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 potent activity against both wild-type and drug-resistant HIV strains.[1]
- DRV coadministered with low-dose RTV 600/100mg bid is approved in many countries including the USA[2] and in Europe[3] for HIV treatment of antiretroviral (ARV)-experienced patients.
- Both DRV and RTV are known substrates for cytochrome P450 (CYP) enzymes, and undergo predominantly hepatic metabolism.[4,5] Coadministration of DRV/r increases both the oral bioavailability of DRV and systemic exposure to DRV.[4]
- The concomitant use of other drugs to treat coexisting diseases is common among HIV-infected patients, therefore evaluating potential interactions between ARVs and other drugs is important.
- The present study (TMC114-C173) 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 CYP2D6) in healthy, HIV-negative volunteers.

Methods

Study design

- TMC114-C173 was an open-label, randomized, two-treatment, crossover, Phase I study conducted in healthy, adult volunteers.
- 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), CYP2D6 (dextromethorphan) and CYP2C19 (omeprazole).
- 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 absence and presence of multiple doses of DRV/r.
- Volunteers were healthy, male or female, aged 18–55 years, with a body mass index of 18–30kg/m^2. Major exclusion criteria for all volunteers included a positive HIV, hepatitis A, B or C screening test; presence of a poor metabolizer genotype (CYP2D6 [*3, *4, *5, *6], 2C9 [*2, *3], and 2C19 [*2, *3, *4, *8]); and history of coagulation or bleeding disorders.
- All volunteers received two treatments
  - Treatment A: single oral dose of the drug cocktail, which consisted of dextromethorphan 30mg, omeprazole 40mg and warfarin 10mg (supplemented with a single dose of vitamin K_1 10mg to reverse the pharmacodynamic effects of warfarin)
  - Treatment B: DRV/r 600/100mg bid for 7 days, with a single oral dose of the drug cocktail on Day 7.
- Volunteers were randomized to one of two treatment sessions: 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

- Plasma concentrations of S-warfarin, dextromethorphan, omeprazole and their metabolites were determined on Day 1 of Treatment A and on Day 7 of Treatment B.
- Descriptive statistics were calculated for the plasma concentrations of DRV, RTV and the compounds in the drug cocktail and their metabolites.
- Statistical analysis was performed for the drug cocktail using PK data obtained on Day 7 of Treatment B as test values and Day 1 of Treatment A as reference values. The least square means (LSM) of the log-transformed primary parameters were estimated with a linear mixed-effects model and a 90% confidence interval (CI) was constructed around the difference between the LSM of test and reference.
- The PK endpoints used to determine drug-metabolizing enzyme activities were
  - CYP2C9: plasma S-warfarin area under the plasma concentration-time curve until the last measured timepoint using linear trapezoidal summation (AUC_{last})
  - CYP2D6: plasma ratio of dextromethorphan to dextrorphan AUC_{last}
  - CYP2C19: plasma ratio of omeprazole to 5-OH-omeprazole AUC_{last}.
- 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.
- 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 into 7-OH-S-warfarin.[6]
- In the presence of DRV/r, S-warfarin AUC_{last} decreased by 21% (Table 1 and Figure 1), suggesting an increase in CYP2C9 activity.
- The induction effect on CYP2C9 observed in this trial can be attributed to the presence of low-dose RTV, and is consistent with observations from literature for RTV and other boosted PIs.[5,7]
- The parent/metabolite (P/M) ratio of S-warfarin and 7-OH-S-warfarin was decreased for both maximum plasma concentration (C_{max}) and AUC_{last} when the cocktail was given in combination with DRV/r (Table 1).

Table 1. PK results of S-warfarin and 7-OH-S-warfarin after administration of cocktail alone and in combination with DRV/r 600/100mg bid.

PK parameter mean ± SD t_{max}: median (range)	Cocktail alone (Treatment A) (n=12)	DRV/r 600/100mg bid + cocktail (Treatment B) (n=12)	LSM ratio (B vs A) (90% CI)
S-warfarin			
C_{max}, ng/mL	383 ± 99	349 ± 75	0.92 (0.86–0.98)
AUC_{last}, ng•h/mL	15,040 ± 6680	11,880 ± 4792	0.79 (0.74–0.86)
t_{max}, hours	3.0 (3.0–6.0)	3.0 (3.0–12.0)	
7-OH-S-warfarin			
C_{max}, ng/mL	30 ± 12	41 ± 15	1.43 (1.24–1.64)
AUC_{last}, ng•h/mL	1494 ± 665	1723 ± 697	1.24 (0.97–1.58)
t_{max}, hours	24.0 (12.0–48.0)	24.0 (6.0–36.0)	
Ratio $C_{max,P/M}$, %	1561 ± 882	994 ± 564	0.64 (0.58–0.72)
Ratio $AUC_{last,P/M}$, %	1552 ± 1676	844 ± 576	0.64 (0.53–0.78)

t_{max} = time to C_{max}; SD = standard deviation

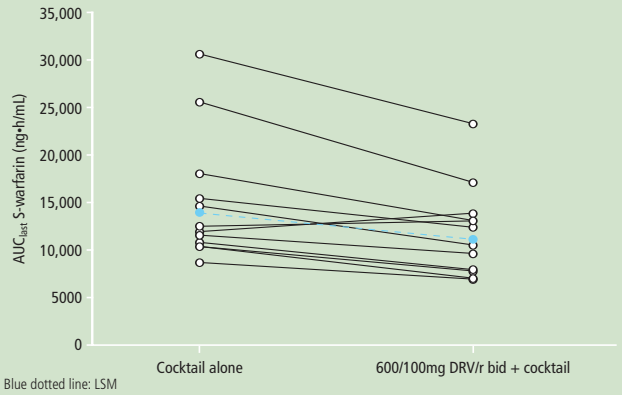

Figure 1. AUC_{last} (individual data and LSM) of S-warfarin after administration of cocktail alone and in combination with DRV/r 600/100mg bid.

Effect of DRV/r on CYP2D6: dextromethorphan and dextrorphan

- CYP2D6 plays a key role in the metabolism of dextromethorphan to dextrorphan.[8] Furthermore, dextromethorphan is also metabolized by CYP3A4.[9]
- In the presence of DRV/r, the P/M AUC_{last} ratio of dextromethorphan and dextrorphan increased by approximately three-fold (Table 2 and Figure 2).
- Although the exposure to dextromethorphan increased, the exposure to dextrorphan (formed via CYP2D6) remained unchanged (Table 2).
- In addition to inhibition of the CYP2D6 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.

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

PK parameter mean ± SD t_{max}: median (range)	Cocktail alone (Treatment A) (n=12)	DRV/r 600/100mg bid + cocktail (Treatment B) (n=12)	LSM ratio (B vs A) (90% CI)
Dextromethorphan			
C_{max}, ng/mL	3 ± 4	6 ± 5	2.27 (1.59–3.26)
AUC_{last}, ng•h/mL	18 ± 25	39 ± 38	2.70 (1.80–4.05)
t_{max}, hours	3.0 (1.5–5.0)	3.0 (2.0–5.0)	
Dextrorphan			
C_{max}, ng/mL	334 ± 117	284 ± 83	0.87 (0.77–0.98)
AUC_{last}, ng•h/mL	1785 ± 611	1676 ± 436	0.96 (0.90–1.03)
t_{max}, hours	3.0 (2.0–5.0)	3.0 (2.0–5.0)	
Ratio $C_{max,P/M}$, %	2 ± 4	3 ± 5	2.63 (1.75–3.95)
Ratio $AUC_{last,P/M}$, %	2 ± 4	3 ± 4	2.81 (1.83–4.30)

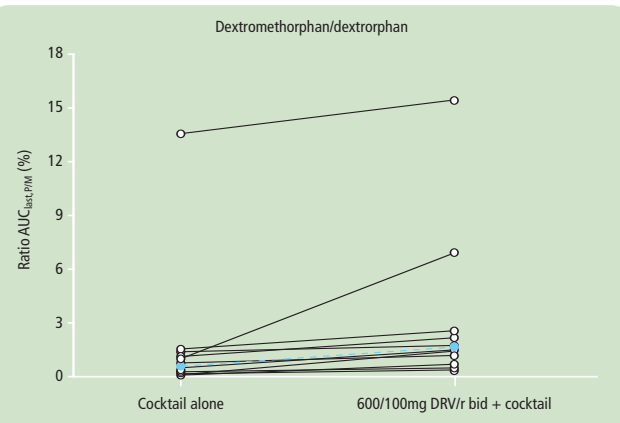

Figure 2. P/M AUC_{last} ratio of dextromethorphan and dextrorphan (individual data and LSM) after administration of cocktail alone and in combination with DRV/r 600/100mg bid.

Effect of DRV/r on CYP2C19: omeprazole and 5-OH-omeprazole

- Omeprazole is predominantly metabolized by CYP2C19 to 5-OH-omeprazole, with CYP3A4 being an additional minor pathway.[10]
- In the presence of DRV/r, the P/M AUC_{last} ratio of omeprazole and 5-OH-omeprazole decreased by 31% (Table 3), suggesting an increase in CYP2C19 activity.
- The induction effect on CYP2C19 can likely be attributed to the presence of RTV, which has been reported to induce this enzyme.[11]

Table 3. PK results of omeprazole and 5-OH-omeprazole after administration of cocktail alone and in combination with DRV/r 600/100mg bid.

PK parameter mean ± SD t_{max}: median (range)	Cocktail alone (Treatment A) (n=12)	DRV/r 600/100mg bid + cocktail (Treatment B) (n=12)	LSM ratio (B vs A) (90% CI)
Omeprazole			
C_{max}, ng/mL	525 ± 321	361 ± 271	0.66 (0.48–0.91)
AUC_{last}, ng•h/mL	1323 ± 1024	813 ± 749	0.58 (0.51–0.67)
t_{max}, hours	3.0 (1.5–5.0)	4.0 (1.0–6.0)	
5-OH-omeprazole			
C_{max}, ng/mL	300 ± 180	254 ± 75	0.94 (0.72–1.22)
AUC_{last}, ng•h/mL	901 ± 386	729 ± 196	0.85 (0.77–0.93)
t_{max}, hours	3.5 (1.5–5.0)	3.0 (1.0–6.0)	
Ratio $C_{max,P/M}$, %	191 ± 110	141 ± 100	0.71 (0.61–0.81)
Ratio $AUC_{last,P/M}$, %	148 ± 94	105 ± 78	0.69 (0.61–0.77)

DRV and RTV pharmacokinetics

- Steady-state plasma concentrations of DRV and RTV were generally reached after 5 days of treatment with DRV/r, before coadministration of DRV/r and the drug cocktail.
- DRV and RTV PK parameters in this study (Table 4) were within the range of those observed in previous studies in healthy volunteers.[12,13]

Table 4. PK results of DRV and RTV after treatment with DRV/r 600/100mg bid for 7 days and a single dose of the drug cocktail on Day 7.

Day 7 PK parameter mean ± SD t_{max}: median (range)	DRV (n=12)	RTV (n=12)
C_{0h}, ng/mL	2558 ± 1126	248 ± 162
C_{min}, ng/mL	2148 ± 1218	159 ± 79
C_{max}, ng/mL	5497 ± 1718	821 ± 508
AUC_{12h}, ng•h/mL	44,900 ± 17,270	5137 ± 2606
t_{max}, hours	3.0 (1.0–4.0)	4.0 (3.0–6.0)

C_{0h} = predose plasma concentration; C_{min} = minimum plasma concentration; AUC_{12h} = area under the plasma concentration-time curve until the last point measured

Safety and tolerability

- In general, the incidence of adverse events (AEs) was similar during Treatments A and B.
- Overall, nine (75%) volunteers reported at least one AE: six (50%) reported at least one AE during treatment with DRV/r alone, four (33%) with the cocktail alone and six (50%) with combined DRV/r and the cocktail.
- The number of volunteers reporting one or more AEs considered at least possibly related to DRV/r or the drug cocktail was seven (58%) and eight (67%), respectively.
- No grade 3 or 4 AEs, serious AEs or AEs leading to discontinuation were reported.
- No clinically relevant changes in laboratory safety assessments were observed.

Conclusions

- Coadministration of a drug cocktail of CYP probes and DRV/r resulted in induction or inhibition of various CYP enzyme activities.
- The observed induction effects on CYP2C9 and CYP219 activities and the increase in dextromethorphan exposure may be attributed to the coadministration of low-dose RTV and are consistent with reports on the interaction profile of RTV.[5,7]
- In addition to inhibition of the CYP2D6 enzyme, the increase in dextromethorphan exposure may be attributable to the inhibition of an alternate metabolic pathway such as CYP3A4. This would be consistent with the interaction profile of DRV and RTV, both of which are CYP3A4 inhibitors.
- The current study demonstrated that DRV/r 600/100mg bid alone or added to a cocktail of CYP probes is generally well tolerated.

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