

# Pharmacokinetic-pharmacodynamic analyses of once-daily darunavir in the ARTEMIS study

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## Introduction

- Darunavir with low-dose ritonavir (DRV/r) at a dose of 600/100mg bid has been approved in the USA<sup>1</sup> and in other countries<sup>2</sup> for the treatment of HIV-1 infection in treatment-experienced adult patients.
- The ARTEMIS trial (TMC114-C211) was designed to compare the efficacy, safety and tolerability, resistance characteristics and pharmacokinetics of DRV/r at a dose of 800/100mg qd versus lopinavir/ritonavir (LPV/r) 800/200mg total daily dose in treatment-naïve, HIV-1-infected patients.
- In ARTEMIS, 84% of DRV/r and 78% of LPV/r patients achieved the primary efficacy endpoint of viral load <50 copies/mL (intent-to-treat/time-to-loss of virologic response) at Week 48.<sup>3</sup>
- The current analysis explored the relationship between DRV pharmacokinetics and efficacy and safety following treatment with DRV/r 800/100mg qd in ARTEMIS.

## Methods

### Patients and study design

- In the ongoing, randomized, controlled, open-label, Phase III ARTEMIS trial, treatment-naïve, HIV-1-infected, adult patients were randomized to receive DRV/r 800/100mg qd or LPV/r 800/200mg total daily dose, plus a standard daily-dose of tenofovir disoproxil fumarate/emtricitabine.
- The study protocol was reviewed and approved by the appropriate institutional ethics committee(s) and health authorities, and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

### Pharmacokinetic (PK) and pharmacodynamic (PD) analysis

- Sparse sampling for the determination of plasma concentrations of DRV and ritonavir was performed in all patients
  - blood samples were drawn at Weeks 4, 8, 24, 48, 72 and 96, with two samples taken at Weeks 4 and 24 (the first sample immediately before DRV/r intake, and the second at least 1 hour after the first was drawn).
- Plasma concentrations of DRV and ritonavir were determined by a validated liquid chromatography-mass spectrometry/mass spectrometry method. The lower limit of quantification was 10.0ng/mL for DRV and 5.00ng/mL for ritonavir.
- Estimates of exposure (area under the curve; AUC) and trough concentrations ( $C_{0h}$ ) of DRV were calculated to perform PK/PD analyses
  - a population PK model was developed for DRV on the basis of data in HIV-1-infected patients and healthy volunteers.<sup>4</sup> This model was then applied to the samples drawn in this trial to derive empirical Bayesian estimates of DRV exposure at steady-state
  - the final population PK model to describe the pharmacokinetics of DRV in this trial was a two-compartmental model with first-order absorption. Apparent total clearance was modeled to be dependent on concentrations of alpha-1 acid glycoprotein (AAG), with a decreasing clearance with higher concentrations of AAG
  - individual estimates of  $AUC_{24h}$  and  $C_{0h}$  were obtained at each visit where plasma samples were obtained, and a median value for each parameter was calculated for each individual patient from these values.

- Relationships between DRV  $AUC_{24h}$  and  $C_{0h}$  and virologic efficacy at Week 48 were assessed using analysis of covariance models. Efficacy measurements tested in the model included change in  $\log_{10}$  viral load from baseline and proportion of patients achieving viral load <50 copies/mL (observed data used for both measurements).
- For relationships between DRV PK and safety, descriptive statistics of DRV  $AUC_{24h}$  and  $C_{0h}$  were used for patients who did or did not present with the following adverse events (AEs): rash-related, cardiac-related, gastrointestinal (GI)-related, liver-related, lipid-related, glucose-related, psychiatric and nervous system-related AEs.

## Results

### Patient characteristics

- A total of 689 patients (n=343 in the DRV/r arm and n=346 in the LPV/r arm) were randomized and treated.
- Baseline characteristics were well-balanced between treatment arms. The trial included a diverse population where women and non-Caucasians were well represented (30% and 58%, respectively).
- Consistent with the treatment-naïve status of patients, few patients (9%) had CDC category C HIV infection. At baseline, 34% of patients had  $\geq 100,000$  copies/mL and median CD4 cell count was 225 cells/mm<sup>3</sup>.

### Pharmacokinetics

- Of the 343 patients randomized and treated with DRV/r, 335 patients with sparse sampling data were included in the population PK analysis for DRV.
- Figure 1 and Table 1 show the Bayesian estimates of the DRV PK parameters from the sparse sampling. For all DRV/r-treated patients, DRV  $C_{0h}$  was consistently above 55ng/mL, which is the protein binding-corrected  $EC_{50}$  value for wild-type virus. The median DRV  $C_{0h}$  was 37-fold greater than this  $EC_{50}$  value.

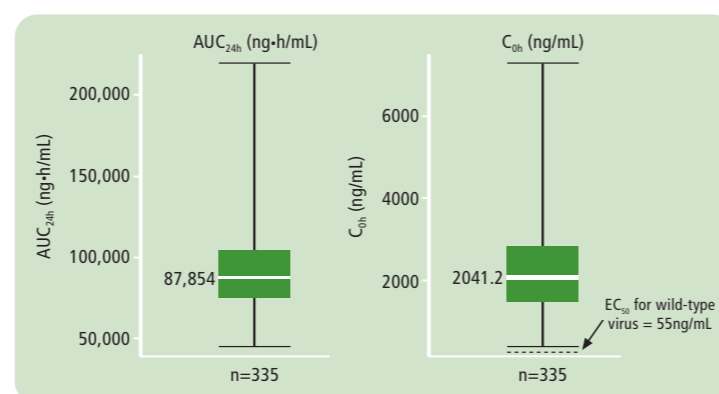


Figure 1. Median, 25% and 75% percentiles, minimum and maximum DRV  $AUC_{24h}$  and  $C_{0h}$ .

Table 1. Population PK estimates of DRV following administration of DRV/r 800/100mg qd (n=335).

PK parameter	Median (range)
$AUC_{24h}$ (ng·h/mL)	87,854 (45,000–219,240)
$C_{0h}$ (ng/mL)	2041.2 (368.0–7242.0)

### Relationship between pharmacokinetics and efficacy

- No apparent relationships were observed between DRV  $AUC_{24h}$  and  $C_{0h}$  quartile ranges and observed change in  $\log_{10}$  viral load from baseline at Week 48 (Figure 2).

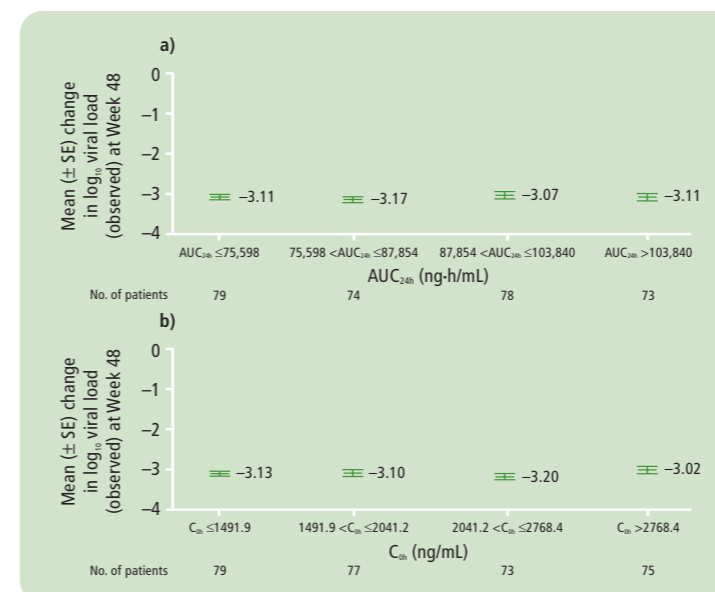


Figure 2. Observed change in  $\log_{10}$  viral load from baseline at Week 48 (observed data) by quartile ranges of: a) DRV  $AUC_{24h}$  and b) DRV  $C_{0h}$ .

- There was no relevant relationship between DRV  $AUC_{24h}$  and  $C_{0h}$  and observed proportion of patients achieving plasma viral load <50 copies/mL at Week 48 (Figure 3).

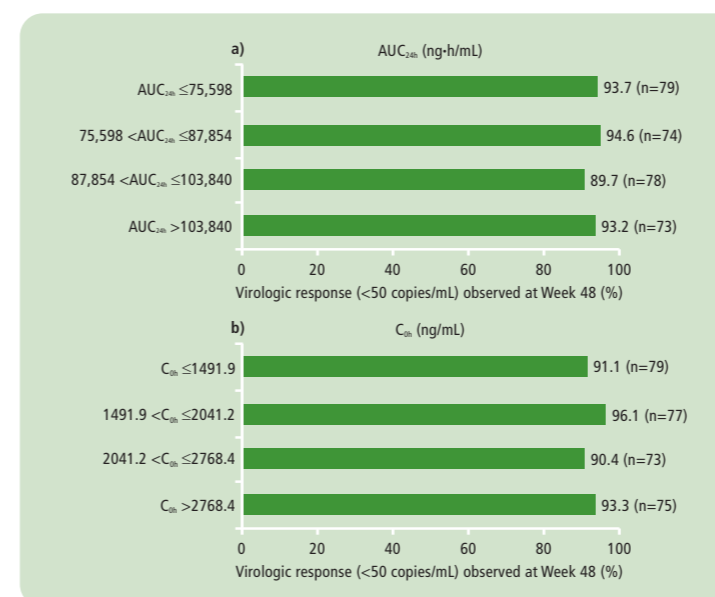


Figure 3. Confirmed virologic response at Week 48 (viral load <50 copies/mL, observed data) by quartile ranges of: a) DRV  $AUC_{24h}$  and b) DRV  $C_{0h}$ .

### Relationship between pharmacokinetics and safety

- No apparent relationships were observed between DRV  $AUC_{24h}$  and  $C_{0h}$  and occurrence of rash, nervous system and psychiatric disorders, or cardiac, GI, liver, lipid and glucose-related AEs (Figure 4).

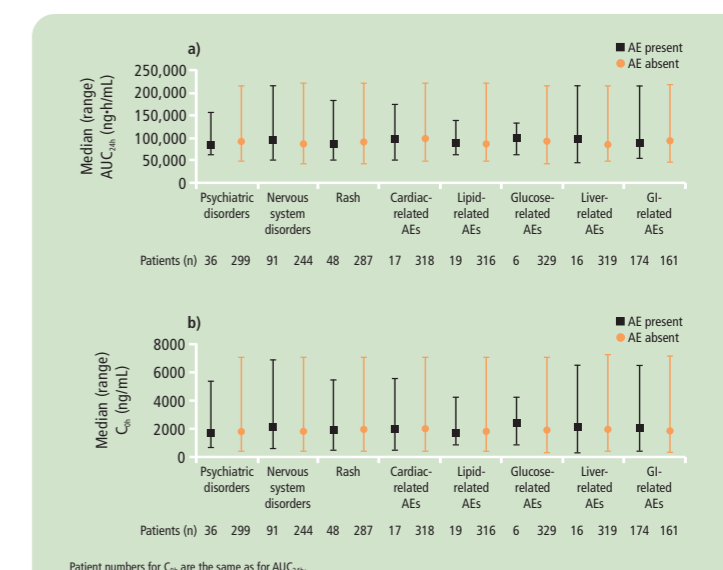


Figure 4. Incidence of AEs of interest (regardless of severity or causality) by DRV PK parameters of: a) median  $AUC_{24h}$  and b) median  $C_{0h}$ .

## Conclusions

- In ARTEMIS, DRV/r 800/100mg qd was shown to be effective and had a favorable tolerability profile at Week 48.
- The current analysis showed that DRV  $C_{0h}$  were consistently above the protein binding-corrected  $EC_{50}$  value for wild-type virus of 55ng/mL in all patients. Furthermore, the median DRV  $C_{0h}$  was 37-fold greater than this  $EC_{50}$  value.
- No relevant relationships between DRV pharmacokinetics and efficacy or safety at Week 48 were observed in antiretroviral-naïve, HIV-1-infected adult patients, at a given dose of DRV/r 800/100mg qd.

## References

1. Tibotec Inc. PREZISTA™ (darunavir) Prescribing Information. October 2006 [accessed January 3, 2008]. Available from: <http://www.prezista.com>.
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4. Vis P, et al. 15th Meeting of the Population Approach Group in Europe, Bruges, Belgium, June 14–16 2006. Abstract 964.