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Efficacy and safety of darunavir/ritonavir 800/100mg once-daily versus lopinavir/ritonavir in treatment-naïve, HIV-1-infected patients at 96 weeks: ARTEMIS (TMC114-C211)

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Summary

ARTEMIS: Summary of Week 96 analysis

- This 96-week analysis of the ARTEMIS (TMC114-C211; **A**nti**R**etroviral **T**herapy with TMC114 **E**xa**mi**ned **I**n Naïve **S**ubjects) trial demonstrates that darunavir with low-dose ritonavir (DRV/r) 800/100mg is an effective treatment option for antiretroviral (ARV)-naïve patients.
- Once-daily DRV/r showed significantly greater virologic response rates than lopinavir with low-dose ritonavir (LPV/r) at 96 weeks
  - 79% of DRV/r patients had HIV-1 RNA <50 copies/mL vs 71% of LPV/r patients (difference = 8.3%, 95% confidence interval [CI]: 1.8–14.7; intent-to-treat/time-to-loss of virologic response [ITT-TLOVR], p=0.012).
- Once-daily DRV/r 800/100mg was generally safe and well tolerated, with few treatment discontinuations
  - grade 2–4 diarrhea at least possibly related to treatment occurred less frequently with DRV/r than LPV/r (4% vs 11%; p<0.001)
  - DRV/r compared with LPV/r was associated with smaller median percent increase in triglycerides (12 vs 50%; p<0.001) and total cholesterol (15 vs 23%; p<0.001) and levels remained below National Cholesterol Education Program (NCEP) cut-offs
  - based on NCEP criteria, fewer DRV/r than LPV/r patients had abnormally high total cholesterol (37% vs 47%; p=0.0058) and triglycerides (41% vs 56%; p<0.0001).
- DRV/r superiority was driven by better virologic response and fewer discontinuations due to adverse events (AEs) compared with LPV/r.
- Once-daily DRV/r offers a new, effective, well tolerated once-daily first-line treatment option for treatment-naïve patients.

ARTEMIS: Phase III study design

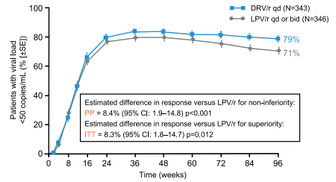
689 ARV-naïve patients from 26 countries viral load >5000 no CD4 cut-off

- DRV/r 800/100mg qd + TDF 300mg and FTC 200mg (N=343)
- LPV/r 800/200mg total daily dose* + TDF 300mg and FTC 200mg (N=346)

LPV dosing		LPV formulation	
qd =	15%	Capsule only =	12%
bid =	75%	Tablet only =	2%
bid/qd =	11%	Capsule/tablet switch =	86%

*qd or bid dosing was based on regulatory approval for naïve patients; switch from capsule to tablet (Meltrex) was made according to local regulatory approval and drug availability
TDF = tenofovir ; FTC = emtricitabine

ARTEMIS: Viral load <50 copies/mL to Week 96 (ITT-TLOVR)*

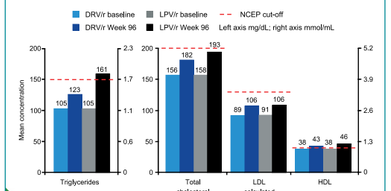


*Estimated from a logistic regression model including treatment and stratification factors (baseline $\log_{10}$ viral load and baseline CD4 cell count)

ARTEMIS: VF analysis over 96 weeks

- The DRV/r arm had a lower VF rate than the LPV/r arm (12%, n=40 vs 17%, n=59; p=0.0437, TLOVR non-VF censored)
  - initial VF analysis was performed on samples with viral load >1000 copies/mL
  - no primary PI mutations developed in VFs in either of the treatment arms
  - all VFs (DRV/r and LPV/r) that had available matching baseline and endpoint phenotypes remained susceptible to all PIs
  - genotyping of VFs with a viral load >50 copies/mL is underway

ARTEMIS: Median lipid levels at baseline and Week 96

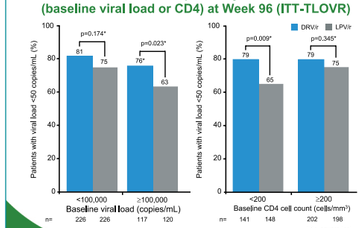


HDL = high-density lipoprotein

ARTEMIS: Study objectives

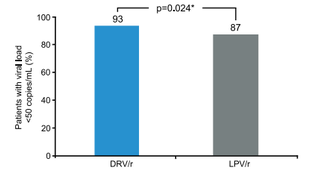
- Primary endpoint
  - proportion of patients with HIV-1 RNA <50 copies/mL
- Primary objective
  - demonstrate non-inferiority of DRV/r qd versus LPV/r based on that primary endpoint
    - non-inferiority of DRV/r versus LPV/r concluded if, at Week 48, the lower limit of the 95% two-sided CI of the difference between DRV/r and LPV/r exceeded –12%
- Secondary objectives
  - evaluate the superiority for virologic response in case DRV/r was non-inferior
  - evaluate long-term safety, tolerability and durability of virologic responses over 192 weeks
  - compare immunologic responses
  - conduct pharmacokinetic evaluations
  - compare quality of life

ARTEMIS: Confirmed response by stratification factor (baseline viral load or CD4) at Week 96 (ITT-TLOVR)



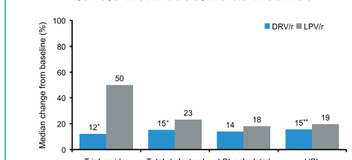
*Chi-square test

ARTEMIS: Virologic response at Week 96 in the TLOVR non-VF censored population‡



*Chi-square test
‡Patients who discontinued treatment due to reasons other than VF were excluded

ARTEMIS: Median percent change in lipid levels from baseline at Week 96



- A similar proportion of patients used lipid-lowering agents in the DRV/r arm (7%) and in the LPV/r arm (8%)

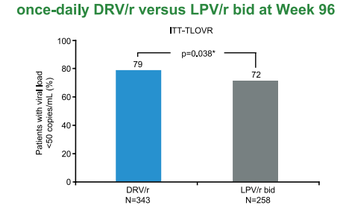
*p<0.001; **p=0.0102 vs LPV/r
Data analyzed by Wilcoxon rank test

ARTEMIS: Baseline characteristics

	DRV/r (N=343)	LPV/r (N=346)
Baseline demographics		
Female, n (%)	104 (30)	105 (30)
Mean age, years (±SD)	36 (9)	35 (9)
Caucasian, n (%)	137 (40)	153 (44)
Black, n (%)	80 (23)	71 (21)
Hispanic, n (%)	77 (22)	77 (22)
Asian, n (%)	44 (13)	38 (11)
Baseline disease characteristics		
Median HIV-1 RNA, copies/mL (range)	70,800 (835–5,580,000)	62,100 (667–4,580,000)
Median CD4 cell count, cells/mm³ (range)	228 (4–750)	218 (2–714)
HBV/HCV co-infected, n (%)	43 (13)	48 (14)
Stratification factors		
CD4 cell count <200 cells/mm³, n (%)	141 (41)	148 (43)
HIV-1 RNA ≥100,000 copies/mL, n (%)	117 (34)	120 (35)

SD = standard deviation; HBV = hepatitis B virus; HCV = hepatitis C virus

ARTEMIS: Virologic response with once-daily DRV/r versus LPV/r bid at Week 96



*Chi-square test

ARTEMIS: Grade 2–4 AEs at least possibly related to treatment over 96 weeks (≥2% incidence)

	DRV/r (N=343)	LPV/r (N=346)
Mean exposure (weeks)	*95.0*	*91.4*
Any grade 2–4 AE at least possibly related‡	**80 (23)**	**119 (34)**
Gastrointestinal AEs (all types), n (%)	23 (7)	52 (15)
Diarrhea	14 (4)*	38 (11)
Nausea	6 (2)	10 (3)
Rash (all types), n (%)	9 (3)	5 (1)

*p<0.001 vs LPV/r; no other AEs showed a statistically significant difference between the two treatment arms; ‡Excludes laboratory abnormalities reported as AEs

- No additional case of grade 2–4 rash was seen for DRV/r after Week 48
- Grade 2–4 treatment-related hepatitis was reported in one patient (<1%) in each arm
- No renal serious AEs and no treatment discontinuations due to renal AEs were reported over 96 weeks

ARTEMIS: Conclusions from 96-week analysis

- The use of once-daily DRV/r 800/100mg + TDF/FTC in treatment-naïve patients
  - resulted in sustained virologic and immunologic responses
  - was generally well tolerated, with a favorable safety profile
  - superiority was driven by better virologic response and fewer discontinuations due to AEs compared with LPV/r
- In comparison to the LPV/r arm in treatment-naïve patients
  - for efficacy, once-daily DRV/r 800/100mg was non-inferior and statistically superior
  - significantly lower rates of diarrhea were seen with DRV/r
  - DRV/r was associated with smaller median increases in triglycerides and total cholesterol

ARTEMIS: Week 48 findings[1]

- At 48 weeks, patients receiving once-daily DRV/r achieved high durable virologic responses rates
  - once-daily DRV/r 800/100mg was non-inferior to LPV/r 800/200mg total daily dose in treatment-naïve patients at 48 weeks
  - 84% of DRV/r vs 78% of LPV/r patients achieved viral load <50 copies/mL
    - Estimated difference in response vs LPV/r for non-inferiority: PP-TLOVR = 5.6% [95% CI: –0.1;11.3], p<0.001
    - Estimated difference in response vs LPV/r for superiority: ITT-TLOVR = 5.5% [95% CI: –0.3;11.2], p=0.062
- Once-daily DRV/r 800/100mg had a low rate of discontinuation due to VF and/or AEs
  - patients receiving DRV/r did not develop PI resistance upon failure
- Once-daily DRV/r 800/100mg was generally safe and well tolerated
  - there was a lower incidence of diarrhea in the DRV/r arm compared with the LPV/r arm
  - triglyceride increases were less frequent with DRV/r than LPV/r

PP = per protocol; VF = virologic failure; PI = protease inhibitor; AEs = adverse events
1. Ortiz R, et al. AIDS 2008;22:1389–97

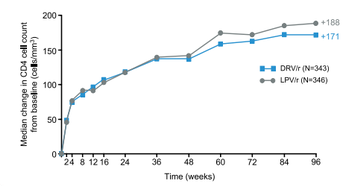
ARTEMIS: Patient disposition at Week 96 analysis

Incidence, n (%)	DRV/r (N=343)	LPV/r (N=346)
Discontinuation	59 (17)	81 (23)
AE*	13 (4)	32 (9)
Lost to follow-up	18 (5)	11 (3)
Withdrawal of consent	11 (3)	10 (3)
VF	3 (1)	8 (2)
Pregnancy	6 (2)	3 (1)
Non-compliance to study protocol	3 (1)	7 (2)
Other	5 (1)	10 (3)

*Includes six deaths (one in DRV/r group; five in LPV/r group)
Table includes all data up to the point when the last patient reached Week 96
Mean exposure was 93 weeks (range 0–130 weeks)

SE = standard error

ARTEMIS: Median change in absolute CD4 cell count to Week 96 (ITT-NC=F)



NC=F = non-completer = failure

ARTEMIS: Grade 2–4 laboratory abnormalities over 96 weeks (≥2% incidence)

n (%)	DRV/r (N=343)	LPV/r (N=346)
Alanine aminotransferase	38 (11)	40 (12)
Aspartate aminotransferase	39 (11)	35 (10)
Neutrophil count	30 (9)	11 (3)
Hyperglycemia	28 (8)	26 (8)
Pancreatic amylase	25 (7)	18 (5)
Alkaline phosphatase	5 (2)	5 (2)
Partial thromboplastin time	8 (2)	9 (3)
Pancreatic lipase	8 (1)	8 (2)
Hyperbilirubinemia	4 (1)	17 (5)
Prothrombin time	2 (1)	7 (2)
Total cholesterol	60 (18)*	95 (28)
Calculated low-density lipoprotein (LDL)‡	62 (18)	50 (15)
Triglycerides	15 (4)*	46 (13)

*p=0.0016 vs LPV/r; *p<0.0001 vs LPV/r; ‡Not calculated where triglycerides were >400mg/dL

- No significant changes in calculated creatinine clearance between baseline and Week 96 visits

Acknowledgments

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