Pharmacokinetics of Multiple-Dose Darunavir in Combination with Low-Dose Ritonavir in Individuals with Impaired Hepatic Function

T. Fomaka,1 BMW Hoetelmans,2 S Spinoza-Guzman,3 E De Paepe,4 T Stevens,4 M De Pauw,2 JM Mrus,3 and VI Sekar1
1Tibotec Inc., Yardley, PA, USA; 2Tibotec BVBA, Mechelen, Belgium; 3Tibotec Therapeutics, Bridgewater, NJ, USA

Introduction

• Darunavir (PREZISTA, DRV) is an HIV protease inhibitor (PI) with potent activity against both wild-type and drug-resistant strains.
• At 24 and 48 hours post-dose, DRV has been shown to achieve therapeutic levels in the high-risk setting of HIV-infected patients receiving standard PI-based therapy (700 mg every 12 hours).
• DRV and low-dose ritonavir (RTV) (600 mg twice daily) were evaluated in a clinical trial in HIV-infected patients with moderate hepatic impairment.
• DRV/r (darunavir co-administered with low-dose ritonavir) (RTV) has been approved as an individual drug for the treatment of HIV/AIDS.

Methods

• This phase I, open-label, parallel, controlled, sequential study (TMC114-134) was designed to investigate the steady-state pharmacokinetics (PK) of DRV in HIV-negative volunteers with mild or moderate hepatic impairment, in comparison with HIV-negative healthy volunteers. Short-term safety and tolerability were evaluated throughout the study.
• Volunteers were male or female, aged 18–60 years. Major exclusion criteria for all volunteers included: positive HIV or hepatitis virus test results, severe concomitant illness, serious liver dysfunction, or significant abnormalities on laboratory testing.
• Inclusion criteria for volunteers with moderate hepatic impairment included: a history of pediatric hepatic disease, liver function impairment (Child-Pugh classification), or candidacy for liver transplantation.

Results

• There were no relevant demographic differences within either panel (Table 1).
• All volunteers with hepatic impairment presented with currently active diseases at screening. None of the considered conditions were considered to have an influence on the outcome of the trial.

Pharmacokinetics of DRV

• The mean PK profile in volunteers with mild or moderate hepatic impairment compared with those of healthy matched controls on Day 7 of combined treatment are shown in Figures 2a and 2b, respectively.

Pharmacokinetics of RTV

• RTV (prophylactic doses on Day 6) were comparable between healthy volunteers and those with mild hepatic impairment (Figures 3a and Table 3). In volunteers with moderate hepatic impairment, RTV plasma concentrations were increased relative to those of healthy volunteers (Figure 3b).

Conclusions

• Following treatment with DRV/r-600/100mg bid, DRV pharmacokinetics in volunteers with mild or moderate hepatic impairment were comparable with those in healthy matched controls.
• RTV pharmacokinetics in volunteers with mild hepatic impairment were comparable to those in healthy volunteers, whereas the mean RTV exposure (AUC0-12h) was approximately 50% higher in volunteers with moderate hepatic impairment compared with healthy volunteers.
• All AEs were Grade 1–2 severity except for one Grade 3 increase in AST reported in a volunteer with mild hepatic impairment.
• No serious AEs or AEs leading to discontinuation were reported during DRV treatment.

References


Figure 1. Study design and PK analysis

Figure 2. Mean (standard deviation [SD]) DRV plasma concentrations on Day 7 for: a volunteers with mild hepatic impairment compared with healthy volunteers (Panel A) and b volunteers with moderate hepatic impairment compared with healthy volunteers (Panel B)

Figure 3. Mean (SD) RTV plasma concentrations on Day 1 for: a volunteers with mild hepatic impairment compared with healthy volunteers (Panel A) and b volunteers with moderate hepatic impairment compared with healthy volunteers (Panel B)
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Introduction

• Darunavir (PREZISTA, DRV) is an HIV protease inhibitor (PI) with potent activity against both wild-type and drug-resistant strains.

• At 24 and 48 hours in the phase I/II trial, randomized, controlled POWER 1 and 2 trials, treatment-experienced HIV-1-infected patients receiving DRV co-administered with low-dose ritonavir (RTV) (DRV 600/100 mg bid) plus either an individualized background regimen achieved greater reductions in viral load and greater increases in CD4 count than patients receiving currently available PI/RTV DRV was generally well tolerated with no specific safety concerns.

• DRV/RTV 600/100 mg has been approved in the US, Europe, and other countries for the treatment of HIV in antiretroviral treatment-experienced adult patients.

• Similar to other members of the PI class, DRV undergoes predominantly hepatic metabolism by the cytochrome P450 (CYP) 3A4 isoenzyme. Co-administration of DRV with low-dose RTV increases both the oral availability of DRV and systemic exposure to DRV.

• As HIV-associated mortality and morbidity decrease, liver impairment in HIV-infected patients is emerging as an important comorbidity and may affect the metabolism of antiretroviral drugs. Liver impairment may be the result of several factors, including injection drug use, alcohol abuse and therapeutic drug hepatotoxicity. Additionally, co-infection with HIV and hepatitis C is common and may lead to liver dysfunction.

• This study assessed the phase III steady-state pharmacokinetics and safety of DRV/RTV 600/100 mg bid in HIV-negative volunteers with mild or moderate hepatic impairment, compared with matched HIV-negative, healthy control volunteers, to determine whether liver function affected exposure to DRV.

Methods

• This phase I, open-label, parallel, controlled, sequential study (TMC114-134) was designed to investigate the steady-state pharmacokinetics (PK) of DRV in HIV-negative volunteers with mild or moderate hepatic impairment, in comparison with HIV-negative healthy volunteers. Short-term safety and tolerability were evaluated throughout the study.

• Volunteers were male or female, aged 18–50 years. Major exclusion criteria for all volunteers included a positive HIV or HBV test at screening; acute hepatitis; or any currently active, acute or chronic, severe disease that might interfere with the results of the study. Volunteers with a history of psychiatric illness were also excluded.

• Use of medication other than that used by volunteers for the management of mild or moderate comorbidities was considered to have an influence on the outcome of the trial.

• The most commonly reported AEs during DRV/r treatment in volunteers with mild hepatic impairment were increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and headache, each reported in two volunteers; these were also each reported in two healthy volunteers.

• The most commonly reported AE during DRV/r treatment in volunteers with moderate hepatic impairment was fatigue, reported in two volunteers, and in none of the healthy volunteers.

• All AEs were Grade 1–2 in severity except for one Grade 3 increase in ALT in a volunteer with mild hepatic impairment (with mild liver derangement secondary to alcoholism).

• No serious AEs were noted during the study and no volunteers prematurely discontinued treatment due to an AE.

• No consistent or clinically relevant changes in laboratory parameters were observed. Most treatment-emergent laboratory abnormalities were Grades 1–2 in severity and no Grade 4 abnormalities were observed during DRV treatment.

Results

Participant disposition

• All 32 volunteers completed the study.

• There were no relevant demographic differences within either panel (Table 1).

• All volunteers with hepatic impairment presented with currently active diseases at screening. None of these conditions were considered to have an influence on the outcome of the trial.

Pharmacokinetics of DRV

• The mean PK profiles in volunteers with mild or moderate hepatic impairment compared with those of healthy matched controls on Days 7 of combined treatment are shown in Figures 2a and 2b, respectively.

• DRV/RTV pharmacokinetic data on Day 7 were comparable between healthy volunteers and those with mild hepatic impairment (Figure 3a and Table 2) in volunteers with moderate hepatic impairment, RTV plasma concentrations were increased relative to those of healthy volunteers (Figure 3b).

Pharmacokinetics of DRV

• The mean 90% confidence interval (CI) DRV plasma concentrations (Cmin, Cmax, AUC12h) were 78%, 73%, and 77% higher in volunteers with mild hepatic impairment and 53%, 27%, and 75% higher in volunteers with moderate hepatic impairment, compared with those of healthy controls (Table 2).

• In volunteers with moderate hepatic impairment the mean AUC0–24 of RTV was approximately 42% higher with healthy volunteers, and RTV Cmax was increased by approximately two-fold (Table 3). Safety and tolerability

• The incidence of adverse events (AE) was similar within each panel during treatment with DRV/RTV.

• In Panel A, 3 volunteers with mild hepatic impairment and 5 healthy volunteers reported at least one AE.

• In Panel B, 4 volunteers with moderate hepatic impairment and 5 healthy volunteers reported at least one AE.

Conclusions

• Following treatment with DRV/RTV 600/100 mg bid, DRV pharmacokinetics in volunteers with mild or moderate hepatic impairment were comparable with those in healthy matched controls.

• RTV pharmacokinetics in volunteers with mild hepatic impairment were comparable to those in healthy volunteers, while the mean RTV exposure (AUC0–24) was approximately 50% higher in volunteers with moderate hepatic impairment compared with healthy volunteers.

• All AEs were Grade 1–2 in severity except for one Grade 3 increase in ALT in a volunteer with mild hepatic impairment. No serious AEs or AEs leading to discontinuation were reported.

• Dose adjustments of DRV are not necessary in individuals with mild or moderate hepatic impairment. Clinical monitoring of individuals with mild to moderate hepatic impairment receiving DRV is considered adequate.

References


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Introduction

- Darunavir (PREZISTA, DRV) is an HIV protease inhibitor (PI) with potent activity against both wild-type and drug-resistant strains
- At 24 and 48 hours in the phase I trial, controlled, randomized POWER 1 and 2 trials, treatment-experienced HIV-1-infected patients receiving DRV co-administered with low-dose ritonavir (RTV) (DRV/r) 600/100 mg bid plus an individually optimized background regimen achieved greater reductions in viral load and greater increases in CD4 count than patients receiving currently available PI/RTV. DRV/r was generally well tolerated with no specific safety concerns
- DRV/r 600/100 mg bid has been approved in the US, Europe, and other countries for the treatment of HIV in antiretroviral treatment-experienced adult patients
- Similar to other members of the PI class, DRV undergoes predominantly hepatic metabolism by the cytochrome P450 (CYP) 3A4 isozyme. Co-administration of DRV with low-dose RTV increases both the oral bioavailability of DRV and systemic exposure to DRV
- As HIV-associated mortality and mortality decrease, liver impairment in HIV-infected patients is emerging as an important comorbidity and may affect the metabolism of antiretroviral drugs. Liver impairment may be the result of several factors, including injection drug use, alcohol abuse and therapeutic drug hepatotoxicity. Additionally, co-infection with HIV and hepatitis C is common and may lead to liver dysfunction
- This study assessed the steady-state pharmacokinetics and safety of DRV/r 600/100 mg bid in HIV-negative volunteers with mild or moderate hepatic impairment, compared with matched HIV-negative, healthy control volunteers, to determine whether liver impairment affected exposure to DRV

Methods

- This phase I, open-label, parallel, controlled, sequential study (TMC114-C14A) was designed to investigate the steady-state pharmacokinetics (PK) of DRV in HIV-negative volunteers with mild or moderate hepatic impairment, in comparison with HIV-negative healthy volunteers. Short-term safety and tolerability were evaluated throughout the study
- Volunteers were male or female, aged 18–60 years. Major exclusion criteria for all volunteers included a positive HIV or HIV 2 test at screening; acute hepatitis; or any currently active, clinically significant disease (excluding liver disease for those with mild or moderate hepatic impairment)
- Healthy volunteers could not have chronic hepatitis B or C virus infection or any predefined liver-related laboratory abnormalities as screening
- Volunteers with hepatic impairment had to have a history of hepatic disease and liver function impairment according to the Child-Pugh and NASH classifications. The main exclusion criteria for volunteers with hepatic impairment were hepatic decompensation, Grade 3 or 4 encephalopathy (Child-Pugh classification), hepatic carcinoma, or candidacy for liver transplantation
- Use of medication other than that used by volunteers for the management of mild or moderate hepatic impairment condition had to be discussed prior to inclusion on an individual basis except for paracetamol (acetaminophen)
- The study design is described in Figure 1

- Statistical analysis for DRV compared PK parameters from volunteers with mild (Panel A) or moderate (Panel B) hepatic impairment (defined as those with matched volunteers) with DRV/r-treated volunteers in the same panel. The primary PK parameters were minimum plasma concentration (Cmin), maximum plasma concentration (Cmax) and plasma concentration-time curve from administration up to 12 hours post-dose (AUC12h) values (in the logarithmic scale). The least squares mean (LSM) ratios of the primary parameters from each panel were estimated with a linear mixed effects model with random treatment effect and individual as a random effect. Confidence intervals (CI) of 90% were constructed around the difference between the LSM ratios of test and reference

Results

Participant disposition

- All 32 volunteers completed the study
- There were no relevant demographic differences within either panel (Table 1)
- All volunteers with hepatic impairment presented with currently active disease at screening. None of these volunteers were considered to be at an increased risk on the outcome of the trial

Pharmacokinetics of DRV

- The mean PK profiles in volunteers with mild or moderate hepatic impairment compared with those of healthy matched controls on Day 7 of combined treatment are shown in Figures 2a and 2b, respectively
- DRV pharmacokinetics and statistical analyses for DRV are summarized in Table 2
- In volunteers with moderate hepatic impairment, LSM ratios for DRV Cmin, Cmax and AUC12h were 1.27, 1.52, and 1.20, respectively, in volunteers with mild hepatic impairment
- In volunteers with moderate hepatic impairment, LSM ratios for DRV Cmin, Cmax and AUC12h were 1.27, 1.52, and 1.20, respectively, relative to healthy volunteers

Pharmacokinetics of RTV

- RTV (propharmacokinetics or Day 7) were comparable between healthy volunteers and those with mild hepatic impairment (Figure 3a and Table 2). In volunteers with moderate hepatic impairment, RTV plasma concentrations were increased relative to those of healthy volunteers (Figure 3b)

Conclusions

- Following treatment with DRV/r 600/100mg bid, DRV pharmacokinetics in volunteers with mild or moderate hepatic impairment were comparable with those in healthy matched controls
- DRV pharmacokinetics in volunteers with mild hepatic impairment were comparable to those in healthy volunteers, while the mean RTV exposure (AUC12h) was approximately 50% higher in HIV-1 infected volunteers with moderate hepatic impairment compared with healthy volunteers.
- All AEs were Grade 1–2 in severity except for one Grade 3 increase in ALT reported for one volunteer with mild hepatic impairment (with mild liver cirrhosis secondary to alcoholism)
- No serious AEs were reported during the study and no volunteers prematurely discontinued treatment due to an AE
- No consistent or clinically relevant changes in laboratory parameters were observed. Most treatment-emergent laboratory abnormalities were Grade 1 or 2 in severity and no Grade 4 abnormalities were observed during DRV/r treatment

References

7. Sekar et al. 4th International AIDS Conference. August 13–18, 2000; Toronto, Canada. Poster 30PUD308

Table 1. PK results of DRV on Day 7

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<th>Parameter</th>
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<td>B</td>
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<tr>
<td>Cmin (ng/mL)</td>
<td>2,840 ± 2,346 ± 0.83</td>
<td>2,053 ± 2,554 ± 1.22</td>
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<td>Cmax (ng/mL)</td>
<td>6,553 ± 5,583 ± 0.88</td>
<td>4,715 ± 5,768 ± 1.22</td>
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<td>1,333 ± 1,186 ± 0.94</td>
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<td>AUC12h (ng/mL)</td>
<td>45,647 ± 41,000 ± 1.24</td>
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Table 2. PK results of RTV on Day 7

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<td>Cmin (ng/mL)</td>
<td>5,809 ± 5,129 ± 0.86</td>
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<td>Cmax (ng/mL)</td>
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<td>963 ± 202 ± 0.86</td>
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<tr>
<td>AUC12h (ng/mL)</td>
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<td>963 ± 202 ± 0.86</td>
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Figure 1. Study design and PK analysis

Figure 2. Mean (standard deviation) (SD) DRV plasma concentration-time curves on Day 7 for: a) volunteers with mild hepatic impairment compared with healthy volunteers (Panel A) and b) volunteers with moderate hepatic impairment compared with healthy volunteers (Panel B)

Figure 3. Mean (SD) RTV plasma concentration-time curves on Day 7 for: a) volunteers with mild hepatic impairment compared with healthy volunteers (Panel A) and b) volunteers with moderate hepatic impairment compared with healthy volunteers (Panel B)

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