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Pharmacokinetic interaction between darunavir in combination with low-dose ritonavir and carbamazepine

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Introduction

- The protease inhibitor darunavir (DRV; TMC114) coadministered with low-dose ritonavir (RTV; DRV/r), at a dose of 600/100mg bid, is approved in many countries including the USA and Europe for the treatment of HIV in antiretroviral-experienced adult patients.[1,2]
- Carbamazepine (CBZ) is an anticonvulsant and a specific analgesic for trigeminal neuralgia.[3] Its active metabolite is carbamazepine-10,11-epoxide (CBZE), which is produced by a reaction catalyzed by cytochrome P450 (CYP) isoenzyme CYP3A4. CBZ can be used as a comedication in HIV-infected individuals.
- A pharmacokinetic (PK) drug interaction may be expected when CBZ, DRV and RTV are coadministered, as they are all metabolized by CYP3A4. Furthermore, RTV is a potent inhibitor of CYP3A4 metabolism, and can increase exposure to CBZ and DRV even at low dosages. DRV is also an inhibitor of CYP3A4. In contrast, CBZ induces CYP3A4, and could reduce plasma concentrations of CYP3A4 substrates.
- The primary objectives of this multiple dose study were to determine the effect of CBZ on the steady-state PK of DRV and RTV in HIV-negative healthy volunteers, and the effects of DRV/r on the steady-state PK of CBZ and CBZE. The secondary objective was to assess the short-term safety and tolerability of the concomitant use of DRV/r and CBZ.
- The study results will provide guidance on dose recommendations for the combined administration of DRV/r and CBZ.

Methods

Study design

- This study (TMC114-TiDP3-C172) was a Phase I, open-label, randomized, two-panel, crossover trial to investigate the PK interaction between DRV/r and CBZ.
- Thirty-two HIV-negative, healthy male and female volunteers, aged 18–55 years were recruited. Written, informed consent was provided by all volunteers.
- Two panels of 16 patients received drug treatments as follows
  - Panel 1: DRV/r alone 600/100mg bid on Days 1–7, then in combination with CBZ (200mg qd on Days 8–10, 200mg bid on Days 11–29) with an additional morning dose of all three drugs on Day 30
  - Panel 2: CBZ 200mg alone Days 1–3 (qd) and Days 4–23 (bid). On Days 24–29: CBZ 200mg bid with DRV/r 600/100mg bid, with an additional morning dose of all three drugs on Day 30.
- DRV, RTV, and CBZ were taken with water within 10 minutes after a meal. During the coadministration phase, CBZ was taken first followed by RTV (within 5 minutes) then DRV (within 5 minutes).
- Total treatment duration was 30 days, with a further follow-up period of up to 32 days.
- Safety and tolerability evaluations were assessed throughout the study and up to 30 days after the last administration of trial medication.

Pharmacokinetic assessments

- DRV, RTV, CBZ and CBZE plasma concentrations were determined using validated liquid chromatography mass spectrometry/mass spectrometry methods. Lower limits of quantification were 5.00ng/mL for DRV and RTV and 0.05µg/mL for CBZ and CBZE.
- PK parameters assessed included: trough concentration (C_{0h}), minimum plasma concentration between 0 hour and the end of the dosing interval (C_{min}), maximum plasma concentration (C_{max}) and area under the curve (AUC) calculated from the time of administration up to 12 hours postdose (AUC_{12h}), time to C_{max} (t_{max}).
- The least square (LS) means of the primary parameters (C_{min}, C_{max}, AUC_{12h}) were calculated with a linear, mixed-effects model, controlling for treatment as fixed effect and subject as a random effect. A 90% confidence interval (CI) was constructed around the difference between the LS means of test and reference.

Results

Participant disposition

- Seventy-four volunteers were screened; 32 (18 males and 14 females) were randomized between the two treatment panels (n=16 per panel). Twenty-seven volunteers completed the trial; five volunteers (in Panel 1) discontinued treatment due to adverse events (AEs).

Pharmacokinetics of DRV

- Steady-state conditions for DRV were achieved prior to full PK blood sampling on Day 7.
- Administration of DRV/r alone or in combination with CBZ (Panel 1) resulted in comparable DRV plasma concentration-time profiles (Figure 1).
- PK parameters of DRV at steady-state when given as DRV/r or as DRV/r plus CBZ are listed in Table 1
  - mean values of C_{min}, C_{max}, and AUC_{12h} of DRV were comparable between treatments. The 90% CIs of the LS means ratios for C_{max} and AUC_{12h} were within the limits of 80–125%; the ratios of the LS means were close to 100%.

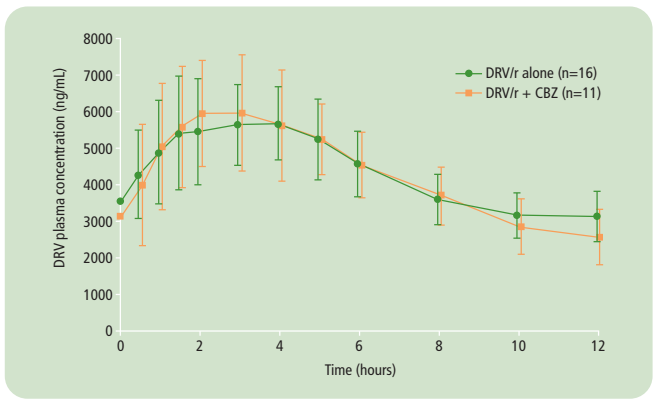

Figure 1. Mean plasma concentration-time curves (including standard deviations [SD]) of DRV after administration of DRV/r alone (Day 7) and in combination with CBZ (Day 30) – Panel 1.

Table 1. PK results of DRV after administration of DRV/r alone (Day 7) and in combination with CBZ (Day 30) – Panel 1.

Pharmacokinetics of DRV (mean ± SD, t_{max}: median [range])	Treatment		LS means ratio of DRV PK parameters % (90% CI)
	DRV/r	DRV/r + CBZ	
n	16	11	–
t_{max}, h	2.0 (0.5–5.0)	3.0 (1.0–5.0)	–
C_{0h}, ng/mL	3527 ± 859.7	3125 ± 1008	–
C_{min}, ng/mL	2901 ± 714.1	2509 ± 772.3	85.45 (73.33–99.57)
C_{max}, ng/mL	6262 ± 1148	6551 ± 1384	103.7 (93.14–115.5)
AUC_{12h}, ngh/mL	52 310 ± 9557	51 800 ± 10,800	98.79 (90.30–108.1)

Pharmacokinetics of CBZ and CBZE

- Individual plots of predose plasma concentrations of CBZ and CBZE demonstrated that steady-state conditions for both compounds were achieved prior to full PK blood sampling (data not shown).
- Compared with CBZ alone, the mean plasma concentration-time curves showed that at steady-state, coadministration of DRV/r resulted in
  - higher mean plasma concentrations of CBZ over the entire dose interval (Figure 2a)
  - lower mean plasma concentrations of CBZE (Figure 2b).

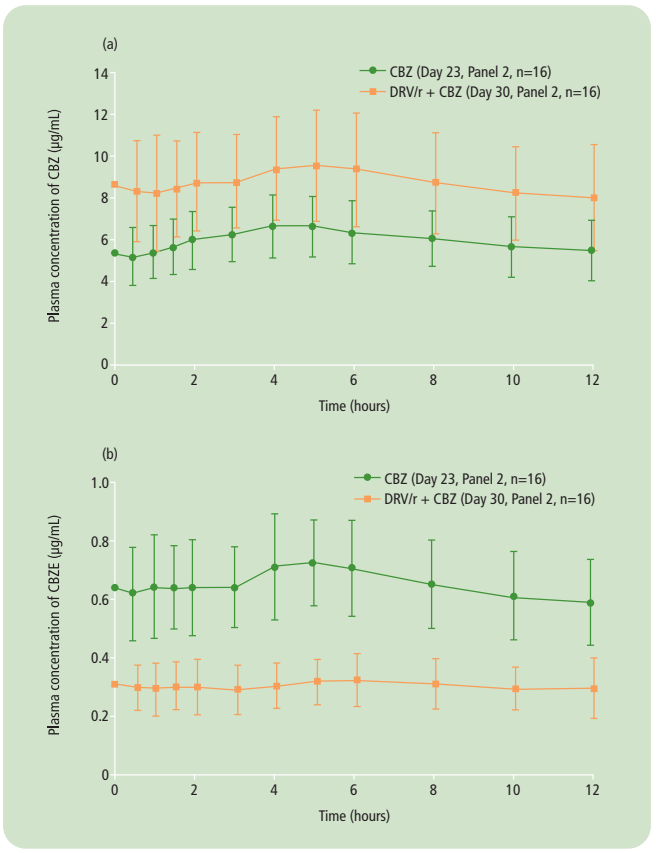

Figure 2. Mean plasma concentration-time curves (including SDs) of CBZ (a) and CBZE (b) after administration of CBZ alone (Day 23) and in combination with DRV/r (Day 30) – Panel 2.

- After combined administration with DRV/r, mean values for CBZ of C_{0h}, C_{min}, C_{max} and AUC_{12h} were higher than those after CBZ administration alone (Table 2)
  - C_{min}, C_{max} and AUC_{12h} of CBZ were increased by 54%, 43% and 45%, respectively, in the presence of DRV/r compared with CBZ alone (LS means).

Table 2. PK results of CBZ after administration of CBZ alone (Day 23) and in combination with DRV/r (Day 30) – Panel 2.

Pharmacokinetics of CBZ (mean ± SD, t_{max}: median [range])	Treatment		LS means ratio of CBZ PK parameters % (90% CI)
	CBZ	DRV/r + CBZ	
n	16	16	–
t_{max}, h	4.5 (2.0–8.0)	5.0 (1.5–8.0)	–
C_{0h}, µg/mL	5.3 ± 1.4	8.7 ± 2.5	–
C_{min}, µg/mL	5.0 ± 1.2	7.8 ± 2.3	154.3 (141.3–168.4)
C_{max}, µg/mL	7.0 ± 1.5	10.0 ± 2.6	142.9 (133.7–152.7)
AUC_{12h}, µgh/mL	72.1 ± 16.2	105.2 ± 28.9	145.3 (134.5–157.1)

- At steady state, mean values of CBZE of C_{0h}, C_{min}, C_{max} and AUC_{12h} were lower following DRV/r + CBZ administration compared with CBZ alone (Table 3)
  - the AUC_{12h} ratio metabolite/parent drug ($AUC_{12h\ met/par}$) was markedly reduced postadministration of DRV/r + CBZ versus CBZ
  - C_{min}, C_{max} and AUC_{12h} of CBZE were reduced by 52%, 54% and 54%, respectively, in the presence of DRV/r compared with CBZ alone.

Table 3. PK results of CBZE after administration of CBZ alone (Day 23) and in combination with DRV/r (Day 30).

Pharmacokinetics of CBZE (mean ± SD, t_{max}: median [range])	Treatment		LS means ratio of CBZE PK parameters % (90% CI)
	CBZ	DRV/r + CBZ	
n	16	16	–
t_{max}, h	5.0 (3.0–8.0)	5.0 (0.0–12.0)	–
C_{0h}, µg/mL	0.6 ± 0.2	0.3 ± 0.1	–
C_{min}, µg/mL	0.6 ± 0.1	0.3 ± 0.1	47.78 (45.07–50.66)
C_{max}, µg/mL	0.8 ± 0.2	0.4 ± 0.1	45.60 (42.52–48.90)
AUC_{12h}, µgh/mL	7.9 ± 1.8	3.7 ± 1.0	46.31 (43.88–48.88)
Percentage ratio $AUC_{12h\ met/par}$	11.1 ± 1.8	3.5 ± 0.5	–

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This poster is available on-line at www.tibotec.com.

Pharmacokinetics of RTV

- At steady state, mean values of C_{0h}, C_{min}, C_{max} and AUC_{12h} of RTV were lower after coadministration of DRV/r and CBZ, compared with those after DRV/r alone (Table 4).

Table 4. PK results of RTV after administration of DRV/r alone (Day 7) and in combination with CBZ (Day 30) – Panel 1.

Pharmacokinetics of RTV (mean ± SD, t_{max}: median [range])	Treatment		LS means ratio of RTV PK parameters % (90% CI)
	DRV/r	DRV/r + CBZ	
n	16	11	–
t_{max}, h	4.0 (1.5–6.0)	5.0 (2.0–8.0)	–
C_{0h}, ng/mL	386.4 ± 198.3	173.1 ± 78.41	–
C_{min}, ng/mL	256.2 ± 104.0	112.6 ± 44.19	44.22 (37.05–52.78)
C_{max}, ng/mL	934.8 ± 248.9	516.5 ± 148.2	56.17 (49.48–63.77)
AUC_{12h}, ngh/mL	6540 ± 2087	3281 ± 914.1	51.17 (46.54–56.25)

- Based on the ratios of the LS means, C_{min}, C_{max} and AUC_{12h} values of RTV decreased by 56%, 44% and 49%, respectively, in the presence of CBZ.

Safety and tolerability

- Overall, 15 (94%) volunteers in Panel 1 and 16 (100%) in Panel 2 reported at least one treatment-emergent AE during this study. The number of individuals with ≥1 AE was: 10 (63%) during treatment with DRV/r alone (Panel 1), 16 (100%) on CBZ alone (Panel 2), and 30/32 (15 [94%] in each panel) during coadministration of DRV/r with CBZ.
- None of the AEs was considered by the investigators to be very likely related to the study medication
  - AEs considered to be possibly related to DRV during treatment with DRV/r alone (Panel 1) were (n: %): headache (3: 18.8%), dizziness, fatigue, and pruritus (2: 12.5% for each), and diarrhea (1: 6.3%)
  - AEs possibly related to CBZ during treatment with CBZ alone (Panel 2) were (n: %): somnolence (7: 43.8%), headache (5: 31.3%), fatigue (4: 25%), paresthesia and nausea (3: 18.8% for each), dizziness and memory impairment (2: 12.5% for each), constipation, upper abdominal pain, and generalized pruritis (2: 12.5% for each), diarrhea and pruritus (1: 6.3% for each)
  - AEs possibly related to DRV during coadministration (Panel 1) were (n: %): fatigue (4: 25.0%), nausea, diarrhea, and generalized rash (3: 18.8% for each), abdominal pain (2: 12.5%), and pruritis (1: 6.3%)
  - AEs possibly related to CBZ during coadministration (Panel 1) were (n: %): dizziness (9: 56.3%), fatigue (5: 31.3%), nausea, diarrhea, generalized rash, blurred vision, and dry eye (3: 18.8% for each), abdominal pain, and disturbance in attention (2: 12.5% for each), headache, pruritis, and somnolence (1: 6.3% for each)
  - AEs possibly related to DRV during coadministration (Panel 2) were (n: %): nausea (10: 62.5%), headache (6: 37.5%), diarrhea (3: 18.8%), fatigue (2: 12.5%), and pruritis (1: 6.3%)
  - AEs possibly related to CBZ during coadministration (Panel 2) were (n: %): nausea (10: 62.5%), headache (5: 31.3%), diarrhea, and dry eye (3: 18.8% for each), memory impairment (2: 12.5%), somnolence, dizziness, upper abdominal pain, fatigue, generalized pruritis, generalized rash, and fatigue (1: 6.3% for each).
- Most AEs were grade 1 or 2 in severity. During treatment, two volunteers (Panel 1) had a grade 3 AE (increased aspartate aminotransferase [AST]; nausea). No grade 4 events were reported.
- There were five AE-related treatment discontinuations in Panel 1, all occurring during coadministration: three due to generalized rash (Day 10, 11 and 18); one for increased AST (Day 21); one with abdominal pain and nausea (Day 11).
- No consistent or clinically relevant changes over time in laboratory parameters were observed.
- The most common graded laboratory abnormalities were hypocalcemia, and elevated low-density lipoprotein (LDL) and total cholesterol levels. Most laboratory abnormalities were grade 1 or 2 in severity in both panels.
- Grade 3 abnormalities were only observed in Panel 1 (hyperkalemia [n=1], increased LDL, AST, ALT (alanine transaminase) levels [n=2]).

Conclusions

- Systemic exposure to DRV, coadministered with low-dose RTV, was largely unchanged in the presence of CBZ.
- The CBZ-induced reduction (approximately 50%) in RTV exposure had no clinically relevant effect on DRV PK in this study.
- Exposure to CBZ was increased by 45% in the presence of DRV/r; consequently, exposure to the active metabolite, CBZE, was reduced.
- DRV in combination with low-dose RTV, with or without coadministration of CBZ, was generally safe and well tolerated in HIV-negative, healthy volunteers.
- If DRV/r and CBZ are combined
  - patients should be monitored for potential CBZ-related AEs
  - CBZ concentrations should be monitored and the dose titrated for adequate response.
- Based upon these study findings, the CBZ dose may need to be reduced by 25% to 50% in the presence of DRV/r.

References

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