


## ORIGINAL ARTICLE

# Methadone and buprenorphine pharmacokinetics and pharmacodynamics when coadministered with fostemsavir to opioid-dependent, human immunodeficiency virus seronegative participants

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**Aims:** Regional human immunodeficiency virus (HIV) prevalence rates are high in people with history of injection drug use, including those managed with maintenance opioids. Fostemsavir (FTR) is an oral prodrug of temsavir, a first-in-class attachment inhibitor that binds HIV-1 gp120, preventing initial HIV attachment and entry into host immune cells. Here we determine the impact of FTR on the pharmacokinetics of opioids methadone (MET: R-, S- and total) or buprenorphine and norbuprenorphine (BUP and norBUP) when coadministered.

**Methods:** Study 206216 (NCT02666001) was a Phase I, open-label study, assessing the effect of FTR 600 mg (extended-release formulation) twice daily on pharmacokinetics of MET or BUP and norBUP, in non-HIV-infected participants on stable maintenance therapy with MET (40–120 mg;  $n = 16$ ) or BUP plus naloxone (8–24 mg plus 2–6 mg;  $n = 16$ ); pharmacodynamic response was assessed using standard opioid rating scales.

**Results:** Following coadministration with FTR, dose-normalized MET (R-, S- and total) exposures (maximum concentration in plasma, area under the plasma concentration–time curve over the dosing interval and concentration in plasma at 24 hours) increased 9–15% and BUP and norBUP exposures increased 24–39%. The 90% confidence interval ranges for MET (1.01–1.21) and BUP and norBUP (1.03–1.69) were within respective no-effect ranges (0.7–1.43 and 0.5–2.0). Opioid pharmacodynamic scores were similar with and without MET/BUP with no symptoms

The authors confirm that the PIs for this study were Debra J. Kelsh, Thomas C. Marbury and Howard A. Hassman and that they had direct clinical responsibility for patients.

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of withdrawal/overdose; no new safety signal for FTR when combined with a stable opioid regimen.

**Conclusions:** FTR did not impact MET and had no clinically significant impact on BUP pharmacokinetics. Standardized assessments of opioid pharmacodynamics were unchanged throughout FTR administration with MET or BUP. FTR can be administered with MET or BUP without dose adjustment.

#### KEYWORDS

antiretrovirals, opioids, pharmacodynamics, pharmacokinetics

## 1 | INTRODUCTION

Antiretroviral (ARV) treatment for human immunodeficiency virus type 1 (HIV) is lifelong, and many ARV agents undergo pharmacokinetic (PK) interactions with recreational drugs or the oral opioid substitutes used to manage addiction to injection drugs.<sup>1,2</sup> Globally, around 13 million people inject drugs, and ~1.7 million of them are living with HIV. Injection drug use accounts for approximately 10% of HIV infections globally and 30% of those outside of Africa. Regional HIV prevalence rates are high in people who inject drugs in all parts of the world (up to 15.5% in East and Southern Africa).<sup>3</sup> The oral opioid analgesics **methadone** (MET) and **buprenorphine** (BUP) are commonly prescribed as maintenance treatment for opioid dependence.<sup>4-6</sup> MET is a chiral compound normally administered as racemic mixture of R- and S-enantiomers, with R-MET as the pharmacologically active enantiomer.<sup>7,8</sup> For maintenance treatment, BUP is usually administered as a sublingual coformulation with the opioid receptor antagonist **naloxone** (NLX), which has poor oral bioavailability, to prevent parenteral abuse.<sup>9</sup> Plasma concentrations of both MET and BUP have a linear relationship with dose, although BUP exposure is not directly dose proportional.<sup>10,11</sup> Both MET and BUP/NLX must be clinically titrated to achieve a stable maintenance state for each individual without symptoms of either opioid withdrawal or overdose, and thus, evaluation of potential drug-drug interactions is important.<sup>12</sup>

Fostemsavir (FTR) is a highly soluble methyl phosphate prodrug of the membrane-permeable but poorly soluble ARV temsavir (TMR), currently under clinical development for treatment-experienced individuals with limited further treatment options. FTR is metabolized by alkaline phosphatase at the luminal surface of the small intestine to yield active TMR a first-in-class, potent HIV-1 attachment inhibitor.<sup>13,14</sup> Presystemic conversion to TMR is supported by the lack of quantifiable FTR observed in blood after FTR administration.<sup>15</sup> TMR binds to the HIV gp120 envelope protein and blocks its subsequent attachment to target cell **CD4 receptors**<sup>16</sup> independent of the co-receptor tropism of the virion.<sup>13,16-19</sup> In vitro data show broad HIV-1 isolate susceptibility to TMR, except for subtype AE and, possibly, group O.<sup>17,18</sup> TMR also has a unique resistance profile with no in vitro cross-resistance to other ARV classes.<sup>16,17</sup>

TMR has a plasma half-life of approximately 11 hours, shows limited accumulation (<2-fold) with twice-daily (BID) dosing of FTR, and

### What is already known about this subject

- Regional human immunodeficiency virus (HIV) prevalence rates are high in people who inject drugs, including those on maintenance opioids.
- Fostemsavir is being evaluated in heavily treatment-experienced HIV-1-infected adults.
- As HIV-1-infected adults receiving methadone or buprenorphine for opioid addiction may be prescribed fostemsavir, it is important to identify potential drug-drug interactions.

### What this study adds

- Methadone and buprenorphine can be administered with fostemsavir without dose adjustments, which is supported by the similar opiate withdrawal and overdose scale scores between methadone or buprenorphine alone and in combination with fostemsavir.
- Coadministration of fostemsavir and maintenance opioids was generally well tolerated.

steady-state TMR exposure is 2–3 days. Food effects on TMR PK are fat- and calorie-dependent, with time to maximum plasma concentration (T<sub>max</sub>) increased from 2 hours fasted to 4 hours with a standard meal and 6.5 hours with a high-fat meal, and an 81% increase in the area under the TMR concentration–time curve noted with a high-fat meal but not with a standard meal. Based on these observations and Phase III clinical data, FTR is considered suitable for administration with or without food.<sup>15,20</sup> FTR is administered as an extended-release (ER) tablet formulation following data from a regional absorption study showing an improved PK profile compared with an earlier immediate-release formulation.<sup>14</sup> Clinical data from the Phase III BRIGHT study (NCT02362503) of FTR 600 mg ER BID, given to heavily treatment-experienced adults with HIV-1 infection susceptible to 1 or 2 active ARV classes, showed a 0.8 log<sub>10</sub> copies/mL decline in HIV-1 RNA during 8 days of functional FTR monotherapy (vs a 0.2 log<sub>10</sub> copies/mL decline on placebo; *P* < 0.0001),<sup>21</sup> and a 54% rate of HIV virological

suppression among those receiving FTR with an optimized background therapy for 24 and 48 weeks.<sup>21,22</sup>

TMR is predominantly metabolized by an esterase-mediated hydrolysis pathway with contributions from a **cytochrome P450 (CYP) 3A4**-mediated oxidative pathway,<sup>23</sup> does not inhibit or induce major CYP or uridine diphosphate glucuronosyltransferase (UGT) enzymes, and is a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate. TMR inhibits BCRP and organic anion transporter protein 1B3. A TMR metabolite, BMS-930644, inhibits CYP3A4, BCRP, MATE2K and **OCT1** with IC<sub>50</sub> values <10 µM; however, circulating BMS-930644 concentrations are low (C<sub>max</sub> of approximately 458 ng/mL [~1 µM]) with FTR 600 mg ER BID dosing, such that clinically significant interactions are unlikely; like its parent compound TMR, BMS-930644 is a substrate for but not an inhibitor of P-gp (data on file), and both MET and BUP are also P-gp and CYP3A4 substrates. Plasma concentrations of MET and BUP increase in a linear manner with dose and for BUP the increase was not directly in proportion to dose.<sup>11</sup> MET is metabolized to an inactive metabolite via *N*-demethylation primarily by CYP3A4 and **CYP2B6**, but contributions from other CYP enzymes (CYP2C19, **CYP2C9** and **CYP2D6**) have been indicated *in vitro*.<sup>24</sup> *R*- and *S*-MET are substrates for CYP3A4, with *S*-MET being preferentially metabolized by CYP2B6.<sup>25–27</sup> BUP has a significant first-pass liver and/or intestinal metabolism by CYP3A4 resulting in low bioavailability even with sublingual administration.<sup>28</sup> BUP is metabolized via *N*-dealkylation to active metabolite norbuprenorphine (norBUP), primarily by CYP3A4, with minor contributions from **CYP2C8** and CYP2C9.<sup>29,30</sup> Both BUP and norBUP also undergo glucuronidation by **UGT1A1**, UGT1A3 and UGT2B7.<sup>29,31,32</sup> Studies indicate that MET and BUP are transported by P-gp, which may play a role in their disposition.<sup>1</sup> This study investigated the PK, pharmacodynamics (PD), safety and tolerability of MET or BUP/NLX when coadministered with FTR in participants on stable opioid maintenance therapy.

## 2 | METHODS

### 2.1 | Study participants

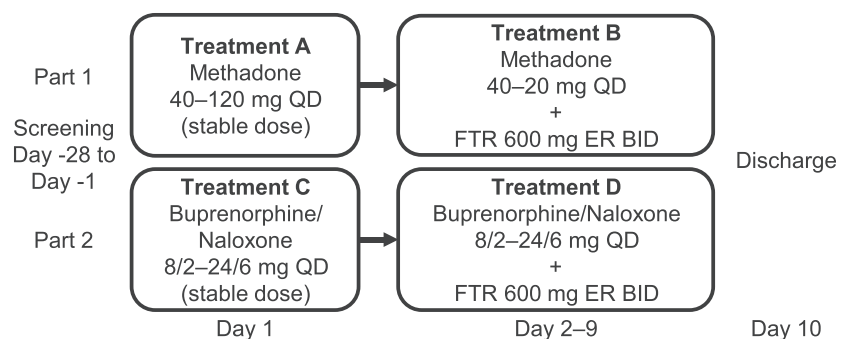
Male and female participants aged 18–65 years, with a body mass index of 18.0–34.0 kg/m<sup>2</sup>, who were receiving MET maintenance therapy or BUP/NLX maintenance therapy were eligible for the study.

Participants were reliably participating in an oral MET or BUP/NLX programme and were on a stable dose. Eligible participants had no clinically significant deviations from normal in medical history, physical examinations, 12-lead electrocardiograms (ECGs), or clinical laboratory determinations typical for this population. Women of childbearing potential (WOCBP) who were not nursing or pregnant, using acceptable methods of contraception and had a negative serum or urine pregnancy test within 24 hours prior to the start of study drug were eligible for inclusion in the study. Investigators advised WOCBP and male participants who were sexually active with WOCBP on the use of highly effective methods of contraception.

Exclusion criteria were related to medical history and concurrent diseases, physical examination findings and clinical laboratory test results, allergies (for example, history of allergy to FTR, HIV-attachment inhibitors or related compounds) and adverse drug reactions, and HIV- and hepatitis B virus-positive participants were excluded; however, a positive test for hepatitis C (HCV) antibodies with documentation of anti-HCV therapy was acceptable. Prohibited and/or restricted medications included prior exposure to FTR, exposure to any investigational drug or placebo within 4 weeks of study drug administration, and use of any prescription drugs or over-the-counter acid controllers within 4 weeks prior to study drug administration except those medications cleared by the medical monitor. No concomitant medications (prescription, over-the-counter or herbal) were to be administered during the study unless prescribed for treatment of specific clinical events.

### 2.2 | Study design and treatments

This was a Phase I, open-label, 2-part, drug–drug interaction (DDI) study (NCT02666001) between FTR 600 mg ER BID and MET (stable doses between 40 and 120 mg once daily [QD] for inclusion in Part 1) or BUP/NLX (stable doses of BUP/NLX between 8/2 and 24/6 mg QD for inclusion in Part 2) (Figure 1). The participants were required to be on a stable dose and formulation of MET or BUP/NLX for at least 30 days before screening and throughout the study. No switching between formulations was allowed. For both parts of the study, screening evaluations to determine eligibility were performed within 28 days before study drug administration. Eligible participants were admitted to the clinic the day before dosing (day -1) and remained confined to the clinic until study discharge on day 10.



**FIGURE 1** Study design. BID, twice daily; ER, extended release; FTR, fostemsavir; QD, once daily

Participants received their usual QD dose of MET or BUP/NLX alone on day 1 and then in combination with FTR 600 mg ER BID on days 2–9. All doses were given with a standard meal of approximately 400–500 calories with approximately 30% calories from fat; meal composition was identical on PK sampling days.

This study was conducted in accordance with: Good Clinical Practice, as defined by the International Council for Harmonisation; the ethical principles underlying European Union Directive 2001/20/EC; the US Code of Federal Regulations, Title 21, Part 50 (21CFR50); and the ethical principles that have their origin in the Declaration of Helsinki. Participants 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.

### 2.3 | Study objectives

The primary objectives of the study were to assess the effect of multiple doses of FTR 600 mg ER BID on PK exposure parameters for MET (*R*-, *S*- and the total) or BUP and norBUP in participants on stable maintenance therapy with MET or BUP/NLX. Secondary objectives were to characterize the PK of TMR (active moiety of FTR) coadministered with MET or BUP/NLX; assess the effect of multiple doses of FTR 600 mg ER BID on the withdrawal and overdose effect of MET and BUP, utilizing the Clinical Opiate Withdrawal Scale (COWS),<sup>33</sup> Subjective Opiate Withdrawal Scale (SOWS),<sup>34</sup> Objective Opiate Withdrawal Scale (OOWS)<sup>34</sup> and Opiate Overdose Assessment (OOA)<sup>35</sup>; and the short-term safety and tolerability.

### 2.4 | PK sampling and analytical methods

Serial blood samples for PK analysis were collected predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h on day 1 and day 9 for MET and BUP, and predose, 1, 2, 3, 4, 5, 6, 8, 10 and 12 h on day 9 for TMR. Concentrations of total MET, *R*-MET, *S*-MET, BUP, norBUP and TMR in plasma were determined by validated liquid chromatography with tandem mass spectrometry assays. Lower limits of quantification were 5 ng/mL for *R*-MET, *S*-MET and TMR, and 20 pg/mL for BUP and norBUP. Calibration standards ranged from 5 to 5000 ng/mL. Plasma samples were analysed at Covance and PPD Laboratories. Individual participant PK parameter values were derived with noncompartmental methods by a validated PK analysis program (Phoenix WinNonlin Version 6.2.1, Certara, Princeton, New Jersey) using actual times. COWS, SOWS, OOWS and OOA assessments were performed predose on each day of the study. Safety was assessed throughout the study, and safety assessments were based on medical review of adverse event (AE) reports and the results of vital sign measurements, ECG, physical examinations and clinical laboratory tests. Physical examinations and ECGs were performed at screening, day 1 and discharge/day 10; blood and urine were taken for clinical laboratory evaluations on day 5 and day 9. Vital signs were measured at screening, days 1, 5 and discharge/day 10.

## 2.5 | Data and statistical analyses

To assess the effect of FTR on the PK of *R*-MET, *S*-MET and total MET and on the PK of BUP and norBUP, a linear mixed-effects model, with treatment as a fixed effect and participant as repeated measures, was fitted to the log-transformed, dose-normalized steady-state PK parameters (area under the plasma concentration–time curve over the dosing interval [AUC<sub>τ</sub>], maximum concentration in plasma [C<sub>max</sub>], and concentration in plasma at 24 hours [C<sub>24</sub>]) for use in the estimation of the effect and construction of confidence intervals (CIs). Kenward–Rogers degrees of freedom were specified in the model. Point estimates and 90% CIs for treatment differences on the log scale were exponentiated to obtain estimates for geometric mean ratios (GMRs) on the original scale. A priori assumptions about clinically relevant effects on opioid exposure were derived from a literature search of drug interaction studies for which no dose modifications were required.<sup>12</sup> In Part 1, no clinically relevant effect of FTR on MET PK was assumed if the 90% CIs of the GMR for AUC<sub>τ</sub> and C<sub>max</sub> of both MET enantiomers were entirely contained within prespecified boundaries of 0.7 and 1.43. In Part 2, no clinically relevant effect of FTR on BUP PK was assumed if the 90% CIs of the GMR for AUC<sub>τ</sub> and C<sub>max</sub> of BUP and norBUP were entirely contained within the prespecified boundaries of 0.5 and 2.0.

A sample size of 14 evaluable participants was estimated to provide 99.9% and 97.3% power with respect to *R*-MET (the pharmacologically active enantiomer) AUC<sub>τ</sub> and C<sub>max</sub>, respectively, and 97.2% overall power with respect to both *R*-MET AUC<sub>τ</sub> and C<sub>max</sub> for the 90% CI of the GMR to be contained within the prespecified boundaries of 0.70 to 1.43, if the true GMR is 1.00 and the within-participant standard deviation (SD) of 0.197 and 0.23, respectively. A sample size of 14 evaluable participants was estimated to provide 99.9% power with respect to each of BUP AUC<sub>τ</sub> and C<sub>max</sub>, and norBUP AUC<sub>τ</sub> and C<sub>max</sub>, and a 99.6% overall power with respect to BUP and norBUP AUC<sub>τ</sub> and C<sub>max</sub>, for the 90% CI of the GMR to be contained within the prespecified boundaries of 0.50–2.00, if the true GMR is 1.00 and the within-participant SDs of 0.19 and 0.278 for BUP, respectively, and AUC<sub>τ</sub> and C<sub>max</sub> the within-participant SDs of 0.285 and 0.288 for norBUP, respectively.

The PD impact of FTR on the withdrawal and overdose effect of MET or BUP/NLX using COWS, SOWS, OOWS and OOA questionnaires was determined using descriptive statistical summary for the total score of each questionnaire.

## 2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,<sup>36</sup> and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.<sup>37–39</sup>

### 3 | RESULTS

#### 3.1 | Participants' disposition and characteristics

Overall, 109 participants were screened, of whom 16 receiving MET were treated in Part 1 of the study and 16 receiving BUP/NLX were treated in Part 2. The 77 participants screened but not treated, the majority (53 [48.6%]) no longer met study criteria, while 5 (4.6%) withdrew consent, and 19 (17.4%) were not treated for other reasons. All treated participants completed the study. Except for 1 participant in Part 2 who did not receive 1 scheduled dose of FTR, all participants received all treatments as specified in the protocol. Participants in this study were predominantly white (81.3%) or black/African American (12.5%) and had a median (range) age of 36.5 (24–63) years. There was a greater number of male (71.9%) than female (28.1%) participants. Mean body mass index at screening was 26.74 kg/m<sup>2</sup> overall and demographics and baseline characteristics were generally similar across the 2 parts.

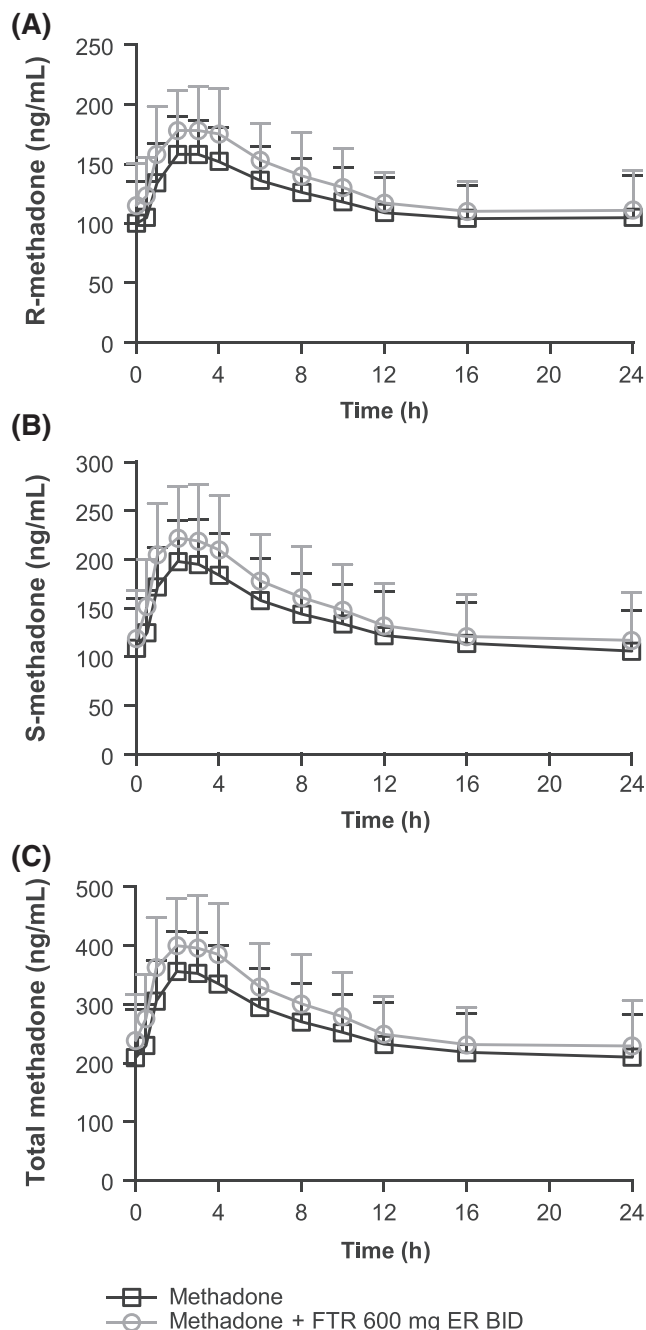
#### 3.2 | PK

##### 3.2.1 | Effect of FTR on R- and S-MET

Mean R- and S- and total MET (normalized to the lowest daily dose of 40 mg) plasma concentration–time profiles with and without FTR are shown in Figure 2. Statistical analysis of dose-normalized R- and S- and total MET PK parameters following administration with and without FTR is also shown in Table 1. Coadministration of MET 40–120 mg with FTR resulted in a 9–15% increase in MET exposure parameters compared with administering MET alone. The 90% CIs of the GMR for each parameter in both enantiomers did not contain 1.0 but were entirely contained within the prespecified range of 0.70–1.43 and, additionally, within the standard 0.8–1.25 range applied to evaluation of bioequivalence, indicating no clinically relevant effect of FTR on MET PK. The median T<sub>max</sub> of MET with FTR was similar to MET administered alone.

##### 3.2.2 | Effect of FTR on BUP and norBUP

Mean BUP and norBUP (normalized to the lowest daily dose of 8 mg/2 mg of BUP/NLX) plasma concentration–time profiles with and without FTR are shown in Figure 3. Statistical analysis of dose-normalized BUP and norBUP PK parameters following administration with and without FTR is also shown in Table 2. Coadministration of BUP/NLX 8/2 to 24/6 mg with FTR 600 mg ER BID increased BUP and norBUP C<sub>max</sub>, AUC<sub>τ</sub> and C<sub>24</sub> by 24–39% compared with administering BUP/NLX alone. The 90% CIs of the GMR for each parameter in both the parental compound and the metabolite did not contain 1.0 but were contained within the prespecified range of 0.50–2.00, indicating no clinically relevant effect of FTR on BUP and norBUP PK. The metabolite to parent AUC<sub>τ</sub> ratio of norBUP/BUP with and without FTR coadministration was similar. The median T<sub>max</sub> of coadministered BUP/NLX was similar to BUP/NLX administered alone.



**FIGURE 2** Mean (+ standard deviation) dose-normalized plasma concentration–time profiles for (A) R-methadone; (B) S-methadone; (C) total methadone with and without FTR. BID, twice daily; ER, extended release; FTR, fostemsavir

##### 3.2.3 | Effect of opioids on TMR

Geometric mean (coefficient of variation [%]) TMR C<sub>max</sub>, AUC<sub>τ</sub> and C<sub>12</sub> were 1498 (41) ng/mL, 9758 (40) ng h/mL and 409 (60) ng/mL, respectively, when FTR 600 mg ER BID was coadministered with MET; and 2052 (39) ng/mL, 13 176 (35) ng h/mL and 468 (80) ng/mL, respectively, when FTR 600 mg ER BID was coadministered with BUP/NLX. TMR exposures and variability were

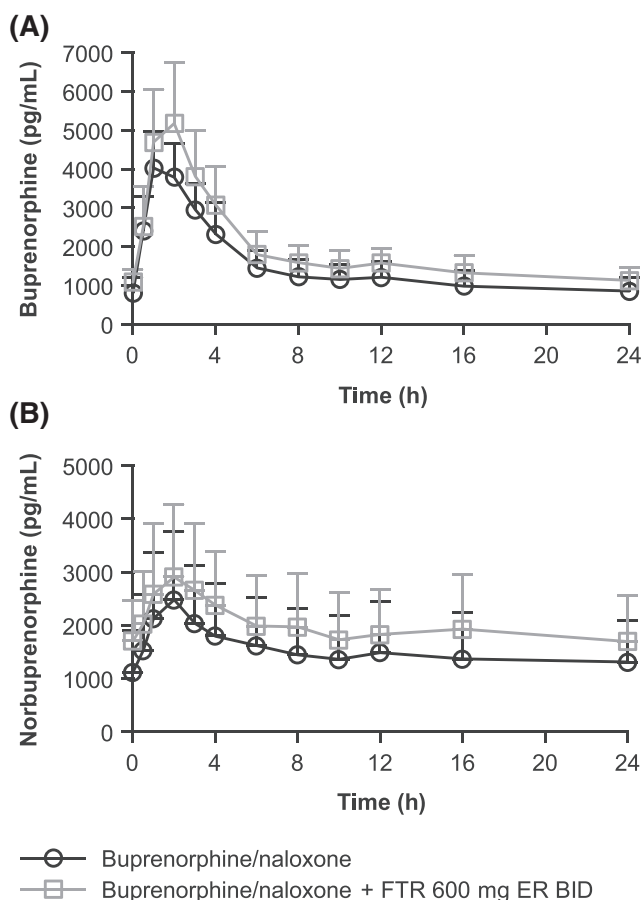


**TABLE 1** Effect of FTR 600 mg ER BID on dose-normalized methadone PK

Analyte	Parameter (unit)	Adjusted geometric mean (90% CI)		GMR (90% CI) Treatment B vs A
		Treatment A (methadone alone)	Treatment B (methadone + FTR 600 mg ER BID)	
<b>R-methadone</b>	C <sub>max</sub> (ng/mL)	162 (149–176)	187 (173–202)	1.15 (1.11–1.20)
	AUC <sub>τ</sub> (ng h/mL)	2707 (2450–2993)	3062 (2804–3343)	1.13 (1.07–1.19)
	C <sub>24</sub> (ng/mL)	98.5 (86.3–113)	107 (94.6–121)	1.09 (1.01–1.17)
<b>S-methadone</b>	C <sub>max</sub> (ng/mL)	199 (180–220)	228 (206–252)	1.15 (1.10–1.19)
	AUC <sub>τ</sub> (ng h/mL)	2967 (2593–3396)	3412 (2974–3915)	1.15 (1.09–1.21)
	C <sub>24</sub> (ng/mL)	97.3 (80.7–117)	107 (87.8–131)	1.10 (1.02–1.19)
<b>Total methadone</b>	C <sub>max</sub> (ng/mL)	362 (332–395)	415 (382–452)	1.15 (1.11–1.19)
	AUC <sub>τ</sub> (ng h/mL)	5702 (5095–6380)	6509 (5849–7244)	1.14 (1.09–1.20)
	C <sub>24</sub> (ng/mL)	197 (170–230)	216 (186–252)	1.10 (1.02–1.18)

AUC<sub>τ</sub>, area under the plasma concentration–time curve over the dosing interval; BID, twice daily; C<sub>24</sub>, concentration in plasma at 24 hours; C<sub>max</sub>, maximum concentration in plasma; CI, confidence interval; ER, extended release; FTR, fostemsavir; GMR, geometric mean ratio; PK, pharmacokinetics; T<sub>max</sub>, time to maximum plasma concentration.

Median (range) T<sub>max</sub> for Treatment A and Treatment B: R-methadone (3.0 h [1.0–4.0] and 3.0 h [1.0–6.0]); S-methadone (3.0 h [1.0–3.1] and 2.5 h [1.0–6.0]); total methadone (3.0 h [1.0–3.1] and 3.0 h [1.0–6.0]).

**FIGURE 3** Mean (+ standard deviation) dose-normalized plasma concentration–time profiles for (A) buprenorphine; (B) norbuprenorphine with and without FTR. BID, twice daily; ER, extended release; FTR, fostemsavir

consistent with historical observations in healthy participants receiving multiple oral doses of FTR 600 mg ER BID with a standard meal.<sup>15,20,40,41</sup>

### 3.3 | PD

Coadministration of FTR 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 (Figure 4). The similar scores, with no symptoms of withdrawal or overdose reported clinically, suggested that the effects of FTR on the PD of MET and BUP/NLX were not clinically relevant.

### 3.4 | Safety

Coadministration of FTR 600 mg ER BID with MET or BUP/NLX was well tolerated. There were no deaths, serious AEs or AEs leading to discontinuation of study therapy. There were no trends in emergent laboratory abnormalities and no AEs related to ECG abnormalities.

In Part 1, 2 participants (12.5%) reported at least 1 AE while receiving MET only and 10 participants (62.5%) reported at least 1 AE while receiving MET with FTR. The most frequently reported AEs were headache, reported in 1 participant (6.3%) while receiving MET only and 2 participants (12.5%) while receiving MET with FTR; and nausea, reported by 1 participant (6.3%) while receiving MET only and 2 participants (12.5%) while receiving MET with FTR. All other AEs were reported by only 1 or 2 participants each across the 2 treatments. An AE of acute HCV was reported for 1 participant in Part 1, subsequent to clinical laboratory abnormalities in levels of alanine aminotransferase/aspartate aminotransferase. The AE was considered mild and unrelated to study drug and was ongoing at the end of the study.

In Part 2, 3 participants (18.8%) reported at least 1 AE while receiving BUP/NLX only and 8 participants (50.0%) reported at least 1 AE while receiving BUP/NLX with FTR. The most frequently reported AEs in Part 2 were headache, reported by 3 participants (18.8%) while

**TABLE 2** Effect of FTR 600 mg ER BID on dose-normalized buprenorphine PK

Analyte	Parameter (unit)	Adjusted geometric mean (90% CI)		GMR (90% CI) Treatment D vs C
		Treatment C (buprenorphine/ naloxone alone)	Treatment D (buprenorphine/ naloxone + FTR 600 mg ER BID)	
Buprenorphine	C <sub>max</sub> (pg/mL)	4187 (3835–4572)	5206 (4534–5977)	1.24 (1.06–1.46)
	AUC <sub>τ</sub> (pg h/mL)	33 867 (30 230–37 942)	44 090 (39 652–49 024)	1.30 (1.17–1.45)
	C <sub>24</sub> (pg/mL)	780 (638–953)	1082 (949–1234)	1.39 (1.18–1.63)
Norbuprenorphine	C <sub>max</sub> (pg/mL)	2152 (1644–2818)	2674 (2171–3295)	1.24 (1.03–1.51)
	AUC <sub>τ</sub> (pg h/mL)	30 219 (22 688–40 252)	41 920 (33 436–52 557)	1.39 (1.16–1.67)
	C <sub>24</sub> (pg/mL)	1104 (843–1447)	1506 (1205–1883)	1.36 (1.10–1.69)
	MR-AUC <sub>τ</sub> <sup>a</sup>	1.009 (50.9)	1.075 (48.8)	1.066 (46.6)

AUC<sub>τ</sub>, area under the plasma concentration–time curve over the dosing interval; BID, twice daily; C<sub>24</sub>, concentration in plasma at 24 hours; C<sub>max</sub>, maximum concentration in plasma; CI, confidence interval; ER, extended release; FTR, fostemsavir; GMR, geometric mean ratio; PK, pharmacokinetics; T<sub>max</sub>, time to maximum plasma concentration.

Median (range) T<sub>max</sub> for Treatment C and Treatment D: buprenorphine (1.0 h [1.0–2.0] and 2.0 h [1.0–2.0]); norbuprenorphine (2.0 h [1.0–2.0] and 2.0 h [1.0–4.0]).

<sup>a</sup>MR-AUC<sub>τ</sub>, ratio of metabolite AUC<sub>τ</sub> to parent AUC<sub>τ</sub> corrected for molecular weight, for norbuprenorphine to buprenorphine presented as geometric mean (coefficient of variation, %).

receiving BUP/NLX only and by 1 participant (6.3%) while receiving BUP/NLX with FTR; and nausea, reported by 3 participants (18.8%) while receiving BUP/NLX with FTR. All other AEs were reported by only 1 or 2 participants each across the 2 treatments. One participant reported rash erythematous while receiving BUP/NLX with FTR, which was considered mild and related to study drug. No treatment was administered, nor action taken with study drug. The event resolved after 3 days.

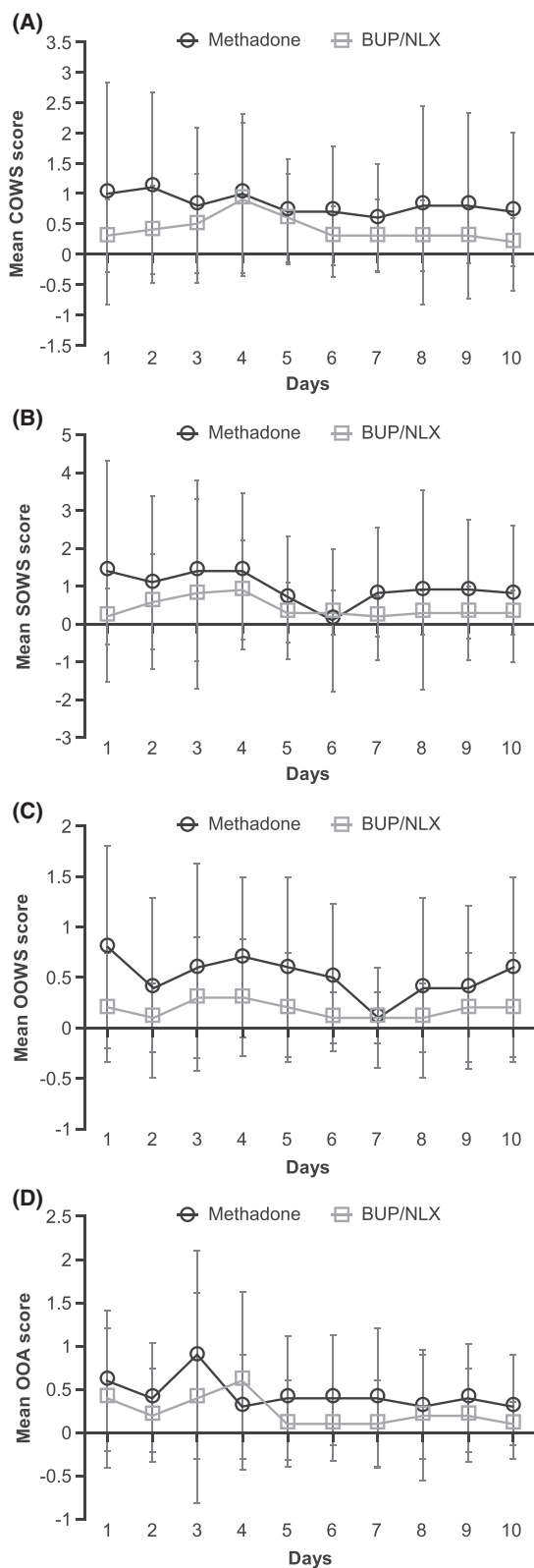
## 4 | DISCUSSION

FTR is being developed for heavily treatment-experienced patients who are infected with HIV-1, some of whom are likely to be on a maintenance regimen of MET or BUP/NLX. Therefore, an assessment of the potential for a DDI was warranted. MET and BUP/NLX doses are highly individualized to titrate effective control of opiate withdrawal symptoms while avoiding symptoms of opiate toxicity; therefore, participants who had been reliably joining in an oral MET or BUP/NLX programme on a stable dose for at least 30 days prior to screening were required to maintain their current stable dose throughout the study. The stable MET and BUP/NLX doses for the study participants ranged from 40 to 120 mg and BUP/NLX 8/2 to 24/6 mg, respectively, requiring PK normalization to the lowest dose to enable comparison of the impact of FTR coadministration to be assessed. However, it is a limitation that dose normalization may confound interpretation to a degree, since MET and BUP PK is not entirely dose proportional. Assessment of the impact of FTR on MET or BUP/NLX PK and safety demonstrated no clinically significant effect defined a priori per respective drug labels and literature on the concomitant administration with selected ARVs.<sup>1,2,9,34</sup>

Coadministration of FTR 600 mg ER BID with MET did not have a meaningful impact on R-, S-, or total MET exposures, with the 90% CIs all contained within the protocol-defined boundaries for no clinically

significant effect, as well as being within the range for bioequivalence. Coadministration of BUP/NLX with FTR 600 mg ER BID increased BUP and norBUP C<sub>max</sub>, AUC<sub>τ</sub> and C<sub>24</sub> by 24–39%. Importantly, BUP and norBUP 90% CIs were contained within the protocol-defined boundaries for no clinically significant effect.

TMR has 2 human plasma metabolites, BMS-646915 and BMS-930644, that constitute ≥10% of TMR concentrations; both lack anti-HIV activity. BMS-930644 has low circulating concentrations compared with TMR but, unlike TMR and BMS-646915, it has been shown in vitro in human liver microsomes to inhibit CYP3A4. TMR and its metabolites, BMS-646915 and BMS-930644, inhibit BCRP and all are P-gp substrates, but not inhibitors. The mechanism of the minor impact of TMR on MET and the modest impact on BUP and norBUP is uncertain and an increase in MET and BUP absorption may be most probable based on the impact of TMR on the early phase of the MET, BUP and norBUP concentration–time profiles. Potential mechanisms may involve modest increases in bioavailability, given that P-gp is implicated in gut absorption and efflux and MET, BUP, TMR and BMS-930644 are all P-gp substrates. Inhibition of hepatic or gut CYP3A4 metabolism by BMS-930644 (IC<sub>50</sub> = 9.9 μM) may play a role, although circulating BMS-930644 concentrations are low (C<sub>max</sub> ≈ 458 ng/mL [~1 μM] for FTR 600 mg BID), making clinically significant interactions unlikely. It is also not clear why there was a modest increase in norBUP exposures with FTR coadministration though the ratio of norBUP/BUP AUC<sub>τ</sub> was similar with or without FTR. If there was significant CYP3A4 inhibition by BMS-930644, the norBUP absolute value and norBUP/BUP AUC<sub>τ</sub> ratio would have been expected to decrease. Given that BUP has a significant first-pass effect resulting in low bioavailability and assuming that the primary impact with FTR coadministration is increased BUP absorption, then norBUP concentrations would be expected to increase, which matches the observed data. The COWS, SOWS, OOWS or OOA scores following coadministration of FTR were similar to those when MET or BUP/NLX were administered alone. Based on this,



**FIGURE 4** Mean (+ standard deviation) predose pharmacodynamic assessments of methadone and buprenorphine/naloxone (BUP/NLX) maintenance before (day 1), during (days 2 to 9) and after (day 10) the period of fostemsavir coadministration by (A) COWS; (B) SOWS; (C) OOWS; (D) OOA. COWS, clinical opiate withdrawal scale; OOA, opiate overdose assessment; OOWS, objective opiate withdrawal scale; SOWS, subjective opiate withdrawal scale

MET and BUP may be coadministered with FTR 600 mg ER BID without dose adjustment.

TMR PK parameters and variability were comparable with prior observations from 4 separate studies in healthy adult volunteers receiving FTR 600 mg ER BID alone with a standard meal where mean values for  $C_{max}$ ,  $AUC_{\tau}$  and  $C_{12}$  ranged from 1643 to 2071 ng/mL, 9695 to 12 190 ng h/mL and 287 to 358 ng/mL, respectively. TMR exposures were slightly higher with BUP/NLX compared with MET; however, given TMR PK parameters were comparable with other study results and that 2 separate cohorts of participants were in the MET and BUP parts of the study by design, it would be difficult to associate any differences to MET or BUP.

Coadministration of FTR 600 mg ER BID with MET or BUP/NLX was well tolerated and produced no new safety signal, including no clinically meaningful impact on trends of opiate withdrawal or overdose effect.

It is likely that heavily treatment-experienced, HIV-1-infected adults may need to take complicated ARV regimens, which include inhibitors and/or inducers of drug metabolism and/or transporters. The complex DDI effects caused by ARV regimens may require a titration of a pre-existing maintenance opioid, which could impact a stable maintenance state without symptoms of either opioid withdrawal or overdose. Additionally, patient adherence to a medication they associate with opiate withdrawal symptoms is likely to be low. Non-adherence, especially in a complex population like heavily treatment-experienced HIV-1-infected patients, could have significant consequences on therapeutic benefit and risk for increased resistance to remaining ARV therapies. The MET or BUP/NLX PK and PD data with FTR indicate that FTR does not have a clinically relevant impact on maintenance opioids; inclusion of FTR as part of a combination ARV regimen does not require titration of MET or BUP/NLX.

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#### COMPETING INTERESTS

K.M., P.A. and C.L. are employees at ViiV Healthcare. Mindy Magee is an employee at GlaxoSmithKline. Ming M.C., S.L. and E.M. are employees at Bristol-Myers Squibb. Heather Sevinsky is an employee at Arbutus Biopharma.

#### CONTRIBUTIONS

All authors have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data and have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final



approval of the version to be published and each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content. All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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