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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 wild-type and drug-resistant HIV strains.[1]
- DRV in combination with low-dose ritonavir (DRV/r; RTV) is now approved as treatment for the following HIV-1-infected patient groups
  - treatment-naïve adults (800/100mg qd) in the USA,[2] Europe[3] and other countries
  - treatment-experienced adults (600/100mg bid) in the USA,[2] Europe[3] and in many more countries
  - treatment-experienced pediatric patients aged 6 years or older (twice-daily bodyweight-based dose) in the USA and European Union.[2]
- 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-TiDP29-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
  - to assess steady-state pharmacokinetics of DRV following administration of the suspension plus low-dose RTV in healthy HIV-negative adults.

Methods

Study design

- TMC114-TiDP29-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 F016 under fed conditions
  - Treatment B: 6mL of a DRV suspension (100mg/mL) formulated as F051 under fasted conditions
  - Treatment C: 6mL of a DRV suspension (100mg/mL) formulated as F051 under fed 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.
- In Part 2, each volunteer received multiple doses of DRV 600mg bid as a suspension
  - Treatment D: 6mL bid of a DRV suspension (100mg/mL, F051) on Days 1–6 with an additional morning dose on Day 7. RTV 100mg bid was administered from Day 1 to 9.
- The dose and volume of suspension of DRV and food recommendations for DRV/r 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 (on Day 3 in Part 1, and on Day 7 in Part 2). Blood sampling times were: predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 12, 24, 48 and 72 hours after study medication intake.
- Plasma concentrations of DRV and RTV were determined using a validated liquid chromatographic-mass spectrometry/mass spectrometry method. The lower limit of quantification was 5.0ng/mL for DRV and RTV.
- Descriptive statistics were calculated for the plasma concentrations of DRV and RTV at each timepoint and for the derived pharmacokinetic parameters.
- The pharmacokinetic parameters calculated for DRV and RTV were: predose plasma concentration (C_{0h}); minimum plasma concentration (C_{min}); maximum plasma concentration (C_{max}); time-to-maximum plasma concentration (t_{max}); terminal elimination half-life ($t_{1/2term}$); area under the plasma concentration-time curve (AUC) extrapolated to infinity (AUC_{∞}); AUC from time of administration up to 12 hours after dosing (AUC_{12h}) and AUC from time of administration up to the last time point with a measurable concentration post-dose (AUC_{last}), AUC_{12h} and AUC_{last} were both calculated by linear trapezoidal summation.
- The least square (LS) means of the primary parameters (C_{max}, AUC_{last} and AUC_{∞}) for each treatment group were estimated with a linear mixed-effects model, controlling for treatment, sequence and period as fixed effects, and subject as a random effect.
- T_{max} of DRV was analyzed by the Mann-Whitney U-test, comparing: Treatment B (Test) versus Treatment A (Reference); Treatment C (Test) versus Treatment A (Reference); Treatment C (Test) versus Treatment B (Reference). The crossover design tool of WinNonlin Professional™ was used for these analyses.
- Pharmacokinetic parameters for DRV and RTV from Part 2 of this trial were compared to historic pharmacokinetic data.
- Safety and tolerability were evaluated continuously throughout the study.

Results

Volunteer disposition

- In Part 1, 20 volunteers were randomized to treatment; of these, 17 completed Part 1 and 15 continued treatment in Part 2. For Part 2, an additional three volunteers were enrolled, thus, a total of 18 volunteers started treatment in Part 2; 16 volunteers completed Part 2 of the trial.
- Baseline demographics were generally well balanced across all treatment arms (n=23). Overall, 78% volunteers were male and 87% were Caucasian. The median age was 30 years (range: 20–53 years).

Part 1

Darunavir pharmacokinetics

- The mean plasma concentration-time profiles showed that the plasma concentrations of DRV given as a single 600mg dose formulated as a tablet under fed conditions (Treatment A), were comparable to those after a single DRV 600mg dose 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), C_{max} was lower and t_{max} was observed earlier compared with administration of DRV under fed conditions (formulated as tablet and suspension, Treatment A and C; Figure 1).

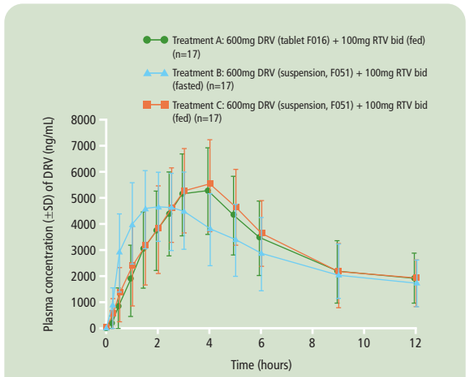

Figure 1. Mean plasma concentration-time curves of DRV after administration of Treatment A, Treatment B, and Treatment C, all in combination with RTV 100mg bid.

- The pharmacokinetic parameters of DRV for Treatments A, B and C are shown in Table 1. The 90% confidence intervals (CIs) of the LS means ratios for C_{max}, AUC_{last}, and AUC_{∞} were all within the 80–125% interval when the suspension (in fed- and fasted-state) was compared with the tablet (fed-state).

Ritonavir pharmacokinetics

- The mean plasma concentration-time profiles demonstrated that steady-state plasma concentrations of RTV, under fed conditions, were comparable during co-administration of a single 600mg dose of DRV formulated as tablet (Treatment A) versus a single 600mg dose of DRV formulated as suspension (Treatment C) (data not shown).
- After administration of DRV/r under fasted conditions, (formulated as a suspension, Treatment B), C_{max} appeared to be higher and t_{max} was observed earlier for RTV compared with Treatments A (formulated as tablet) and C (formulated as a suspension) (data not shown).

Table 1. Pharmacokinetic results of single-dose DRV when co-administered with RTV 100mg bid in Treatments A, B, and C.

DRV PK parameter (mean ±SD, t_{max}: median [range])	Treatment A: DRV 600mg tablet + RTV 100mg bid (fed) (Reference)	Treatment B: DRV 600mg suspension + RTV 100mg bid (fasted) (Test)	Treatment C: DRV 600mg suspension + RTV 100mg bid (fed) (Test)	LS means ratio (90% CI) A vs B	B vs C	A vs C
n	17*	17	17	17†	17	17†
C_{max}, ng/mL	5654 ± 1478	5176 ± 1411	5885 ± 1724	0.91 (0.85–0.98)	1.14 (1.06–1.23)	1.04 (0.99–1.10)
t_{max}, hours	3.0 (2.5–5.0)	2.0 (1.0–3.0)	4.0 (1.5–4.0)	–	–	–
AUC_{last}, ng•h/mL	85,240 ± 38,020	83,510 ± 33,540	88,410 ± 32,590	1.00 (0.92–1.08)	1.07 (1.00–1.14)	1.08 (1.01–1.14)
AUC_{∞}, ng•h/mL	87,330 ± 40,890	88,520 ± 35,570	92,270 ± 33,540	1.02 (0.93–1.11)	1.06 (0.99–1.13)	1.07 (1.00–1.14)
$t_{1/2term}$, hours	15.04 ± 7.88*	16.08 ± 7.24	15.36 ± 6.44	–	–	–

*n=16 for AUC_{∞} and $t_{1/2term}$; †n=16 for AUC_{∞} for Reference; PK = pharmacokinetic

Part 2

Darunavir pharmacokinetics

- Mean maximum DRV plasma concentration was reached 3 hours after intake of DRV 600mg bid, formulated as a suspension, in the presence of RTV 100mg bid.
- Mean values of C_{max}, C_{min}, and AUC_{12h} for DRV formulated as a suspension compared with DRV formulated as tablet were within the range of those previously observed (Table 2). The range of t_{max} values was comparable for both formulations.

Table 2. Pharmacokinetic results of multiple doses of DRV when co-administered with RTV 100mg in Treatment D compared with historic control data.

DRV PK parameter (mean ±SD, t_{max}: median [range])	Treatment D: DRV 600mg suspension bid + RTV 100mg bid (fed)	Historic control data DRV/r 600/100mg bid (TMC114-C171)	DRV/r 600/100mg bid (TMC114-C123)	DRV/r 600/100mg bid (TMC114-C163)
n	17	17	17	16*
C_{0h}, ng/mL	4029 ± 1677	3450 ± 944	2742 ± 625	2768 ± 1077
C_{max}, ng/mL	3345 ± 1172	3132 ± 1006	2353 ± 744	2349 ± 1006
C_{min}, ng/mL	7390 ± 1540	6894 ± 1654	5908 ± 917	5874 ± 1637
t_{max}, hours	3.0 (2.0–4.0)	3.0 (1.0–5.0)	3.0 (2.0–5.0)	4.0 (1.0–9.0)
AUC_{12h}, ng•h/mL	58,550 ± 17,570	58,550 ± 17,200	44,750 ± 7773	46,720 ± 15,430

*n=15 for C_{0h}

Ritonavir pharmacokinetics

- Mean values of RTV pharmacokinetic parameters after co-administration with DRV 600mg bid formulated as a suspension (Treatment D) were comparable with historic data from TMC114-C123, C163, and C171 studies, in which patients received DRV/r 600/100mg bid, where DRV was formulated as an oral tablet (data not shown).

Safety and tolerability

- Overall, adverse events (AEs) considered at least possibly related to DRV by the investigator were reported for 16 (69.6%) 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 3.
- The most frequently reported AEs were: dysgeusia (n=4) following a single dose of DRV in Treatment B (DRV suspension, fasted); headache (n=4), diarrhea (n=3), and rash (n=3) following administration of multiple doses of DRV in Treatment D (DRV suspension, fed).
- No serious AEs occurred in this trial. Four (17.4%) volunteers discontinued trial medication due an AE (nausea [n=1] and rash [n=3; mandatory discontinuation for grade 2 rash was specified in the trial protocol]).
- All laboratory abnormalities were grade 1 or 2. No consistent or clinically relevant changes over time in median laboratory parameters were observed.

Table 3. The incidence of treatment-emergent AEs considered at least possibly related to DRV reported by >1 volunteer, regardless of severity.

System Organ Class, preferred term, n (%)	Single DRV dose (Part 1) Treatment A: DRV 600mg tablet + RTV 100mg bid (fed) (n=17)	Treatment B: DRV 600mg suspension + RTV 100mg bid (fasted) (n=17)	Treatment C: DRV 600mg suspension + RTV 100mg bid (fed) (n=17)	Multiple DRV doses (Part 2) Treatment D: DRV 600mg suspension bid + RTV 100mg bid (fed) (n=18)
Any AE	*5 (29.4)*	*9 (52.9)*	*3 (17.6)*	*12 (66.7)*
Abdominal pain	0	2 (11.8)	0	2 (11.1)
Diarrhea	1 (5.9)	0	1 (5.9)	3 (16.7)
Flatulence	0	0	0	2 (11.1)
Nausea	0	1 (5.9)	0	2 (11.1)
Headache	2 (11.8)	2 (11.8)	1 (5.9)	4 (22.2)
Somnolence	1 (5.9)	0	0	2 (11.1)
Dysgeusia	0	4 (23.5)	0	0
Rash	0	0	0	3 (16.7)

Conclusions

- The criteria for bioequivalence were met when comparing the rate and extent of absorption (C_{max}, AUC_{last}, AUC_{∞}) of a single dose of DRV 600mg following treatment with DRV as a tablet (fed) or as an oral suspension (fasted or fed) in the presence of low-dose RTV.
- DRV and RTV steady-state pharmacokinetics were comparable to historic data (DRV/r 600/100mg bid [DRV tablet formulation]), following administration of the DRV 600mg suspension formulation in the presence of low-dose RTV under fed conditions.
- The DRV suspension formulation was well tolerated in healthy HIV-negative adults.
- DRV 100mg/mL as a suspension formulation, in combination with low-dose RTV, will be further evaluated in 3–5-year-old, HIV-1-infected patients.

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