MOPEB034

Effects of once-daily darunavir/ritonavir versus lopinavir/ritonavir on lipid parameters and anthropometrics in treatment-naïve, HIV-1-infected ARTEMIS patients at Week 96

Ezio Baraldi,[1] Javier Morales-Ramírez,[2] Stefan Schneider,[3] Albrecht Stoehr,[4] Anna Orani,[5] Carline Vanden Abeele,[6] Ludo Lavreys[6]

[1]Embassy Drive Medical Centre, Pretoria, South Africa; [2]Clinical Research Puerto Rico, San Juan, Puerto Rico; [3]Living Hope Clinical Foundation, Long Beach, CA, USA; [4]Institute for Interdisciplinary Medicine, Hamburg, Germany; [5]Division of Infectious Diseases, General Hospital, Lecco, Italy; [6]Tibotec BVBA, Mechelen, Belgium

Address correspondence to: Ezio Baraldi, MD, Embassy Drive Medical Centre, Pretoria, South Africa; Fax: +27 (0)12 420 4555; E-mail: eziob@qw.co.za

Introduction

- The efficacy and safety of the protease inhibitor (PI) darunavir (DRV) combined with low-dose ritonavir (DRV/r) has been assessed in the Phase III, open-label, randomised ARTEMIS (TMC114-C211; **A**nti**R**etroviral **T**herapy with TMC114 **E**xa**M**ined **I**n naïve **S**ubjects) trial.[1] In this study, HIV-1-infected, treatment-naïve patients received DRV/r 800/100mg qd or lopinavir/r (LPV/r) 800/200mg (total daily dose), plus fixed-dose tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC).
- Based on the results of the Week 48 primary analysis of the ARTEMIS study, once-daily DRV/r 800/100mg was approved in the USA and Canada[2] and Europe[3] for use in treatment-naïve patients.
- In a pre-planned analysis of ARTEMIS at Week 96, 79% of DRV/r vs 71% of LPV/r patients achieved HIV-1 RNA <50 copies/mL, and statistical non-inferiority (primary objective) and superiority (secondary objective) of DRV/r over LPV/r was observed (estimated difference = 8.3%, 95% confidence interval [CI]: 1.8–14.7; intent-to-treat [ITT]-time to loss of virological response [TLOVR]; p=0.012 for superiority).[4]
- A meta-analysis of 12 clinical trials of first-line highly active antiretroviral therapy suggests that the choice of PI can affect lipid elevations.[5] Significantly greater elevations were seen in patients receiving LPV/r or fosamprenavir/r versus DRV/r, atazanavir/r or saquinavir/r.
- With regard to safety, in the ARTEMIS primary Week 48 analysis, DRV/r had a favourable lipid profile, with smaller increases in triglycerides and total cholesterol than with LPV/r.[6]
- This analysis reports the lipid profile and anthropometric changes seen in ARTEMIS patients at Week 96.

Methods

Study design

- The ARTEMIS study methodology has been reported in detail previously.[1] Treatment-naïve, HIV-1-infected adult patients with HIV-1 RNA >5,000 copies/mL were randomised in a 1:1 ratio to receive DRV/r 800/100mg qd or LPV/r 800/200mg (total daily dose [qd or bid]).
- All patients also received a fixed-dose background regimen of TDF 300mg qd and FTC 200mg qd.

Assessments and endpoints

- Safety assessments were performed at screening, baseline, Week 2 and every 4 weeks until Week 16, at Week 24 and every 12 weeks thereafter to Week 96. Patients were required to fast for at least 10 hours prior to blood sampling for biochemistry tests.
- The ITT population was used for the safety analysis. Incidence and severity of adverse events (AEs) and laboratory abnormalities were evaluated throughout the study.
- Lipid parameters assessed included triglycerides, total cholesterol, low-density lipoprotein (LDL) (calculated) and high-density lipoprotein (HDL)
  - results of lipid-associated parameters were classified as being above or below the US National Cholesterol Education Program (NCEP) cut-offs at any time from baseline to last available treatment timepoint
  - post-hoc Wilcoxon rank tests were used to test for differences between groups.
- Anthropometric measurements (weight, body mass index [BMI], and waist, hip, chest and neck circumferences) were taken at screening, baseline and Weeks 24, 48, 72 and 96.
- Certain lipid-lowering drugs (atorvastatin, rosuvastatin and fibrates) were permitted as comedications during the trial
  - lovastatin, pravastatin and simvastatin were disallowed in the DRV/r group due to potential interactions with DRV/r.
- Written informed consent was obtained from all patients. The study protocol was reviewed and approved by the appropriate institutional ethics committees and health authorities, and was conducted in accordance with the Declaration of Helsinki.

Results

Patient disposition and baseline characteristics

- In total, 689 patients were randomised to receive DRV/r 800/100mg qd (n=343) or LPV/r 800/200mg total daily dose (n=346) plus fixed-dose TDF/FTC qd.
- Baseline demographics and disease characteristics were well balanced between treatment arms (Table 1) and have been described in detail elsewhere.[1] Mean exposure to treatment was 95.0 weeks for DRV/r and 91.4 weeks for LPV/r.

AEs of interest

- Overall safety data at Week 96 are reported elsewhere.[4] AEs of interest in this analysis were: lipid-, lipodystrophy- and anthropometric-associated AEs.
- No patients in the DRV/r arm permanently discontinued due to a lipid-associated AE. Two patients (0.6%) in the LPV/r group discontinued due to lipid-associated AEs (hypercholesterolaemia and hypertriglyceridaemia [n=1] and hypertriglyceridaemia [n=1]).
- Lipid-associated AEs, regardless of causality and severity, were reported in fewer DRV/r (8.2%) than LPV/r patients (15.9%)
  - this difference did not appear to be attributable to the use of lipid-modifying drugs which were used in similar numbers of DRV/r: 8.2% (statins: 5.5%; fibrates: 1.5%; other [including ezetimibe and fish oil]: 2.3%) and LPV/r patients: 11.3% (statins: 4.9%; fibrates: 3.5%; other [including benfluorex hydrochloride and fish oil]: 4.3%)
  - the most frequent lipid-associated AEs considered by the investigator to be at least possibly related to treatment were hypertriglyceridaemia (2.0% with DRV/r and 5.8% with LPV/r), hypercholesterolaemia (1.5% and 4.0%) and hyperlipidaemia (0.6% and 3.2%)

Table 1. Baseline demographics and disease characteristics.

	DRV/r (n=343)	LPV/r (n=346)
Male, n (%)	239 (69.7)	241 (69.7)
Mean age, years	35.5	35.3
Race, n (%)		
Black	80 (23.4)	71 (20.6)
Caucasian/White	137 (40.1)	153 (44.5)
Hispanic	77 (22.5)	77 (22.4)
Asian	44 (12.9)	38 (11.0)
Other	4 (1.2)	5 (1.5)
Missing	1	2
Disease characteristics		
Mean known duration of infection, years (SD)	2.4 (3.6)	2.5 (3.6)
Mean HIV RNA, $\log_{10}$ copies/mL (SD)	4.86 (0.64)	4.84 (0.60)
Median CD4 cell count, cells/mm³ (range)	228 (4–750)	218 (2–714)
Hepatitis B and/or C co-infection, n (%)	43 (12.5)	48 (13.9)
CDC class, n (%)		
A	226 (65.9)	217 (62.7)
B	91 (26.5)	95 (27.5)
C	26 (7.6)	34 (9.8)
Median lipid levels, mg/dL (mmol/L)		
Triglycerides	105 (1.2)	105 (1.2)
Total cholesterol	156 (4.0)	158 (4.1)
LDLc	89 (2.3)	91 (2.3)
HDL	38 (1.0)	38 (1.0)

SD = standard deviation; CDC = Centers for Disease Control and Prevention; LDLc = calculated LDL

- grade 2–4 lipid-associated AEs at least possibly related to treatment were reported in fewer patients in the DRV/r arm (6.1%) compared with the LPV/r arm (11.3%)
- further details are provided in actual laboratory abnormalities below.

- Few lipodystrophy- or anthropometric-associated AEs were reported in either group (Table 2). No cases of metabolic syndrome as an AE were reported.

Table 2. Lipodystrophy and anthropometric-associated AEs overall and considered at least possibly related to treatment* at Week 96.

	DRV/r (n=343)		LPV/r (n=346)	
Mean exposure, weeks	95.0		91.4	
AE of interest, n (%)	Overall, regardless of cause	At least possibly related to treatment	Overall, regardless of cause	At least possibly related to treatment
Any lipodystrophy-associated AE, n (%)	**6 (1.7)**	**4 (1.2)**	**10 (2.9)**	**7 (2.0)**
Fat tissue increased	0	0	1 (0.3)	1 (0.3)
Facial wasting	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Lipomatosis	0	0	2 (0.6)	2 (0.6)
Lipoma	1 (0.3)	0	4 (1.2)	1 (0.3)
Lipoatrophy	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Lipodystrophy acquired	3 (0.9)	2 (0.6)	0	0
Lipohypertrophy	0	0	1 (0.3)	1 (0.3)
Any anthropometric-associated AE, n (%)				
Anorexia	11 (3.2)	5 (1.5)	16 (4.6)	9 (2.6)
Weight decreased	6 (1.7)	1 (0.3)	6 (1.7)	0
Obesity	1 (0.3)	0	2 (0.6)	1 (0.3)
Weight increased	4 (1.2)	1 (0.3)	1 (0.3)	1 (0.3)

*As considered by the investigator

Lipid-associated laboratory abnormalities

- At Week 96, fewer DRV/r than LPV/r patients had grade 2–4 treatment-emergent abnormalities of triglycerides (4% vs 13%; p<0.0001) or total cholesterol (18% vs 28%; p=0.0019; Table 3)
  - these differences were not thought to be attributable to the use of lipid-modifying drugs, which were used similarly in both groups
  - the above finding was also confirmed by analysis of triglyceride and total cholesterol levels in patients who were not receiving lipid-lowering agents: the incidence of grade 2–4 treatment-emergent abnormalities of triglycerides was 2.9% in DRV/r patients vs 9.1% in LPV/r patients, and total cholesterol was 13.7% in DRV/r patients vs 24.4% in LPV/r patients (Table 3).
- The proportion of patients with increases in LDL and decreases in HDL was similar between the treatment groups.

Table 3. Treatment-emergent, lipid-associated laboratory abnormalities at Week 96.

	In all patients			In patients not receiving lipid-lowering agents		
Laboratory parameter, n (%)*	DRV/r (n=343)	LPV/r (n=346)	p value	DRV/r (n=315)	LPV/r (n=307)	p value
Mean exposure, weeks	95.0	91.4	–	–	–	–
Grade 2–4‡						
Triglycerides	15 (4.4)	46 (13.3)	<0.0001	9 (2.9)	28 (9.1)	0.0010
Total cholesterol	60 (17.5)	95 (27.5)	0.0019	43 (13.7)	75 (24.4)	0.0006
LDLc§	62 (18.1)	50 (14.5)	NS	47 (14.9)	39 (12.7)	NS
Non-graded¶						
HDL	61 (17.9)	71 (20.7)	NA	58 (18.4)	62 (20.2)	NA

*The number of patients with data can vary per parameter, but the % reflects the true percentage of observed abnormalities; ‡Worst grade, based on the Division of AIDS table for grading the severity of adult and paediatric AEs 2004, which does not have a grade 1 classification for triglycerides and grade 4 for total cholesterol and LDL; §LDL calculated by the method of Friedewald et al[7] (LDLc = total cholesterol – HDL – triglycerides/5). LDL was not calculated where triglycerides >400mg/dL (>4.52mmol/L); ¶Below normal: <40mg/dL (<1.03mmol/L); NS = not significant; NA = not assessed;
All p values were determined in post-hoc analyses

- Treatment-emergent abnormalities in triglycerides and total cholesterol classified according to NCEP criteria were less frequent with DRV/r than with LPV/r at Week 96 (Table 4).
- The proportion of patients with abnormally low HDL and abnormally high LDL levels was similar between the treatment groups (Table 4).

Table 4. Treatment-emergent, lipid-associated laboratory abnormalities of interest at Week 96 according to NCEP criteria.

Laboratory parameter, n (%)*	NCEP criteria mg/dL (mmol/L)	DRV/r (n=343)	LPV/r (n=346)
Triglycerides	High, ≥150 (≥1.69) Warranting intervention, ≥200 (≥2.25)	140 (41.1) 72 (21.1)	191 (55.8) 141 (41.2)
Total cholesterol	High, ≥200 (≥5.13) Warranting intervention, ≥240 (≥6.16)	125 (36.7) 40 (11.7)	161 (47.1) 68 (19.9)
LDLc‡	High, ≥130 (≥3.33)	108 (31.7)	110 (32.2)
HDL	Low, Male: ≤40 (1.03), Female: ≤50 (1.28)	69 (20.2)	67 (19.6)

*The number of patients with data can vary per parameter, but the % reflects the true percentage of observed abnormalities. ‡LDL calculated by the method of Friedewald et al[7] (LDLc = total cholesterol – HDL – triglycerides/5). LDL was not calculated where triglycerides >400mg/dL (>4.52mmol/L)

Change in median lipid levels up to Week 96

- The changes in median levels to Week 96 are shown for all lipid parameters (Figure 1).
- The median percentage increase in triglycerides from baseline to Week 96 was lower for DRV/r (12%) compared with LPV/r (50%; p<0.001)
  - in the DRV/r group, median levels of triglycerides remained within NCEP cut-offs; in the LPV/r group, triglyceride levels exceeded cut-offs as early as Week 2 and remained above the cut-off throughout (Figure 1).
- For total cholesterol, the median percentage increase was less pronounced for DRV/r (15%) compared with LPV/r (23%; p<0.001)
  - despite higher median levels of total cholesterol over time in the LPV/r group, median levels remained within the recommended NCEP limits (Figure 1).
- Median changes for HDL and LDL calculated at Week 96 were less pronounced relative to the other lipid parameters (Figure 1).

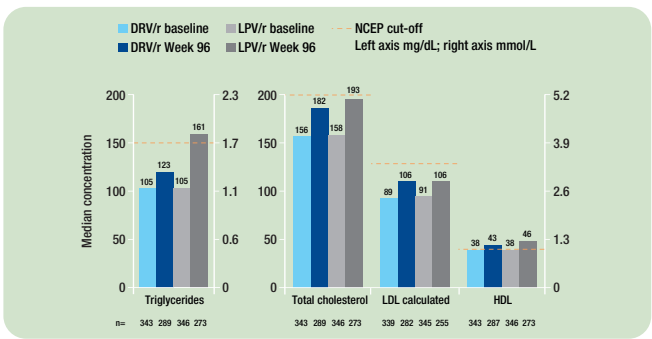

Figure 1. Median lipid levels at baseline and Week 96.

Anthropometric measurements

- Median mid-waist/hip ratio at Week 96 was comparable to baseline in both DRV/r and LPV/r treatment groups (baseline: 0.9; median increase: 0.0, in both arms).
- Median changes in anthropomorphic measurements were as follows:
  - BMI: DRV/r: 0.9kg/m² (lower/upper quartile ranges: –0.1 to 2.2kg/m²; baseline: 23.6); LPV/r: 0.4kg/m² (–0.4 to 1.6kg/m²; 23.4)
  - bodyweight: DRV/r: 2.5kg (lower/upper quartile ranges: –0.2 to 6.1kg; baseline: 68.0kg); LPV/r: 1.3kg (–1.0 to 5.0kg; 69.9kg)
  - chest: DRV/r: 1.8cm (baseline: 92.0cm); LPV/r 1.4cm (93.6cm)
  - hip: DRV/r 1.5cm (baseline: 95.0cm); LPV/r 1.0cm (96.0cm)
  - mid-waist circumference: DRV/r 2.1cm (baseline: 85.1cm); LPV/r 1.0cm (85.0cm)
  - neck circumference: DRV/r 0.2cm (baseline: 36.5cm); LPV/r –0.1cm (37.0cm).
- Although differences were observed between arms for certain measurements, these were small and not considered to be clinically relevant.

Conclusions

- Lipid-associated AEs were reported in fewer DRV/r than LPV/r patients over 96 weeks.
- There were relatively few lipodystrophy and anthropometric-associated AEs reported in either arm over 96 weeks.
- Over 96 weeks, fewer DRV/r than LPV/r patients had grade 2–4 treatment-emergent abnormalities of triglycerides and total cholesterol; these differences were also seen in patients who were not receiving lipid-lowering agents.
- The median percentage increase in triglycerides and total cholesterol from baseline to Week 96 was greater for LPV/r compared with DRV/r; median levels of triglycerides remained within NCEP cut-offs in the DRV/r group, but not in the LPV/r group, where levels exceeded cut-offs as early as Week 2. LDL increases were small and similar in the DRV/r and LPV/r groups and remained below NCEP cut-offs.
- At Week 96, median mid-waist/hip ratio was comparable to baseline in both treatment groups
  - no clinically relevant changes were seen with other anthropometric measurements.
- Safety and tolerability results from Week 48 were corroborated at Week 96, and confirm that once-daily DRV/r 800/100mg is well tolerated and has a more favourable lipid profile than LPV/r in treatment-naïve, HIV-infected patients.

References

1. Ortiz R, et al. AIDS 2008;22:1389–97.
2. PREZISTA™ (darunavir) Prescribing Information. Tibotec Inc. Revised June 2009 [accessed 03 July 2009]. Available from: http://www.prezista.com/prezista/documents/us_package_insert.pdf.
3. PREZISTA™ (darunavir). EPARs for authorised medicinal products for human use, 12 February 2009 [accessed 12 May 2009]. Available from: http://www.emea.europa.eu/humandocs/Humans/EPAR/prezista/prezista.htm.
4. Mills AM et al. AIDS 2009. In press.
5. Hill A, et al. HIV Clin Trials 2009;10:1–12.
6. Arathoon E, et al. 17th International AIDS conference, Mexico City, Mexico, 3–8 August 2008. Poster THPE0151.
7. Friedewald WT, et al. Clin Chem 1972;18:499–502.

Presented at the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Cape Town, South Africa, 19–22 July 2009.

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

Editorial support provided by Gardiner-Caldwell Communications; this support was funded by Tibotec