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ARTEMIS: Week 96 safety and efficacy of darunavir/r by gender, age and race

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Introduction

- The protease inhibitor (PI) darunavir (DRV; TMC114) in combination with low-dose ritonavir (DRV/r) is now approved for the treatment of the following HIV-1-infected patient groups
  - treatment-naïve adults (800/100mg qd) in the USA,[1] Europe[2] and other countries
  - treatment-experienced adults (600/100mg bid) in the USA,[1] Europe[2] and in many more countries
  - treatment-experienced paediatric patients aged 6 years or older (twice-daily bodyweight-based dose) in the USA.[1] Approval in the EU is also expected soon.
- Recently updated HIV treatment guidelines now list DRV/r as a preferred PI component of therapy for treatment-naïve patients (US Department of Health and Human Services [DHHS],[3] International AIDS Society-USA[4] and French guidelines[5]).
- ARTEMIS (TMC114-C211; **A**nti**R**etroviral **T**herapy with TMC114 **E**xa**M**ined **I**n naïve **S**ubjects) is an ongoing, randomised, controlled, Phase III trial evaluating the efficacy and safety of once-daily DRV/r 800/100mg versus lopinavir with low-dose ritonavir (LPV/r: 800/200mg total daily dose) in treatment-naïve, HIV-1-infected patients across 26 countries.[6,7]
- The 96-week analysis of the overall population in ARTEMIS demonstrated that[7]
  - significantly more patients in the DRV/r arm achieved HIV-1 RNA <50 copies/mL than those in the LPV/r group (79% vs 71%, respectively; p<0.001 [non-inferiority test; primary objective], p=0.012 [superiority test; secondary objective])
  - DRV/r patients had a lower incidence of grade 2–4 treatment-related diarrhoea (4% vs 11% [per investigator assessment]; post-hoc p<0.001), and smaller median increases in triglycerides (0.1mmol/L vs 0.6mmol/L, p<0.0001) and total cholesterol (0.6mmol/L vs 0.9mmol/L; post-hoc p<0.0001) than LPV/r patients.
- Subgroup analyses of the efficacy and tolerability of DRV/r 800/100mg qd at Week 48 in the ARTEMIS trial demonstrated no clinically meaningful differences due to gender, age or race.[8]
- The aim of the present analyses of ARTEMIS data was to evaluate the effect of gender, age and race on the safety and efficacy of once-daily DRV/r (800/100mg) at Week 96.

Methods

- Details of the ARTEMIS study methodology have been reported previously.[6,7]

Patients and study design

- Treatment-naïve, HIV-1-infected adult patients with HIV-1 RNA >5,000 copies/mL were randomised to receive either DRV/r 800/100mg qd or LPV/r 800/200mg total daily dose.
- All patients also received a fixed-dose background regimen of tenofovir disoproxil fumarate (TDF) 300mg qd and emtricitabine (FTC) 200mg qd. TDF/FTC was provided by Gilead.
- Written informed consent was obtained from all patients. Study protocols were reviewed and approved by the appropriate institutional ethics committees and health authorities, and were conducted in accordance with the Declaration of Helsinki.

Assessments and endpoints

- Safety and efficacy assessments were conducted at screening, baseline, Week 2 and every 4 weeks until Week 16, at Week 24 and every 12 weeks thereafter until Week 96.
- Virological response (defined as viral load <50 copies/mL) at Week 96 was determined using the time-to-loss of virological response (TLOVR) algorithm, in the intent-to-treat (ITT) population.
- Initial safety analyses examined the incidence of adverse events (shown on abstract). However, to better assess clinical relevant safety findings, further analyses focused on examining the incidence of adverse drug reactions (ADRs) and laboratory abnormalities, considered ADRs, included in the product information[1]
  - data are presented on ADRs of grade 2 or more in severity, and considered at least possibly treatment-related by the investigators
  - laboratory abnormalities, considered ADRs, of grade 3–4 were included in this analysis.
- Safety findings and Week 96 efficacy data were analysed according to gender (male or female), baseline age (≤30, 31–45 or >45 years) and race (Asian, Black, Caucasian/White or Hispanic)
  - this poster describes an exploratory sub-group analysis to examine the contribution of each of these factors, however, the ARTEMIS trial was not specifically designed to examine the reasons for any variability.

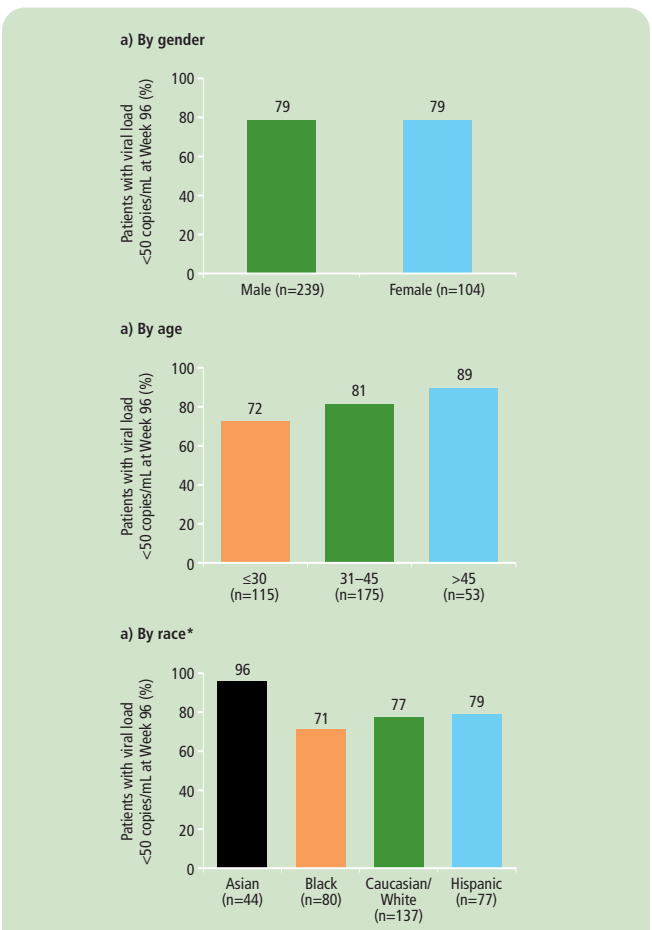
Results

Subgroup baseline disease characteristics

- A diverse group of treatment-naïve patients, broadly representative of the general clinical population with HIV-1 infection, were enrolled into ARTEMIS: 30% women; 60% non-Caucasian; mean age 34 years (range 18–70).
- For the overall patient population in the DRV/r group, mean viral load was 4.86 (standard deviation: 0.64) $\log_{10}$ copies/mL and median CD4 cell count was 228 (range: 4–750) cells/mm^3 at baseline.
- Baseline disease characteristics were generally similar between the subgroups (Table 1).

Efficacy

- The relatively small numbers of patients in some subgroups as well as the post-hoc exploratory analyses should be considered when interpreting the following results.
- Virological response at Week 96 (percentage of patients with viral load <50 copies/mL) was generally similar across the analysed subgroups and consistent with that of the overall population (79%), however, variability among subgroups was observed (Figures 1a–c)
  - response rates were identical in male and female patients (Figure 1a)
  - higher responses were seen with increasing age (Figure 1b)
  - the highest response rate (96%) was observed in Asian patients; although the number of patients in this group was small (n=44)
  - Black patients had a slightly lower virological response rate (71%) compared with other races (Figure 1c).
- Logistic regression analyses showed that baseline HIV-1 RNA, race, region and mean adherence as possible explanatory factors did not account for this observed variability. However, age was shown to correlate with response, but this finding could not be explained by the analyses that were conducted.



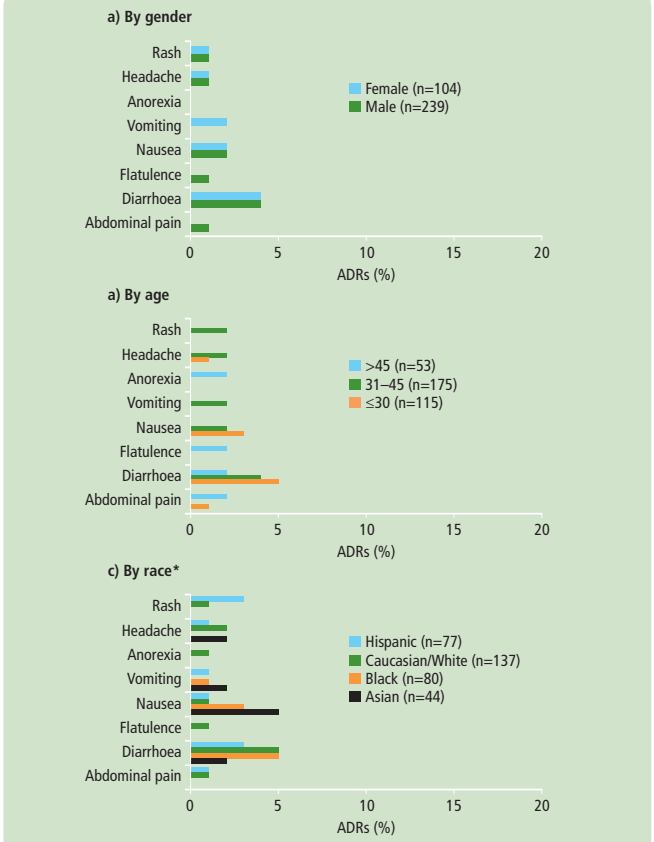
*Data for four patients with race classified as Other were not included due to low numbers (n=4)

Figure 1. Virological response (percentage of patients with viral load <50 copies/mL) at Week 96 (ITT-TLOVR) according to gender, age and race of patients receiving DRV/r 800/100mg qd.

Safety

Adverse drug reactions

- The relatively small numbers of patients in some subgroups should be considered when interpreting the following results.
- No meaningful differences in incidence of serious ADRs or rate of treatment discontinuation due to ADRs were seen for any of the subgroups.
- The most frequently reported ADRs at least grade 2 in severity and possibly related to DRV/r by the investigators (≥2% incidence in any subgroup) in the DRV/r arm by gender, age and race subgroups are shown in Figure 2.
- The incidence of ADRs at least grade 2 was below 5% and were generally comparable across the subgroups analysed. Although some relatively small differences were observed in certain subgroups, these were not considered clinically relevant.
- The following ADRs, which occurred in <2% of any subgroup, were not included in the comparisons given the low number of events: asthenia, diabetes, fatigue, hepatitis, pruritis, lipodystrophy, myalgia and Stevens-Johnson syndrome.



*Data for four patients with race classified as Other were not included due to low numbers (n=4)
Laboratory abnormalities reported as ADRs are not shown in this figure

Figure 2. Overview of the most frequently reported ADRs at least grade 2 and possibly related to DRV/r treatment by the investigators (≥2% incidence in any subgroup) according to gender, age and race in patients receiving DRV/r 800/100mg qd.

Laboratory abnormalities, considered ADRs

- The majority of treatment-emergent laboratory abnormalities in all subgroups were grade 1 or 2.
- With the exception of low-density lipoprotein (LDL) increases seen in patients >45 years of age (17%), the incidence of grade 3–4 laboratory abnormalities was <10%. Although small differences in the incidence (Table 2) were observed for certain parameters, these were not considered to be clinically relevant.

Table 1. Baseline disease characteristics according to gender, age and race of patients receiving DRV/r 800/100mg qd (N=343).

Subgroup	n (%)	Mean known duration of HIV infection (years [SE])	Mean $\log_{10}$ viral load (copies/mL [SE])	Median CD4 cell count (cells/mm^3 [range])	CDC classification n (%) A	B	C
Gender							
Male	239 (70)	2.50 (0.26)	4.94 (0.04)	226 (4–742)	164 (69)	55 (23)	20 (8)
Female	104 (30)	2.33 (0.26)	4.69 (0.07)	240 (13–750)	62 (60)	36 (35)	6 (6)
Age, years (range)							
≤30	115 (34)	2.10 (0.22)	4.75 (0.06)	268 (9–750)	73 (64)	38 (33)	4 (4)
31–45	175 (51)	2.44 (0.27)	4.95 (0.05)	218 (4–748)	119 (68)	38 (22)	18 (10)
>45	53 (15)	3.24 (0.76)	4.82 (0.08)	227 (11–686)	34 (64)	15 (28)	4 (8)
Race*							
Asian	44 (13)	1.82 (0.34)	4.91 (0.09)	196 (13–552)	27 (61)	12 (27)	5 (11)
Black	80 (23)	2.92 (0.54)	4.81 (0.07)	225 (5–748)	50 (63)	22 (28)	8 (10)
Caucasian/White	137 (40)	2.86 (0.31)	4.97 (0.06)	228 (4–750)	82 (60)	46 (34)	9 (7)
Hispanic	77 (22)	1.67 (0.32)	4.71 (0.07)	246 (13–624)	63 (82)	10 (13)	4 (5)
Other	4 (1)	1.27 (0.89)	4.59 (0.24)	153 (49–353)	3 (75)	1 (25)	0 (0)

*Race for one patient was not reported; SE = standard error; CDC = US Centers for Disease Control and Prevention

Table 2. Incidence of grade 3–4 treatment-emergent laboratory abnormalities, considered ADRs, observed in >2 patients in any subgroup through Week 96 according to gender, age and race in patients receiving DRV/r 800/100mg qd.

Laboratory parameter, n (%)	Worst grade[‡]	Gender Male (n=238)	Gender Female (n=104)	Age (years) ≤30 (n=114)	Age (years) 31–45 (n=175)	Age (years) >45 (n=53)	Race* Asian (n=44)	Race* Black (n=80)	Race* Caucasian/ White (n=137)	Race* Hispanic (n=76)
ALT (increased)	4	9 (4)	4 (4)	7 (6)	5 (3)	1 (2)	1 (2)	2 (3)	7 (5)	3 (4)
AST (increased)	4	15 (6)	3 (3)	9 (8)	6 (3)	3 (6)	0	3 (4)	10 (7)	5 (7)
Pancreatic amylase (increased)	4	9 (4)	0	1 (1)	3 (2)	5 (9)	0	1 (1)	5 (4)	3 (4)
Hyperglycaemia	3	1 (<1)	2 (2)	0	3 (2)	0	0	1 (1)	1 (1)	1 (1)
LDL calculated (increased)	3	11 (5)	5 (5)	1 (1)	6 (3)	9 (17)	4 (9)	6 (8)	3 (2)	3 (4)
Total cholesterol (increased)	3	3 (1)	1 (1)	1 (1)	0	3 (6)	0	2 (3)	1 (1)	1 (1)
Triglycerides (increased)	4	5 (2)	1 (1)	2 (2)	4 (2)	0	2 (5)	0	4 (3)	0

Treatment-emergent laboratory abnormalities examined in this analysis were those included in the product information[1]
*Data for four patients with race classified as Other were not included due to low numbers (n=4)
[‡]Based on the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events 2004, which does not have a grade 4 classification for total cholesterol and LDL
ALT = alanine aminotransferase; AST = aspartate aminotransferase

Conclusions

- The diverse population of treatment-naïve patients enrolled into ARTEMIS allowed for an exploration of potential gender, age and race effects on efficacy and safety outcomes.
- Although some variability was observed, the efficacy (HIV-1 RNA <50 copies/mL) of DRV/r at Week 96 was generally similar across the subgroups (gender: 79%; age: 72–89%; race: 71–96%) and was comparable to the overall population (79%).
- No clinically meaningful differences were observed when comparing ADRs and laboratory abnormalities, considered ADRs, with DRV/r 800/100mg qd across gender, age or race subgroups.
- Most ADRs and laboratory abnormalities in all subgroups were mild-to-moderate in severity and were infrequently associated with treatment discontinuation.
- These results at Week 96 support the findings previously reported at Week 48.[8]
- Once-daily DRV/r (800/100mg) is an effective, well-tolerated treatment option for treatment-naïve patients.

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