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ARTEMIS 96-week comparison of liver tolerability of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve patients

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Introduction

- ARTEMIS (**A**nti**R**etroviral **T**herapy with TMC114 **E**xa**M**ined **I**n naïve **S**ubjects) is a randomised, open-label, controlled, Phase III trial comparing the efficacy and safety of darunavir (DRV; TMC114) with low-dose ritonavir (DRV/r) 800/100mg qd versus lopinavir with low-dose ritonavir (LPV/r) 800/200mg (total daily dose) in HIV-1-infected, treatment-naïve adult patients.
- The 96-week analysis of ARTEMIS demonstrated the statistical non-inferiority (primary objective) and superiority (secondary objective) of DRV/r (HIV-1 RNA <50 copies/mL) versus LPV/r.[1] At this timepoint, more DRV/r (79%) than LPV/r (71%) patients had HIV-1 RNA <50 copies/mL (estimated difference = 8.3%, 95% confidence interval: 1.8–14.7; intent-to-treat (ITT)/time-to-loss of virological response, p=0.012 for superiority).[1]
- In ARTEMIS, once-daily DRV/r also demonstrated a favourable safety and tolerability profile over 96 weeks.[1]
- Once-daily DRV/r 800/100mg is approved in the USA,[2] the EU[3] and other countries for the treatment of antiretroviral (ARV)-naïve, HIV-1-infected patients.
- Liver-related adverse events (AEs) are a potential concern with many classes of ARVs including protease inhibitors (PIs), and therefore it is important to monitor these types of AEs and liver-related laboratory abnormalities.[4]
- Furthermore, co-infection of HIV and hepatitis B and/or C virus (HBV/HCV) is common and can lead to liver dysfunction
  - in patients taking PIs, co-infection with HBV and/or HCV is associated with an increased risk of elevated liver enzymes compared with patients who are not co-infected.[4]
- In the present analyses, the 96-week hepatic tolerability of DRV/r and LPV/r in treatment-naïve patients in ARTEMIS are presented.

Methods

- Detailed methodology on ARTEMIS has been reported previously.[5]

Study population

- Treatment-naïve, HIV-1-infected adult patients with HIV-1 RNA ≥5,000 copies/mL were randomised to receive DRV/r 800/100mg qd (n=343) or LPV/r 800/200mg total daily dose (qd or bid; n=346).
- All patients received a fixed-dose background regimen of tenofovir 300mg qd and emtricitabine 200mg qd.
- Patients co-infected with HBV and/or HCV were included in the trial if their condition was clinically stable and if they were not expected to receive treatment for hepatitis infection during the trial period.

Safety assessments

- The ITT population was used for the safety analysis.
- The type and incidence of AEs and laboratory abnormalities were assessed throughout the treatment period. These were examined by severity, drug-relatedness and outcome.
- Hepatitis A, B and C antibody testing was performed at screening. After screening, testing was only performed on a visit if a patient was suspected of having hepatitis.
- Blood samples for biochemistry testing were taken at screening, baseline, Weeks 2, 4, 8, 12, 16, 24 and every 12 weeks thereafter to Week 96. Patients were required to fast for at least 10 hours prior to blood sampling. If a patient had not fasted, a blood sample after fasting was collected at an unscheduled visit.
- Liver-related AEs included all AEs suggestive of potential hepatobiliary impact, including abnormal laboratory parameters reported as AEs.
- Liver-related laboratory parameters included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin and indirect bilirubin
  - abnormal parameters were evaluated according to the sponsor-enhanced Division of AIDS (DAIDS) grading severity list[6] and tabulated per group by the worst toxicity grade after baseline
  - post-hoc p values were generated using Fisher's exact test.
- The study protocol was reviewed and approved by the appropriate institutional ethics committee(s) and 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 689 patients were randomised and treated: n=343 in the DRV/r arm and n=346 in the LPV/r arm.
- Baseline demographics and disease characteristics were well balanced across the treatment arms.[1]
- A total of 12.5% patients in the DRV/r group and 13.9% in the LPV/r group were co-infected with HBV or HCV at baseline.
- Mean exposure to treatment was 95.0 weeks for DRV/r and 91.4 weeks for LPV/r.

Safety

Overall AEs

- Overall, most AEs were grade 1 or 2 in severity. There were few discontinuations due to AEs (Table 1)
  - fewer patients in the DRV/r than LPV/r group discontinued due to an AE
  - serious AEs (SAEs) were reported in 9.9% of DRV/r and 15.9% of LPV/r patients.

Table 1. Summary of safety.

Parameter, n (%)	DRV/r (n=343)	LPV/r (n=346)
Mean treatment exposure (weeks)	*95.0*	*91.4*
≥1 AE	316 (92.1)	331 (95.7)
≥1 SAE	34 (9.9)	55 (15.9)
≥1 grade 3 or 4 AE	82 (23.9)	89 (25.7)
≥1 AE leading to permanent discontinuation	19 (5.5)	35 (10.1)

- The most common grade 2–4 AEs considered (by the investigator) to be at least possibly related to treatment (occurring in ≥2% of patients) were diarrhoea (4.1% and 11.0% with DRV/r and LPV/r, respectively), hypertriglyceridaemia (1.7% and 5.2%), hypercholesterolaemia (1.5% and 3.2%), nausea (1.7% and 2.9%), increased ALT (1.5% and 2.9%), increased AST (1.2% and 2.0%), and increased low-density lipoprotein (2.3% and 0.9%).

Liver-related AEs

- Three DRV/r patients and 10 LPV/r patients discontinued due to ≥1 grade 3 or 4 liver-related AE. A grade 2 liver-related AE also led to treatment discontinuation in one LPV/r patient.
- Liver-related SAEs, regardless of causality, were reported in two patients in the DRV/r group and nine patients in the LPV/r group
  - of these, none in the DRV/r group were considered treatment-related
  - in the LPV/r group, these were considered treatment-related in four patients, leading to permanent treatment discontinuation in two patients (grade 4 increased ALT and AST [Day 27] plus grade 4 increased transaminases [Day 29]). Both of these patients were co-infected with HBV.
- Overall, 5.8% of patients in the DRV/r group and 11.0% in the LPV/r group reported liver-related AEs (including laboratory abnormalities) (p=0.019; Table 2)
  - only half of these were considered (by the investigator) to be at least possibly treatment-related (Table 2).
- The most frequently reported treatment-related liver-related AEs were increased ALT and AST (Table 2).
- During treatment, seven patients in the LPV/r group developed hepatitis (HCV: n=5; hepatitis A virus: n=2); four of these were grade 3–4 in severity.

Table 2. Summary of liver-related AEs overall and at least possibly related to treatment (occurring in ≥1% of patients in either treatment group).

Parameter, n (%)	DRV/r (n=343) All	DRV/r (n=343) Related	LPV/r (n=346) All	LPV/r (n=346) Related
Any liver-related AE	*20 (5.8)*	*9 (2.6)*	*38 (11.0)*	*17 (4.9)*
HCV (new infections during trial)	0	0	5 (1.4)	1 (0.3)
ALT increased	8 (2.3)	6 (1.7)	15 (4.3)	11 (3.2)
AST increased	8 (2.3)	4 (1.2)	12 (3.5)	8 (2.3)
Blood ALP increased	1 (0.3)	0	5 (1.4)	2 (0.6)
Hepatic enzyme increased	3 (0.9)	1 (0.3)	4 (1.2)	2 (0.6)

- Grade 2–4 liver-related AEs considered by the investigator to be at least possibly related to treatment occurred in 2.3% of patients in the DRV/r group and 4.3% in the LPV/r group (Table 3)
  - of these, the most commonly reported AEs were asymptomatic liver-related laboratory abnormalities: increased ALT and AST
  - all other liver-related AEs occurred in <1% of patients in either treatment group.

Table 3. Grade 2–4 at least possibly treatment-related liver-related AEs (in ≥1% of patients in either treatment group).

Parameter, n (%)	DRV/r (n=343)	LPV/r (n=346)	p value
Any liver-related AE	*8 (2.3)*	*15 (4.3)*	*0.2024*
Increased ALT*	5 (1.5)	10 (2.9)	0.2975
Increased AST*	4 (1.2)	7 (2.0)	0.5456

*Laboratory abnormalities reported as AEs

- In both groups, HBV/HCV co-infected patients experienced more liver-related AEs versus non-co-infected patients (14.0% and 39.6% with DRV/r and LPV/r, respectively, in co-infected patients, vs 4.7% and 6.4%, respectively, in non-co-infected patients)
  - liver-related AEs in co-infected patients were lower with DRV/r (6/43, 14.0%) versus LPV/r (19/48, 39.6%)
    - fewer co-infected patients in the DRV/r than the LPV/r group had increased ALT (11.6% [5/43] vs 22.9% [11/48] for DRV/r and LPV/r, respectively) or AST (9.3% [4/43] vs 22.9% [11/48]).

Liver-related laboratory abnormalities

- Most liver-related laboratory abnormalities were grade 1–2 in severity (Table 4).
- The most frequently reported laboratory abnormalities (increased ALT and AST) occurred in a similar proportion of patients in both groups (Table 4)
  - grade 2–3 hyperbilirubinaemia occurred more frequently in LPV/r (5%) than DRV/r (1.2%) patients (p=0.0064; grade 2: 0.9% of DRV/r and 4.4% of LPV/r patients; grade 3: 0.3% of DRV/r vs 0.6% of LPV/r patients). No cases of grade 4 hyperbilirubinaemia were reported in either group.

Table 4. Treatment-emergent liver-related laboratory abnormalities of interest (worst grade).*

Parameter, n (%)‡	Worst grade	DRV/r (n=343)	LPV/r (n=346)	p value
Increased ALT	All grades	71 (20.7)	66 (19.3)	
	Grade 2–4	38 (11.1)	40 (11.7)	0.9045
Increased AST	All grades	72 (21.0)	66 (19.3)	
	Grade 2–4	39 (11.4)	35 (10.2)	0.6240
Hyperbilirubinaemia	All grades	8 (2.3)	31 (9.1)	
	Grade 2–3§	4 (1.2)	17 (5.0)	0.0064

*Liver biochemistry assessed in blood samples as part of clinical laboratory evaluations; ‡The number of patients with data can vary per parameter, but percentage reflects the true percentage of observed abnormalities; §Grade 4 hyperbilirubinaemia was not observed

- Non-graded laboratory abnormalities were reported in few patients in either group
  - direct bilirubin levels were reported as being above normal in 0.9% of DRV/r patients and 5.0% of LPV/r patients
  - 0.9% of DRV/r and 4.7% of LPV/r patients had above normal levels of indirect bilirubin.
- Overall, the incidence of increased AST and ALT was high in co-infected patients (DRV/r: 58.1%; LPV/r: 75.0%), although the majority of these were grade 1–2 in severity
  - grade 2–4 increases in ALT were observed in 37.2% (16/43) DRV/r and 56.3% (27/48) LPV/r HBV/HCV co-infected patients
  - grade 2–4 AST elevations in this population were also seen in fewer DRV/r than LPV/r patients (27.9% [12/43] and 47.9% [23/48], respectively).
- In the LPV/r group, hyperbilirubinaemia was reported more frequently in co-infected (12.5% [6/48]) than in non-co-infected patients (9.1% [31/346])
  - in the DRV/r group, the incidence of hyperbilirubinaemia was low and similar in co-infected and non-co-infected patients (2.3% [1/43] vs 2.3% [8/343], respectively).

Conclusions

- Over 96 weeks in ARTEMIS, the incidence of liver-related AEs and laboratory abnormalities was low in both arms
  - fewer liver-related AEs and laboratory abnormalities were seen with once daily DRV/r 800/100mg vs LPV/r 800/200mg (total daily dose)
  - the most common liver-related AEs and laboratory abnormalities in either group were increased ALT and AST
  - seven patients in the LPV/r group developed acute viral hepatitis infection during treatment; this could potentially have affected liver-related AEs or laboratory abnormalities.
- There were no liver-related SAEs considered (by the investigator) to be related to treatment with DRV/r.
- In both treatment groups, patients co-infected with HBV and/or HCV experienced more liver-related AEs or laboratory abnormalities than patients not co-infected
  - fewer HBV and/or HCV co-infected patients in the DRV/r than the LPV/r group experienced liver-related AEs or laboratory abnormalities.
- Data from ARTEMIS confirm the favourable liver tolerability profile of once-daily DRV/r 800/100mg in treatment-naïve HIV-infected patients.

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