ARTEMIS: WEEK 48 SAFETY AND EFFICACY OF DARUNAVIR/R BY GENDER, AGE AND RACE

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Keywords

protease inhibitor, HIV-1, Darunavir

Introduction: Once-daily DRV/r 800/100mg is being examined in ARTEMIS (TMC114-C211; AntiRetroviral Therapy with TMC114 Examined In Naïve Subjects), an ongoing, open-label, Phase III study comparing the efficacy and safety of DRV/r versus lopinavir with low-dose ritonavir (LPV/r) in treatment-naïve, HIV-1-infected adult patients. The aim of the present analysis was to determine the influence of gender, age and race on the safety and efficacy at Week 48 of patients receiving DRV/r 800/100mg qd in the ARTEMIS trial.

Methods: All patients received a fixed background regimen of tenofovir disoproxil fumarate (TDF) 300mg qd and emtricitabine (FTC) 200mg qd. Safety and efficacy assessments were performed at screening, baseline, Week 2 and every 4 weeks until Week 16, at Week 24 and every 12 weeks thereafter.

Results: No clinically meaningful differences were observed in the tolerability of DRV/r 800/100mg qd in treatment-naïve patients at Week 48, irrespective of gender, age or race.

The majority of AEs and laboratory abnormalities observed in all subgroups were of mild-to-moderate severity. These incidences were similar to those reported for the overall population and were infrequently associated with treatment discontinuation.

The efficacy of DRV/r through Week 48 was similar across the subgroups, and was comparable to the overall population.

DRV/r 800/100mg qd is an effective, well-tolerated once-daily treatment option for treatment-naïve patients regardless of gender, age or race.

Introduction

The protease inhibitor darunavir (DRV; TMC114) with low-dose ritonavir (DRV/r) at a dose of 600/100mg bid has been approved in the USA[1] and Europe[2] for the treatment of HIV-1 infection in treatment-experienced adult patients. Based on the 24-week dose-finding results from the POWER 1 and 2 (TMC114-C213 and C202) studies[3,4] once-daily DRV/r 800/100mg was selected as the dose for evaluation in treatment-naïve, HIV-1-infected patients.

Once-daily DRV/r 800/100mg is being examined in ARTEMIS (TMC114-C211; AntiRetroviral Therapy with TMC114 Examined In Naïve Subjects), an ongoing, open-label, Phase III study comparing the efficacy and safety of DRV/r versus lopinavir with low-dose ritonavir (LPV/r) in treatment-naïve, HIV-1-infected adult patients across 26 countries.

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In ARTEMIS, the primary 48-week analysis showed that 84% of patients in the DRV/r arm achieved HIV-1 RNA <50 copies/mL at Week 48 vs 78% of patients in the LPV/r arm (time-to-loss of virologic response [TLOVR], p value for non-inferiority, p<0.001).5 Furthermore, patients in the DRV/r arm compared with those in the LPV/r arm had a lower incidence of grade 2-4 gastrointestinal adverse events (AEs) at least possibly related to treatment (7% vs 14%, p<0.01) and grade 2-4 triglyceride elevations (3% vs 11%).

The aim of the present analysis was to determine the influence of gender, age and race on the safety and efficacy at Week 48 of patients receiving DRV/r 800/100mg qd in the ARTEMIS trial.

Methods

Patients and study design

In ARTEMIS, treatment-naïve, HIV-1-infected adult patients with HIV-1 RNA >5000 copies/mL were randomized to receive DRV/r 800/100mg qd or LPV/r 800/200mg total daily dose.

All patients received a fixed background regimen of tenofovir disoproxil fumarate (TDF) 300mg qd and emtricitabine (FTC) 200mg qd.

Assessments and endpoints

Safety and efficacy assessments were performed at screening, baseline, Week 2 and every 4 weeks until Week 16, at Week 24 and every 12 weeks thereafter.

The intent-to-treat (ITT) population was used for the analysis.

Virologic response (defined as viral load <50 copies/mL) at Week 48 was determined using the TLOVR algorithm.

The incidence of AEs and laboratory abnormalities were evaluated. For laboratory abnormalities the cut-off was at least two abnormalities in any subgroup.

All available safety data and Week 48 efficacy data were analyzed according to gender (male or female), baseline age (<30, 31–45 or >45 years) and race (Oriental/Asian, Black, Caucasian/White or Hispanic).

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.

Results

Baseline disease characteristics according to subgroup

The trial included a diverse group of patients broadly representative of the general clinical population with HIV-1 infection: 30% were women; 60% were non-Caucasian; mean age was 34 years (range: 18-70).

Subgroup	n (%)	Mean known duration of HIV infection (years [SE])	Mean log10 viral load (copies/mL [SE])	Median CD4 cell count (cells/mm3 [range])
Gender				
Male	239 (70)	2.50 (0.26)	4.94 (0.04)	226 (4-742)
Female	104 (30)	2.33 (0.26)	4.69 (0.07)	240 (13-750)
Age, years (range)				
<30	115 (34)	2.10 (0.22)	4.75 (0.06)	268 (9-750)
31-45	175 (51)	2.44 (0.27)	4.95 (0.05)	218 (4-748)
>45	53 (15)	3.24 (0.76)	4.82 (0.08)	227 (11-686)
Race*				
Oriental/Asian	44 (13)	1.82 (0.34)	4.91 (0 09)	196 (13-552)
Black	80 (23)	2.92 (0.54)	4.81 (0 07)	225 (5-748)
Caucasian/White	137 (40)	2.86 (0.31)	4.97 (0 06)	228 (4-750)
Hispanic	77 (22)	1.67 (0.32)	4.71 (0 07)	246 (13-624)
Other	4(1)	1.27 (0.89)	4.59 (0 24)	153 (49-353)

*Race for one patient was not reported; SE = standard error

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

Baseline disease characteristics were generally similar between the subgroups (Table 1).

Overall, the mean viral load was 4.86 (standard deviation [SD]: 0.64) $\log_{10}$ copies/mL and the median CD4 cell count was 228 (range: 4-750) cells/mm3 at baseline for patients randomized to DRV/r treatment.

Efficacy

Virologic response at Week 48 (percentage of patients with viral load <50 copies/mL) was similar across the analyzed subgroups and consistent with that of the overall population (84%) (Figures 1a-c). The highest response rate (100%) was observed in Oriental/Asian patients; although the number of patients in this group was small (n=44).

Safety

The most frequently reported AEs regardless of severity or causality (>10% incidence in any subgroup) in the DRV/r arm by gender, age and race subgroups are shown in Figures 2a-c.

Conclusions

ARTEMIS enrolled a broad and diverse population of treatment-naïve patients.

No clinically meaningful differences were observed in the tolerability of DRV/r 800/100mg qd in treatment-naïve patients at Week 48, irrespective of gender, age or race.

The majority of AEs and laboratory abnormalities observed in all subgroups were of mild-to-moderate severity. These incidences were similar to those reported for the overall population and were infrequently associated with treatment discontinuation.

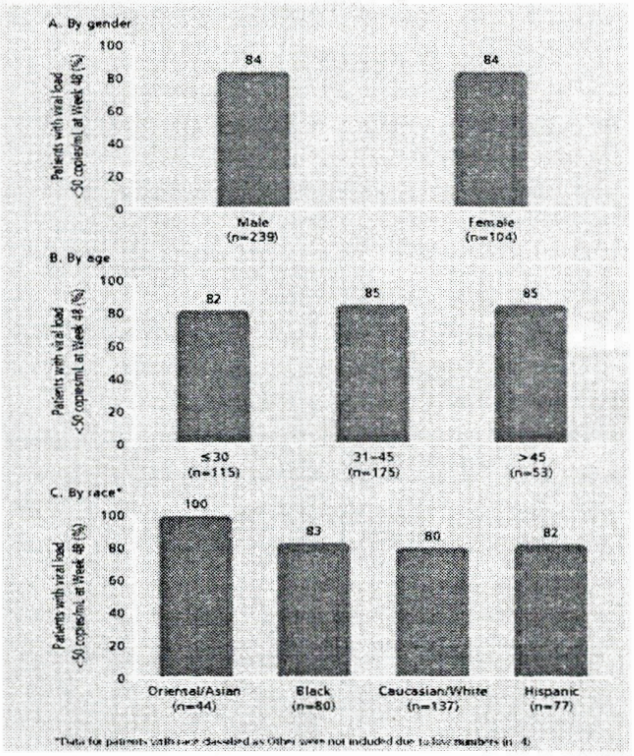

Figure 1. Virologic response (percentage of patients with viral load <50 copies/mL) at Week 48 (ITT-TLOVR) according to gender, age and race of patients receiving DRV/r 800/100mg qd.

The efficacy of DRV/r through Week 48 was similar across the subgroups, and was comparable to the overall population.

DRV/r 800/100mg qd is an effective, well-tolerated once-daily treatment option for treatment-naïve patients regardless of gender, age or race.

Irrespective of severity and causality, the most common AEs in the overall population[5]

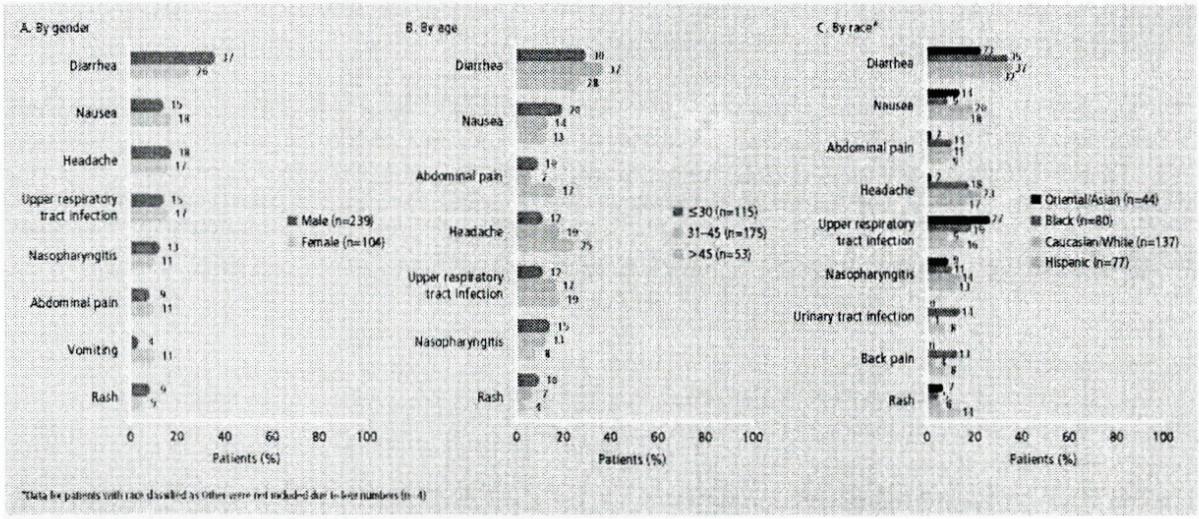

Figure 2. Overview of the most frequently reported AEs regardless of severity or causality (>10% incidence in any subgroup) according to gender, age and race of patients receiving DRV/r 800/100mg qd.

were generally also those most frequently observed in the gender, age and race subgroups

Diarrhea, nausea, headache, upper respira/tory tract infection, nasopharyngitis, abdominal pain, vomiting and cough were the most common AEs in the overall population.

With the exception of diarrhea (observed more frequently in males than in females) and vomiting (observed more frequently in females than males), the incidence of AEs was similar between the two sexes.

The incidence of diarrhea was slightly higher for patients 31-45 years old, and patients >45 years had a slightly higher incidence of headaches than the other age groups. However, overall, clinically relevant differences in the incidence of AEs in the different age subgroups were not observed.

Although some differences were observed in the incidence of AEs in the different age subgroups (abdominal pain: 7% [31-45] vs 10-17%; headache: 12% [≤30] vs 19-25%; rash: 4% [>45] vs 7-10%; nasopharyngitis: 8% [>45] vs 13-15%), these were considered not to be clinically relevant.

Some differences were also observed in the incidence of AEs in the different races, and all of these were considered not to be clinically relevant

- a lower incidence of nausea and higher incidence of back pain in Black patients (9% vs 14-20% and 13% vs 0-8%, respectively)
- a lower incidence of headache, diarrhea and abdominal pain in Oriental/Asian patients

		Gender		Age (years)			Race*			
Laboratory parameter n (%)	Worst grade‡	Male (n=239)	Female (n=104)	<30 (n=115)	31–45 (n=175)	>45 (n=53)	Oriental/ Asian (n=44)	Black (n=80)	Caucasian/ White (n=137)	Hispanic (n=77)
Amylase (increased)	3	9 (4)	0	1 (1)	3 (2)	5 (9)	0	1 (1)	5 (4)	3 (4)
ALT (increased)	3	8 (3)	2 (2)	7 (6)	2 (1)	1 (2)	1 (2)	2 (3)	5 (4)	2 (3)
	4	0	2 (2)	0	2 (1)	0	0	0	1 (1)	1 (1)
AST (increased)	3	8(3)	2(2)	5 (4)	3 (2)	2 (4)	0	1 (1)	6 (4)	3 (4)
	4	2(1)	1 (1)	2(2)	1(1)	0	0	0	1 (1)	2 (3)
LDL (increased)	3	4 (2)	1 (1)	1 (1)	1 (1)	3 (6)	1 (2)	2 (3)	1 (1)	1 (1)
Total cholesterol (increased)	3	3 (1)	1 (1)	1 (1)	0	3 (6)	0	2 (3)	1 (1)	1 (1)
Triglycerides (increased)	3	4 (2)	0	2 (2)	2 (1)	0	1 (2)	0	3 (2)	0
	4	1 (0)	0	0	1 (1)	0	0	0	1 (1)	0
Hyperglycemia	3	1 (0)	2 (2)	0	3 (2)	0	0	1 (1)	1 (1)	1 (1)
Hypophosphatemia	3	2 (1)	2 (2)	2 (2)	1 (1)	1 (2)	0	1 (1)	3 (2)	0
Neutrophils (decreased)	3	4 (2)	3 (3)	1 (1)	6 (3)	0	0	6 (8)	1 (1)	0
	4	0	1	0	1 (1)	0	0	1 (1)	0	0

*Data for patients with race classified as Other were not included due to low numbers (n=4); ‡Based on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events 2004, which does not have a grade 4 classification for total cholesterol and LDL

ALT = alanine aminotransferase;
AST = aspartate aminotransferase

Table 2. Incidence of grade 3-4 treatment-emergent laboratory abnormalities observed in ≥ 1 patient in any subgrup through Week 48 according to gender, age and race of patients receiveng DRV/r 800/100 mg qd

(2% vs 17-23%, 23% vs 32-37% and 2% vs 9-11%, respectively)
- a higher incidence of upper respiratory tract infections in Oriental/Asian patients (27% vs 9-19%)
- a higher incidence of rash in Hispanic patients (14% vs 5-7%)
- a lower incidence of urinary tract infections in Oriental/Asian and Caucasian/White patients (0-1% vs 8-14%).

No meaningful differences in incidence of serious AEs or rate of treatment discontinuation due to AEs were seen for any of the subgroups.

Although more grade 3 amylase increases (9% vs 1-2%), grade 3 low-density lipoprotein (LDL) increases (6% vs 1%) and grade 3 total cholesterol increases (6% vs 0-1%) were observed in patients >45 years and more grade 3 neutrophil decreases (8% vs 0-1%) observed in Black patients, these were not considered clinically relevant (Table 2).

Few other relevant or consistent differences in the incidence of grade 3-4 treatment-emergent laboratory abnormalities were seen in the subgroups (Table 2).

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