Cocktail study to investigate the in vivo drug interaction potential of darunavir coadministered with low-dose ritonavir (DRV/r; RTV) on cytochrome P450 enzymes 2D6, 2C9 and 2C19

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Introduction

Darunavir (DRV; TMC114) is a protease inhibitor (PI), with potential activity both against wild-type and drug-resistant HIV strains.1–3

DRV coadministered with low-dose RTV 600/100mg bid is approved in many countries including the USA and in Europe for treatment of advanced HIV-experienced patients.4–5 Both DRV and RTV are known substrates for cytochrome P450 (CYP) enzymes, and are potential substrates for multiple CYP isoforms, which are involved in the metabolic pathways of complex pharmaceuticals.6–7 Coadministration of DRV increases both the oral bioavailability of DRV and systemic exposure to RTV.8–9

The concomitant use of other drugs that treat coexisting diseases is common among HIV-positive patients, thus an evaluation of potential drug-drug interactions (DDIs) is important.9–10

The present study (TMC114-117) was designed to determine the effect of DRV/r on the single dose pharmacokinetics of a cocktail of representative probes of CYP enzymes (CYP2C9, CYP2C19 and CYP3A4) in healthy, non-smoking volunteers.

Methods

Study design

TMC114-117 was a randomized, open-label study, two-treatment, crossover, Phase I study of healthy volunteers with normal renal and hepatic function, able to comply with all study requirements.11–12

The drug interaction potential of DRV/r was investigated using a drug cocktail with several well-selected probes, known to be substrates for CYP2C9 (S-warfarin), CYP3A4 (dextromethorphan) and CYP2C19 (omeprazole).13

The single-dose pharmacokinetics of each probe (S-warfarin, dextromethorphan and omeprazole) and its main metabolite (7-OH-s-warfarin, dextrorphan and 5-OH-omeprazole, respectively) were measured in the presence and absence of multiple doses of DRV/r.

Eligible volunteers were healthy, male or female, aged 18–55 years, with a body mass index of 18–30kg/m². Major exclusion criteria for all volunteers included a positive HIV, hepatitis B or C screening test, presence of a major comorbidity or condition (e.g. diabetes, cancer, history of ileostomy or colostomy, history of allergy to any study drug or any component of the drug cocktail).11–12

All volunteers were randomized to two treatment sequences; Treatment A followed by Treatment B or Treatment B followed by Treatment A. Each session was separated by a wash-out period of at least 14 days.

Pharmacokinetic (PK) and safety evaluation

CYP2C9 plasma concentrations of S-warfarin, dextromethorphan and omeprazole and their metabolites were determined on Day 1 of Treatment A and on Day 7 of Treatment B.11–12

The drug levels were measured at the trough concentrations (C₀) and at the maximum plasma concentration (Cmax) after a single dose of vitamin K (10mg) to reverse the pharmacodynamic effects of warfarin.5

Safety and tolerability were assessed throughout the study.

Results

Volunteer disposition

Of 37 volunteers screened, 12 were randomized to receive treatment and completed the study.11–12

Baseline demographics were generally well-balanced across treatments.

Effect of DRV/r on CYP2C9: S-warfarin and 7-OH-S-warfarin

S-warfarin is predominantly metabolized by CYP2C9 to 3-OH-s-warfarin (C₀ and Cmax).13

The induced effect of CYP2C9 observed in this trial can be attributed to the presence of low-dose RTV and is consistent with observations from literature for DRV and other boosted PIs.13

The paremeters (PH) ratio of S-warfarin and 7-OH-S-warfarin was decreased by 26% (Table 1 and Figure 2), suggesting an increase in CYP2C9 activity.

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In the presence of DRV/r, the PHmax,AUCratio of omeprazole and 5-OH-omeprazole increased by 31% (Table 1), suggesting an increase in CYP2C9 activity.13

The induction effect on CYP2C9 can be attributed to the presence of RTV which has been reported to induce this enzyme.13


day 7 PK parameter mean ± SD (Treatment B) (n=12) (90% CI)

| C₀, ng/mL | 15,776 ± 14,730 | 12,038 ± 12,140 | 0.80 (0.71–0.90) |
| Cmax, ng/mL | 24,600 ± 19,030 | 16,890 ± 13,870 | 0.84 (0.76–0.94) |
| AUC₀–∞, h/mL | 74,868 ± 41,550 | 61,100 ± 39,570 | 0.65 (0.59–0.71) |

**Table 2. PK results of dextromethorphan and dextrorphan after administration of cocktail alone and in combination with DRV/600/100mg bid.**

Effect of DRV/r on CYP3A4: dextromethorphan and dextrorphan

Dextromethorphan is a probe substrate of CYP3A4 and dextrorphan is a major metabolite.14

Due to a significant increase in dextromethorphan exposure, the dose of dextromethorphan was reduced by 50%.

In the presence of DRV/r, the PHmax,AUC ratio of dextromethorphan and dextrorphan increased by approximately three-fold (Table 2 and Figure 2).13

Although the exposure to dextromethorphan increased, the exposure to dextrorphan (formed via CYP3A4 mediated reduction) remained unchanged (Table 2).13

In addition to inhibition of the CYP2C9 enzyme, this may suggest inhibition of an alternate metabolic pathway such as CYP3A4, consistent with the interaction profile of DRV and RTV, which are both CYP3A4 inhibitors.13

Safety and tolerability

Overall, nine (75%) volunteers reported at least one AE (45%) reported at least one AE during treatment with DRV alone, four (33%) with the cocktail and six (50%) with DRV/r.11–12

The number of volunteers reporting one or more AEs considered at least possibly related to DRV or the drug cocktail was seven (58%) and eight (67%), respectively.11–12

No grade 3 or 4 AEs, serious AEs or AEs leading to discontinuation were reported.11–12

No clinically relevant changes in laboratory safety assessments were observed.11–12

Conclusions

Coadministration of a drug cocktail of CYP probes and DRV resulted in induction or inhibition of various CYP enzyme activities.11–12

The observed induction effects on CYP2C9 and CYP3A4 activities and the increase in dextromethorphan exposure may be utilised to the coadministration of low-dose RTV and is consistent with reports on the interaction profile of RTV.11–12

In addition to inhibition of the CYP3A4 enzyme, the increase in dextromethorphan exposure may be attributable to the inhibition of an alternate metabolic pathway such as CYP3A4 which would be consistent with the interaction profile of DRV and RTV, both of which are CYP3A4 inhibitors.13

The current study demonstrated that DRV/600/100mg bid alone or added to a cocktail of CYP probes is generally well-tolerated.

References