**Effect of the HIV protease inhibitor darunavir (TMC114), coadministered with low-dose ritonavir, on the pharmacokinetics of digoxin in healthy volunteers**

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**Introduction**

- Darunavir (DRV; TMC114) is a new protease inhibitor (PI), coadministered with low-dose ritonavir (RTV) to achieve adequate plasma concentrations.
- The primary objective of this study was to examine the pharmacokinetics of digoxin in healthy volunteers during DRV and DRV/RTV coadministration.

**Methods**

- This was a Phase I, open label, randomized, two-way crossover study (TMC114-C1108) in healthy volunteers (aged 18–55) to assess the effect of DRV/RTV on the pharmacokinetics of digoxin. The effect of digoxin on the pharmacokinetics of DRV/RTV was not evaluated in this study, as DRV/RTV is not metabolized by the CYP3A4 enzyme and is not a known inhibitor or inducer of this enzyme.

**Pharmacokinetic analysis**

- Digoxin plasma profiles and urinary excretion were determined up to 96 hours after dosing on Day 1 of Treatment A and Day 8 of Treatment B. Plasma concentrations of DRV and digoxin were determined using validated liquid chromatography/mass spectrometry methods.

**Statistical analysis**

- Statistical analyses were performed using the combined data of Treatment A (2) and Treatment B (2) for each treatment group. The pharmacokinetics of DRV and digoxin were determined using validated liquid chromatography/mass spectrometry methods. All observations for both treatment and control groups were included in the statistical analysis. To ensure that study data were achieved for DRV and for Digoxin plasma concentrations, 

**Results**

- No grade 3 or 4 AEs were reported.
- All AEs leading to discontinuation were reported for eight (47%) volunteers, all during Treatment B (two volunteers).
- The most common AEs during combined digoxin and DRV/r treatment were pruritus and headache.
- All events leading to discontinuation were grade 1 or 2 in severity and considered at least possibly related to DRV/r.
- One case of grade 1 increase in eosinophils was reported as a laboratory abnormality during DRV/r treatment (reported as grade 2A leading to treatment discontinuation), after all laboratory abnormalities were grade 1 or 2 (except for one case of grade 3 skin toxicity [erythematous eruptions] and not reported in more than one volunteer (except for grade 1 increase in white blood cell abnormalities, reported in two volunteers).

**Conclusions**

- When a single dose of digoxin 0.4mg was coadministered with DRV 600/100mg bid, the exposure to digoxin increased by 77% (90% CI: 0.90–3.50), with substantial interindividual variability between individuals, it is recommended that the lowest possible dose of digoxin should initially be prescribed, with careful titration of the dose and monitoring of digoxin concentrations.

**References**


2. Ten volunteers dropped out before study completion: eight due to adverse events (AEs) and two due to treatment discontinuation.

3. The total amount of digoxin excreted in urine as a percentage of the dose was comparable between DRV/r plus an OBR and DRV/r alone.

4. No grade 3 or 4 AEs were reported.

5. An increase in digoxin exposure when coadministered with DRV/r and the degree of interindividual variability between individuals, it is recommended that the lowest possible dose of digoxin should initially be prescribed, with careful titration of the dose and monitoring of digoxin concentrations.