



# Pharmacokinetics (PK) of AMD11070, a CXCR4 Antagonist, in HIV-infected Patients Carrying X4-tropic Virus

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## Abstract

**Background:** AMD11070 (070) is a specific and reversible CXCR4 antagonist undergoing phase IIa studies. Activity has been demonstrated in the first dose cohort in an ongoing proof-of-activity study. The aim of this analysis was to assess the plasma PK of AMD11070 when administered BID to HIV-infected patients and investigate its relationship with virological response.

**Methods:** A single arm, open label, dose-escalating study was conducted in HIV-infected patients carrying X4-tropic virus (determined by a luciferase activity of  $\geq 2000$  rlu on the Monogram HIV Coreceptor Tropism Assay). Eight patients were administered AMD11070 at 200mg BID and two patients at 100mg BID for 10 days. Sampling for plasma AMD11070 concentration determinations were performed at multiple time points following the morning and afternoon doses on the last day of administration (Day 10). Samples were also obtained immediately prior to the morning dose on Days 1-10 for trough level analysis. PK analysis was performed using a non-compartmental extravascular input model provided by WinNonlin V.4.0.1.

**Results:** When AMD11070 was administered at 100 and 200 mg BID, the average times to reach C<sub>max</sub> were 180 $\pm$ 60 min and 108.8 $\pm$ 23min (median = 105 min) respectively. Mean AUC<sub>0-24h</sub> values were 1123.5 $\pm$ 145.0 ng $\cdot$ h/mL and 6471.8 $\pm$ 1511.2

(median = 5650.2 ng $\cdot$ h/mL); and mean C<sub>max</sub> were 346.5 $\pm$ 26.5 ng/mL and 1271.2.1 $\pm$ 234.2 ng/mL (median = 1350.0 ng/mL) respectively. AUC<sub>0-24h</sub> coefficient of variation was 66.0%. The 100 to 200 mg AUC<sub>0-24h</sub> ratio was 5.7, suggesting a greater than proportional increase in exposure. For the 200 mg dose group, the median C<sub>12h</sub> on Day 10 was 84.1 ng/mL (mean  $\pm$  SEM = 97.8  $\pm$  24.3 ng/mL), which was close to the protein-adjusted *in vitro* IC<sub>50</sub> (~100 ng/mL) of 070. Half-life was 5.5 $\pm$ 0.7h (n=5 on 200mg BID). Trough levels analysis suggested that steady-state was not achieved in all patients after 10 days of BID dosing. At the 100 and 200 mg BID dose levels, no significant relationship was observed between AUC<sub>0-24h</sub> or C<sub>12h</sub> and X4 log rlu reduction at Day 10 (results presented in poster no. 511).

**Conclusions:** AMD11070 is orally bioavailable and exhibits evidence of accumulation following repeated administration. Pharmacokinetic data suggested that the AMD11070 PK parameters in HIV-infected patients are comparable to those in healthy volunteers. At doses studied to date, no relationship was observed between AMD11070 PK parameters and virological response. Future dose escalating studies will continue to assess the PK/PD relationship of this novel antiretroviral compound.

*Note: AMD11070 was recently placed on clinical hold by the FDA due to liver histology changes observed in longer term pre-clinical toxicity experiments. These findings are currently under investigation.*

## Results

Figure 1: Plasma Concentration vs. Time Profiles Following a.m. Dose (Day 10)

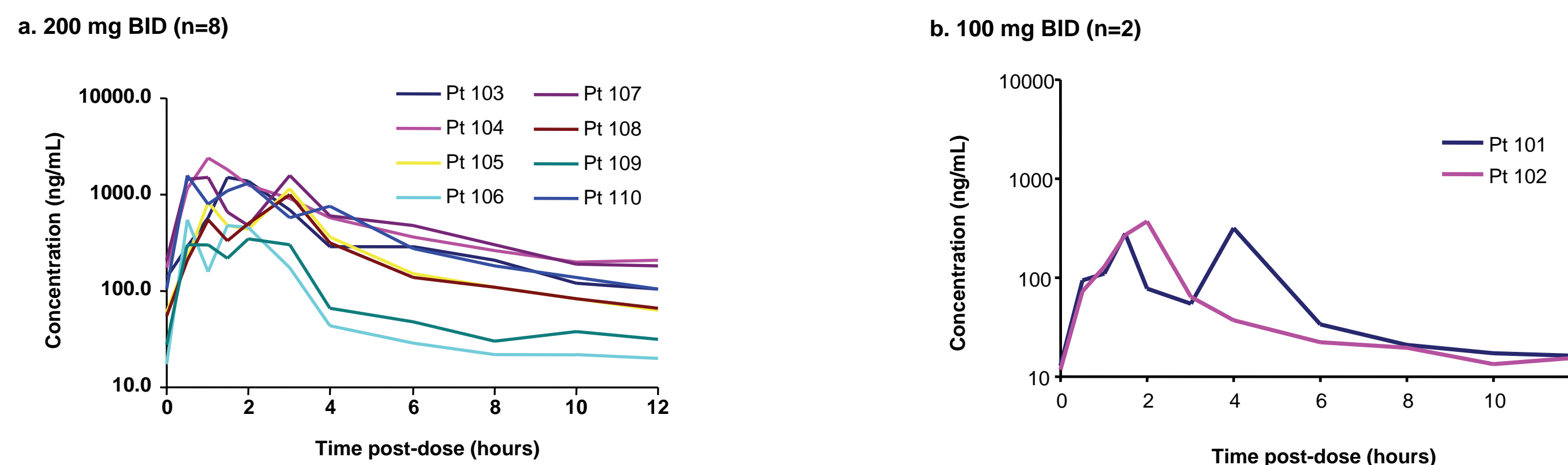


Figure 2: AMD11070 Trough Concentration (Days 1-10) (Pts 101, 102 = 100 mg BID; Pts 103-110 = 200 mg BID)

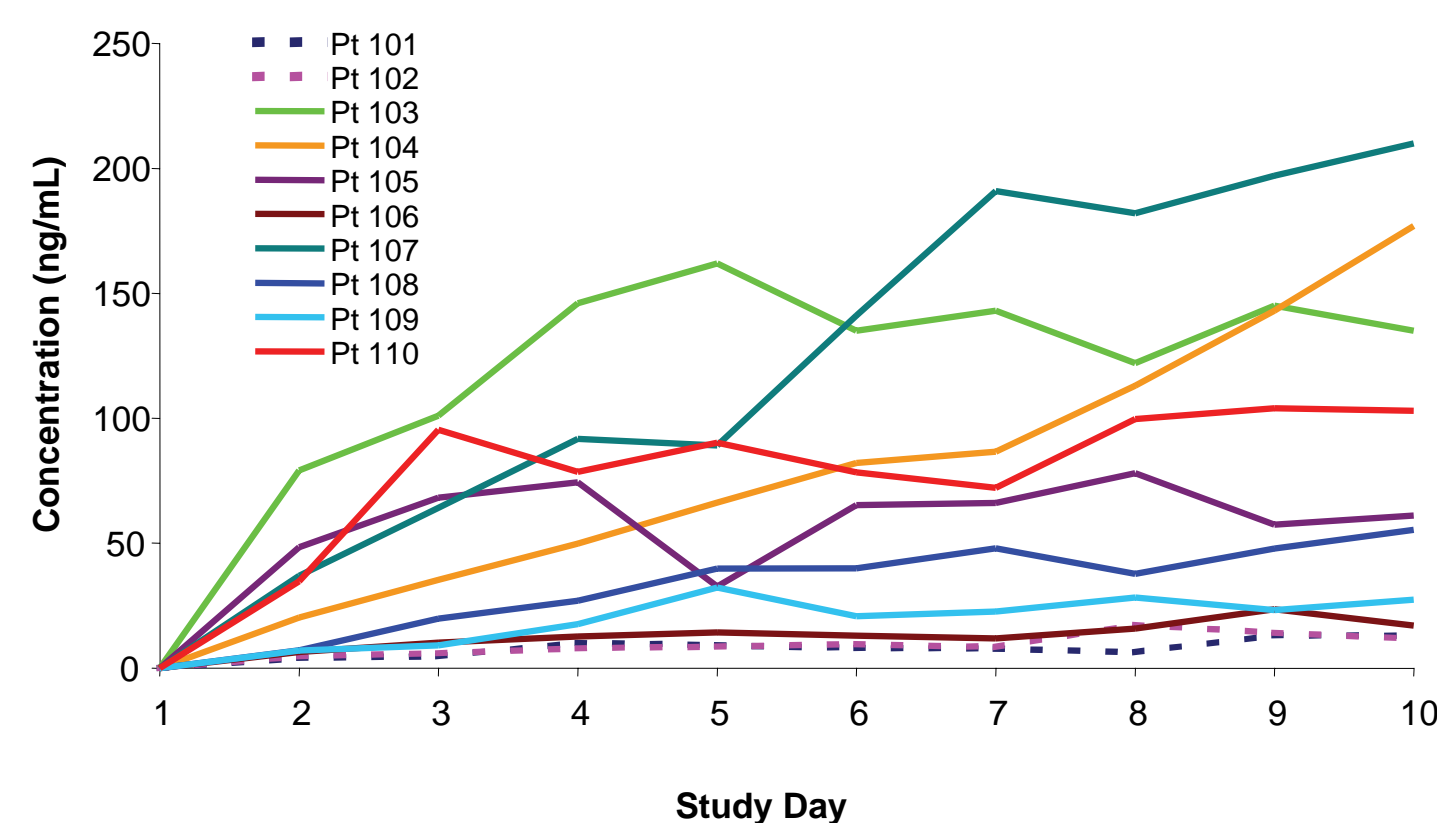


Table 1: Pharmacokinetic Parameters Determined Following a.m. Dose in XACT (Day 10) and A5191 (Day 4)

	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (min)	AUC <sub>0-12h</sub> (ng $\cdot$ h/mL) mean (SEM)	AUC <sub>0-24h</sub> (ng $\cdot$ h/mL) mean (SEM)
100 mg BID (XACT; n=2)	346.5 (26.5)	180 (60)	880.6 (116.6)	1123.5 (145.0)
200 mg BID (XACT; n=8)	1271.3 (234.2)	108.8 (23.3)	4250.4 (816.6)	6471.8 (1511.1)
200 mg BID (A5191; n=6)	1088.2 (482.7)	73.6 (0)	2537.2 (1146.8)	--

all values represent mean (SEM)

Figure 3: Exposure Comparison Following 7 Doses (A5191) and 19 Doses (XACT) at 200 mg BID

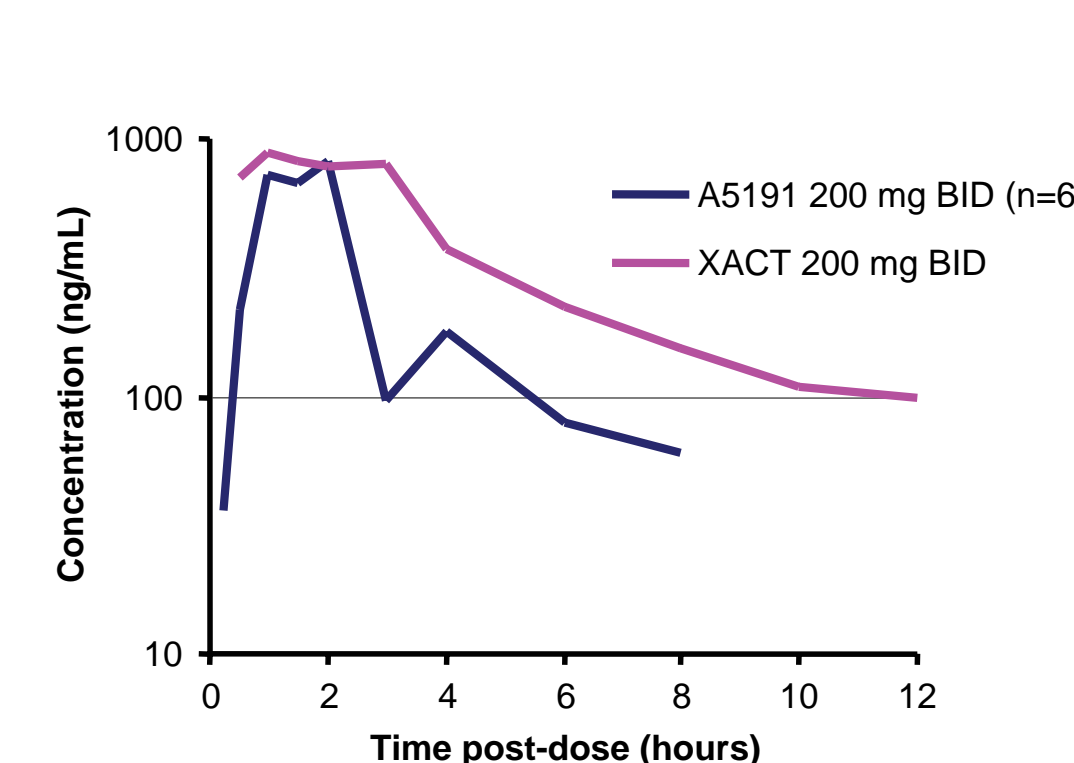


Table 2: Pre-dose and C<sub>max</sub> Comparison Between a.m. and p.m. Doses on Day 10 (XACT)

Pre-dose (trough) conc. (ng/mL) mean (SEM)	Day 10 dose	
	a.m.	p.m.
98.2 (25.0)	98.2 (25.0)	97.8 (24.3)
C <sub>max</sub> (ng/mL) mean (SEM)	1271.3 (234.2)	369.5 (249.1)

all values represent mean (SEM)

<sup>1</sup>calculated values for AUC<sub>0-24h</sub> are considered to be underestimated due to an insufficient number of sampling time points after the p.m. dose; this is also reflected by the lower mean C<sub>max</sub> value for the p.m. compared to the a.m. dose (Table 2)

## Summary of Results

- AMD11070 was well absorbed following oral administration and cleared from plasma in a bi-exponential manner (Figure 1)
- A greater-than-proportional increase in AUC<sub>0-12h</sub> was observed in comparing 100 mg BID and 200 mg BID doses, with increases of approximately 3.6-fold and 4.8-fold for C<sub>max</sub> and AUC<sub>0-12h</sub>, respectively, observed with dose doubling (Table 1); this finding is consistent with previous results from a phase 1 dose escalation study conducted in healthy volunteers (ACTG Study No. A5191) in which AMD11070 was administered as single doses or for 7 consecutive doses using a BID regimen
- Accumulation of AMD11070 is indicated by the observed increases in trough concentrations seen in the current study (Figure 2) and by comparison of observed C<sub>max</sub> and AUC values in the current study in HIV patients with results obtained following single doses or short-term (7 doses) in Study A5191 (Figure 3); the increasing trend in trough plasma concentrations suggests that steady-state may not be achieved following 10 days of administration using a BID regimen
- Plasma AMD11070 concentrations at the 200 mg BID dose exceed the protein-binding adjusted *in vitro* IC<sub>50</sub> for X4-tropic virus in PBMCs with the suggestion this dose level will be associated with antiviral activity *in vivo* (note; antiviral activity and safety findings from this study are presented at this meeting in poster no. 511)

## Conclusion

AMD11070 is a novel CXCR4 inhibitor that inhibits HIV replication *in vitro*, with an IC<sub>50</sub> of 30 nM in PBMCs. AMD11070 is absorbed following oral administration and eliminated from plasma in a bi-exponential manner. Greater than proportional increases in plasma AMD11070 concentrations are observed when comparing results from the 100 mg BID and 200 mg BID dose levels in HIV patients in the current study. This finding is consistent with previous results obtained in a phase 1 study in healthy volunteers. Accumulation of AMD11070 is indicated by increasing plasma trough concentrations in the current 10-day study, and by comparison of exposures seen on day 10 (200 mg BID) with those obtained in a previous study following the 7th consecutive dose. Plasma AMD11070 levels following 10 days of administration at 200 mg BID exceed the protein-binding adjusted *in vitro* IC<sub>50</sub> value (100 ng/mL) at all time points with the suggestion that this dose may result in antiviral activity (antiviral activity and safety findings from this study are presented at this meeting in poster no. 511).

*Note: AMD11070 was recently placed on clinical hold by the FDA due to liver histology changes observed in longer term pre-clinical toxicity experiments. These findings are currently under investigation.*

## Acknowledgements

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## References

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## Introduction

HIV entry into cells occurs through a series of steps beginning with binding of virus to the human CD4 receptor. Binding to CD4 results in a conformational change in the viral envelope glycoprotein, gp120, that allows it to bind to a cell surface chemokine co-receptor, ultimately leading to fusion of viral and cell membranes and viral entry (1). Two chemokine receptor subtypes, CXCR4 and CCR5, are utilized by HIV for entry into human cells. Virus that utilize the CXCR4 receptor are the T-lymphocyte tropic (T-tropic) X4 strains, and those that utilize the CCR5 receptor are the macrophage tropic (M-tropic) R5 strains. In addition, 'dual tropic' virus strains exist that are capable of using either the CXCR4 or CCR5 receptor.

AMD11070 is a first-in-class, small molecule inhibitor of the CXCR4 chemokine receptor that is currently under investigation for treatment of HIV infection. A previously investigated small molecule CXCR4 inhibitor, AMD3100, demonstrated antiviral activity in HIV patients in a phase 2 study in which AMD3100 was administered by 24 hour continuous intravenous infusion for 10 consecutive days (2). One participant harboring pure X4 virus showed a 0.87 log<sub>10</sub> reduction in HIV RNA, and 9 out of 19 patients harboring both X4 and R5 virus showed reductions in the level of X4 virus following treatment. This observed efficacy validated blockade of the CXCR4 receptor as an antiviral strategy.

AMD11070 is an orally bioavailable CXCR4 inhibitor that exhibits potent antiviral activity *in vitro* (3). The safety and pharmacokinetics of AMD11070 were initially evaluated in a phase 1 study in healthy volunteers (Study No. ACTG A5191; reference 3). In that study, AMD11070 was well tolerated without serious adverse events when administered as single doses (50, 100, 200, and 400 mg) or for up to 7 doses using a BID regimen (100, 200, and 400 mg BID). Plasma AMD11070 concentrations increased in a dose-dependent manner, with greater-than-proportional increases in exposure observed across the dose ranges tested in both single and multiple dose cohorts.

Pharmacokinetic results are presented from XACT(X4 Antagonist Concept Trial), a multicenter, dose finding safety and activity study of AMD11070 in HIV-infected adults. Ten patients harboring X4-tropic virus received AMD11070 as a single agent for 10 consecutive days at doses of either 100 mg BID or 200 mg BID. Pharmacokinetic findings are compared with previous results from the aforementioned phase 1 study in healthy volunteers.

## Methods

**Study Design:**

XACT (Multicenter, Dose-Finding Safety and Activity Study of AMD11070 in HIV-Infected Patients Carrying X4-Tropic Virus) is a single arm, open label, dose-escalating/de-escalating study designed to examine the safety, pharmacokinetics, and antiviral activity of AMD11070 in HIV-infected adults harboring X4-tropic virus strains. Patients (men and women  $\geq 18$  years of age) were required to demonstrate an HIV-1 RNA level of  $\geq 5000$  copies/mL, CD4+ cell count  $\leq 200$  cells/mm<sup>3</sup>, and presence of X4 tropic virus of  $\geq 2000$  rlu, as determined using a commercially available tropism assay (Monogram Biosciences). Use of CYP450 3A4 or P-gp inhibitors or inducers was not permitted. Use of CYP450 substrates were permitted with the exception of agents whose clearance is dependent on CYP2D6 and/or CYP2C8. Activity was evaluated based on levels of X4 viral load determined using the tropism assay. Antiviral activity and safety results are presented in poster 511.

**Pharmacokinetics:**

Patients received AMD11070 at dose levels of 100 mg BID (n=2) or 200 mg BID (n=8) for 10 consecutive days. AMD11070 was administered in capsules, with a.m. and p.m. doses administered at approximately 12 hours apart on an empty stomach. Blood sampling for plasma AMD11070 determinations was performed at multiple time points (0-24 hours) following the last 2 consecutive doses (a.m. and p.m.) on Day 10. In addition, samples were obtained prior to each morning dose for trough plasma level determinations.

Plasma AMD11070 concentrations were determined using a validated HPLC-MS/MS method. Briefly, heparinized plasma samples (100  $\mu$ L) were extracted with methyl *tert*-butyl ether (MTBE) following addition of internal standard and pH adjustment with NaOH. The MTBE layer was decanted and evaporated to dryness, and the extract reconstituted in 5/95/0.1% water/acetonitrile/TFA. Analysis was performed by isocratic reversed-phase HPLC-MS/MS using an Inertsil ODS-3 column. The validated calibration range was 0.50 to 500 ng/mL. Pharmacokinetic parameters were calculated using WinNonlin V.4.1 (Pharsight).

