), with the nucleotide NS5B polymerase inhibitor sofosbuvir (3), and with asunaprevir and the nonnucleoside NS5B inhibitor beclabuvir (BMS-791325) (22). DCV has linear, time-independent PK, and its plasma exposure reaches steady state after 3 to 4 days of once-daily dosing (23). DCV is also a substrate and inhibitor of the P-glycoprotein transporter and a substrate of, and very weak inducer of, CYP3A4 with minimal effects on the levels of the sensitive CYP3A4 probe midazolam in plasma (24). Given the importance of maintaining stable individual opioid exposures in maintenance therapy and the potential for unanticipated drug interactions, the effects of steady-state DCV on opioid exposure were evaluated in non-HCV-infected subjects receiving stable maintenance doses of MET or BUP-NLX.

MATERIALS AND METHODS

Subjects. Eligible subjects were adults aged 18 to 65 years with a body mass index of 18 to 32 kg/m² who had a negative screening test for HCV antibodies and who had been reliably participating in an oral opioid maintenance program with MET or BUP-NLX for at least 28 days prior to screening. Eligible subjects had no clinically significant deviation from normal in medical history, examination, electrocardiograph findings, or clinical laboratory parameters. Women of childbearing potential (WOCBP) must have had a negative pregnancy test within 24 h prior to the start of DCV administration, could not be breastfeeding, and must have agreed to use effective barrier methods of birth control for up to 4 weeks before and 8 weeks after receiving DCV. Sexually active men with WOCBP partners must have agreed to use effective barrier contraception during and for 90 days after the study.

Major exclusion criteria included current prescription drug or alcohol use that, in the opinion of the investigator, compromised the subject’s safety or compliance with study procedures. This included a positive urine test for drugs of abuse with the exception of MET or BUP, and tetrahydrocannabinol. Other major exclusion criteria included current treatment for hepatitis B virus or human immunodeficiency virus, although untreated subjects with either infection were permitted, and previous or current gastrointestinal conditions or surgery likely to affect DCV PK.

Study design and conduct. This was an open-label, 2-part, phase 1 drug-drug interaction study (study AH44-064) between steady-state DCV (60 mg once daily) and individually titrated stable doses of either MET (study part 1) or BUP-NLX (part 2) in non-HCV-infected subjects receiving opioid maintenance treatment. For both parts of the study, subjects underwent screening within 28 days of study dosing. Subjects were admitted to the clinic on study day −1 and remained in the clinic until discharge on day 10. Subjects received their usual once-daily dose of MET or BUP-NLX alone on day 1 and then in combination with DCV 60 mg once daily on days 2 to 9. From day 10 onward, subjects continued to receive their usual dose of opioid.

Subjects received both their opioid dose and DCV with 240 ml of water in the morning following a fast of at least 10 h. On PK sampling days (days 1 and 9), subjects continued to fast until they received a standard lunch (~4 h postdose. On other days, subjects received a standard light meal at ~2 h postdose, followed by a standard lunch at ~4 h. On all study days, subjects received a standard dinner at ~10 h postdose, followed by a snack at 12 h.

The study was conducted in accordance with good clinical practice defined by the International Conference on Harmonisation and with the ethical principles underlying European Union Directive 2001/20/EC, the U.S. Code of Federal Regulations (title 21, part 50 [21CFR50]), and the principles originating in the Declaration of Helsinki. The study was conducted at 2 clinical sites in the United States between December 2012 and April 2013 (part 1) and between January 2013 and December 2013 (part 2). All subjects provided written informed consent. The study protocol, amendments, and informed-consent documents were approved by the relevant institutional review board for each site prior to study initiation.

Endpoints and assessments. The primary study objective was to assess the effect of steady-state oral administration of DCV on stable MET or BUP PK. Secondary objectives were to assess the PK of DCV coadministered with MET or BUP-NLX and to assess the effect of steady-state DCV on the pharmacodynamics (PD) of methadone and BUP-NLX using standardized measures of opiate withdrawal and overdose, specifically the Clinical Opiate Withdrawal Scale (COWS) (25), the Subjective Opiate Withdrawal Scale (SOWS) (26), the Objective Opiate Withdrawal Scale (OOWS) (26), and the Opiate Overdose Assessment (OOA) (27).

Primary study endpoints were the area under the plasma concentration-time curve over the dosing interval (AUCr) and maximum concentration in plasma (Cmax) for R- and S-MET enantiomers in part 1 and the AUCr and Cmax for BUP and norBUP in part 2. Secondary endpoints included other PK parameters for these analytes, PD endpoints (COWS, SOWS, OOWS, and OOA scores), and adverse events (AEs).

Serial blood samples for PK analysis were drawn predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h on day 1 (opioid PK) and day 9 (opioid and DCV PK). Concentrations of total MET, R-MET, S-MET, BUP, norBUP, and DCV in plasma were determined by validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assays. The assay for DCV has been fully described elsewhere (28).

MET (LC-MS/MS) and BUP and norBUP assays (ultra performance liquid chromatography with electrospray ionization tandem mass spectrometry [UPLC-ESI-MS/MS]) were undertaken by Pharmaceutical Product Development (PPD; Richmond, VA, and Middleton, WI). Analytes were extracted by liquid-liquid solvent extraction using dichloromethane for MET and a 1:1:1 by-volume mixture of hexane, methyl tert-butyl ether, and dichloromethane for BUP, norBUP, and their internal standards BUP-d4 and norBUP-d3.

Liquid chromatography of MET was performed by isocratic separation on a Chrom Tech Chiral-AGP 2.0-mm by 50-mm column with a particle size of 5 μm (Chrom Tech, Inc., Apple Valley, MN), using a mobile phase of 12% isopropanol in 10 mM ammonium acetate. Liquid chromatography of BUP and norBUP was performed by gradient separation on a Waters XBridge C18 5.0-mm by 150-mm column also with a particle size of 5 μm (Waters Corporation, Milford, MA), using 100% acetonitrile and 0.1% ammonium hydroxide in 10 mM ammonium bicarbonate as the mobile phases.

MET mass analysis was performed on an API 4000 triple quadruple LC-MS/MS system (AB SCIEX, Framingham, MA) operating in positive polarity mode with an m/z transition of 310/265 and an assay detection range of 5.0 to 1,000 ng/ml. BUP and norBUP mass analysis was performed on a Xevo TQ-S tandem quadrupole system (Waters Corp.) in
positive-polarity mode with m/z transitions of 468/396 and 414/101, respectively, and an assay range of 0.02 to 10 ng/ml for both analytes. Individual subject PK parameters were derived from plasma analyte concentrations by noncompartmental methods using Kinetica version 5.0 in the eToolbox application (Thermo Electron, Philadelphia, PA). As individual opioid doses varied, opioid pharmacokinetic data were dose normalized to 40 mg of methadone or 8 mg/2 mg of BUP-NLX before analysis.

COWS, SOWS, OOWS, and OOA assessments were performed pre-dose on each day of the study. Safety was assessed throughout the study, and safety assessments were based on medical review of AE reports and the results of vital sign measurements, electrocardiograms, physical examinations, and clinical laboratory tests. Physical examinations and electrocardiograms were performed, and blood and urine were taken for clinical laboratory evaluations at screening, day −1, and discharge/day 10. Vital signs were measured at screening, days −1, 1, and 9, and discharge/day 10.

**Statistical analysis and study power.** To assess the effect of steady-state DCV on the stable dose-normalized pharmacokinetics (AUC_{cmax} and concentration at 24 h [C_{24}] of R- and S-MET (part 1) and BUP and norBUP (part 2), general linear mixed-effect models were fitted to log-transformed pharmacokinetic parameters for administration with or without DCV, with treatment as a fixed effect and subject as repeated measures, utilizing Kenward-Roger degrees of freedom. From these models after back-transformation, 90% confidence intervals (CIs) around the geometric mean ratio (GMR) of opioid pharmacokinetic parameters for dosing with versus without DCV were computed. A *priori* assumptions about clinically relevant effects on opioid exposure were made on the basis of a literature search of drug interaction studies for which no *a priori* dose modifications were required. In part 1, no clinically relevant effect of DCV on MET PK was assumed if the 90% CIs of the GMR for AUCr and C_{max} of both methadone enantiomers were entirely contained within prespecified boundaries of 0.7 and 1.43. These boundaries were derived from established interactions between methadone and ritonavir-boosted darunavir and fosamprenavir, both HIV protease inhibitors and inhibitors of CYP3A4 for which no MET dose adjustment was suggested under coadministration. These two antiretrovirals gave similar reductions in total MET AUC GMR (mean, 0.83), with similar 90% CIs (mean, 0.76 to 0.92). To allow for a similar degree of effect by CYP3A4 inducers, the 0.7 and 1.43 boundaries were selected.

In part 2, no clinically relevant effect of DCV on BUP pharmacokinetics was assumed if the 90% CIs of the GMR for AUCr and C_{max} of both BUP and norBUP were entirely contained within the prespecified boundaries of 0.5 and 2.0. These boundaries were derived from a literature search of established interactions not requiring a dose adjustment between BUP and antiretrovirals that were either inducers or inhibitors of CYP3A4: specifically, full-dose ritonavir; ritonavir-boosted darunavir, tipranavir, and lopinavir; unboosted neflavin; efavirenz; and delavirdine. Changes in BUP AUC and/or C_{max} GMR ranged from 0.51 with efavirenz to 4.25 with delavirdine. However, as delavirdine is little used and is unapproved in Europe, few clinical data on its use with opioids exist. The next largest change in BUP AUC/C_{max} with no recommended dose adjustment was 1.6 to 1.8 for full-dose ritonavir. The no-effect boundaries of 0.5 and 2.0 were therefore chosen as reasonable, based on existing recommendations. No significant effect of either MET or BUP-NLX on DCV pharmacokinetics was anticipated. DCV parameters on day 9 were compared visually with pooled historical data on file from 8 studies of DCV given for 5 or 14 days to fasted healthy volunteers. No formal statistical comparison was performed.

During the study, the sublingual tablet formulation of BUP-NLX stipulated by the original study protocol was discontinued by the manufacturer, and the protocol was amended to allow administration of a replacement film formulation. However, due to potential bioavailability differences between the formulations, it was made a requirement that any subject who changed their formulation from the tablet to the film over the 10-day dosing period be discontinued from the study, and that the primary PK analysis population in both the MET and BUP parts of the study be defined as those subjects with PK data from both dosing periods (opioid with and without DCV). On study completion, it was determined that all BUP subjects had received the sublingual tablet throughout, and a supplementary analysis was performed in part 2 using all evaluable subjects from each dosing period.

Target enrollment for each part of the study was 14 subjects, to allow for a final sample of 12 after dropouts. Assuming DCV had no effect on the pharmacokinetics of either methadone or BUP (GMR = 1.0 for each parameter), a sample size of 12 in each part of the study was calculated to provide a power of ≥97% that the 90% CI for AUCr and C_{max} would be within the prespecified intervals. In part 1, the overall power was 99.3%, with individual powers of 99.9% for both R-MET AUCr and C_{max} and 99.7% and 99.8% for S-MET AUCr and C_{max}, respectively. In part 2, the overall power was 97.1%, with individual powers of 99.9% and 99.8% for BUP AUCr and C_{max}, respectively, and 99.8% and 99.6% for norBUP AUCr and C_{max}.

These power calculations were derived from the approach of Diletti et al. (29) and assumed that the log-transformed values of each parameter tested were normally distributed and had an intrasubject standard deviation similar to that derived from published literature. For part 1, the assumed log-transformed intrasubject standard deviations for AUCr and C_{max} were 0.134 and 0.1275, respectively, for S-MET. For part 2, the assumed log-transformed intrasubject standard deviations for AUCr and C_{max} were 0.2311 and 0.2871, respectively, for BUP and 0.3531 and 0.3579 for norBUP.

All statistical analyses were carried out using SAS version 8.2 or higher (SAS Institute, Cary, NC) and S-PLUS version 8.1.1 (TIBCO Software Inc., Palo Alto, CA).

**RESULTS**

**Patient disposition and characteristics.** Overall, 49 subjects were screened, of whom 14 receiving MET were treated in part 1 of the study and 11 receiving BUP-NLX were treated in part 2. Due to difficulty in recruiting subjects on stable BUP-NLX, the target of 14 treated subjects in part 2 was not met. Of the 24 subjects screened but not treated, the majority (15/24 [63%]) did not meet entry criteria, while 4/24 (17%) were lost to follow-up, 3/24 (13%) were noncompliant, 1/24 (4%) withdrew consent, and 1/24 (4%) was not treated for other reasons.

Subjects in part 1 received between 40 mg and 120 mg of oral MET per day; subjects in part 2 received between 8 mg/2 mg and 24 mg/6 mg of oral BUP-NLX per day. All treated subjects completed the study. In part 2, two patients were excluded from the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Part 1 (MET)</th>
<th>Part 2 (BUP-NLX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean yr (SD)</td>
<td>26.9 (6.2)</td>
<td>31.8 (5.6)</td>
</tr>
<tr>
<td>Male, %</td>
<td>71.4</td>
<td>90.9</td>
</tr>
<tr>
<td>BMI, mean kg/m² (SD)</td>
<td>24.7 (3.5)</td>
<td>28.6 (2.9)</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>92.9</td>
<td>100</td>
</tr>
<tr>
<td>Chinese</td>
<td>7.1</td>
<td>0</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>42.9</td>
<td>27.3</td>
</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>57.1</td>
<td>72.7</td>
</tr>
</tbody>
</table>

*Abbreviations: BMI, body mass index; BUP-NLX, buprenorphine/naloxone; MET, methadone.*
primary analysis due to having received their day 10 BUP-NLX dose before their 24-h PK sample on day 9 was taken.

Baseline and demographic characteristics for both parts of the study are shown in Table 1. Although permitted, no HIV-infected or HBV-infected subjects were enrolled and treated.

**Pharmacokinetics. (i) Effect of DCV on R- and S-MET.** Dose-normalized (to 40 mg of MET) plasma concentration-versus-time curves for R-MET and S-MET with and without concomitant DCV are shown in Fig. 1. Dose-normalized pharmacokinetic parameters for both enantiomers are shown in Table 2.

Statistical comparisons (primary analysis population) of dose-normalized R- and S-MET $C_{\text{max}}$ and AUC$_{\text{T}}$ for administration with versus without DCV are also shown in Table 2. The 90% CIs of the GMR for both parameters in each enantiomer were entirely contained within the prespecified range of 0.70 to 1.43, indicating no clinically relevant effect of DCV on MET pharmacokinetics.

(ii) Effect of DCV on BUP and norBUP. Dose-normalized (to 8 mg/2 mg of BUP-NLX) BUP and norBUP plasma concentration-versus-time curves for administration with versus without DCV are shown in Fig. 2. Dose-normalized pharmacokinetic parameters for BUP and norBUP and statistical comparisons of dose-normalized BUP and norBUP $C_{\text{max}}$ and AUC$_{\text{T}}$ for administration with versus without DCV are shown in Table 3. In the primary statistical analysis—in which calculation of the GMR and 90% CI for AUC$_{\text{T}}$ was restricted to the 9 subjects who had valid $C_{24}$ measurements with DCV—BUP $C_{\text{max}}$ and AUC$_{\text{T}}$ were increased by 30% and 37%, respectively, and norBUP $C_{\text{max}}$ and AUC$_{\text{T}}$ increased by 65% and 62%, respectively. The upper 90% CI bound of 102% for norBUP AUC$_{\text{T}}$ GMR (1.62 [90% CI, 1.3 to 2.02]) was just outside the prespecified range of no clinically relevant effect (50% reduction to 100% increase).

(iii) Effect of opioids on DCV. Neither MET nor BUP-NLX appeared to influence exposure to DCV. With both opioids the DCV pharmacokinetic parameters were numerically similar to historical data for healthy volunteers (Table 4).

**Pharmacodynamics.** Coadministration of DCV with either MET or BUP-NLX had no effect on measures of opioid withdrawal or toxicity. Mean predose COWS, SOWS, OOWS, and OOA scores did not indicate any loss of stable opioid maintenance over the period of coadministration (Fig. 3).

**Safety.** Coadministration of DCV with MET or BUP-NLX was generally well tolerated. There were no deaths, serious AEs, or discontinuations for AEs. There were no clinically relevant changes in laboratory parameters, no laboratory-related AEs, and no clinically relevant electrocardiograph findings.

In part 1, six subjects reported at least 1 AE. All events were mild or moderate in intensity. Only nausea and pruritus occurred in more than 1 subject ($n = 2$ each). Three subjects had AEs considered by the investigator to be related to DCV treatment: hand dermatitis ($n = 1$), pruritus ($n = 1$), and abdominal distension and flatulence ($n = 1$). All treatment-related AEs were mild in intensity and resolved spontaneously without treatment.

In part 2, nine patients receiving BUP-NLX reported at least 1 AE. All AEs were mild or moderate in intensity. Five events oc-

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**TABLE 2** Dose-normalized (MET, 40 mg daily) PK parameters and statistical comparisons for R-MET and S-MET enantiomers, with and without concomitant DCV (60 mg daily)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value for drug</th>
<th>R-MET ($n = 14$)</th>
<th>S-MET ($n = 14$)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Without DCV</td>
<td>With DCV</td>
<td>GMR (90% CI)</td>
</tr>
<tr>
<td>AUC$_{\text{T}}$, ng · h/ml$^a$</td>
<td>1,570 (58)</td>
<td>1,700 (55)</td>
<td>1.08 (0.94–1.24)</td>
</tr>
<tr>
<td>$C_{\text{max}}$, ng/ml$^b$</td>
<td>96.6 (56)</td>
<td>104 (52)</td>
<td>1.07 (0.97–1.18)</td>
</tr>
<tr>
<td>$T_{\text{max}}$, h$^c$</td>
<td>2.0 (1.0–4.0)</td>
<td>2.0 (1.0–4.0)</td>
<td></td>
</tr>
<tr>
<td>$C_{24}$, ng/ml$^d$</td>
<td>52.5 (60)</td>
<td>56.7 (57)</td>
<td>1.08 (0.93–1.26)</td>
</tr>
</tbody>
</table>

* Abbreviations: AUC$_{\text{T}}$, area under the plasma concentration-time curve over the dosing interval; CI, confidence interval; $C_{\text{max}}$, maximum concentration in plasma; $C_{24}$, concentration at 24 h; DCV, daclatasvir; GMR, geometric mean ratio; MET, methadone; $T_{\text{max}}$, time to $C_{\text{max}}$.

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![FIG 1 Dose-normalized (methadone, 40 mg) 24-h plasma concentration-time profiles for R-methadone (R-MET) (A) and S-methadone (S-MET) (B), with and without concomitant DCV (60 mg daily).](http://aac.asm.org/)

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![FIG 2 Dose-normalized (BUP-NLX, 8 mg/2 mg) 24-h plasma concentration-time profiles for BUP and norBUP (BUP-NLX) with and without concomitant DCV (60 mg daily).](http://aac.asm.org/)

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![FIG 3 Dose-normalized (MET, 40 mg) 24-h plasma concentration-time profiles for R-methadone (R-MET) (A) and S-methadone (S-MET) (B), with and without concomitant DCV (60 mg daily).](http://aac.asm.org/)
occurred in more than 1 patient, and none were considered treat-
ment related: fatigue \((n = 5)\), constipation \((n = 3)\), upper abdom-
inal pain, headache, and hyperhidrosis \((n = 2)\) each. One subject
had an AE considered to be related to DCV administration (mild rash)
that resolved spontaneously without treatment.

**DISCUSSION**

Steady-state administration of DCV at its standard dose of 60 mg
daily to HCV-uninfected subjects on MET maintenance treat-
ment resulted in small increases in the AUC\(_{\text{max}}\) and C\(_{\text{max}}\) GMRs
\((1.07 \text{ to } 1.13)\) for R-MET and S-MET, with 90% CIs that all
crossed 1.0. Similar administration of DCV to subjects on BUP-
NLX maintenance resulted in larger increases in BUP and norBUP
AUC\(_{\text{max}}\) and C\(_{\text{max}}\) (GMR range, 1.30 to 1.65) than what was seen
with MET, with 90% CIs that did not include 1.0. These BUP and
norBUP 90% CIs were all contained within the prespecified range
over which no clinically relevant effect would be considered likely
\(\text{a priori}\), with the exception of the CI for norBUP C\(_{\text{max}}\) GMR,
whose upper limit fell marginally outside this range.

Based on the known metabolic pathways for MET and DCV, it
was not considered likely that there would have been a significant
pharmacokinetic interaction. MET is cleared predominantly by
CYP3A4—which appears minimally affected by DCV \(\text{in vivo}\) in
drug interaction studies with midazolam \((24)\) or other CYP3A4
substrates \((30–32)\) —and by CYP2B6, which DCV does not affect.

As anticipated, concomitant administration of steady-state DCV
did not alter stable plasma exposure of R-MET or S-MET to any
clinically relevant extent among subjects on MET maintenance
treatment. Although C\(_{\text{max}}\) and AUC\(_{\text{max}}\) for both enantiomers were
\(\approx 10\%\) higher with DCV than without, the 90% CIs around these
GMRs were entirely contained within a literature-derived range
\((0.7 \text{ to } 1.43)\) within which no MET retitration would be anticipated
on the basis of current recommendations. Consistent with
this assumption, standardized measures of opioid withdrawal or
toxicity administered throughout the period of concomitant dos-
ing did not indicate any loss of clinical maintenance.

It was also considered unlikely that there would be a CYP-
mediated interaction between DCV and BUP. DCV weakly inhib-
its UGT 1A1 \(\text{in vitro}\) but has little effect on the PK of the UGT 1A1
substrate ethinyl estradiol \(\text{in vivo}\) \((30)\). A previous drug-drug in-
teraction study with healthy subjects found that concomitant
DCV increased the AUC\(_{\text{max}}\) and C\(_{\text{max}}\) of the UGT 1A1-substrate HIV
integrate inhibitor dolutegravir by approximately 30% \((33)\).
However, this increase is not considered clinically relevant and is
believed to be the result of altered dolutegravir transport by P-
glycoprotein and breast cancer resistance protein, both of which are
inhibited by DCV. It was therefore considered unlikely that DCV
would significantly alter the glucuronidation of BUP or norBUP.
The observed 30% to 37% increase in BUP and 62% to 65% in-

![Dose-normalized (8 mg/2 mg of buprenorphine-naloxone daily) 24-h plasma concentration-time profiles for buprenorphine (BUP) (A) and norbu-
prenorphine (norBUP) (B), with and without concomitant DCV (60 mg daily).](image)

**TABLE 3** Dose-normalized \((8 \text{ mg/2 mg BUP/NLX daily) PK parameters and statistical comparisons for BUP and norBUP, with and without concomitant DCV (60 mg daily).**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value for drug</th>
<th>BUP ((n = 11))</th>
<th>GMR (90% CI)</th>
<th>norBUP ((n = 11))</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(_{\text{max}}), ng·h/ml(^{a})</td>
<td></td>
<td>19.2 ((54))(^{a})</td>
<td>25.7 ((50))(^{b})</td>
<td>1.37 ((1.24–1.52))</td>
</tr>
<tr>
<td>C(_{\text{max}}), ng/ml(^{b})</td>
<td></td>
<td>2.6 ((51))</td>
<td>3.3 ((51))</td>
<td>1.30 ((1.03–1.64))</td>
</tr>
<tr>
<td>T(_{\text{max}}), h(^{b})</td>
<td></td>
<td>1.0 ((0.5–2.0))</td>
<td>1.5 ((0.5–2.4))</td>
<td>ND(^{c})</td>
</tr>
<tr>
<td>C(_{24}), ng/ml(^{d})</td>
<td></td>
<td>0.4 ((51))</td>
<td>0.5 ((51))</td>
<td>1.17 ((1.03–1.32))</td>
</tr>
</tbody>
</table>

\(^{a}\) BUP AUC\(_{\text{max}}\) = 18.8 ng·h/ml \((n = 9)\) and BUP C\(_{\text{max}}\) = 0.4 ng/ml \((n = 9)\) for analysis of GMR.

\(^{b}\) NorBUP AUC\(_{\text{max}}\) = 25.4 ng·h/ml \((n = 9)\) and norBUP C\(_{\text{max}}\) = 0.9 ng/ml \((n = 9)\) for analysis of GMR.

\(^{c}\) \(n = 9\).

\(^{d}\) Geometric mean (percent coefficient of variation).

\(^{e}\) Median (range).

\(^{f}\) ND, not determined.
crease in norBUP AUC and $C_{\text{max}}$ were therefore unanticipated on the basis of the known or assumed metabolic interactions of DCV, but they are unlikely to be clinically significant. As was observed for subjects maintained on MET, no loss of BUP-NLX maintenance was observed across the DCV dosing period by any standardized measure. Furthermore, recent data have shown that the all-oral HCV combination of ombitasvir (an NS5A inhibitor), dasabuvir (a nonnucleoside NS5B inhibitor), and ritonavir-boosted paritaprevir (an NS3 protease inhibitor) increases BUP and norBUP exposure to a greater degree than DCV without loss of clinical maintenance in either HCV-infected or non-HCV-infected subjects. Specifically, at steady state in healthy subjects, this combination increased BUP $C_{\text{max}}$ and AUC by 118% and 107%, respectively, and norBUP $C_{\text{max}}$ and AUC by 107% and 84%, respectively (34). No opioid adjustments were required over 12 weeks of treatment with this combination plus ribavirin in a phase 2 study with genotype-1-infected patients on stable MET ($n = 19$) or BUP-NLX ($n = 19$) maintenance (35). Thus, the increases in BUP and norBUP exposure observed with DCV would not indicate an a priori need for BUP-NLX retitration with DCV-based regimens.

The mechanism for the modest increase in plasma concentrations of both BUP and its metabolite observed with DCV is not entirely clear but may be, at least in part, the result of increased BUP bioavailability under coadministration. The sublingual BUP-NLX tablet is eventually swallowed, and although BUP normally has poor gastrointestinal bioavailability, it is possible that DCV inhibition of P-glycoprotein efflux transporters may contribute to greater-than-normal absorption through the gut wall. The slightly greater increase in norBUP exposure relative to that of methadone

<table>
<thead>
<tr>
<th>Studies or administration</th>
<th>$C_{\text{max}}, \text{ng/ml}^a$</th>
<th>$T_{\text{max}}, \text{h}^b$</th>
<th>AUC$_1$, ng · h/ml$^a$</th>
<th>$C_{\text{min}}/C_{24}, \text{ng/ml}^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled historical studies, day 5$^c$</td>
<td>1,548.93 [43] (29)</td>
<td>1.00 [43] (1.0–4.0)</td>
<td>13,203 [15] (29)</td>
<td>230.95 [43] (48)</td>
</tr>
<tr>
<td>Pooled historical studies, day 14$^d$</td>
<td>1,582.0 (37)</td>
<td>1.5 (1.5–3.0)</td>
<td>15,666.5 (47)</td>
<td>295.8 (67)</td>
</tr>
<tr>
<td>DCV 60 mg + methadone, day 9</td>
<td>1,620 [14] (35)</td>
<td>1.25 [14] (0.9–4.0)</td>
<td>14,935 [14] (49)</td>
<td>215 [14] (77)</td>
</tr>
</tbody>
</table>

$^a$ Geometric mean [number] (percent coefficient of variation).
$^b$ Median [number] (range).
$^c$ Summary of steady-state day 5 data in fasted healthy volunteers: studies AI444-009, AI444-012, AI444-023, AI444-024, AI444-039, AI444-044, AI444-065, and AI444-084.
$^d$ Summary of steady-state day 14 data in fasted healthy subjects: studies AI444-003, AI444-005, AI444-007, and AI444-009.

FIG 3 Predose pharmacodynamic assessments of methadone and BUP-NLX maintenance before (days 1 and 2), during (days 3 to 9) and after (day 10) the period of DCV coadministration, by COWS (A), SOWS (B), OOWS (C), and OOA (D).
its parent suggests that other mechanisms may also be involved but that CYP3A4 inhibition by DCV is not responsible. This increase does not appear to be clinically significant. Both BUP and norBUP are pharmacologically active but possess a number of differing receptor specificities and pharmacological properties in cell culture and animal models that are not well studied at the clinical level and that render it difficult to establish their relative contributions to stable maintenance (36–40).

MET, BUP, and NLX are not potent inhibitors or inducers of CYP3A4, and as would be anticipated, DCV exposure parameters in both parts of the study were similar to historical values for people who inject drugs in the Kinondoni municipality in Dar Es Salaam, Tanzania, abstr 473/poster 113. 75th Ann Meet College Problems Drug Dependence, San Diego, CA, 15 to 20 June 2013.


