Effect of Telaprevir on the Pharmacokinetics of Buprenorphine in Volunteers on Stable Buprenorphine/Naloxone Maintenance Therapy

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This was an open-label, single-sequence trial in hepatitis C virus-negative volunteers on stable, individualized, buprenorphine maintenance therapy. Telaprevir at 750 mg every 8 h was coadministered with buprenorphine/naloxone (4:1 ratio as sublingual tablets) for 7 days with food. Pharmacokinetic profiles of buprenorphine, norbuprenorphine, and naloxone were measured over the 24-hour dosing interval on day -1 (buprenorphine/naloxone alone, reference) and day 7 of telaprevir coadministration (test). Geometric least-squares mean ratios and associated 90% confidence intervals of treatment ratios (test/reference) were calculated using log-transformed pharmacokinetic parameters. Opioid withdrawal symptoms were evaluated throughout the study (via questionnaires and pupillometry). Pharmacokinetic data were available for 14 and 13 volunteers on day -1 and day 7, respectively. The area under the concentration-time curve (AUC) for buprenorphine was unchanged and the maximum concentration of drug in serum (C_{max}) for buprenorphine, C_{max} and AUC for norbuprenorphine, and C_{max} naloxone were modestly decreased during coadministration with telaprevir. Geometric least-squares mean ratios (90% confidence intervals) for buprenorphine were 0.80 (0.69, 0.93) for the C_{max} and 0.96 (0.84, 1.10) for the AUC from 0 to 24 h (AUC_{0-24}); for norbuprenorphine, values were 0.85 (0.66, 1.09) for C_{max} and 0.91 (0.71, 1.16) for AUC_{0-24} ; for naloxone, the C_{max} was 0.84 (0.62, 1.13). Coadministration of telaprevir did not increase withdrawal symptom frequency, and there were no serious adverse events reported during or after completion of telaprevir coadministration. Results suggest dose adjustment may not be necessary when telaprevir and buprenorphine/naloxone are coadministered.

Telaprevir is an orally administered inhibitor of the nonstructural 3/4A (NS3/4A) protease of the hepatitis C virus (HCV) (10). Telaprevir in combination with pegylated interferon and ribavirin was recently approved in the United States, Canada, European Union, and Japan for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (8, 12, 18, 19).

Buprenorphine is a synthetic narcotic analgesic and a partial opioid agonist that is often prescribed for maintenance therapy in patients with opioid dependence; some of these patients have chronic hepatitis C and may be in need of treatment. In the United States, buprenorphine is commercially available as a sublingual tablet or film (Suboxone) that also contains naloxone, an opioid antagonist (14). Such an opioid agonist and antagonist combination is intended to prevent illicit intravenous use of the formulation. While buprenorphine is rapidly absorbed via the sublingual route, naloxone undergoes poor absorption, resulting in subtherapeutic systemic exposure. However, if the sublingual tablet or film is used illicitly via the intravenous route, the pharmacodynamic effects of buprenorphine can be blocked by the systemic exposure attained for naloxone.

Cytochrome P450 (CYP) enzymes, primarily CYP3A4 and to a lesser extent CYP2D6, have been identified *in vitro* to play a role in the conversion of buprenorphine to norbuprenorphine (13). Norbuprenorphine, an active metabolite, and buprenorphine can undergo glucuronidation, and these metabolites have been identified as major metabolites of buprenorphine in humans and shown to be excreted mainly in urine (2). Telaprevir is both a substrate and inhibitor of CYP3A (6, 8, 18, 19). This suggests that coadministration of telaprevir may increase systemic exposure to buprenorphine because of the drug-drug interaction (DDI). The present study was designed to investigate the effect of telaprevir on the steady-state pharmacokinetic (PK) parameters of buprenor-

phine and norbuprenorphine, to measure opiate withdrawal symptoms, and to determine whether dose adjustment is needed for patients who are concomitantly treated with telaprevir.

MATERIALS AND METHODS

Volunteers. The protocol and informed consent form were approved by the ethics committee at Vince and Associates Clinical Research (Overland Park, KS) and Lifetree Clinical Research (Salt Lake City, UT) in accordance with U.S. procedures. All volunteers provided written informed consent before participating in the study. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations. Eligibility requirements included the following: being male or female (nonchildbearing potential) volunteers between 18 and 64 years of age (inclusive) on the date of consent; having a body mass index (BMI) between 18 and 30 kg/m² (inclusive) and a weight of more than 50 kg at screening visit; receiving once-daily buprenorphine/naloxone maintenance therapy at a stable individualized dose, at a ratio of 4:1, formulated as commercially available sublingual tablets or films (Suboxone), up to a maximum dose of 24 mg/6 mg daily, for at least 2 weeks prior to screening visit.

Study design. This was a phase I, open-label, single-sequence study. See Fig. 1 for a schematic of the study design.

During the run-in period, volunteers received their stable, individualized maintenance dose of buprenorphine/naloxone (individualized dose up to a maximum dose of 24 mg/6 mg daily). Volunteers visited the study site on days -14, -7, -4, and -3 for supervised administration of bu-

Received 13 January 2012 Returned for modification 25 February 2012

Accepted 29 April 2012

Published ahead of print 7 May 2012

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doi:10.1128/AAC.00077-12

FIG 1 Schematic of the study design.

prenorphine/naloxone and scheduled study procedures. On all other days from days -14 to -5 (inclusive), volunteers self-administered their buprenorphine/naloxone daily individualized dose and, for treatment compliance, recorded the date, time, and dose on a diary card. From days -14 to -7, timing of the dose was gradually adjusted, such that by day -7 through day 38, the dose was taken between 6 a.m. and 10 a.m. Volunteers were admitted to the study site on day -2. All volunteers were inpatients when they received telaprevir at 750 mg every 8 h (q8h) for 7 days (days 1 through 7) coadministered with their stable buprenorphine/naloxone maintenance treatment. The ongoing buprenorphine/naloxone dose was not to be changed from screening visit until day 8 (inclusive) unless warranted by the investigator's clinical judgment of the volunteer's safety. Volunteers were discharged on day 8 after supervised administration of the buprenorphine/naloxone individualized dose and completion of scheduled study procedures. All volunteers continued to receive their buprenorphine/naloxone treatment for 31 ± 1 day (day 38 ± 1) subsequent to the last telaprevir dose administration (day 7). After day 8, the dose of buprenorphine/naloxone was allowed to be adjusted if deemed necessary by the investigator.

Volunteers were not to use cocaine, amphetamines and methylenedioxymethamphetamine (MDMA), barbiturates, benzodiazepines, tricyclic antidepressants, methadone or opiates (apart from buprenorphine), or any other drugs of abuse (excluding marijuana) deemed relevant by the investigator or after discussion with the sponsor. Volunteers were to have stopped consumption of herbal medications, dietary supplements (e.g., St. John's Wort, ginkgo biloba, garlic supplements), vitamins, grapefruit or grapefruit juice, apple juice, or orange juice, as well as alcohol and alcohol-containing beverages from screening through the final follow-up visit. Volunteers were advised to consume no more than five 240-ml servings of caffeinated beverages per day starting from screening until admission and were not allowed to consume any caffeinated beverages during the inpatient period. No significant changes in smoking habits were to occur during the study.

Determination of sample size. Intersubject variability (percent coefficient of variation [CV%]) of the buprenorphine/norbuprenorphine maximum concentration of drugs in serum ($C_{\max}$) and area under the time-concentration curve (AUC) ranged from 30% to 45% (14). Assuming an intraindividual variability of 30% for the log-transformed AUC from 0 to 24 h (AUC_{0-24}), $C_{\max}$, and $C_{\min}$ pharmacokinetic (PK) parameters of buprenorphine with and without telaprevir, a sample size of at least 12 volunteers was considered sufficient to estimate the mean ratio to within 80% to 125% of the true mean ratio with 90% confidence. To allow for dropouts, 19 volunteers were enrolled in the study.

Drugs administered. Telaprevir was administered orally in doses of 750 mg q8h in the fed state (30 min after the start of a meal [standard breakfast for morning dose] or snack [for afternoon and evening dose]). During the inpatient period, buprenorphine/naloxone was administered

sublingually within 30 min after the start of breakfast from day -1 to day 8. When coadministered with telaprevir (days 1 through day 7, inclusive), buprenorphine/naloxone was administered immediately after telaprevir administration. The fat content and caloric values of the standard breakfast given on inpatient days -1 through 8 (including the days of intensive PK measurements) were as follows: 21 g of fat, 533 total kcal, 189 kcal from fat, 268 kcal from carbohydrates, and 76 kcal from proteins.

All administrations of telaprevir and buprenorphine/naloxone during inpatient and outpatient visits were supervised by the investigator, and between outpatient visits diary cards were to be used by the volunteers to document treatment compliance. Individual buprenorphine/naloxone dosages ranged from 4/1 to 24/6 mg/day (median, 12 mg/day buprenorphine and 3 mg/day naloxone).

Bioanalytical methods. Plasma concentrations of telaprevir, buprenorphine, naloxone, and norbuprenorphine were determined using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods at Covance Laboratories Inc. (Madison, WI). Detailed bioanalytical procedures for telaprevir have been previously published (7). The assays for buprenorphine, naloxone, and norbuprenorphine were performed by Covance Laboratories Inc., using fully validated methods (details of the methods are proprietary). Briefly, analytes and their internal standards were extracted from human plasma by liquid-liquid extraction (telaprevir) or supported liquid extraction (buprenorphine, naloxone, and norbuprenorphine). After evaporation under nitrogen, the residue was reconstituted and analyzed using LC-MS/MS with selected ion monitoring in the positive ion mode.

The lower limit of quantitation for telaprevir was 2.00 ng/ml, and the calibration curves ranged from 2.00 to 1,000 ng/ml for the low curve method and 20.0 to 5,000 ng/ml for the high curve method. The lower limit of quantitation for buprenorphine and norbuprenorphine was 50.0 pg/ml, and the calibration curve ranged from 50.0 to 2,500 pg/ml. The lower limit of quantitation for naloxone was 5.00 pg/ml, and the calibration curve ranged from 5.00 to 500 pg/ml. The inter- and intrarun variabilities were $\leq 15\%$.

Pharmacokinetic analyses. Blood samples obtained to determine buprenorphine and norbuprenorphine plasma C_{trough} values were collected predose on days -4 through -2 (inclusive), days 1 to 6 (inclusive), day 14 ± 1 , day 21 ± 1 , day 28 ± 1 , and day 38 ± 1 . Blood samples to determine buprenorphine and norbuprenorphine plasma PK parameters were collected predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, and 24 h after the buprenorphine/naloxone dose on days -1 and 7.

Blood samples to determine naloxone plasma concentrations were collected at 0.5, 1, 1.5, and 2 h after the buprenorphine/naloxone dose on day -1 and day 7.

Blood samples to determine telaprevir plasma C_{trough} values were collected predose on days 1 to 6. Blood samples to determine telaprevir

plasma PK parameters were collected predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 h after the morning dose of telaprevir on day 7.

PK analyses were carried out using WinNonlin version 5.3 (Pharsight Corporation, Mountain View, CA). PK parameters were determined using standard noncompartmental methods.

PK parameters were estimated for buprenorphine, norbuprenorphine, and telaprevir. $C_{\max}$ and the time to maximum drug concentration in the serum ($T_{\max}$) were the only parameters for naloxone PK evaluation.

In general, the following procedures were utilized for computation of the AUC: (i) the AUC was computed using the linear trapezoidal rule between increasing drug concentrations and the logarithmic trapezoidal rule between decreasing drug concentrations; (ii) at least 4 quantifiable concentration-time values were available to compute the AUC; (iii) the AUC_{τ} was computed as the cumulative AUC to the time (τ), where τ was a dosing interval (i.e., τ of 24 h for buprenorphine-norbuprenorphine with naloxone; τ of 8 h for telaprevir). If the concentration level at the τ time was missing or below the limit of quantitation, then the AUC_{τ} could be estimated to the last quantifiable concentration.

Analysis of variance (ANOVA) was performed with the SAS (version 9.2 or later; SAS Institute, Cary, NC) PROC MIXED function on log-transformed variables with a fixed effect for period and subject fitted as a random effect. The 90% confidence intervals (CIs) were calculated for the ratios of geometric least-squares means (GLSMR) of $C_{\max}$ and AUC. No significant drug interaction was concluded if the 90% CI for the ratios of the 2 treatments was within the no-effect range of 0.80 to 1.25 (4).

Additionally, a separate statistical PK analysis was conducted that included only volunteers who completed the coadministration period ($n = 13$). Because the analysis gave similar results as for a volunteer who discontinued on day 6 of the coadministration period, only data for the analyses of volunteers who entered the run-in period on day -1 ($n = 14$) are reported herein.

A separate statistical PK analysis stratified by buprenorphine/naloxone dose level, grouped into either the lower dose group (4/1 or 8/2 mg/day; $n = 6$) or higher dose group (12/3, 20/5, or 24/6 mg/day; $n = 8$) was also performed. The GLSM ratios of PK parameters obtained were comparable across groups and with the value obtained for all groups (see Tables 1, 2, and 3, below), although 90% CIs were wider due to the smaller number of volunteers analyzed per group. For example, for the buprenorphine AUC_{0-24} , the GLSM ratio (90% CI) for the lower dose group was 1.05 (0.793, 1.79; $n = 6$) and for the higher dose group it was 0.900 (0.769, 1.05; $n = 8$). When dose group (described as above) and interaction of dose group and treatment term were added to the linear mixed-effects model, neither the dose group nor the dose group and treatment interaction term was significant. Thus, the effect of telaprevir on the buprenorphine AUC_{0-24} was minimal regardless of dose of buprenorphine-naloxone given within this study. Similar conclusions were made for the other PK parameters analyzed in this study (data not shown).

Pharmacodynamic evaluations. The following pharmacodynamic (PD) analyses were performed to monitor for symptoms of withdrawal and/or subjective changes in desire for drugs: the clinical opiate withdrawal scale (COWS) (16, 20), desires for drug questionnaire (DDQ) (5), and pupillometry. COWS assessments evaluate withdrawal symptoms based on the following parameters: resting pulse rate, sweating, restlessness, pupil size, bone or joint aches, runny nose or tearing, gastrointestinal upset, tremor, yawning, anxiety or irritability, and gooseflesh skin. The DDQ is a subjective measurement of a volunteer's desire for drugs, distinct from a volunteer's need for the drug to prevent unpleasant physical symptoms, and may not correlate with withdrawal symptoms. Pupillometry is an insensitive method for detecting mild withdrawal symptoms, but increased pupil size is associated with severe withdrawal symptoms. For pupillometry assessments, resting pupil diameter was assessed with a validated pupillograph.

For PD variables, the baseline value for the buprenorphine/naloxone treatment administered during the run-in period was defined as the day -7 value. The baseline value for the buprenorphine/naloxone and tel-

aprevir coadministration period and buprenorphine/naloxone follow-up period was defined as the day 1 predose value.

As with the PK data, an additional analysis of the PD data that included only the 13 volunteers who completed the coadministration period showed no meaningful difference from that for all volunteers who entered the run-in period at day -1. For these reasons, only data for all volunteers who entered the run-in period on day -1 are presented herein.

Safety assessments and analysis. Adverse events, vital signs and electrocardiograms (ECGs), clinical chemistry, hematology, and physical examinations were monitored during this clinical study.

Safety analyses were presented for three treatment periods: the run-in period, which included the time from first dose on day -14 through day 1 predose; the coadministration/follow-up period, which included the time from the first dose on day 1 up to but not including the day 14 $\pm$ 1 safety follow-up; the extended follow-up period, which included the time starting at the day 14 $\pm$ 1 safety follow-up through the end of the follow-up period.

RESULTS

Volunteer disposition. Nineteen volunteers enrolled in this study and were included in safety assessments: 16 completed the run-in period, 14 completed the telaprevir and buprenorphine/naloxone coadministration period, and 13 completed both follow-up visits at days 14 and 38. Six volunteers prematurely discontinued study drug treatment: 4 volunteers prematurely discontinued (on days -14, -2, 5, and 28) due to positive drug tests, and 2 volunteers withdrew consent (on days -13 and 6).

Sixteen volunteers received at least one dose of telaprevir during the coadministration period from day 1 to day 7. Two of these volunteers were not included in the PK analysis: one volunteer was withdrawn (on day 5) due to a positive drug test, and the other needed to adjust their buprenorphine-naloxone dose (on days -1 and day 1) based on adverse events that suggested withdrawal symptoms and therefore was not considered to be on stable buprenorphine/naloxone therapy. Another volunteer withdrew consent on day 6 but was included in the PK analysis. Thus, the PK analysis set included 14 volunteers on day 1 and 13 volunteers on day 7.

Seventeen volunteers were assessed for PD responses on day -7 (baseline values for the run-in period) and 16 were assessed on day -1. For the coadministration and follow-up periods, 16 volunteers were assessed for PD responses on day 1 (predose, baseline), and responses were compared 4 h postdose on days 1, 2, and 3 ($n = 16$), 4 h postdose on day 7 ($n = 14$), and predose on days 14 ($n = 14$), 21 ($n = 14$), 28 ($n = 13$), and 38 ($n = 13$).

All volunteers self-identified as white by race. Overall, the mean (and standard deviation [SD]) age of volunteers was 32.3 (12.01) years, mean (SD) height was 179.0 (8.20) cm, mean (SD) weight was 79.5 (11.70) kg, and mean (SD) BMI was 24.8 (3.00) kg/m². The majority of the volunteers (17) were male, and 2 were female.

Effect of telaprevir on pharmacokinetics of buprenorphine. The mean plasma buprenorphine concentration versus time profiles alone or when it was coadministered with steady-state telaprevir are shown in Fig. 2, and the PK parameters are summarized in Table 1.

Upon coadministration with telaprevir, the area under the curve during the dosing period (AUC_{0-24}) for buprenorphine was not affected; $C_{\max}$ was about 20% lower, and $C_{\min}$ was about 6% higher. The median (range) $T_{\max}$ of buprenorphine was similar,

FIG 2 Mean (SE) plasma concentration-time profiles of buprenorphine after administration of buprenorphine/naloxone with and without telaprevir ($n = 14$ without telaprevir; $n = 13$ with telaprevir).

with (1.50 h [1.02, 4.00]) or without (1.75 h [1.00, 2.50]) coadministration of telaprevir.

The mean C_{trough} of buprenorphine declined during the run-in period from day -4 to day -2 but remained stable from day -1 to day 7 (data not shown). Thus, the concentrations of buprenorphine were considered to have reached steady state at day 7 when intensive PK measurements were taken for PK assessment. There was a trend of increasing buprenorphine C_{trough} values during the follow-up period from day 8 to day 14 (data not shown); however, the variability around the mean C_{trough} during the follow-up period was large.

Effect of telaprevir on pharmacokinetics of norbuprenorphine. The mean plasma norbuprenorphine concentration versus time profiles alone or when norbuprenorphine was coadministered with steady-state telaprevir are shown in Fig. 3, and the PK parameters are summarized in Table 2.

Upon coadministration with telaprevir, the AUC_{0-24} for norbuprenorphine was about 9% lower; C_{max} was about 15% lower, and C_{min} was about 9% lower (Table 2). The median (range) T_{max} of norbuprenorphine increased from 2.78 (1.50, 12.0) hours to 7.98 (1.00, 24.0) hours upon coadministration of telaprevir (Table 2).

The ratios of C_{max} ($R_{Cmax, m}$) and AUC_{0-24} ($R_{AUC, m}$) for the metabolite of buprenorphine, norbuprenorphine, to the parent were similar following buprenorphine/naloxone administration

FIG 3 Mean (SE) plasma concentration-time profiles of norbuprenorphine after administration of buprenorphine/naloxone with and without telaprevir ($n = 14$ without telaprevir; $n = 13$ with telaprevir).

alone compared to buprenorphine/naloxone and telaprevir coadministration (Table 2).

Norbuprenorphine C_{trough} (predose) concentrations fluctuated widely but were relatively stable from day 4 to day 7 of telaprevir coadministration with buprenorphine/naloxone (data not shown). Thus, the concentrations of norbuprenorphine were considered to have reached steady state at day 7, when intensive measurements were taken for PK assessment.

Effects of telaprevir on pharmacokinetics of naloxone. The mean plasma naloxone concentration versus time profiles alone or when coadministered with steady-state telaprevir are shown in Fig. 4, and the PK parameters are summarized in Table 3. Upon coadministration with telaprevir, the naloxone C_{max} was 16% lower than buprenorphine/naloxone dosed alone; however, the variability (as seen from the standard deviations around the mean) was large.

Plasma pharmacokinetics of telaprevir. A comparison of predose concentrations of telaprevir on days 2 through day 7 indicated that the steady state was maintained during these days. The telaprevir C_{max} was 3,051 ng/ml, and the AUC_{0-8} was 19,074 h · ng/ml following administration of telaprevir at 750 mg q8h on day 7.

TABLE 1 Buprenorphine PK parameters after administration of buprenorphine/naloxone with and without telaprevir

PK parameter	Mean (SD) value		GLS mean ratio ^b (90% CI)
	Without telaprevir (day -1) ($n = 14$)	With telaprevir (day 7) ($n = 13$)	
AUC_{0-24} (pg · h/ml)	57,500 (43,800)	53,200 (30,600)	0.962 (0.844, 1.10)
C_{max} (pg/ml)	7,510 (6,210)	5,620 (3,380)	0.800 (0.690, 0.927)
C_{min} (pg/ml)	1,070 (830)	1,086 (707)	1.06 (0.868, 1.30)
T_{max} (h) ^a	1.75 (1.00, 2.50)	1.50 (1.02, 4.00)	NA ^c

^a Median (minimum, maximum) values are reported.
^b The GLSM ratio is the value of the analyte during coadministration with telaprevir (day 7) over the value for the analyte when buprenorphine/naloxone was administered without telaprevir (day -1).
^c NA, not available.

TABLE 2 Norbuprenorphine PK parameters after administration of buprenorphine/naloxone with and without telaprevir

PK parameter	Mean (SD) value		GLSM ratio ^d (90% CI)
	Without telaprevir (day -1; $n = 14$)	With telaprevir (day 7; $n = 13$)	
AUC_{0-24} (pg · h/ml)	83,700 (75,300)	83,000 (75,900)	0.907 (0.707, 1.16)
C_{max} (pg/ml)	4,760 (4,260)	4,200 (3,610)	0.845 (0.657, 1.09)
C_{min} (pg/ml)	2,570 (2,190)	2,600 (2,440)	0.913 (0.665, 1.25)
T_{max} (h) ^a	2.78 (1.50, 12.0)	7.98 (1.00, 24.0)	NA ^c
$R_{AUC, m}$ ^b	1.52 (0.72)	1.50 (0.82)	NA
$R_{Cmax, m}$ ^c	0.71 (0.39)	0.74 (0.36)	NA

^a Median (minimum, maximum) values are reported.
^b Ratio of the AUC_{0-24} values for norbuprenorphine and buprenorphine.
^c Ratio of the C_{max} values for norbuprenorphine and buprenorphine.
^d GLSM ratio is the value of analyte during coadministration with telaprevir (day 7) over the value of analyte when buprenorphine/naloxone was administered without telaprevir (day -1).
^e NA, not available.

FIG 4 Mean (SE) plasma concentration-time profiles of naloxone after administration of buprenorphine/naloxone with and without telaprevir ($n = 14$ without telaprevir; $n = 13$ with telaprevir).

Pharmacodynamics based on COWS data. No volunteer had moderate or severe withdrawal symptoms as assessed by COWS throughout the study.

During the run-in period, 1 volunteer had mild withdrawal symptoms on days -1 and 1 (COWS score ranging from 6 to 8) accompanied by adverse events of mild flushing, mild hyperhidrosis, and mild nausea on day -1 . Consequently, the doses of buprenorphine/naloxone were adjusted for this volunteer from 12 mg/3 mg to 16 mg/4 mg on day -1 , with a further increase in doses to 18 mg/4.5 mg on day 1 . This volunteer was not included in the PK analysis set but was allowed to continue in the study, as their COWS scores were normal (between 0 and 4) for the rest of the study.

Another volunteer had mild withdrawal symptoms during the run-in period (COWS score of 8 on day -7 and COWS score of 6 on day -2). No further withdrawal symptoms were reported for this volunteer.

During the follow-up period, 1 volunteer (001010) showed mild withdrawal symptoms (COWS score of 5 on day 14). No further withdrawal symptoms were reported for this volunteer throughout the study.

All other volunteers had normal COWS scores (COWS scores between 0 and 4) throughout the study.

Pharmacodynamics based on the DDQ. For questions relevant to desire and intention, which reflect craving for drugs, a median score of 0 for all volunteers was observed throughout the study, including the time around the C_{max} of telaprevir (i.e., 4 h postdose during the telaprevir and buprenorphine/naloxone coadministration period). Results from the other DDQ assessments (i.e., negative reinforcement and self-control) also did not detect any meaningful differences from baseline values during the period of coadministration with telaprevir. These results show that coadministration with telaprevir did not affect a volunteer's desire for drugs while on stable buprenorphine/naloxone treatment.

Pharmacodynamics based on pupillometry. Larger decreases in pupil diameters were observed when pupillometry was performed 4 h after coadministration of telaprevir and buprenorphine/naloxone (median range, -1.40 to -0.85 mm) than with administration of buprenorphine/naloxone alone at 4 h postdose

on day -1 (medians of -0.60 mm for left eye and -0.30 mm for right eye). However, the values at 4 h after administration of telaprevir on day 7 were similar to those observed at the safety follow-up visits on days 14 and 38 and so were unlikely to be caused by telaprevir.

Safety. There were no reports of serious or severe adverse events, and no volunteers discontinued the study due to adverse events.

The most frequent adverse events that occurred in at least 2 volunteers during the telaprevir and buprenorphine/naloxone coadministration and follow-up periods were headache (4 out of 16 volunteers) and nausea and abdominal discomfort (each occurred in 2 out of 16 volunteers). Headache (5 out of 19 volunteers) and nausea (2 out of 19 volunteers) also occurred during the buprenorphine/naloxone run-in period. The majority of the volunteers had adverse events that were considered mild in severity. Two out of 19 volunteers had adverse events that were considered moderate in severity; 1 volunteer had a moderate toothache in the run-in period, and 1 volunteer had moderate axillary pain and moderate eczema that developed into a mild rash during the telaprevir and buprenorphine/naloxone coadministration/follow-up period. All adverse events resolved by the end of the study.

One volunteer had adverse events related to withdrawal (mild flushing, mild hyperhidrosis, and mild nausea) on day -1 , and so the doses of buprenorphine/naloxone were adjusted for this volunteer from 12 mg/3 mg to 16 mg/4 mg on day -1 , with a further increase in doses to 18 mg/4.5 mg on day 1 . Thereafter, this volunteer did not show symptoms of withdrawal throughout the study.

DISCUSSION

This study was designed to investigate the effect of telaprevir on the steady-state PK parameters of buprenorphine in volunteers on stable buprenorphine/naloxone therapy.

Total exposure (the AUC_{0-24}) to buprenorphine was not changed upon coadministration with telaprevir (GLSMR [90% CI], 0.96 [0.84, 1.10]). The buprenorphine C_{min} was slightly increased (GLSMR [90% CI], 1.06 [0.87, 1.30]), while the C_{max} for buprenorphine (GLSMR [90% CI], 0.80 [0.69, 0.93]) was slightly decreased upon coadministration of telaprevir. The C_{max} (GLSMR [90% CI], 0.85 [0.66, 1.09]), C_{min} (GLSMR [90% CI], 0.91 [0.67, 1.25]), and AUC_{0-24} (GLSMR [90% CI], 0.91 [0.71, 1.16]) for norbuprenorphine were all slightly decreased upon coadministration of telaprevir. Consistent with the small changes in buprenorphine and norbuprenorphine PK parameters compared to the overall variability in these parameters, no clinically relevant phar-

TABLE 3 Naloxone PK parameters after administration of buprenorphine/naloxone with and without telaprevir

PK parameter	Without telaprevir (day -1 ; $n = 14$)	With telaprevir (day 7; $n = 13$)	GLSM ratio ^c (90% CI)
C_{max} (pg/mL) ^a	281 (256)	213 (163)	0.835 (0.617, 1.13)
T_{max} (h) ^b	0.50 (0.50, 1.50)	1.00 (0.45, 2.00)	NA ^d

^a Mean (SD) values are reported.

^b Median (minimum, maximum) values are reported.

^c The GLSM ratio is the value of analyte during coadministration with telaprevir (day 7) over the value of analyte when buprenorphine/naloxone was administered without telaprevir (day -1).

^d NA, not available.

macodynamic effects were detected, as measured by median COWS and DDQ scores. Therefore, the reductions in $C_{\max}$ of buprenorphine and norbuprenorphine and in the AUC of norbuprenorphine were considered not clinically relevant.

Buprenorphine has significant effects on pain tolerance, sedation, and other psychomotor performances, such as the digit symbol substitution test (DSST) score. The onset of the PD effect is usually delayed following the peak drug concentrations, and the effects may remain up to the elimination phase of buprenorphine, possibly due to the high affinity of buprenorphine for the μ -opioid receptors. This may explain the lack of withdrawal symptoms despite the decreased peak concentrations of buprenorphine (3, 9). The lack of withdrawal symptoms associated with decreased buprenorphine exposure was also observed in other drug interaction studies between buprenorphine/naloxone and antiretroviral agents (11).

Although the naloxone $C_{\max}$ was decreased when telaprevir was coadministered, the degree of decrease was quite modest compared to the large variability in naloxone concentrations. Naloxone has no clinically significant effect when administered by the sublingual route. It is an opioid antagonist, and it is added in the sublingual formulation of buprenorphine to prevent opioid effects upon injection of buprenorphine (14). Naloxone is administered in a 1:4 ratio to buprenorphine, and the overall naloxone exposure is very low; therefore, the small effect of telaprevir on the naloxone $C_{\max}$ is unlikely to be clinically significant.

In the current study, pupil diameters were decreased more with telaprevir coadministration than with buprenorphine/naloxone administration alone. The observations cannot be explained by the decreased concentrations of buprenorphine or norbuprenorphine, since these would result in increased pupil diameters. However, potentially better adherence with these medications during inpatient telaprevir coadministration may have resulted in more consistent plasma drug concentrations and may have been a factor in the observed effects. Additionally, the values at 4 h after administration of telaprevir on day 7 were similar to those observed at the safety follow-up visits on days 14 and 38 and were therefore unlikely to be caused by telaprevir.

The ratios of the $C_{\max}$ and AUC_{0-24} for norbuprenorphine to the parent, buprenorphine, were similar following buprenorphine-naloxone administration alone compared to buprenorphine/naloxone and telaprevir coadministration. All three analytes, buprenorphine, norbuprenorphine, and naloxone, had similar magnitudes of reduction in the $C_{\max}$. This further indicated that the proportion of buprenorphine metabolism to norbuprenorphine was not changed. As telaprevir is a strong inhibitor of CYP3A, these results were somewhat unexpected. Buprenorphine is metabolized by CYP3A and CYP2C8, as well as non-CYP-mediated pathways (1), and it has been suggested that other metabolic pathways, such as glucuronidation, become the predominant pathway for buprenorphine clearance when CYP3A is inhibited (11). Variable results have been observed with other CYP3A inhibitors. When coadministered with darunavir-ritonavir, buprenorphine exposure was unchanged while norbuprenorphine exposures increased significantly (15), whereas in the presence of delavirdine, buprenorphine exposure increased significantly while norbuprenorphine exposure decreased (11).

Telaprevir may slightly affect the overall rate of absorption of the buprenorphine/naloxone sublingual formulation. Although buprenorphine/naloxone was administered sublin-

gually, buprenorphine and norbuprenorphine may be absorbed or reabsorbed by enterohepatic recirculation (11), which was observed in the current study, based on individual and mean drug concentration time profiles. The median $T_{\max}$ of norbuprenorphine shifted significantly from 2.78 to 7.98 h in the current study. This has also been reported previously (5). Since norbuprenorphine has much lower activity, this $T_{\max}$ change is unlikely to be of clinical significance. The reason for this delay in $T_{\max}$ is not clear; however, since telaprevir can inhibit P-glycoprotein (18), it may affect the biliary elimination of buprenorphine and norbuprenorphine glucuronides and the subsequent reabsorption process of buprenorphine and norbuprenorphine.

The current study also monitored the C_{trough} (predose) levels of buprenorphine and norbuprenorphine. The C_{trough} levels varied greatly, and there was a trend for higher trough concentrations of buprenorphine during the run-in and follow-up periods. However, the day -1 to day 8 predose levels were stable. This suggests that C_{trough} levels were not affected by telaprevir coadministration, but rather by the variability in the dosing time by volunteers. Based on review of drug administration records, the study drug was dosed within the window required in the protocol: ± 30 min in the outpatient setting and ± 5 min in the inpatient setting. Because of the long elimination half-life of buprenorphine, such small changes in the windows of administration are unlikely to affect trough levels; however, it is possible that the self-reported times of administration by volunteers during outpatient visits may not have been accurate. Higher naloxone levels, along with higher buprenorphine levels, could also have been due to intravenous administration by some of the volunteers, although this cannot be confirmed. The study drugs were taken with food in the inpatient setting but without food restrictions in the outpatient setting. These factors may have impacted the buprenorphine and norbuprenorphine trough concentrations. There were no withdrawal symptoms or other pharmacodynamic or adverse effects associated with the fluctuations in the C_{trough} levels in outpatient settings.

The telaprevir PK measures in the current study ($C_{\max}$, 3,050 ng/ml; AUC_{0-8} , 19,100 ng · h/ml) were similar to those reported in study VX-950-TiDP24-C124 (17), where the mean AUC_{0-8} for telaprevir was approximately 18,900 h · ng/ml to 19,500 h · ng/ml, and the mean $C_{\max}$ was approximately 3,060 ng/ml to 3,100 ng/ml. These results suggest that telaprevir exposure was not affected by coadministration with buprenorphine/naloxone.

Coadministration of telaprevir with buprenorphine-naloxone was well-tolerated in volunteers on stable buprenorphine/naloxone maintenance therapy. No serious adverse events occurred throughout the study, and no adverse events led to premature discontinuation of study drug treatment. The majority of the volunteers had adverse events that were considered mild in severity: 1 volunteer had severe headache during the buprenorphine/naloxone run-in period, 1 volunteer had a moderate toothache in the run-in period, and 1 volunteer had moderate axillary pain, moderate eczema, and mild rash during the telaprevir and buprenorphine/naloxone coadministration period. Rashes have previously been associated with telaprevir administration (8, 12, 18, 19).

These results suggest that dose adjustments may not be necessary when telaprevir and buprenorphine/naloxone are coadministered.

ACKNOWLEDGMENTS

This study was supported by Vertex Pharmaceuticals Incorporated and Janssen Infectious Diseases BVBA (formerly Tibotec BVBA). X.L., J.T., F.S., and V.G. are employees and stock owners of Vertex, and R.V.H. is an employee of Janssen Pharmaceuticals and stock owner of Johnson & Johnson.

We acknowledge the contributions of Vince and Associates Clinical Research (Overland Park, KS) and Lifetree Clinical Research (Salt Lake City, UT), the study sites for this study; Lauren Alexander, for study coordination and support; and Jaya Vatsyayan and Megan Melch for help in the preparation of the manuscript. Susan Wu and Kristin Stephan provided manuscript and editorial coordination support, and Jonathan Kirk provided graphical design support. All of these support personnel are employees and stock owners of Vertex Pharmaceuticals Incorporated.

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