WEPE0115

Effects of once-daily versus twice-daily darunavir/ritonavir on lipid parameters at Week 48 in treatment-experienced, HIV-1-infected patients with no darunavir resistance-associated mutations in the ODIN study

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Introduction

- The efficacy and safety of the protease inhibitor (PI) darunavir (DRV) with low-dose ritonavir (DRV/r) at a dose of 800/100mg qd has been demonstrated in treatment-naïve patients in the ARTEMIS trial.[1]
- DRV/r 800/100mg qd is approved in combination with other antiretrovirals (ARVs), for the treatment of HIV-1 infection in treatment-naïve adults.[2,3]
- The 48-week, Phase IIIb, randomised, open label ODIN (TMC114-C229; **O**nce-daily **D**arunavir In treatment-experie**N**ced patients) trial compared the efficacy, safety and tolerability of DRV/r 800/100mg qd versus DRV/r 600/100mg bid in treatment-experienced, HIV-1-infected patients with no DRV resistance-associated mutations (RAMs) at screening.
- The primary objective of the ODIN trial was to demonstrate non-inferiority in virological response of once-daily DRV/r versus twice-daily DRV/r at 48 weeks.
- At Week 48, 72.1% of once-daily and 70.9% of twice-daily DRV/r patients achieved HIV-1 RNA <50 copies/mL (intent-to-treat/time-to-loss of virological response); the difference in response was 1.2% (95% confidence interval: –6.1 to 8.5%; p<0.001), establishing non-inferiority of once-daily DRV/r.[4]
- Once- and twice-daily DRV/r were generally well tolerated with most adverse events (AEs) being grade 1 or 2 in severity
  - the rate of discontinuation due to AEs was low; 10 patients (3.4%) in the once-daily arm and 14 patients (4.7%) in the twice-daily arm discontinued.
- Previous studies have shown an association between ARV therapy and changes in lipid metabolism, especially with PIs,[5,6] and particularly with ritonavir.[7]
- This analysis reports the 48-week lipid profile of patients treated with once-daily DRV/r versus twice-daily DRV/r in ODIN.

Patients and methods

- Treatment-experienced, HIV-1-infected patients with HIV-1 RNA >1,000 copies/mL at baseline and on a stable highly active ARV therapy regimen for >12 weeks with no DRV RAMs at screening, were randomised to receive either DRV/r 800/100mg qd or DRV/r 600/100mg bid.
- Patients also received an investigator-selected optimised background regimen consisting of ≥2 NRTIs, based on ARV history and resistance testing.

Assessments and endpoints

- The intent-to-treat population was used for the safety analysis.
- Lipid parameters (triglycerides, total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein [HDL]) were assessed at screening, baseline and Weeks 4, 8, 12, 24, 36 and 48.
- Patients fasted for at least 8 hours prior to each blood sample being taken for biochemistry testing.
- Incidence and severity of lipid-related AEs (clinical significance considered by the investigator) and laboratory abnormalities were assessed during each visit.
- Results of lipid-related parameters were classified as above or below the National Cholesterol Education Program (NCEP) cut-offs at any time during the observation period, which was between baseline and a mean of 44.8 (once-daily DRV/r) or 43.1 (twice-daily DRV/r) weeks.
- Lipid-lowering agents were allowed during the study, with the exception of lovastatin and simvastatin, due to potential drug interactions with DRV/r.
- The study protocol and amendments were reviewed and approved by the appropriate institutional review board health authorities, and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Results

Patient disposition and baseline characteristics

- A total of 590 treatment-experienced, HIV-1-infected patients were randomised: 294 to the once-daily DRV/r arm, and 296 to the twice-daily DRV/r arm.
- Baseline demographics, disease characteristics and lipid levels were generally well balanced between treatment arms (Table 1).

Lipid-related AEs

- Lipid-related AEs were reported less frequently in the once-daily DRV/r group (4.8%) than in the twice-daily DRV/r group (7.1%) (Table 2).
- Grade 3–4 lipid-related AEs considered at least possibly related to treatment occurred in <1% (once-daily DRV/r) and 2% (twice-daily DRV/r) of patients.
- One patient in the twice-daily DRV/r arm reported hypercholesterolaemia as a serious AE, which was considered to be related to treatment.
- One patient in the once-daily DRV/r arm discontinued treatment due to hyperlipidaemia, which was considered not to be treatment-related.

Table 1. Demographics, disease characteristics and lipid levels at baseline.

	DRV/r 800/100mg qd (n=294)	DRV/r 600/100mg bid (n=296)
Demographics		
Male, n (%)	179 (60.9)	198 (66.9)
Median age, years (range)	40 (18–70)	40 (18–77)
Median BMI (kg/m²), (range)	24 (16–50)	24 (13–45)
Race, n (%)		
Black	83 (28.2)	72 (24.3)
Caucasian/White	102 (34.7)	110 (37.2)
Hispanic	47 (16.0)	59 (19.9)
Asian	48 (16.3)	41 (13.9)
Other	14 (4.8)	14 (4.7)
Disease characteristics		
Mean HIV RNA, $\log_{10}$ copies/mL (SE)	4.19 (0.05)	4.13 (0.05)
Median CD4 cell count, cells/mm³ (range)	219 (24–1,306)	236 (44–864)
Mean known duration of infection, years (SE)	8.4 (0.29)	8.5 (0.30)
Median lipid levels, mg/dL (mmol/L)		
Triglycerides	133 (1.50)	133 (1.50)
Total cholesterol	178 (4.60)	178 (4.60)
LDL calculated*	101 (2.61)	104 (2.69)
HDL	42.54 (1.1)	42.54 (1.1)

*Calculated by the method of Friedewald WT, et al.[8] (LDLc = total cholesterol – HDL – triglycerides/5) if triglycerides were <400mg/dL. If it was not possible to calculate LDL cholesterol due to a high triglyceride level, a direct measure was performed; BMI = body mass index; SE = standard error

Table 2. Lipid-related AEs overall and at least possibly related to DRV/r during the treatment period (regardless of severity).

	DRV/r 800/100mg qd* (n=294)		DRV/r 600/100mg bid‡ (n=296)	
AE, n (%)	Overall, regardless of cause	At least possibly related to treatment	Overall, regardless of cause	At least possibly related to treatment
Any lipid-related AE	*14 (4.8)*	*7 (2.4)*	*21 (7.1)*	*14 (4.7)*
Blood cholesterol increased	1 (0.3)	1 (0.3)	5 (1.7)	3 (1.0)
Blood triglycerides increased	0	0	3 (1.0)	2 (0.7)
LDL increased	1 (0.3)	1 (0.3)	2 (0.7)	1 (0.3)
Dyslipidaemia	2 (0.7)	1 (0.3)	0	0
Hypercholesterolaemia	2 (0.7)	2 (0.7)	6 (2.0)	3 (1.0)
Hyperlipidaemia	3 (1.0)	0	4 (1.4)	3 (1.0)
Hypertriglyceridaemia	5 (1.7)	2 (0.7)	8 (2.7)	5 (1.7)

*Mean exposure 44.8 weeks; ‡Mean exposure 43.1 weeks

Lipid-related laboratory abnormalities

- The majority of lipid-related laboratory abnormalities were grade 1 or 2 in severity.
- The most frequent lipid-related laboratory abnormality was increased total cholesterol
  - grade 2 or 3 increases in total cholesterol occurred in 10.1% of patients in the once-daily DRV/r arm compared with 20.6% of patients in the twice-daily DRV/r arm (Table 3).

Table 3. Treatment-emergent, lipid-related laboratory abnormalities.

Treatment-emergent grade 2–4 lipid-related laboratory abnormalities (≥2% incidence), n (%)*	DRV/r 800/100mg qd (n=294)	DRV/r 600/100mg bid (n=296)	p value‡
Triglyceride elevations	15 (5.2)	31 (11.0)	<0.014
Total cholesterol elevations	29 (10.1)	58 (20.6)	<0.0007
LDL calculated§ elevations	28 (9.8)	47 (16.7)	<0.019
Non-graded lipid-related laboratory abnormalities, n (%)			
HDL below the lower normal limit	57 (19.9)	52 (18.4)	0.67

*Based on the Division of AIDS table for grading the severity of adult and paediatric AEs, which does not have a grade 1 classification for triglycerides or grade 4 for total cholesterol and LDL; ‡Calculated using the Fisher's exact test; §Calculated by the method of Friedewald WT, et al.[8] (LDLc = total cholesterol – HDL – triglycerides/5) if triglycerides were <400mg/dL. If it was not possible to calculate LDL cholesterol due to a high triglyceride level, a direct measure was performed

- At Week 48, the incidence of grade 2–4 triglyceride elevations with once-daily DRV/r was approximately half that of twice-daily DRV/r (5.2% vs 11%, respectively).
- Based on NCEP criteria, treatment-emergent abnormalities in triglycerides and total cholesterol were less frequent with once-daily DRV/r than twice-daily DRV/r in patients not receiving lipid-lowering agents (Table 4)
  - in the once- and twice-daily DRV/r arms, 5.8% and 11.5% of patients received lipid-lowering agents, respectively
  - lipid-lowering agents included (once-daily DRV/r versus twice-daily DRV/r): statins 4.1% vs 6.1% and fibrates 1.7% vs 6.1%.

Change in median lipid levels to Week 48

- For all lipid-related parameters, only small increases were seen from baseline to Week 48 for both once- and twice-daily DRV/r (Figure 1).

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- The median increases from baseline to Week 48 in triglycerides were smaller for once-daily DRV/r compared with twice-daily DRV/r
  - the median triglyceride levels in the once-daily DRV/r arm remained below the NCEP cut-off throughout the treatment period.
- For total cholesterol, the median percentage increases from baseline to Week 48 were smaller for once-daily versus twice-daily DRV/r
  - median cholesterol levels remained below the NCEP cut-off for both treatment groups.
- Similar small changes from baseline were observed in median levels of LDL calculated and HDL for both treatment arms.

Table 4. NCEP treatment-emergent lipid-related laboratory abnormalities of interest to Week 48 in patients not receiving lipid-lowering agents.

Laboratory parameter, n (%)	NCEP criteria mg/dL (mmol/L)	DRV/r 800/100mg qd (n=270)	DRV/r 600/100mg bid (n=248)	p value*‡
Triglycerides	High: ≥150 (1.69)	68 (25.2)	85 (34.3)	0.0266
Total cholesterol	High: ≥200 (5.17)	53 (19.6)	68 (27.4)	0.0382
LDL calculated§	High: ≥130 (3.36)	55 (20.4)	62 (25.0)	0.2473
HDL	Low: male: ≤40 (1.03); female: ≤50 (1.29)	85 (31.5)	68 (27.4)	0.3357

*Comparison of once-daily DRV/r vs twice-daily DRV/r at Week 48; ‡Calculated using the Fisher's exact test; §Calculated by the method of Friedewald WT, et al.[8] (LDLc = total cholesterol – HDL – triglycerides/5) if triglycerides were <400 mg/dL. If it was not possible to calculate LDL cholesterol due to a high triglyceride level, a direct measure was performed

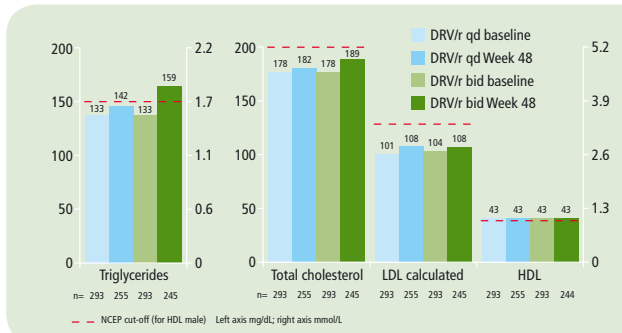

Figure 1. Median lipid levels at baseline and Week 48.

Conclusions

- Lipid-related AEs were reported less frequently in the once-daily DRV/r group than in the twice-daily DRV/r group.
- The incidence of grade 2–4 triglyceride elevations with once-daily DRV/r was approximately half that of twice-daily DRV/r.
- At Week 48, the incidence of NCEP treatment-emergent triglyceride and total cholesterol laboratory abnormalities was significantly lower with once-daily DRV/r compared with twice-daily DRV/r in patients not receiving lipid-lowering agents.
- Overall, only small increases in median lipid levels for all lipid parameters were seen in both the once- and twice-daily DRV/r arms
  - from baseline to Week 48, the median increases in triglycerides were smaller for once-daily DRV/r compared with twice-daily DRV/r.
- Safety and tolerability data from ODIN confirm that once-daily DRV/r was well tolerated with a favourable lipid profile in treatment-experienced, HIV-1-infected patients over 48 weeks.

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