

Comparison of gastrointestinal adverse events of darunavir/ritonavir and lopinavir/ritonavir at Week 96 in ARTEMIS

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Introduction

- The protease inhibitor (PI) darunavir (DRV; TMC114) with low-dose ritonavir (DRV/r) at a dose of 800/100mg qd is approved in Europe,¹ the USA² and other countries for the treatment of antiretroviral (ARV)-naïve, HIV-1-infected adult patients.
- ARTEMIS (AntiRetroviral Therapy with TMC114 ExaMined In naïve Subjects) is a Phase III, open-label, randomised, controlled trial, evaluating the efficacy, safety and tolerability of 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.
- Analyses of this study at 96 weeks showed that
 - 79% of patients in the DRV/r arm achieved HIV-1 RNA <50 copies/mL vs 71% of patients in the LPV/r arm, confirming statistical non-inferiority of DRV/r versus LPV/r ($p < 0.001$; per-protocol-time-to-loss of virological response)³
 - once-daily DRV/r had a favourable tolerability profile in treatment-naïve patients.
- Gastrointestinal adverse events (GI AEs) are known to be associated with the use of PIs, and are often the reason for discontinuation of treatment.⁴
- Previously, the 48-week GI tolerability of DRV/r 800/100mg qd in treatment-naïve ARTEMIS patients was reported⁵
 - DRV/r was associated with a significantly lower rate of grade 2–4 treatment-related diarrhoea than LPV/r (4% vs 10%; $p < 0.01$)
 - no patients treated with DRV/r permanently discontinued due to grade 2–4 GI AEs.
- As long-term tolerability of ARV treatment is essential for treatment success, we now report the 96-week GI tolerability of DRV/r 800/100mg qd versus LPV/r in ARTEMIS.

Methods

Study design

- ARTEMIS is planned for 192 weeks and compares the long-term efficacy, safety and tolerability of DRV/r with LPV/r in treatment-naïve, HIV-1-infected adult patients with HIV-1 RNA >5,000 copies/mL.
- Patients were randomised to receive DRV/r 800/100mg qd ($n=343$) or LPV/r 800/200mg total daily dose (qd or bid, $n=346$), plus a fixed-dose background regimen of once-daily tenofovir 300mg and emtricitabine 200mg.
- LPV/r was given as soft-gel capsules; patients were allowed to switch (in case of intolerance) to tablets later in the study, subject to availability and local approval.³
- Detailed methodology was reported previously.⁶

Safety assessments

- All data collected at the time that all patients reached Week 96 ($n=689$) were included in the safety analysis.
- The type and incidence of all AEs, HIV-related events, and AIDS-defining illnesses were reported. These parameters were examined by severity, drug relationship and outcome.
- The incidences of grade 2–4 GI AEs determined by the investigator at least possibly related to treatment were also reported.
- AEs were assessed and tabulated per treatment group
 - special attention was given to patients who discontinued the trial due to an AE/HIV-related event, or who experienced a grade 3 or 4 AE or a serious AE.
- Chi-square test was used for drug comparisons of AE incidences.
- The study protocol and amendments were reviewed and approved by the appropriate institutional review board, 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

- At baseline, demographical data and disease characteristics were well balanced across the treatment arms (Table 1)
 - patients had a median age of 34 years (range 18–70 years)
 - mean baseline \log_{10} HIV-1 RNA was 4.85 copies/mL.

Information on treatments

- In total, 86% of LPV/r patients switched from capsule to tablet formulation, 12% started and remained on capsules, and 2% started and remained on tablets.³ Overall treatment duration was greater for the tablet versus the capsule formulation.

Table 1. Demographic and baseline characteristics.

	DRV/r (n=343)	LPV/r (n=346)
Demographic parameter		
Sex, n (%)		
Female	104 (30)	105 (30)
Male	239 (70)	241 (70)
Median age, years (range)	34 (18–70)	33 (19–68)
Disease characteristics		
Mean baseline \log_{10} HIV-1 RNA, copies/mL (SD)	4.86 (0.638)	4.84 (0.604)
Baseline HIV-1 RNA $\geq 100,000$ copies/mL, n (%)	117 (34)	120 (35)
Median CD4 cell count, cells/mm ³ (range)	228 (4–750)	218 (2–714)
CD4 cell count <200 cells/mm ³ , n (%)	141 (41)	148 (43)
Mean duration of infection, years (SD)	2.4 (3.63)	2.5 (3.56)
CDC class C (%)	26 (8)	34 (10)

SD = standard deviation; CDC = Centre for Disease Control and Prevention

- Anti-diarrhoeals and anti-motility agents (loperamide [HCl] and co-phenotrope) were taken half as often by DRV/r (13%) versus LPV/r (27%) patients (Figure 1).

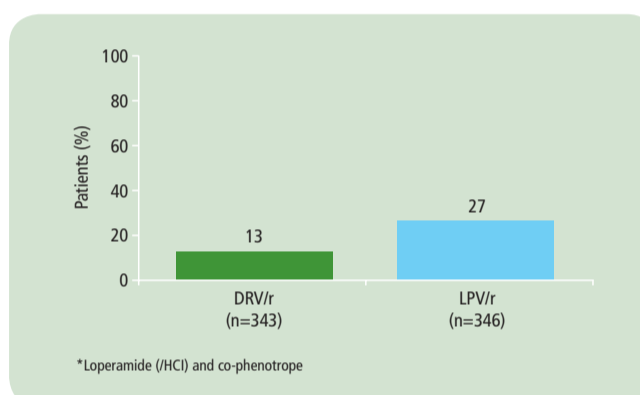


Figure 1. Patients receiving anti-diarrhoeals and anti-motility agents* during the treatment period of ARTEMIS.

Overall safety

- In ARTEMIS, the mean study drug exposure to DRV/r and LPV/r was comparable (Table 2).
- Most AEs were grade 1 or 2 in severity, and discontinuations due to AEs were infrequent
 - there was a statistically significantly lower incidence of serious AEs and AEs leading to permanent discontinuation in the DRV/r versus LPV/r arm.

Table 2. Summary of safety.

Incidence, n (%)	DRV/r (n=343)	LPV/r (n=346)	p value
Mean treatment exposure (weeks)	95	91	
≥ 1 AE	316 (92)	331 (96)	$p=0.0524$
≥ 1 serious AE	34 (10)	55 (16)	$p=0.0192$
≥ 1 grade 3 or 4 AE	82 (24)	89 (26)	$p=0.5811$
≥ 1 AE leading to permanent discontinuation	19 (6)	35 (10)	$p=0.0254$
Death*	1 (<1)	5 (1)	$p=0.1032$

*None of the deaths were considered related to study treatment

Gastrointestinal AEs

- The overall incidence of grade 2–4 treatment-related (investigator determined) GI AEs was lower in the DRV/r arm compared with the LPV/r arm at Week 96 (7% vs 15%, respectively, $p=0.0005$; Figure 2).

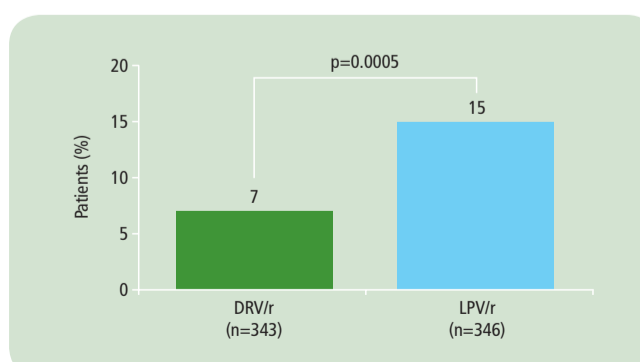


Figure 2. Incidence of overall grade 2–4 GI AEs at least possibly related to study treatment.

- Grade 2–4 treatment-related diarrhoea occurred less frequently with DRV/r (4%) than with LPV/r (11%; $p < 0.001$), while nausea, abdominal pain, vomiting and gastritis occurred with similar frequency (Figure 3).
- Treatment-related serious GI AEs were reported in one DRV/r patient (grade 2 nausea), and in two LPV/r patients (grade 4 vomiting and diarrhoea [$n=1$], and grade 2 pancreatitis [$n=1$]).

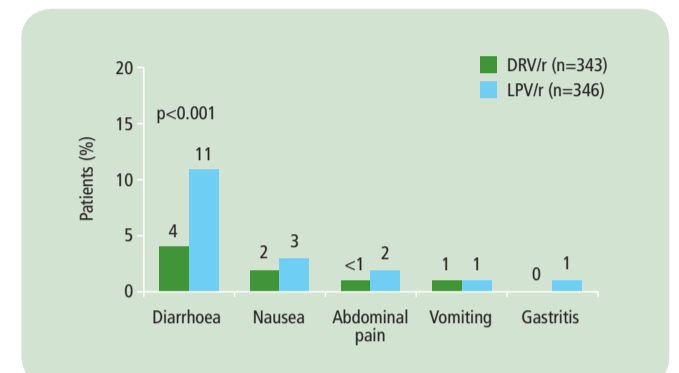


Figure 3. Grade 2–4 treatment-related individual GI AEs reported in $\geq 1\%$ of patients.

Treatment discontinuations due to GI AEs

- No DRV/r patients discontinued due to treatment-related GI AEs, while five LPV/r patients discontinued due to treatment-related GI AEs
 - four LPV/r patients discontinued for grade 1–2 GI-related AEs (pancreatitis [$n=1$], diarrhoea [$n=2$], diarrhoea, flatulence and nausea [$n=1$]), and one discontinued for grade 3 abdominal pain and grade 2 diarrhoea.

Conclusions

- At 96 weeks, grade 2–4 treatment-related GI AEs were significantly lower with DRV/r versus LPV/r
 - in addition, a significantly lower incidence of treatment-related grade 2–4 diarrhoea was shown with once-daily DRV/r than with LPV/r in treatment-naïve, HIV-1-infected adult ARTEMIS patients.
- Furthermore, the use of concomitant anti-diarrhoeal and anti-motility agents support these findings, as fewer patients in the DRV/r versus the LPV/r arm used these medications during the trial.
- There were no discontinuations due to treatment-related GI AEs in patients treated with DRV/r, while five LPV/r patients discontinued treatment for these types of AEs.
- It is unlikely that the higher rate of GI AEs observed in the LPV/r group was related to the use of the largely superseded capsule formulation
 - overall treatment duration on the tablet formulation was greater than that on the capsules
 - bioequivalence of the capsule and tablet formulations has been demonstrated.⁷
- Results from the ARTEMIS study at 96 weeks have shown a favourable safety and GI tolerability profile of once-daily DRV/r in treatment-naïve, HIV-1-infected adult patients.

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Acknowledgements and disclosures

- Editorial support provided by Caroline Waterhouse and Catherine Bragg of Gardiner-Caldwell Communications, Macclesfield, UK; this support was funded by Tibotec.
- The authors have the following conflicts of interest to declare:
 - JF has received research funds from Tibotec for this study as well as TMC278 studies, and has also received research funding from Gilead and Pfizer; BR, PI and GC have declared no conflicts of interest; CVA, RDM, and LL are full-time employees of Tibotec; EL is a full-time employee of Janssen-Cilag.