EFFICACY OF DARUNAVIR/RITONAVIR IN TREATMENT-EXPERIENCED HIV-1-INFECTED PATIENTS AT 96 WEEKS IN THE POWER 1 AND 2 TRIALS

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Keywords

protease inhibitor, HIV, Darunavir, Ritonavir

Introduction: Darunavir (DRV; TMC114) is a HIV protease inhibitor (PI) with potent activity against both wild-type and resistant HIV strains, including multidrug- and cross-resistant strains, and has a high genetic barrier to the development of resistance. The present study combined analysis of POWER 1 and 2 evaluated the efficacy of DRV/r 600/100mg bid compared with CPI(s) at Week 96.

Methods: Patients were male or female, aged >18 years, with HIV-1 RNA >1,000 copies/mL and >1 primary PI mutation (D30N, M46I/L, G48V, I50V/L, V82A/F/T/S, I84V and L90M)9 at screening. Hepatitis B or C co-infected patients were included in POWER 1 if clinically stable and not requiring treatment, but such patients were excluded from POWER 2.

The primary efficacy endpoint was confirmed viral load reduction >1.0 $\log_{10}$ copies/mL at Week 96 from baseline (time-to-loss of virological response [TLOVR] algorithm). The efficacy analysis was based on the intent-to-treat (ITT) population.

The secondary efficacy endpoints were the proportion of patients reaching a viral load <50 copies/mL (TLOVR), change in viral load from baseline (non-completer=failure [NC=F] analysis) and change in CD4 cell count from baseline (last observation carried forward analysis [LOCF]).

Conclusions: Treatment with DRV/r 600/100mg bid led to sustained virological and immunological responses in treatment-experienced patients with advanced HIV infection over 96 weeks.

Patients receiving DRV/r 600/100mg bid had statistically significantly greater reductions in viral load and increases in CD4 cell count at Week 96 than patients receiving CPI(s)

These results support and extend the findings of POWER 1 and 2 at both Weeks 24 and 48, confirming that DRV/r 600/100mg bid is a highly effective treatment option in treatment-experienced patients.

Introduction

Darunavir (DRV; TMC114) is a HIV protease inhibitor (PI) with potent activity against both wild-type and resistant HIV strains, including multidrug- and cross-resistant strains, and has a high genetic barrier to the development of resistance.[1]

DRV with low-dose ritonavir (DRV/r) at a dose of 600/100mg bid has been approved in Europe,[2] the USA[3] and other countries for the treatment of HIV-1 infection in treatment-experienced adults.

POWER 1 and 2 (TMC114-C213 and C202) are randomised, controlled, Phase IIb, 144-week trials designed to evaluate the efficacy and safety of DRV/r in comparison with currently available (control) PIs (CPIs) in treatment-experienced patients, in combination with an optimised background regimen (OBR).[4,5]

At both 24 and 48 weeks, patients receiving DRV/r 600/100mg bid had significantly greater virological and immunological responses than pa-

tients receiving CPIs [4–6]

The proportion of patients with a viral load <50 copies/mL was maintained at 45% over 48 weeks in the DRV/r group, compared with 10% at Week 48 in the CPI group.[6]

DRV/r 600/100mg bid was generally well tolerated, with incidences of adverse events lower than or similar to those in patients receiving CPI(s).[6]

DRV/r is also being evaluated in Phase III trials

- in the TITAN (TMC114-C214) trial in treatment-experienced, lopinavir (LPV)-naïve patients, DRV/r 600/100mg bid was demonstrated to be statistically superior to ritonavir-boosted LPV (LPV/r) at Week 48 for the endpoint of viral load <400 copies/mL (77% vs 67%; p<0.008 for superiority)[7]
- in treatment-naïve patients in the ARTEMIS (TMC114-C211) trial at Week 48, more patients receiving the once-daily dose of DRV/r 800/100mg than those receiving LPV/r (once or twice daily) achieved a viral load <50 copies/mL (84% vs 78%; p<0.001).[8]

The present combined analysis of POWER 1 and 2 evaluated the efficacy of DRV/r 600/100mg bid compared with CPI(s) at Week 96.

Methods

Patients

Patients were male or female, aged >18 years, with HIV-1 RNA >1,000 copies/mL and >1 primary PI mutation (D30N, M46I/L, G48V, I50V/L, V82A/F/T/S, I84V and L90M)[9] at screening.

Patients had received a PI-containing regimen for at least 8 weeks prior to screening, and had previously used >1 NRTI for >3 months, >1 NNRTI and >1 PI for at least 3 months. Previous use of enfuvirtide was permitted.

Major exclusion criteria included acute hepatitis A; any currently active AIDS-defining illness, use of a treatment interruption schedule at screening, previous randomisation to a DRV treatment arm, and use of investigational antiretroviral therapy at screening.

Hepatitis B or C co-infected patients were included in POWER 1 if clinically stable and not requiring treatment, but such patients were excluded from POWER 2.

The study protocol was reviewed and approved by the appropriate institutional ethics committee(s) and health authorities, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Study design

Randomisation at baseline was to either DRV/r (400/100mg qd, 800/100mg qd, 400/100mg bid, or 600/100mg bid), or to one or more investigator-selected CPI(s) (excluding tipranavir [TPV], which was not commercially available at the time of study initiation). All patients also received an OBR (two or more NRTIs, with or without enfuvirtide), selected on the basis of screening genotypic resistance and treatment history.

Following the 24-week dose-finding phase and primary efficacy analysis, all patients receiving lower doses of DRV/r were switched to the 600/100mg bid dose; patients in the CPI group continued their selected treatment regimen

The 96-week pooled efficacy analysis only included patients who had received DRV/r 600/100mg bid or CPIs from baseline.

The primary efficacy endpoint was confirmed viral load reduction >1.0 $\log_{10}$ copies/mL at Week 96 from baseline (time-to-loss of virological response [TLOVR] algorithm). The efficacy analysis was based on the intent-to-treat (ITT) population.

The secondary efficacy endpoints were the proportion of patients reaching a viral load <50 copies/mL (TLOVR), change in viral load from baseline (non-completer=failure [NC=F] analysis) and change in CD4 cell count from baseline (last observation carried forward analysis [LOCF]).

Statistical analyses were adjusted for the stratification factors: number of primary PI mutations, use of enfuvirtide in the OBR, and baseline $\log_{10}$ viral load.

Results

Patient disposition

This updated analysis included 131 patients who had received DRV/r 600/100mg bid from baseline and 124 patients who had received CPI(s) from baseline, all of whom had reached Week 96 or discontinued earlier at the time of analysis.

In total, 43 (33%) of patients receiving DRV/r and 108 (87%) patients receiving CPI(s) discontinued

The high rate of virological failure in the CPI group (89 patients [72%]) compared with the DRV/r group (14 patients [11%]) led to a longer mean treatment duration in the DRV/r group (104.7 weeks)

than in the CPI group (39.8 weeks).

Baseline and demographic characteristics were similar between the two treatment groups (Table 1). Use of enfuvirtide in the OBR (stratified but not randomised) was similar between treatment groups: enfuvirtide was used for the first time by 42 (32%) patients in the DRV/r group and 37 (30%) in the CPI group, and was re-used by 18 (14%) and 15 (12%) patients, respectively.

Parameter	DRV/r 600/100mg bid (N=131)	CPI(s) (N=124)
Demographics		
Male, n (%)	117 (89)	109 (88)
Mean age, years (SD)	43.9 (8.57)	44.4 (7.05)
Caucasian, n (%)	106 (81)	90 (73)
Baseline disease characteristics		
Mean HIV infection duration, years (SD)	12.0 (4.43)	12.9 (4.68)
Mean viral load, $\log_{10}$ copies/mL (SD)	4.61 (0.69)	4.49 (0.78)
Median CD4 cell count, cells/mm3 (range)	153 (3-776)	162.5 (3-1,274)
CDC category C, n (%)	47 (36)	53 (43)
Previous treatment experience		
Median duration previous NRTIs, months (range)	92 (5-238)	98 (6-219)
Median duration previous NNRTIs, months (range)	21 (2-164)	17 (0-67)
Median duration previous PIs, months (range)	63 (5-150)	73 (5-107)
Previous TPV use, n (%)	6 (5)	12 (10)
Previous enfuvirtide use, n (%)	26 (20)	21 (17)
Baseline genotype and phenotype, median (range)		
Number of primary PI mutations	3.0 (0-7)	3.0 (0-8)
Number of PI resistance-associated mutations	12.0 (1-17)	11.5 (2-20)
Median DRV FC (range)	4.3 (0.2-503.2)	3.3 (0.2-362.9)
Median LPV FC (range)	83.9 (0.8-125.4)	82.7 (0.4-130.5)

SD = standard deviation
FC = fold change in EC50

Table 1. Patient demographics and baseline disease characteristics for patients receiving DRV/r 600/100mg bid or CPI(s) from baseline in POWER 1 and 2.

Virological responses

At Week 96, 74 (56%) patients receiving DRV/r and 12 (10%) patients receiving CPI(s) achieved viral load reduction ≥1 $\log_{10}$ copies/mL from baseline (primary efficacy endpoint; p<0.001)

The difference in virological response between the treatment groups was maintained regardless of subgroup (number of primary PI mutations, enfuvirtide use in the OBR and baseline viral load).

This response was better maintained in the DRV/r group than in the CPI group (Figure 1). A smaller proportion of patients never achieved a decrease in viral load of ≥1 $\log_{10}$ copies/mL in the DRV/r group compared with the CPI group (15% vs 56%, respectively).

A viral load <50 copies/mL was reached by 51 (39%) patients in the DRV/r group and 11 (9%) patients in the CPI group (p<0.001), with the difference between the groups sustained over 96 weeks (Figure 2) – this difference was maintained regardless of subgroup (number of primary PI mutations, enfuvirtide use in the OBR and baseline

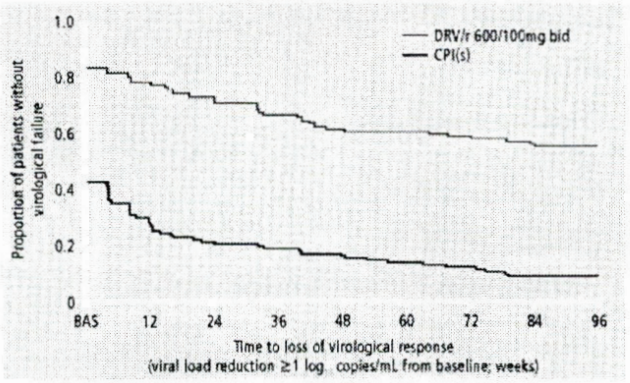

Figure 1. Time to loss of virological response (viral load reduction ≥1 $\log_{10}$ copies/mL from baseline) over time to 96 weeks in POWER 1 and 2 (ITT-TLOVR).

viral load).

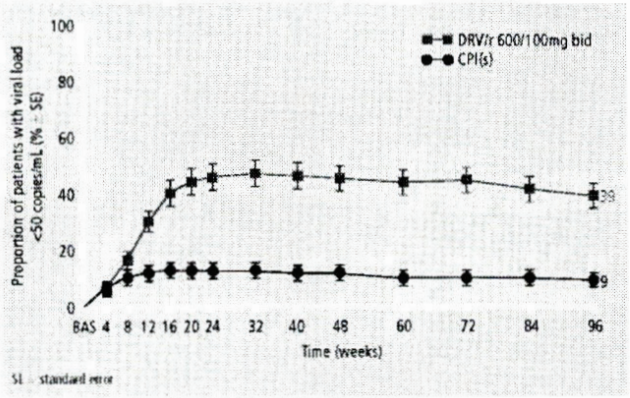

Figure 2. Proportion of patients with viral load <50 copies/mL over time to Week 96 in POWER 1 and 2 (ITT-TLOVR).

Of the 59 patients (45%) in the DRV/r group who had a viral load <50 copies/mL at Week 48, 47 (80%) maintained this response to Week 96. Of the 14 patients (11%) in the CPI group with a viral load <50 copies/mL at Week 48,11 patients (79%) maintained the response to Week 96.

The mean decrease in viral load was greater for the DRV/r group than for the CPI group at all timepoints (Figure 3). At Week 96, the mean change in viral load from baseline was -1.58 (SE 0.12) $\log_{10}$ copies/mL in the DRV/r group and -0.25 (SE 0.06) $\log_{10}$ copies/mL in the CPI group (p<0.001)

The difference between treatment groups was maintained over 96 weeks, regardless of subgroup (number of primary PI mutations, enfuvirtide use in the OBR and baseline viral load).

In the DRV/r group, an increase in mean CD4 cell count from baseline was observed at all timepoints, with the CD4 cell count increasing progressively over time. Conversely, in the CPI group, there

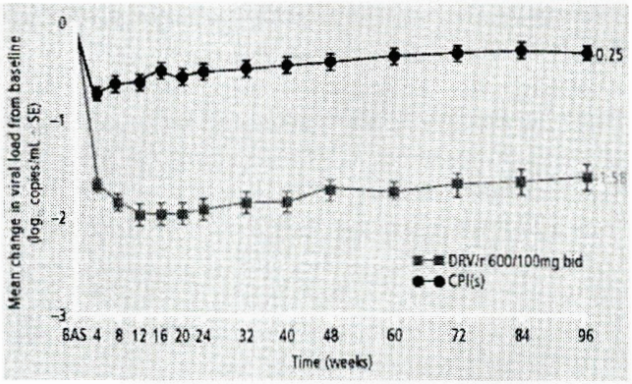

Figure 3. Mean change in viral load from baseline over time to Week 96 in POWER 1 and 2 (NC=F). Immunological response

was little change in mean CD4 cell count at any timepoint over the 96-week period.

At Week 96, the mean absolute CD4 cell count increased from baseline by 133 (SE 15) cells/mm3 in the DRV/r group and 15 (SE 9) cells/mm3 in the CPI group (p<0.001 for difference between groups; Figure 4)

As was observed for the virological responses, the difference between treatment groups was

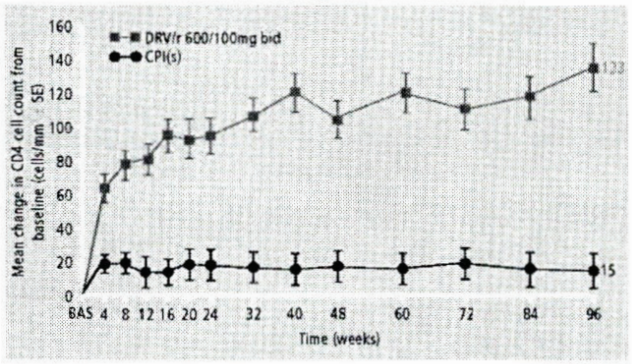

Figure 4. Mean change in CD4 cell count over time to Week 96 in POWER 1 and 2 (LOCF).

maintained over 96 weeks, regardless of subgroup (number of primary PI mutations, enfuvirtide use in the OBR and baseline viral load).

Safety and tolerability

DRV/r was generally well tolerated over 96 weeks by treatment-experienced patients in POWER 1 and 2, with no new safety concerns identified.[11]

Conclusions

Treatment with DRV/r 600/100mg bid led to sustained virological and immunological responses

in treatment-experienced patients with advanced HIV infection over 96 weeks.

Patients receiving DRV/r 600/100mg bid had statistically significantly greater reductions in viral load and increases in CD4 cell count at Week 96 than patients receiving CPI(s)

39% of DRV/r patients achieved a viral load <50 copies/mL compared with 9% of patients receiving CPI(s).

These results support and extend the findings of POWER 1 and 2 at both Weeks 24 and 48, confirming that DRV/r 600/100mg bid is a highly effective treatment option in treatment-experienced patients.

Recent data from Phase III studies demonstrated that DRV/r is effective in patients with a broad range of treatment experience.

References

1. **De Meyer S, et al.** Antimicrob Agents Chemother 2005;49:2314–21.
2. **PREZISTA™ (darunavir)** Summary of Product Characteristics. February 2007 (accessed 20 September 2007). Available from: http://www.emea.eu.int/humandocs/Humans/EPAR/prezista/prezista.htm.
3. **Tibotec Inc.** PREZISTA™ (darunavir) Prescribing Information. October 2006 (accessed 20 September 2007). Available from: www.prezista.com.
4. **Katlama C, et al.** AIDS 2007;21:395–402.
5. **Haubrich R, et al.** AIDS 2007;21:F11–18.
6. **Clotet B, et al.** Lancet 2007;369:1169–78.
7. **Valdez Madruga J, et al.** Lancet 2007;370:49–58.
8. **DeJesus E, et al.** 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, USA, September 17–20, 2007. Abstract H-718b.
9. **D'Aquila RT, et al.** Top HIV Med 2003;11:92–6.
10. **Johnson VA, et al.** Top HIV Med 2006;14:125–30.
11. **Yeni P, et al.** 11th European AIDS Conference, Madrid, Spain, October 24–27, 2007. Abstract P7.2/04.