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Pharmacokinetic Interactions Between Buprenorphine/Naloxone and Tipranavir/Ritonavir in HIV-Negative Subjects Chronically Receiving Buprenorphine/Naloxone

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Abstract

HIV-infected patients with opioid dependence often require opioid replacement therapy. Pharmacokinetic interactions between HIV therapy and opioid-dependence treatment medications can occur.

HIV-seronegative subjects stabilized on at least 3 weeks of buprenorphine/naloxone (BUP/NLX) therapy sequentially underwent baseline and steady-state pharmacokinetic evaluation of open-label, twice daily tipranavir 500 mg co-administered with ritonavir 200 mg (TPV/r).

Twelve subjects were enrolled and 10 completed the study. Prior to starting TPV/r, the geometric mean BUP AUC0-24h and Cmax were 43.9 ng▪hr/mL and 5.61 ng/mL, respectively. After achieving steady-state with TPV/r (≥7 days), these values were similar at 43.7 ng▪hr/mL and 4.84 ng/mL, respectively. Similar analyses for norBUP, the primary metabolite of BUP, demonstrated a reduction in geometric mean for AUC0-24h [68.7 to 14.7 ng▪hr/mL; ratio=0.21 (90% CI 0.19–0.25)] and Cmax [4.75 to 0.94 ng/mL; ratio=0.20 (90% CI 0.17–0.23)]. The last measurable NLX concentration (Clast)

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Author Disclosures

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Conflict of Interest

R. Douglas Bruce: None, Frederick L. Altice: Boehringer Ingelheim Pharmaceuticals, Inc. (grant funding), David E. Moody: None, Shen-Nan Lin: None, Wenfang B. Fang: None, John P. Sabo: employee of Boehringer Ingelheim Pharmaceuticals, Inc., Jan M. Wruck: employee of Boehringer Ingelheim Pharmaceuticals, Inc., Peter J. Piliero: employee of Boehringer Ingelheim Pharmaceuticals, Inc., Carolyn Conner: employee of Boehringer Ingelheim Pharmaceuticals, Inc., Laurie Andrews: None, Gerald H. Friedland: None

in the concentration-time profile, never measured in previous BUP/NLX interaction studies with antiretroviral medications, was decreased by 20%. Despite these pharmacokinetic effects on BUP metabolites and NLX, no clinical opioid withdrawal symptoms were noted. TPV steady-state AUC0-12h and Cmax decreased 19% and 25% respectively, and Cmin was relatively unchanged when compared to historical control subjects receiving TPV/r alone.

No dosage modification of BUP/NLX is required when co-administered with TPV/r. Though mechanistically unclear, it is likely that decreased plasma RTV levels while on BUP/NLX contributed substantially to the decrease in TPV levels. BUP/NLX and TPV/r should therefore be used cautiously to avoid decreased efficacy of TPV in patients taking these agents concomitantly.

Keywords

pharmacotherapy; HIV/AIDS; pharmacokinetics; antiviral treatment; maintenance; opiates

1. 0 Introduction

Substantial advances in the treatment of opioid dependence have been made in recent years. These have had a favorable impact on clinical and public health outcomes of patients with both opioid dependence and HIV/AIDS (Bruce, 2007). Medication-assisted treatment with methadone or buprenorphine (BUP) are evidenced-based therapies that have proven to be effective for both primary and secondary HIV prevention (Altice et al., 2006; Kerr et al., 2004) and cost-effective to society (Doran et al., 2003). Moreover, medication assisted therapy is likely to increase access to and retention on antiretroviral and other therapies (Lucas et al., 2006). BUP, unlike the full opioid-agonist methadone, is a partial *mu*-receptor agonist. This results in a plateau of its agonist effects at higher doses which diminishes the risk of respiratory depression, thereby improving its safety profile compared to methadone (Fiellin and O'Connor, 2002). To reduce diversion, buprenorphine is most commonly prescribed in a sublingual co-formulation with naloxone (NLX). Unlike methadone treatment that is limited in availability and provided only in highly structured treatment settings, BUP can be prescribed by any physician who has completed eight hours of required training and obtains a waiver to prescribe. This potentially allows for the expansion of drug treatment and integration of substance abuse treatment into HIV and other clinical care settings (Basu et al., 2006).

The number of persons eligible for and receiving treatments for both opioid dependence and HIV infection has increased. Co-administration of these therapies, however, has been associated with both pharmacokinetic and pharmacodynamic interactions, with important clinical consequences (Bruce and Altice, 2006; Bruce et al., 2006a; Bruce et al., 2006b; Spire et al., 2007). The concern about such interactions may deter some patients or providers from initiating potentially life-saving therapy (Lucas et al., 2002). For patients currently on both therapies, real or perceived interactions may reduce therapeutic effectiveness for either or both diseases (Basu et al., 2006). Such interactions may lead to non-adherence with antiretroviral regimens, development of viral resistance, and lack of efficacy of HIV therapy (Bruce et al., 2006a; Lucas et al., 2007). Opioid-dependent patients may also experience adverse effects from HIV treatment that mimic opioid withdrawal and may relapse to using opioids (Altice et al., 1999) or other illicit substances (e.g., cocaine, alcohol) to alleviate symptoms. The occurrence of unrecognized drug interactions may therefore lead to a lack of success of treatment for HIV, opioid dependence, or both (Bruce and Altice, 2007).

Tipranavir (TPV), a non-peptidic protease inhibitor used for the treatment of HIVinfected patients resistant to more than one protease inhibitor, has unique pharmacological properties including marked induction of CYP3A4 and UGT1A1. To counteract the induction of CYP3A4

by TPV, it must be co-administered with ritonavir (RTV), a potent inhibitor of CYP3A4. The net effect of co-administration of tipranavir/ritonavir (TPV/r) 500/200 BID is an increase in TPV concentrations to therapeutic levels (Tipranavir Package Insert 2005; MacGregor et al., 2004; McCallister et al., 2002; Vourvahis and Kashuba, 2007).

BUP is oxidatively metabolized to norbuprenorphine (norBUP) by CYP3A4 and both are glucuronidated (Cone et al., 1984). Because CYP3A4 and UGT1A1 (Bruce et al., 2006b; Chang et al., 2006; King et al., 1996), have primary roles in the metabolic pathway of BUP, the potential exists for both pharmacokinetic interactions between BUP and TPV/r, when co-administered. This study was therefore undertaken to ascertain if interactions exist when TPV/r and BUP/NLX are co-administered in individuals receiving chronic BUP/NLX maintenance therapy.

2.0 Methods

2.1 Study Design

This was a multiple dose, open-label, sequential, non-randomized study in BUP-maintained HIV-negative subjects stabilized on at least 3 weeks of BUP/NLX therapy. Subjects were eligible if they were 1) HIV-seronegative; 2) ≥18 years old; 3) not being treated with concomitant medications that might alter drug disposition; 4) without clinically significant medical conditions as determined by medical history, physical examination, ECG, complete blood count, hepatic transaminases, creatinine, and were not pregnant. Urine toxicology was performed at baseline, and repeated prior to conducting drug disposition studies. Urine toxicology screened for amphetamines, benzodiazepines, cocaine, marijuana, methadone, opiates, and oxycodone. Subjects who screened positive for any substance in the urine toxicology were excluded from further evaluation.

Subjects served as their own controls. At baseline, subjects on steady state BUP/NLX were hospitalized and underwent pharmacokinetic (PK) investigation over a 24-hour inpatient period. Blood specimens were drawn at baseline (10 minutes before BUP/NLX dosing; nominal time 0 hours), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after dosing. All subjects were on 16 mg daily of BUP/NLX except for one patient on 24 mg daily.

Subsequently, TPV/r 500 mg/200 mg twice daily was administered for a minimum of seven days under direct observation to insure adherence and to monitor for adverse events. A minimum of 7 days is necessary to achieve steady-state of TPV (Valdez, 2004). After achieving TPV steady-state, serial blood samples were collected from each subject over a 24-hour inpatient period to determine the plasma drug concentration-time profile of TPV and RTV, and for BUP, norBUP, NLX, and its major metabolite, nornaloxone (norNLX).

Study procedures included standardized measures of opioid withdrawal and opioid excess utilizing the objective opioid withdrawal scale (OOWS), subjective opioid withdrawal scale (SOWS)(Handelsman et al., 1987), and the opioid overdose assessment scale (OOAS) (Friedland, 2005). These scales were administered on a daily basis by trained nursing staff prior to the morning dose administration of BUP/NLX and TPV/r. Adverse symptoms were recorded in a standardized manner.

2.2 Bioanalytical procedures

The concentrations of TPV and RTV in heparinized plasma were determined using a validated liquid chromatography-tandem mass spectrometry method at Bioanalytical Systems Inc., West Lafayette, IN. For TPV, accuracy and precision were −5.2% to 4.8% and 1.9% to 7.8%, respectively. For RTV, accuracy and precision were −16.9% to 6.4% and 3.9% to 11.1%, respectively. The lower limit of quantitation for TPV and RTV was 25.0 ng/mL.

The concentrations of BUP, norBUP, NLX and norNLX in heparinized plasma were determined using validated bioanalytical methods at the Center for Human Toxicology, University of Utah, Salt Lake City UT. All drugs and their metabolites discussed were measured using a validated liquid chromatography-tandem mass spectrometry method. BUP and norBUP were determined as previously described, (Moody et al., 2002) the method has a lower limit of quantitation (LLOQ) of 0.1 ng/mL for both analytes. NLX and norNLX were determined using a recently described method (Fang et al., 2009) unpublished method that uses naltrexone-d_3 and oxymorphone-d_3 as the respective internal standards, solid-phase extraction and has a LLOQ of 0.025 ng/mL for NLX and 0.5 ng/mL for norNLX.

2.3 Pharmacokinetic and Statistical Analysis

Non-compartmental methods were used for PK analysis (WinNonlin Professional, version 5.2; Pharsight Corporation, Mountain View, CA). Cmax was defined as the highest observed concentration of a drug in plasma; the corresponding sampling time defined Tmax. Plasma drug concentrations at 12 and 24 h after the initial dose were defined as Cp12h and Cp24h. The elimination rate constant (λz) was determined by least-squares linear regression analysis (log concentration versus time) of the last concentration-time points ($n \geq 3$). The $t_{1/2}$ was calculated as $\ln 2/\lambda z$. The area under the plasma drug concentration-time curve (AUC; from 0 to 24 h [AUC_{0-24}] for BUP, norBUP, NLX and norNLX; and AUC_{0-12} for TPV and RTV) was estimated using the linear-log trapezoidal rule (linear up/log down). Apparent oral clearance (CL/F) was calculated as the drug dose/AUC ratio.

BUP, norBUP, NLX, and norNLX parameters were calculated following sublingual administration of BUP/NLX only and then again following steady-state of TPV/r 500 mg/200 mg twice daily. Statistical analysis was performed with SAS (release 8.2, SAS Institute Inc., Cary, NC). The pharmacokinetic parameters were transformed to the natural logarithm. The difference between the expected means for log(T)-log(R) were estimated by the difference in the corresponding Least Square Means (point estimate) and two-sided 90% confidence intervals based on the t-distribution were computed. These quantities were then back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the median intra-subject ratio between response under test and response under reference. Similar analyses were performed for norBUP, NLX and norNLX.

SAS Proc Multtest was used to compare TPV pharmacokinetics in the present study to TPV AUC_{0-12}, Cmax, and Cp12h PK results for 161 healthy volunteers from eight previous clinical studies (Cooper, 2005; la Porte, 2007a, b; MacGregor et al., 2004; Pham, 2008; Sabo, 2008; van Heeswijk, 2004a, b). Bootstrap arithmetic means (20,000 re-samples) were determined, and the ratios of the means for the test regimen to those for the reference regimen were used to assess the interaction and determine the point estimate. The 5th and 95th percentiles of the distribution of the ratios provided the 90% confidence intervals.

3.0 Results

3.1 Study Disposition

Twenty subjects were screened for this study, with 12 individuals (8 males and 4 females; 8 Caucasian and 4 Black) enrolled. Median (min–max) age, height, weight and body mass index were 44 (21–53) years, 177.8 (165.1–188.0) cm, 75.9 (65.8–112.0) kg, and 25.7 (21.7–35.4) kg/m^2, respectively. Of the 12 subjects treated, two developed adverse events leading to study drug discontinuation before completing the final PK assessment, resulting in 10 evaluable subjects. One subject withdrew due to perioral numbness and lightheadedness likely due to RTV after the first day of study drug administration (Ritonavir Package Insert 2007) and one subject withdrew due to elevated hepatic transaminases (>5x ULN; DAIDS Grade 3) detected

during routine screening on day 4 which was attributed to known hepatic effects of tipranavir (2005). All adverse reactions resolved with study drug discontinuation.

3.2 Pharmacokinetic Outcomes

The steady-state pharmacokinetics for BUP, norBUP, and NLX in the presence and absence of steady-state TPV/r are summarized in Table 1. BUP AUC and Cp_{24h} were not affected by co-administered TPV/r (< 6% change relative to BUP/NLX alone) while C_{max} decreased 14% (Table 1). In contrast, steady-state norBUP, the major BUP metabolite, $AUC_{0–24h}$, C_{max} and Cp_{24h} were significantly decreased, approximately 80%, in the presence of steady-state TPV/r (Table 1). NLX AUC and C_{max} were decreased by 44% and 36%, respectively. Plasma NLX concentrations were less than the lower limit of detection for the assay by 24 hours and therefore not considered further.

The steady-state pharmacokinetics for TPV for subjects receiving TPV/r + BUP/NLX and historical healthy volunteer controls receiving TPV/r alone are summarized in Table 2. $AUC_{0–12h}$ and C_{max} mean ratio decreased 19% and 25%, respectively, with relatively no change in the mean ratio for C_{min} (3% increase). Variability of the C_{min} ratio, as expressed by the 5^{th} and 95^{th} percentiles of the distribution of the ratios (90% CI) was 0.58 and 1.53, respectively.

The steady-state pharmacokinetics for RTV for subjects receiving TPV/r + BUP/NLX and historical healthy volunteer controls receiving TPV/r are summarized in Table 3. RTV steady-state pharmacokinetics were characterized by a geometric mean (minimum – maximum) C_{max} of 0.81 μg/mL (0.14–1.74 μg/mL), AUC of 3.88 h•μg/mL (0.41–9.71 h•μg/mL) and C_{min} of 0.111 μg/mL (0.033–0.804 μg/mL), with 8 of 10 subjects having quantifiable plasma RTV concentrations at 12 h after dosing.

3.3 Clinical Outcomes

Clinical opioid withdrawal and excess scales were utilized to determine whether there were any adverse clinical effects of TPV/r in patients receiving BUP/NLX combined with TPV/r. Using the Objective Opiate Withdrawal Scale (OOWS), the mean value of this over all subjects with reportable data (89 of 119 possible data points) was 0.618 (±0.8726) with a range among subjects from a minimum of 0 to a maximum of 4 (maximum score is 13). The mean value of 0.618 reveals no overall clinically significant opioid withdrawal and none of the subjects fulfilled criteria for opioid withdrawal nor required modification of their BUP/NLX dose. The main reported symptoms were nonspecific and included anxiousness, perspiration, and rhinorrhea. Occasional yawning, restlessness, and hot flashes were reported. One subject reported abdominal cramps on one morning. None of these symptoms necessitated discontinuing treatment or increasing buprenorphine dosing. The Subjective Opiate Withdrawal Scale (SOWS) mean value over all subjects with reportable data (89 of 119 possible data points) was 1.157 (±1.507) with a range among subjects from a minimum of 0 to a maximum of 6 (maximum score 64). The mean value of 1.157 reveals no overall clinically significant opioid withdrawal and none of the subjects developed significant signs of opioid withdrawal. The Opiate Overdose Assessment Scale (OOAS) was utilized to evaluate opioid excess. The mean value of this over all subjects with reportable data (89 of 119 possible data points) was 0.6023 (±0.9889) with a range from 0 to 3. The OOAS is an 11-question instrument combining both subjective symptoms of opioid excess with objective signs as assessed by a nurse with a range from 0 to 40. The mean value of 0.6023 reveals no clinically significant opioid excess. None of the individual patients exhibited clinically significant signs of opioid excess as defined by a maximum score of 3 out of 40 on the OOAS. The main reported symptoms were nonspecific and included fatigue and sweating. None of these symptoms necessitated dose modification or cessation of treatment.

4.0 Discussion

In this pharmacokinetic study examining steady-state BUP/NLX in HIV-seronegative subjects, co-administration of TPV/r did not appreciably affect the AUC and Cp_{24h} of BUP. TPV/r co-administration did, however, reduce the level of norBUP, the major BUP metabolite. The mechanism by which plasma norBUP is reduced by TPV/r is unclear. Such a reduction in norBUP may be the result of the known *in vitro* induction of UGT1A1 by TPV/r (Vourvahis and Kashuba, 2007); however, for this to affect only norBUP seems unlikely as both BUP and norBUP are conjugated by UGT1A1 and 1A3 (Chang and Moody, 2009). TPV is known to affect multiple other CYPs; it is possible that the reduction in norBUP may represent induction of the recently described hydroxylations of norBUP (Chang et al., 2006). Although norBUP is an active BUP metabolite, it is reported to possess less than 2% of the analgesic potency of buprenorphine. Therefore, its contribution to clinical efficacy is believed to be low(Elkader and Sproule, 2005) and a reduction in norBUP should not clinically compromise the treatment of opioid dependence.

This is the first study to ascertain naloxone concentrations in the evaluation of the BUP/NLX tablet interactions with an antiretroviral medication. NLX is metabolized by both UGTs (specificity unknown) and CYPs, the latter recently identified as CYP2C18 and 2C19 (Fang et al. 2009). The inclusion of NLX PK assessments was prompted by the difficulty in predicting TPV metabolic effects. The reduction of NLX may be due to induction at UGT1A1 (Vourvahis and Kashuba, 2007); induction of CYP2C18 and/or 2C19 is also a possibility, but less likely, as the combination of TPV/r is more often associated with inhibition of CYP. Because NLX is an opioid antagonist included in the co-formulated tablet for the purpose of reducing diversion in the setting of BUP/NLX injection, a reduction in plasma concentration of NLX will not compromise the efficacy of BUP/NLX in the treatment of opioid dependence. It is unclear if such a reduction in NLX levels would impede its ability to produce opioid withdrawal in the context of BUP/NLX injection.

The 3 validated scales administered to subjects daily confirmed the lack of a clinical effect associated with these pharmacokinetic changes. No symptoms meeting the predetermined definition of withdrawal or opioid excess were documented. Moreover, this was clinically confirmed by the absence of a need to adjust BUP/NLX dosing and no discontinuations from the study due to symptoms of opioid withdrawal.

Because the study design could not include treatment with TPV/r alone, it was not possible to definitively determine the effect of BUP/NLX treatment on the pharmacokinetics of TPV and RTV. RTV is necessary to increase TPV plasma concentrations to therapeutic levels. The subjects in this study were all HIV negative and, as presented in Table 3, the steady-state Cmin for RTV was similar between these subjects and other HIV negative subjects receiving TPV/r 500 mg/200 mg twice daily. Tipranavir has a complex metabolic pathway and it is possible that the presence of BUP may result in unanticipated changes in this metabolic pathway. This finding is unique among BUP PK studies as, until recently, BUP has been thought to have fewer pharmacological interactions of significance with HIV therapeutics. Further investigations would be necessary to elucidate the metabolic pathways to explain our findings.

The results from this study are subject to several limitations. First, the sample size was small, though within the range of similar drug-drug interaction studies. Second, this study utilized a within-subject design with patients acting as their own controls and thereby resulting in less intra-patient variability in the analysis of BUP/NLX. The study design, however, did not allow for such within-subject comparison to be made with TPV/r before and after BUP/NLX administration and thus comparison was made to historical controls. Finally, because of the limited population of subjects maintained with BUP/NLX and eligible for participating in this

clinical pharmacokinetic study, it was not possible to limit BUP/NLX dosing to a single BUP/NLX dose group. However, exclusion of the single subject that received buprenorphine 24 mg/naloxone 6 mg from the statistical analysis did not result in statistically or clinically important changes, or their interpretation, in the mean ratio or confidence intervals.

In conclusion, with the stated limitations of this study, the results indicate that no dosage modification of BUP/NLX is required when it is co-administered with TPV/r. Compared to historical controls, TPV/r $AUC_{0–12h}$ and C_{max} mean ratio decreased 19% and 25%, respectively. Based on these provocative findings, TPV/r and BUP/NLX should be coadministered with caution as TPV may be less effective due to decreased TPV plasma concentrations in patients taking these medications concomitantly.

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Table 1

Summary of steady-state pharmacokinetics for BUP, norBUP and NLX in the presence and absence of steady-state TPV/r

	BUP		norBUP		NLX	
PK Parameter	**BUP/NLX**	**BUP/NLX + TPV/r**	**BUP/NLX**	**BUP/NLX + TPV/**	**BUP/NLX**	**BUP/NLX + TPV/r**
AUC_{0-24h} (h·ng/mL)	43.9 (47.2, 20.8 – 106.9)	43.7 (41.6, 16.4 – 112.7)	68.7 (63.1, 33.2 – 149.5)	14.7 (12.3, 8.8 – 31.9)	0.35 (0.26, 0.04 – 1.51)	0.20 (0.17, 0.04 – 1.89)
Mean Ratio (90% CI)	0.99 (0.80, 1.23) 0.96 (0.76, 1.21)*		0.21 (0.19, 0.25) 0.21 (0.18, 0.25)*		0.56 (0.39, 0.81) 0.51 (0.36, 0.74)*	
Cmax (ng/mL)	5.61 (5.09, 2.23 – 11.61)	4.84 (4.94, 2.04 – 8.72)	4.75 (4.81, 2.29 – 8.68)	0.94 (0.96, 0.55 – 1.64)	0.131 (0.123, 0.047 – 0.452)	0.084 (0.085, 0.028 – 0.349)
Mean Ratio (90% CI)	0.86 (0.68, 1.10) 0.86 (0.65, 1.12)*		0.20 (0.17, 0.23) 0.20 (0.17, 0.24)*		0.64 (0.47, 0.87) 0.63 (0.44, 0.89)*	
Cmin (ng/mL)	1.07 (1.05, 0.35 – 3.68)	1.00 (0.82, 0.32 – 3.56)	2.28 (2.25, 0.74 – 5.46)	0.46 (0.40, 0.27 – 1.05)	0.041 (0.035, 0.027 – 0.099)	0.033 (0.030, 0.025 – 0.090)
Mean Ratio (90% CI)	0.94 (0.74, 1.19) 0.86 (0.70, 1.06)*		0.20 (0.16, 0.25) 0.20 (0.16, 0.25)*		NA	
Tmax (h)	0.9 (0.9, 0.5 – 2.2)	1.3 (1.4, 0.4 – 10.2)	1.8 (1.5, 0.8 – 10.3)	2.0 (1.7, 0.5 – 12.2)	1.0 (0.8, 0.5 – 5.2)	0.8 (0.6, 0.4 – 10.2)
$t_{1/2}$ (h)	16.6 (15.4, 8.8 – 45.8)	21.4 (14.5, 12.7 – 107.7)	44.2 (30.5, 15.9 – 238.3)	29.1 (27.3, 19.7 – 66.1)	2.6 (2.5, 0.6 – 9.4)	3.1 (3.3, 0.6 – 11.5)
CL/F (L/h)	379 (339, 150 – 770)	382 (386, 142 – 978)	NA	NA	11979 (15183, 2793 – 97912)	21282 (23336, 3175 – 106477)
V (L)	9059 (7174, 3603 – 37647)	11787 (10430, 2610 – 60576)	NA	NA	46954 (36287, 12571 – 204426)	84599 (89681, 36890 – 169342)

PK parameter values are geometric mean (median, min-max); plasma naloxone concentrations at the end of the 24 h buprenorphine/naloxone dosing interval were not evaluated as nearly all concentrations were less than the lower limit of quantitation for the assay

The mean ratio (90% CI) represents the geometric mean ratio and 90% confidence interval of the pharmacokinetic parameter for the treatments BUP/NLX + TPV/r to BUP/NLX alone

All subjects (N = 10) received buprenorphine 16 mg/naloxone 4 mg qd, except one subject who received buprenorphine 24 mg/naloxone 6 mg qd $t_{1/2}$ for NLX could not be calculated for 3 subjects with BUP/NLX and for 2 subjects with BUP/NLX+TPV/r

Cmin for BUP, norBUP was the plasma drug concentration at 24 h after dosing; for NLX, Cmin was the last measured concentration above the assay LOQ (Tlast (h): BUP/NLX 6.2 (5.6, 1.7 – 24.3); BUP/NLX+TPV/r, 4.5 (4.0, 1.4 – 24.1))

* Indicates mean ratio (90% CI) for 9 subjects that received buprenorphine 16 mg/naloxone 4 mg qd.

Table 2

Summary of steady-state pharmacokinetics for TPV/r in the presence and absence of steady-state BUP/NLX

Treatment	N	Arithmetic mean (median, minimum - maximum)[a]		
		AUC_{0-12h}	Cmax	Cmin
TPV/r + BUP/NLX	10	694 (688, 413 – 1141)	95.7 (95.5, 71.7 – 125.8)	34.6 (34.2, 7.4 – 75.6)
TPV/r alone	161	859 (859, 756 – 979)	128.1 (128.1, 112.4 – 143.5)	33.6 (33.6, 26.9 – 42.2)
Mean Ratio (90% CI)[b]		0.81 (0.63, 1.02)	0.75 (0.65, 0.86)	1.03 (0.58, 1.53)

[a] Represents the arithmetic mean, median, minimum and maximum values for the resampled data sets.

[b] Represents the arithmentic mean ratio for the comparison of the pharmacokinetic parameter and the respective 5^{th} and 95^{th} percentiles of the distribution of the ratio; a value of 1.00 indicates no change.

Table 3

Effect of steady-state buprenorphine/naloxone on steady-state ritonavir (TPV/r 500/200 mg bid)

	Treatment[1]	Mean	SD	Median	Geometric Mean
Tmax (h)	Historical (fasted)	3.0	1.1	3.0	2.7
	Historical (fed)	3.3	2.0	4.0	2.7
	BUP+TPV/r	2.18	1.05	1.83	1.95
Cmax (μg/mL)	Historical (fasted)	2.08	1.19	1.89	1.67
	Historical (fed)	1.66	1.09	1.34	1.32
	BUP+TPV/r	0.97	0.51	0.83	0.81
Tmax (h)	Historical (fasted)	11.1	1.8	12.0	10.9
	Historical (fed)	11.2	1.8	12.0	11.0
	BUP+TPV/r	11.31	1.98	11.99	11.09
Clast (μg/mL)	Historical (fasted)	0.071	0.047	0.064	0.060
	Historical (fed)	0.095	0.087	0.061	0.073
	BUP+TPV/r	0.160	0.241	0.068	0.084
AUC_{0-12h}(h·g/mL)	Historical (fasted)	7.7	4.5	7.4	6.1
	Historical (fed)	7.3	7.3	6.1	5.9
	BUP+TPV/r	5.10	2.92	4.72	3.88

[1]Note: Historical results represent the steady-state ritonavir non-compartmental pharmacokinetics for 32 HIV-negative male and female volunteers receiving TPV/r 500/200 mg bid without and with food (BI Study 1182.100); BUP+TPV/r = buprenorphine/naloxone + TPV/r.