Bioavailability and food effect of darunavir following administration of an oral suspension

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Introduction

• Darunavir (DRV; TMC114) is a protease inhibitor, with potent activity against both HIV-1 type and drug-resistant HIV strains.

• DRV in combination with low-dose ritonavir (DRV/r) is now approved as treatment for the following HIV-1-infected patient groups:
  - treatment-naïve adults (800/100 mg qd) in the USA, Europe and many other countries
  - treatment-experienced adults (600/100 mg bid) in the USA, Europe and many other countries
  - treatment-experienced pediatric patients aged 6 years or older (twinco-daily weight-based dose) in the USA and European Union.

• The commercial DRV formulation is currently supplied as a tablet in 75, 150, 300, 400 and 600mg strengths. An oral suspension of DRV is currently in development for use in pediatric patients.

• The present study (TMC114-290-C169) was designed to:
  - compare the oral bioavailability of the DRV suspension with that of the 300mg commercial tablet in the presence of low-dose RTV
  - assess steady-state pharmacokinetics of DRV following administration of the suspension plus low-dose RTV in healthy HIV-negative adults.

Methods

Study design

• TMC114-290-C169 was a Phase I, open-label, randomized, crossover study conducted in healthy HIV-negative adults.

• The trial was divided into two parts that were conducted sequentially. Part 1 results were evaluated before the start of Part 2.

• In Part 1, during three sessions, each volunteer received a single dose of DRV 600mg:
  - Treatment A: two tablets of DRV 300mg formulated as F051 under fed conditions
  - Treatment B: 6mL of a DRV suspension (100mg/mL) formulated as F051 under fasted conditions
  - Treatment C: DRV 600mg suspension (100mg/mL) formulated as F051 under fasted conditions

• In Treatments A, B, and C, a single dose of DRV 600mg was administered on Day 3, while RTV 100mg bid was administered from Day 1 to 5. Each treatment was separated by a washout period of at least 7 days.

• Part 2. Each volunteer received multiple doses of DRV 600mg as a suspension
  - Treatment D: 6mL of a DRV suspension (100mg/mL) formulated as F051 under fed conditions

• In Treatments A, B, C, and D, a single dose of DRV 600mg was administered on Day 3, while RTV 100mg bid was administered from Day 1 to 5. Each treatment was separated by a washout period of at least 7 days.

• In Part 1, each volunteer received multiple doses of DRV 600mg bid as a suspension
  - Treatment D: 6mL of a DRV suspension (100mg/mL) formulated as F051 under fasted conditions

• In Treatments A, B, and C, a single dose of DRV 600mg was administered on Day 3, while RTV 100mg bid was administered from Day 1 to 5.

• The dose and volume of suspension of DRV and food recommendations for DRV intake for Part 2 were based on the results of Part 1 of the trial.

Pharmacokinetic and safety evaluation

• For each treatment group, full pharmacokinetic profiles of DRV and RTV were determined up to 72 hours after administration (Day 3 in Part 1 and in Day 7 in Part 2). Blood sampling times were: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours after each dose.

• Plasma concentrations of DRV and RTV were determined using a validated liquid chromatographic mass spectrometry method. The lower limit of quantification was 5.0 ng/mL for DRV and RTV.

• Descriptive statistics were calculated for the plasma concentrations of DRV and RTV at each time point and for the derived pharmacokinetic parameters.

• The pharmacokinetic parameters calculated for DRV and RTV were: plasma concentration (C0), minimum plasma concentration (Cmin), maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), terminal elimination half-life (T1/2), area under the plasma concentration-time curve (AUC) extrapolated to infinity (AUC∞), AUC from time of administration up to the last time point (AUClast), mean residence time (MRT), and steady-state volume of distribution (VSS).

• The least square (LS) means of the primary parameters (Cmax, AUC0-∞) were compared to historic pharmacokinetic data. The criteria for bioequivalence were met when comparing the least square (LS) means for DRV and RTV from Part 1 and Part 2 of this trial were comparable to historic pharmacokinetic data.

Results

Volunteer disposition

• In Part 1 and Part 2, 20 volunteers were randomized to treatment; of these, 17 completed Part 1 and 15 continued treatment in Part 2, for a total of 19 volunteers enrolled in Part 1 and 16 volunteers completed Part 2 of the trial.

• Baseline demographics were generally well balanced across all treatment arms (n=17). Overall, 78% volunteers were male and 22% were Caucasian. The median age was 30 years (range: 20–30 years).

Part 1 Darunavir pharmacokinetics

• The mean plasma concentration-time profiles showed that the plasma concentrations of DRV given as a single dose of DRV formulated as a tablet under fed conditions (Treatment A) were comparable to those after a single dose of DRV 600mg formulated as suspension under-fed conditions (Treatment C), both in the presence of RTV (Figure 1).

• After administration of DRV under fasted conditions (formulated as a suspension), Treatment B, Cmax was lower and Tmax was observed earlier compared with administration of DRV under fed conditions (formulated as tablet and suspension, Treatment A and C; Figure 1).

• Safety and tolerability were evaluated continuously throughout the study.

Conclusions

• The criteria for bioequivalence were met when comparing the rate and extent of absorption (Cmax, AUC0-∞) of a single dose of DRV 600mg formulated as a suspension compared with the tablet (formulation A) (Figure 1).

• Mean values of RTV pharmacokinetic parameters after co-administration of DRV 600mg bid formulated as a suspension (Treatment D) were comparable with historic data from TMC114-C123, C169, and C171 studies, in which patients received DRV/r 600/100mg bid (formulation B). DRV was formulated as an oral tablet (data not shown).

• Overall, adverse events (AEs) considered at least possibly related to DRV were reported for 16 (68.6%) volunteers; all AEs were grade 1 or 2 in severity.

• The incidence of treatment-emergent AEs considered at least possibly related to DRV reported by ≥1 volunteer by treatment arm are shown in Table 2.

• The most frequently reported AEs were: nausea (n=4), diarrhea (n=3), rash (n=3), and insomnia (n=3). The frequencies of these AEs were comparable to those previously observed in Table 2. The range of tmax values observed earlier for RTV compared with Treatments A (formulated as tablet) and C (formulated as a suspension) was comparable with those previously observed (Table 2). The range of tmax values observed earlier for RTV compared with Treatments A (formulated as tablet) and C (formulated as a suspension) was comparable with those previously observed (Table 2).

References


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