**PREZISTA® (darunavir)**
**Pharmacokinetics of PREZISTA**

## SUMMARY


- In the ARTEMIS study, plasma concentrations of darunavir (DRV) in patients receiving PREZISTA/ritonavir (r) 800/100 mg once daily (QD) were consistently above the in-vitro protein-binding corrected median effective concentration ($EC_{50}$) for wild-type virus (55 ng/mL).[1]
- The median DRV minimum concentration ($C_{0h}$) exceeded the $EC_{50}$ for protease inhibitor (PI)-resistant virus (550 ng/mL) for each treatment group in the pooled POWER 1 and 2 studies and in both arms of the ODIN study.[2,3]
- The $EC_{50}$ for PI-resistant virus (550 ng/mL) was exceeded in all patients in the POWER 3, TITAN, and GRACE studies, all of whom received PREZISTA/r 600/100 mg twice daily (BID).[4-6]
- No direct relationship between DRV pharmacokinetics (PK) and safety or efficacy was observed in the ARTEMIS, ODIN, TITAN, GRACE, and POWER 1, 2, and 3 studies.[1-6]
- **Lloret-Linares et al (2018)**[7] conducted a prospective, single-center study to compare the steady state plasma concentrations of DRV in normal and overweight human immunodeficiency virus (HIV) infected adult patients treated with PREZISTA/r 800/100 mg QD. DRV concentrations tended to be higher in patients with body mass index (BMI) ≥25 kg/m$^2$ than in patients with BMI <25 kg/m$^2$ (2896.7±1689 vs 2091.9±1038, respectively, *P*=0.09) and was positively correlated with fat mass (*r*=0.32, *P*=0.02).
- **Calza et al (2017)**[8] conducted an observational, open-label study in HIV-1 infected patients treated with PREZISTA/r 800/100 mg QD plus emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) 200/300 mg QD. The geometric mean (GM) plasma trough concentration ($C_{trough}$) of DRV was significantly higher among patients aged ≥60 years (older patients) than among patients aged ≤40 years (younger patients) (2209 ng/mL [139%] vs 1876 ng/mL [162%], respectively; geometric mean ratio [GMR] 1.56; 95% confidence interval [CI]: 1.22-1.88; *P*=0.004).[8]
- **Tyrberg et al (2021)**[9] conducted a cross-sectional study to evaluate the differences in steady state concentrations of DRV, atazanavir (ATV), or efavirenz (EFV) following the administration of DRV/r 800/100 mg, ATV/r 300/100 mg, or EFV 600 mg QD in HIV-1 infected patients aged ≥65 years (study group, n=100) and ≤49 years (control group, n=99). Compared with the control group (n=30), DRV steady-state concentrations were significantly higher in the study group (n=25; *P*=0.047).[9]


## CLINICAL DATA

### Treatment-Naïve Patients

#### *ARTEMIS Study*

The ARTEMIS (AntiRetroviral Therapy with TMC114 ExaMined In naïve HIV-1 infected Subjects) study was a randomized, controlled, open-label, 192-week phase 3 study comparing PREZISTA/r 800/100 mg QD versus either lopinavir/r (LPV/r) 800/200 mg QD or LPV/r 400/100 mg BID in treatment-naïve patients. All patients received a fixed-dose background regimen of FTC/TDF 200/300 mg QD (N=689).[10]

*Study Design/Methods*

- Sparse blood sampling for PK/pharmacodynamic (PD) analysis was carried out at weeks 4, 8, 24, and 48 in DRV/r patients.[1]

*PK/PD Results*

- PK data were available for 335 patients (Figure: Exposure Estimates for DRV 800 mg QD).
- Median (range) DRV population PK parameters:
  - Area under the concentration-time curve from t=0-24h ($AUC_{24h}$) (ng·h/mL)=87,854 (45,000–219,240)
  - Trough concentration ($C_{0h}$) (ng/mL)=2041 (368–7242)

**Exposure Estimates for DRV 800 mg QD**

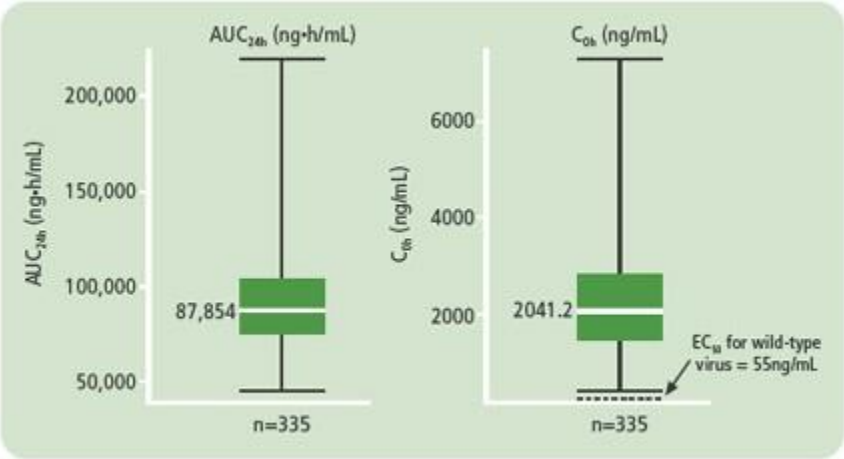


Figure 1. Median, 25% and 75% percentiles, minimum and maximum DRV $AUC_{24h}$ and $C_{0h}$.

**Abbreviations**: $AUC_{24h}$, area under the concentration-time curve from t=0-24h; $C_{0h}$, trough concentration; DRV, darunavir; $EC_{50}$, median effective concentration; QD, once daily.

- $C_{trough}$ was consistently above the $EC_{50}$ for wild-type virus (55 ng/mL) in all patients.
  - Median $C_{0h}$ was 37-fold greater than the $EC_{50}$.
- No relationship was observed between DRV exposure ($AUC_{24h}$ and $C_{0h}$) and virologic response (VR) at week 48.
  - Mean reductions in viral load (VL) and the proportion of patients achieving VL <50 copies/mL were consistently similar across the range of $AUC_{24h}$ and $C_{0h}$ values measured through week 48.
- No relationship was observed between DRV exposure ($AUC_{24h}$ and $C_{0h}$) and the occurrence of rash, nervous system, psychiatric, cardiac, gastrointestinal (GI), liver, lipid, and glucose-related adverse events (AEs).

*Effect of Different Covariates on DRV/r PK Exposure*

- Female patients had higher DRV exposures compared to male patients.[11]
  - Mean $AUC_{24h}$ was 96,364 ng·h/mL and 84,754 ng·h/mL in female and male patients, respectively.
  - Mean $C_{0h}$ was 2288 ng/mL and 1918 ng/mL in female and male patients, respectively.
- Mean DRV exposure and $C_{trough}$ was lowest in Asian patients compared to other ethnic subgroups.[11]
  - Mean $AUC_{24h}$ and $C_{0h}$ were 79,824 ng·h/mL and 1763 ng/mL, respectively.
- The differences observed in DRV exposure with respect to gender and race were not considered clinically relevant.[11]
- Age, body weight, and hepatitis B and/or C coinfection had no effect on DRV exposure.[11]

**Treatment-Experienced Patients**

***ODIN Study***

The ODIN (**O**nce-daily **D**arunavir **I**n treatment-experie**N**ced patients) study was a randomized, open-label, parallel assignment, 48-week phase 3 study comparing PREZISTA/r 800/100 mg QD or PREZISTA/r 600/100 mg BID, each in combination with an optimized background regimen (OBR) consisting of ≥2 investigator-selected nucleoside reverse transcriptase inhibitors (NRTIs), in 590 treatment-experienced patients with no DRV resistance-associated mutations (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V).[12]

*Study Design/Methods*

- Sparse blood sampling for PK/PD analysis was carried out at weeks 4, 8, 24, and 48.[3]

*PK/PD Results*

- Data were available for 280 patients in the QD arm and 278 patients in the BID arm (Table: DRV PK at Week 48 in the ODIN Study).

**DRV PK at Week 48 in the ODIN Study**[3]

| PK Parameter, Median (range) | PREZISTA/r 800/100 mg QD (n=280) | PREZISTA/r 600/100 mg BID (n=278) |
|---|---|---|
| $AUC_{24h}$, ng·h/mL[a] | 87,788 (45,456–236,920) | 109,401 (48,934–323,820) |
| $C_{0h}$, ng/mL | 1896 (184–7881) | 3197 (250–11,865) |

**Abbreviations**: $AUC_{12h}$, 12-hour area under the plasma concentration-time curve; AUC24h, 24-hour area under the plasma concentration-time curve; BID, twice daily; $C_{0h}$, trough concentration; DRV, darunavir; PK, pharmacokinetic; QD, once daily; r, ritonavir.
[a]Calculated as $AUC_{12h}$ x 2 in the BID group.

- $C_{0h}$ and $AUC_{24h}$ of DRV were lower with QD dosing than with BID dosing.
- The entire range of plasma concentrations for DRV QD and BID were above the $EC_{50}$ (55 ng/mL) for wild-type HIV (adjusted for protein binding).
- No clinically relevant relationships between DRV PK and efficacy were found.
- No relationships between DRV PK and laboratory lipid abnormalities or rash, cardiac, GI, liver, lipid, or glucose-related AEs were found.

*Effect of Different Covariates on DRV PK Exposure*

- Age, body weight, and hepatitis coinfection status did not affect DRV exposure.
- Differences in DRV exposure with respect to gender and race were not considered to be clinically relevant.
  - Mean DRV $AUC_{24h}$ was higher in females (QD regimen: 94,780 ng·h/mL; BID regimen: 111,744 ng·h/mL) than in males (QD regimen: 84,031 ng·h/mL; BID regimen: 107,810 ng·h/mL).
  - DRV exposure was highest in blacks, followed by Caucasians and Hispanics, and lowest in Asians.

***TITAN Study***

The TITAN (**T**MC114/r **I**n **T**reatment-experienced p**A**tients **N**aive to lopinavir) study was a randomized, controlled, open-label, 96-week phase 3 study comparing PREZISTA/r 600/100 mg BID or LPV/r 400/100 mg BID, each in combination with an investigator-selected OBR that consisted of ≥2 antiretrovirals (NRTIs ± non-nucleoside reverse transcriptase inhibitors [NNRTIs]), in treatment-experienced, LPV-naïve patients (N=595).[13]

*Study Design/Methods*

- Sparse blood sampling for PK analysis was carried out at weeks 4, 8, 24, and 48 in PREZISTA/r patients (n=285).[5]

*PK/PD Results*

- Median (range) $C_{0h}$ was 3306 (1517–13,198) ng/mL, which consistently exceeded the $EC_{50}$ value for PI-resistant HIV-1 strains (550 ng/mL).
- Median (range) 12-hour area under the plasma concentration-time curve ($AUC_{12h}$): 55,816 (32,437–177,680) ng·h/mL.
- No relationship was observed between DRV exposure ($AUC_{12h}$, $C_{0h}$) and VR (VL <400 copies/mL).
- No relationship was observed between the incidence of AEs of interest experienced by patients and DRV exposure.

*Effect of Different Covariates on DRV PK Exposure*

- DRV $AUC_{12h}$ was not affected by coadministration of nevirapine or EFV, age, body weight, or hepatitis B or C coinfection.[14]
- The differences observed in DRV exposure ($AUC_{12h}$) with respect to gender and race were not considered to be clinically relevant.[14]
  - DRV $AUC_{12h}$ was 8% higher in females (59,072 ng·h/mL) compared to males (54,547 ng·h/mL).
  - DRV exposure was highest in blacks (62,280 ng·h/mL) and lowest in Asian/Orientals (45,749 ng·h/mL).
- Patients with higher baseline alpha 1-acid glycoprotein (AAG) levels experienced higher exposure to DRV compared to those with lower baseline AAG levels.[14]
  - Differences in exposure may be related to the high binding affinity of DRV to AAG protein.

***GRACE Study***

The GRACE (Gender, Race And Clinical Experience) study was an open-label, multicenter, 48-week phase 3b study which evaluated gender and race differences in the efficacy, safety, PK, and tolerability of PREZISTA/r 600/100 mg BID plus an OBR in treatment-experienced men (n=142) and women (n=287).[15]

*Study Design/Methods*

- PK analysis was conducted using the following 2 sampling methods:
  - Sparse PK sampling was performed for DRV in all patients at weeks 4, 8, 24, and 48.
  - Intensive PK sampling was performed for DRV and ritonavir in a subset of patients at weeks 4, 24, and 48.
    - At each of the timepoints, a sample was collected 15 minutes predose and 1, 2, 3, 4, 6, 9, and 12 hours postdose.
- Relationship of DRV PK with efficacy and safety was assessed at week 48.

*PK Substudy Results*

- Sparse PK sampling was undertaken in 376 patients:
  - Women 66% (n=248); black 60% (n=226); Hispanic 22% (n=84).
- Intensive PK sampling was undertaken in 37 patients:
  - Women (n=25); black (n=25); Hispanic (n=10); Caucasian (n=2).

*PK — Sparse sampling*

- Based on the PK data available, the median (range) DRV $AUC_{12h}$ and $C_{0h}$ were 60,642 (26,117-128,790) ng·h/mL and 3624 (931-9570) ng/mL, respectively.
  - DRV $C_{trough}$ exceeded the $EC_{50}$ for resistant virus (550 ng/mL) for all patients (median $C_{0h}$=6.5 x $EC_{50}$).

*PK — Intensive sampling*

- The plasma concentrations of DRV and ritonavir did not show a time-dependent relationship over 48 weeks.
- DRV and ritonavir exposures were comparable to population PK data.

*Effect of Different Covariates on DRV PK Exposure*

- Based on univariate analysis, DRV PK did not differ between women and men or by ethnic subgroups.
- Based on multivariate analysis, higher DRV exposure was statistically correlated with female gender and age; however, these were not considered clinically relevant (as seen in the univariate analysis).
- No relationship was observed between DRV $AUC_{12h}$ or $C_{0h}$ and change in VL from baseline to week 48, the proportion of patients that achieved VL <50 copies/mL, or incidence of AEs such as rash, cardiac, GI, liver, glucose, nervous system, or psychiatric-related disorders.

### *POWER 1, 2, and 3 Studies*

The POWER 1, POWER 2, and POWER 3 studies were 144-week phase 2b studies that evaluated the efficacy and safety of PREZISTA/r in highly treatment-experienced HIV-1 infected patients.[16-18]

*Study Design/Methods*

- The POWER 1 and 2 studies were randomized, controlled, partially blinded studies evaluating the safety and efficacy of various dosing regimens of PREZISTA/r (400/100 mg QD, 800/100 mg QD, 400/100 mg BID, or 600/100 mg BID) in comparison with other PIs, each in combination with an OBR.[16,17]
- POWER 3 was an analysis of two open-label, single-arm trials evaluating the efficacy and safety of PREZISTA/r 600/100mg bid plus an OBR.[19,20]
- PK data for the POWER 1, 2, and 3 studies were based on population PK modeling on sparse samples.

*PK Results*

**DRV PK through Week 24**[2, 4]

| PK Parameter, Median (range) | Pooled POWER 1 and 2 | | | | POWER 3 |
|---|---|---|---|---|---|
| | PREZISTA/r 400/100 mg QD(n=118) | PREZISTA/r 800/100 mg QD(n=118) | PREZISTA/r 400/100 mg BID(n=113) | PREZISTA/r 600/100 mg BID(n=119) | PREZISTA/r 600/100 mg BID(n=292) |
| $AUC_{24h}$, ng·h/mL[a] | 56,576 (13,035–163,950) | 89,845 (25,828–214,040) | 95,592 (37,030–197,186) | 123,336 (67,714–212,980) | 119,858 (56,128-295,000) |
| $C_{0h}$, ng/mL | 1258 (140–5380) | 1840 (256–5868) | 2806 (646–6391) | 3539 (1255-7368) | 3806 (1233-10,761) |

**Abbreviations**: $AUC_{12h}$, 12-hour area under the plasma concentration-time curve; AUC24h, 24-hour area under the plasma concentration-time curve; BID, twice daily; $C_{0h}$, predose concentration; DRV, darunavir; PK, pharmacokinetic; QD, once daily; r, ritonavir.
[a]$AUC_{24h}$ for the BID regimens were calculated by $AUC_{12h}$ multiplied by 2.

- No direct relationship was observed between DRV PK and VR or AEs.

### *Effect of Body Weight and Composition*

**Lloret-Linares et al (2018)**[7] conducted a prospective, single-center study in France to compare the steady-state PK of DRV in normal and overweight HIV infected adult patients

receiving PREZISTA/r 800/100 mg QD combined with at least 2 NRTIs and determined the relationship between concentrations and fat mass.

*Study Design/Methods*

- Patients received the PREZISTA/r QD regimen for at least 6 months prior to study enrollment.
- Blood samples were collected 24 hours (±1 hour) after the last PREZISTA/r dose.

*PK Results*

- A total of 48 patients were enrolled in the study.
- DRV concentrations tended to be higher in patients with BMI ≥25 kg/m$^2$ (*P*=0.09) and was positively correlated with fat mass (*r*=0.32, *P*=0.02). Clusters of differentiation (CD)4+ T cell count and the percentage of patients with a VL of <20 copies/mL did not differ according to the BMI group (Table: Antiretroviral Drug Concentration and Immune Status of Patients Treated with DRV with Respect to BMI).
- According to BMI quartiles, the DRV concentrations were:
  - BMI 17.4-18.3 (n=4): 2174.0±864.2 µg/L
  - BMI 18.5-24.8 (n=23): 2077.6±1082 µg/L
  - BMI 25.3-29.9 (n=14): 2701.1±1410.3 µg/L
  - BMI 30.3-35.4 (n=7): 3287.7±223.1 µg/L
- In a subgroup analysis, the effect of fat mass on serum concentrations was significant in the 52.1% of patients from Sub Sahara Africa (*r*=0.4, *P*=0.04).

**Antiretroviral Drug Concentration and Immune Status of Patients Treated with DRV with Respect to BMI**[7]

| | **BMI <25 kg/m$^2$ (n=27)** | **BMI ≥25 kg/m$^2$ (n=21)** |
|---|---|---|
| Mean drug concentration±SD, µg/L | 2091.9±1038 | 2896.7±1689 |
| Mean CD4 cell count±SD, cells/mm$^3$ | 537±193 | 577±189 |
| Viral load <20 cells/mm$^3$, % | 74.1% | 81% |
| **Abbreviations:** BMI, body mass index; CD, clusters of differentiation; DRV, darunavir; SD, standard deviation. | | |

### *Older vs Younger Patients*

**Calza et al (2017)**[8] conducted a observational, open-label study to evaluate the plasma concentrations of DRV following administration of PREZISTA/r 800/100 mg QD in combination with FTC/TDF in HIV-1 infected patients ≥60 years old (older patients; n=21) in comparison with those ≤40 years old (younger patients; n=25).

*Study Design/Methods*

- The plasma $C_{trough}$ of DRV and ritonavir were assessed at steady state (>4 weeks after the start of treatment).
- Blood samples were obtained before the morning dose and 23-25 hours after the previous morning dose of PREZISTA/r.

*PK Results*

- The GM plasma $C_{trough}$ (coefficient of variation [CV%]) of DRV was 2017 ng/mL (145%), and was significantly higher in older patients than in younger patients (Table: DRV Plasma Concentrations in Younger and Older Patients).
- Overall, the mean DRV $C_{trough}$ (CV%) was significantly higher in female patients (2144 ng/mL; 143%) than in male patients (1991 ng/mL; 128%; GMR 1.48; 95% CI: 1.21-1.89; *P*=0.041), in patients with BMI <24 kg/m$^2$ (2219 ng/mL; 119%) than in those with BMI ≥24 kg/m$^2$ (1887 ng/mL; 152%; GMR 1.57; 95% CI: 1.29-1.78; *P*=0.039), and in patients with albumin concentration <3.5 g/dL (2144 ng/mL; 167%)

than in those with albumin concentration ≥3.5 g/dL (1914 ng/mL; 148%; GMR 1.66; 95% CI: 1.26-1.98; *P*=0.019).
- Similar results were observed with mean ritonavir $C_{trough}$ levels (data not shown).

**DRV Plasma Concentrations in Younger and Older Patients**[8]

| | DRV $C_{trough}$ (ng/mL) | | *P*-value |
|---|---|---|---|
| | Age ≤40 Years (n=25) | Age ≥60 Years (n=21) | |
| Overall | 1876 (162%) | 2209 (139%) | 0.004 |
| Male patients | 1855 (152%) | 2158 (144%) | <0.001 |
| Female patients | 1921 (134%) | 2246 (153%) | <0.001 |
| BMI ≥24 kg/m$^2$ | 1709 (141%) | 2156 (119%) | 0.021 |
| BMI <24 kg/m$^2$ | 1915 (133%) | 2417 (135%) | 0.019 |
| Albumin ≥3.5 g/dL | 1754 (147%) | 2145 (102%) | <0.001 |
| Albumin <3.5 g/dL | 1922 (121%) | 2327 (125%) | 0.042 |

**Abbreviations**: BMI, body mass index; $C_{trough}$, plasma trough concentration; CV, coefficient of variation; DRV, darunavir.
Data are presented as geometric mean (CV; %).

*Effect of Different Covariates on DRV/r PK Exposure*

- Female gender and BMI <24 kg/m$^2$ were significantly associated with increased plasma concentrations of DRV ($C_{trough}$ >2200 ng/mL) by univariate and multivariate analysis.
- Albumin concentration <3.5 g/dL was significantly associated with increased plasma levels of DRV by both analyses (Table: Univariate and Multivariate Logistic Regression Analyses of Factors Associated with Increased Plasma Concentrations of DRV).

**Univariate and Multivariate Logistic Regression Analyses of Factors Associated with Increased Plasma Concentrations of DRV**[8]

| Factor | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P*-value | OR | 95% CI | *P*-value |
| Female gender | 1.49 | 1.21-1.77 | 0.012 | 1.45 | 1.25-1.87 | 0.031 |
| BMI <24 kg/m$^2$ | 1.76 | 1.39-1.98 | <0.001 | 1.62 | 1.38-1.85 | 0.029 |
| Albumin <3.5 g/dL | 1.54 | 1.28-1.82 | 0.044 | 1.35 | 1.12-1.57 | 0.037 |

**Abbreviations**: BMI, body mass index; CI, confidence interval; $C_{trough}$, plasma trough concentration; DRV, darunavir; OR, odds ratio.
Increased plasma concentrations defined as $C_{trough}$ >2200 ng/mL.

**Tyrberg et al (2021)**[9] conducted a cross-sectional study to evaluate the differences in steady state concentrations of DRV, ATV, or EFV following the administration of DRV/r 800/100 mg, ATV/r 300/100 mg, or EFV 600 mg QD in HIV-1 infected patients aged ≥65 years (study group, n=100) and ≤49 years (control group, n=99).

*Study Design/Methods*

- HIV-1 infected patients aged ≥65 years (study group) and ≤49 years (control group) who were on stable treatment with ATV, DRV, or EFV for more than 6 months were included from 4 HIV centers in Sweden.
- Blood samples were collected on the day of inclusion for the measurement of plasma drug levels.
- For the analysis of steady-state drug levels, blood samples were collected between 6 and 36 hours after the last dose of the drug.

*PK Results*

- Between November 2013 and August 2015, 100 (DRV, n=35; ATV, n=19; EFV, n=46) and 99 patients (DRV, n=37; ATV, n=18; EFV, n=44) were included in the study and control groups, respectively.

- Compared with the control group (n=30), the DRV steady-state concentrations were significantly higher in the study group (n=25; *P*=0.047).
- Compared with the control group, the GM steady-state concentration was 48% higher in the study group.

## LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 23 March 2023.

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