WEPEB038

Effect of baseline and on-treatment mutations on the antiretroviral activity of darunavir/ritonavir and lopinavir/ritonavir: results of a randomised, controlled, Phase III study (TITAN)

De Meyer S,[1] De Paepe E,[1] Vangeneugden T,[1] Van Baelen B,[1] Spinosa-Guzman S,[1] Lefebvre E,[2] Tomaka F,[3] Lathouwers E,[1] de Béthune MP[1]

[1]Tibotec BVBA, Mechelen, Belgium; [2]Janssen-Cilag, Amsterdam, The Netherlands; [3]Tibotec Inc, Yardley, PA, USA

Address correspondence to: Marie-Pierre de Béthune, PhD, Tibotec BVBA, Generaal De Wittelaan L11 B3, B2800 Mechelen, Belgium; Fax: +32 15 444 290; E-mail: mdbethun@tibbe.jnj.com

Introduction

- The emergence of resistance to highly active antiretroviral therapy (HAART) presents a significant challenge to managing HIV-1 infection.
- Darunavir (DRV; TMC114) is a protease inhibitor (PI) that exhibits significant in-vitro activity against both wild-type and drug-resistant HIV isolates, including multi-drug resistant strains.[1]
- DRV possesses a high genetic barrier to resistance development,[1] defined as the drug's ability to delay resistance development and to retain antiviral activity despite the occurrence of mutations within the viral target protein.
- In the POWER 1 and 2 trials (TMC114-C213 and C202), significant virological and immunological improvement was shown in treatment-experienced patients using DRV with low-dose ritonavir (RTV; DRV/r) compared with currently available PIs.[2] Similar efficacy was confirmed in a larger patient population in the non-comparative POWER 3 (TMC114-C215/C208) analysis.[3]
- DRV/r at a dose of 600/100mg bid has been approved in the USA[4] and other countries including those in Europe[5] for the treatment of HIV-1 infection in treatment-experienced adult patients.
- TITAN (TMC114-C214; **T**MC114/r **I**n **T**reatment-experienced p**A**tients **N**aïve to lopinavir) is an ongoing Phase III trial designed to assess the efficacy and safety of DRV/r in a broad range of treatment experience commonly encountered in the clinical setting. Primary 48-week data are presented at this congress.[6]
- This analysis examined the influence of baseline and on-treatment resistance-associated mutations (RAMs) on the antiretroviral activity of DRV/r and lopinavir with low-dose RTV (LPV/r) in the TITAN trial.

Methods

Design and patient population

- TITAN is a Phase III, randomised, controlled, open-label, 96-week trial comparing the efficacy and safety of DRV/r and LPV/r in treatment-experienced, LPV-naïve, HIV-infected patients.
- Patients from 159 centres in 26 countries with HIV-1 RNA >1,000 copies/mL and treated with a current highly active antiretroviral therapy regimen for ≥12 weeks were randomised to receive an optimised background regimen (OBR, consisting of NRTIs ± one NNRTI) plus either DRV/r 600/100mg bid or LPV/r 400/100mg bid (Figure 1). Initially, patients on a structured treatment interruption (STI) of at least 4 weeks were permitted to be enrolled.
- Patients with previous or current use of LPV, DRV, tipranavir or enfuvirtide and current use of investigational antiretroviral drugs were excluded from the trial.

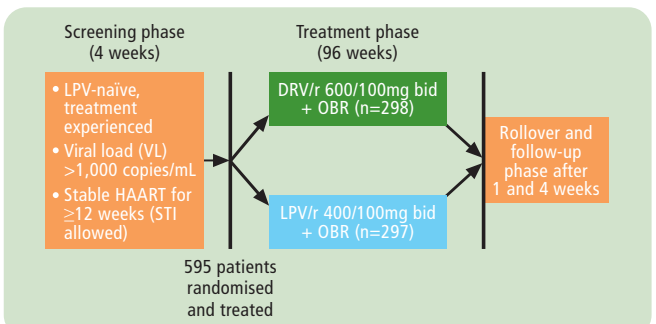

Figure 1. Study flow of the TITAN trial.

Virological analysis

- Analyses were performed on the dataset from the primary analyses with a cut-off date of 17 January 2007, at which time all patients had reached Week 48 of treatment or discontinued.
- The primary efficacy endpoint was the proportion of patients with VL <400 HIV-1 RNA copies/mL at Week 48. A secondary endpoint was the proportion of patients with VL <50 HIV-1 RNA copies/mL at Week 48.
- Viral phenotypic and genotypic determinations were performed using Antivirogram® and Virco®TYPE HIV-1 assays (Virco BVBA, Mechelen, Belgium), respectively.
- Phenotypic resistance was defined as having a fold change in EC_{50} (FC) above the biological/clinical cut-off (Antivirogram). The clinical cut-off of 10 was used for both DRV[7] and LPV.[8]
- All lists of mutations were based on the IAS-USA list of mutations (Fall 2006),[9] DRV RAMs were V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V and L89V.[9] LPV RAMS were L10F/I/R/V, K20M/R, L24I, V32I, L33F, M46I/L, I47V/A, I50V, F53L, I54V/L/A/M/T/S, L63P, A71V/T, G73S, V82A/F/T/S, I84V and L90M.[9]
- In the analyses where baseline genotype was associated with virological response, the time-to-loss of virological response (TLOVR) non-virological failure (VF) imputation was used. For patients who discontinued for reasons other than VF (non-VF), data were not imputed at timepoints after discontinuation.
- The development of resistance at endpoint (i.e. the last available timepoint with a genotype/phenotype during the treatment period) was studied in patients who experienced VF (rebounders and non-responders), defined as loss of, or never achieved, a plasma VL <400 copies/mL. The TLOVR (non-VF censored) imputation method was used for the identification of VF. Patients who discontinued before Week 16 were not taken into account to determine VF.

Results

Baseline data

- Of 595 patients randomised and treated, 31% were PI-naïve. Eighty-two per cent of baseline isolates were susceptible to ≥4 PIs.
- Overall baseline characteristics were balanced between both arms.[6]
- Virological baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics.

Median (range)	DRV/r	LPV/r	All patients
Phenotypic sensitivity score of OBR	2 (0–3)	2 (0–4)	2 (0–4)
Mutations at baseline[9]			
Primary PI mutations	0 (0–6)	0 (0–6)	0 (0–6)
PI RAMs	4 (0–17)	4 (0–14)	4 (0–17)
DRV RAMs	0 (0–5)	0 (0–4)	0 (0–5)
LPV RAMs	1 (0–11)	1 (0–9)	1 (0–11)
NRTI RAMs	2 (0–7)	2 (0–8)	2 (0-8)
FC at baseline			
DRV	0.60 (0.1–37.4)	0.60 (0.1–43.8)	0.60 (0.1–43.8)
LPV	0.70 (0.4–74.4)	0.80 (0.3–74.5)	0.75 (0.3–74.5)

- The frequency of DRV RAMs was low
  - 83% of patients' baseline isolates had no DRV RAMs
  - only 4% of patients' baseline isolates had ≥3 DRV RAMs.

Efficacy analysis results

- Overall efficacy results in the TITAN trial at 48 weeks showed that DRV/r was non-inferior to LPV/r, as determined by the primary endpoint (VL < 400 copies/mL). Results of a secondary analysis showed that DRV/r was superior to LPV/r at this timepoint.[6]
- Higher response rates were observed at 48 weeks in the DRV/r arm compared with the LPV/r arm regardless of the number of DRV RAMs at baseline (Figure 2)
  - a diminished response to DRV/r was observed in patients with ≥3 DRV RAMs at baseline; this subgroup with ≥3 DRV RAMs at baseline had a median number of 13 IAS-USA PI RAMs[9]
  - the virological response to LPV/r was already reduced (response <75% of the overall response) in patients with two DRV RAMs at baseline.

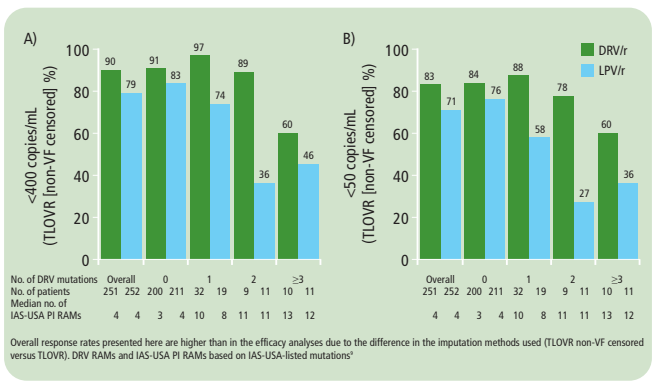

Figure 2. Virological response by baseline DRV RAMs (TLOVR non-VF censored). (A) VL <400 copies/mL, (B) VL <50 copies/mL.

- Higher response rates were observed at 48 weeks in the DRV/r arm compared with the LPV/r arm regardless of the number of LPV RAMs[9] at baseline (Figure 3)
  - the virological response to LPV/r was reduced in patients with ≥6 LPV RAMs at baseline
  - the presence of ≥6 LPV RAMs at baseline had no influence on response to DRV/r; this subgroup had a median number of 12 IAS-USA PI RAMs.[9]

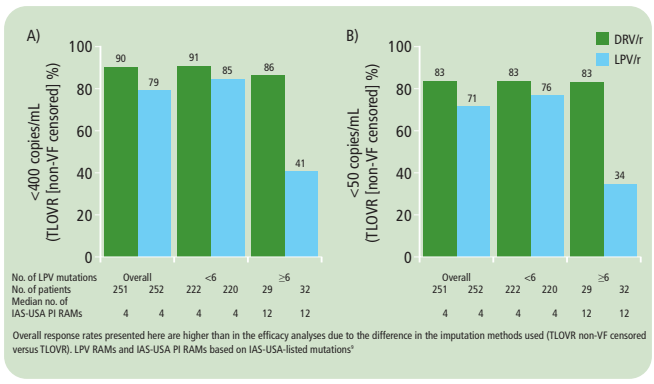

Figure 3. Virological response by baseline LPV RAMs (TLOVR non-VF censored). (A) VL <400 copies/mL, (B) VL <50 copies/mL.

Development of resistance in VF

- VF was observed in 31 (10%) patients in the DRV/r arm and 65 (22%) patients in the LPV/r arm (the numbers of VF in the abstract represent VF at Week 48)
  - after excluding patients with LPV FC >10, the VF rate in the LPV/r arm (19%) was still twice that of the DRV/r arm (10%).
- Proportionally fewer patients with VF on DRV/r than on LPV/r developed primary PI mutations or NRTI RAMs (Figure 4). In addition, fewer patients with VF developed DRV or LPV RAMs in the DRV/r arm compared with those in the LPV/r arm
  - after excluding patients with LPV FC >10, the proportion of patients with VF developing primary PI mutations or NRTI RAMs was still higher in the LPV/r arm compared with the DRV/r arm (33% vs 4%, and 23% vs 13%, respectively).

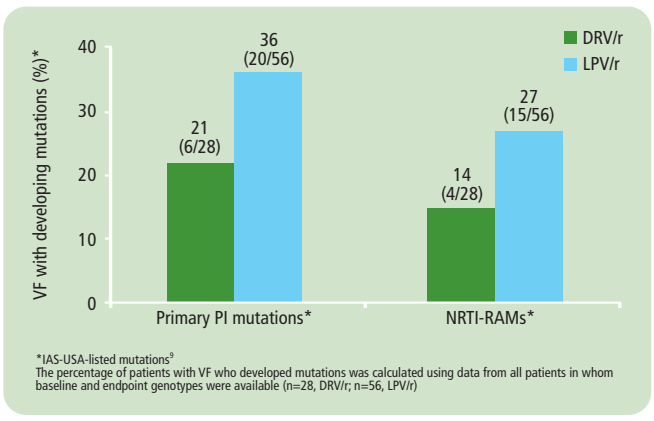

Figure 4. Development of primary PI mutations and NRTI RAMs in patients with VF at endpoint.

- The V32I mutation developed in >10% of patients with VF (3/28; 11%) on DRV/r treatment.
- Fewer patients with VF on DRV/r than on LPV/r lost susceptibility compared with baseline to the PI or an NRTI used in the treatment regimen (Figure 5).

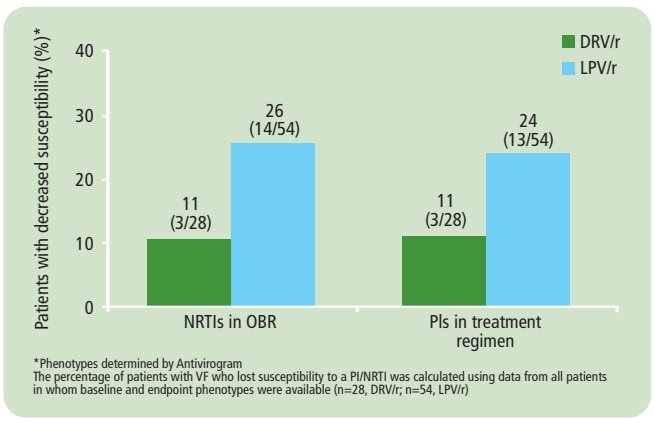

Figure 5. Loss of susceptibility in patients with VF at endpoint.

Conclusions

- In the treatment-experienced, LPV-naïve TITAN patient population, higher response rates were observed at 48 weeks in the DRV/r arm compared with the LPV/r arm, regardless of the number of DRV RAMs or LPV RAMs at baseline.
- The number of baseline DRV RAMs was low in this population.
- Virological response to DRV/r was correlated with the number of DRV RAMs at baseline, confirming the results of the POWER trial analysis.[2,3] The highest virological responses (VL <50 or <400 copies/mL) were seen in patients with 0–1 DRV RAMs.
- DRV/r-treated patients experienced less VF and developed less resistance upon VF than LPV/r-treated patients.
- Compared with LPV/r, fewer primary PI mutations and NRTI RAMs and lower rates of loss of susceptibility to the PI or NRTI(s) in the treatment regimen occurred following VF with DRV/r. DRV-based therapy thus preserved future PI-based treatment options and protected the antiretroviral treatment 'backbone' in TITAN more effectively than LPV/r.
- Findings from this analysis confirmed the high genetic barrier to resistance of DRV, and suggested its ability to preserve future therapeutic options against HIV-1.

References

1. De Meyer S, et al. Antimicrob Agents Chemother 2005;49:2314–21.
2. Clotet B, et al. Lancet 2007;369:1169–78.
3. Molina JM, et al. JAIDS 2007. In press.
4. Tibotec Inc. PREZISTA™ (darunavir) Prescribing Information. October 2006 [cited 21 May 2007]. Available from: http://www.prezista.com.
5. PREZISTA™ (darunavir) Summary of Product Characteristics. February 2007 (accessed 13 June 2007). Available from: http://www.emea.eu.int/humandocs/Humans/EPAR/prezista/ prezista.htm
6. Valdez-Madruga J, et al. 4th International AIDS Society Conference, Sydney, Australia, 22–25 July 2007. Abstract TUAB101.
7. De Meyer S, et al. 15th International HIV Drug Resistance Workshop, Sitges, Spain, 13–17 June 2006. Abstract 73.
8. Abbott Laboratories. Kaletra® (lopinavir/ritonavir) Prescribing Information. Revised April 2005 [cited 21 May 2007]. Available from: www.kaletra.com.
9. Johnson VA, et al. Top HIV Med 2006;14:125–30.

Supported by Tibotec

Presented at the 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, Australia, 22–25 July 2007.

This poster is available on-line at www.tibotec.com.