Pharmacokinetic interaction between darunavir in combination with low-dose ritonavir and buprenorphine/naloxone

Sekar V1, Tomaka F2, Meyvisch P4, De Paew M3, Spinosa-Guzman S2, Vangeneugden T1, Hoetelmans R2
1Tibotec Inc., Yardley, PA, USA; 2Tibotec BVBA, Mechelen, Belgium

Introduction

- Substance abuse is a common comorbidity among HIV-infected subjects and, untreated, can pose serious HIV treatment challenges.1 The most effective treatment for opioid dependence is opioid maintenance therapy, which helps to reduce cravings and prevent the use of illicit substances.
- Buprenorphine (BUP) is a partial opioid receptor agonist, and naloxone (NLX) is an opioid antagonist. In combination, BUP and NLX are an effective maintenance strategy for opioid dependence.2
- The HIV-1 protease inhibitor darunavir (DRV) in combination with low-dose ritonavir (DRV/RTV) is an approved treatment for treatment-naive, HIV-1-infected adults (900/100 mg in the USA, Europe and other countries) and treatment-experienced, HIV-1-infected patients aged ≥ 46 years (bodyweight-based dosing) in the USA and the EU.3
- Pharmacokinetic drug-drug interactions between BUP/NLX and DRV/RTV might be expected based on their hepatic metabolism. All of these drugs are metabolized by cytochrome P450 (CYP) enzymes.4 DRV is a potent and main, and active, metabolite of BUP is norbuprenorphine (norBUP).5 RTV and DRV inhibit of CYP3A4 metabolism, with RTV being the most potent.6
- The primary objective of this study was to investigate the effect of multiple doses of DRV on the steady-state pharmacokinetics of BUP, norBUP and NLX. Secondary objectives included assessing the effect of BUP/NLX on the pharmacokinetics of DRV and RTV, evaluating pharmacodynamic effects (opioid withdrawal or excess), and determining the short-term safety and tolerability.

Methods

Study design

- TAM11-TDP1-C17 V1 was a Phase I, open-label, add-on trial in treatment-naive adults in the USA, Europe and in many other countries and treatment-experienced, HIV-1-infected, adult patients aged ≥ 46 years (bodyweight-based dosing) in the USA and the EU.
- Thirty-seven volunteers were screened; 19 were eligible, and two were discontinued to start. Seventeen volunteers on stable BUP/NLX received DRV/RTV (six discontinued post to follow-up), and 11 completed the study.

Pharmacokinetics of BUP

- Mean (± SD) plasma concentration of norBUP (ng/mL) shown in Table 1. Exposure to DRV and RTV in the presence of BUP/NLX and DRV/r 600/100mg bid (Day 7).

Results

- Thirty-seven volunteers were screened; 19 were eligible, and two were discontinued to start. Seventeen volunteers on stable BUP/NLX received DRV/RTV (six discontinued post to follow-up), and 11 completed the study.
- Most volunteers were male (12/17, 71%), with a median age of 45 years (range: 21–53 years). All (except one) were Caucasian or Black (eight, 47% each), and all were smokers (except one).
- BUP/NLX maintenance therapy was either 164mg (n=10) or 82mg (n=12) qd.

Pharmacokinetics of DRV and RTV

- The combination of BUP/NLX and DRV/r was generally well tolerated. However, nausea was the most common AE during the trial, occurring in eight volunteers (47%) when BUP/NLX was coadministered with DRV and in two volunteers (11.8%) during BUP/NLX alone.
- During coadministration, physical examinations and questionnaires showed that volunteers experienced either no or mild opiate withdrawal symptoms, and no-to-slight opiate excess symptoms.
- No BUP/NLX dose adjustments were necessary during continued treatment with BUP/NLX and DRV/RTV for any volunteer.

Conclusions

- Based on the LSM ratios, mean values of norBUP C20, Cmax and AUC0–24h increased by 8%, 71%, 36% and 47%, respectively, with DRV compared to BUP/NLX alone (Table 2). The inter-individual variability was comparable between treatments for C20, Cmax and AUC0–24h, and CV 87–102% for non-normalized data and 61–70% when the data were normalized for dosing.

Pharmacokinetics of NLX

- Mean plasma concentration-time curves of NLX were comparable when BUP/NLX was administered with DRV/RTV (Figure 3). DRV/RTV coadministration with BUP/NLX had no apparent influence on NLX pharmacokinetic parameters (data not shown).

Table 3. Pharmacokinetic results of DRV and RTV after coadministration of DRV/RTV and BUP/NLX 600/100mg bid (Day 7).

References