5-year efficacy and safety of maraviroc versus efavirenz, each in combination with zidovudine/lamivudine, in treatment-naïve HIV-1-infected patients: open-label extension of the randomized, double-blind MERIT study

TUPE026

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Background

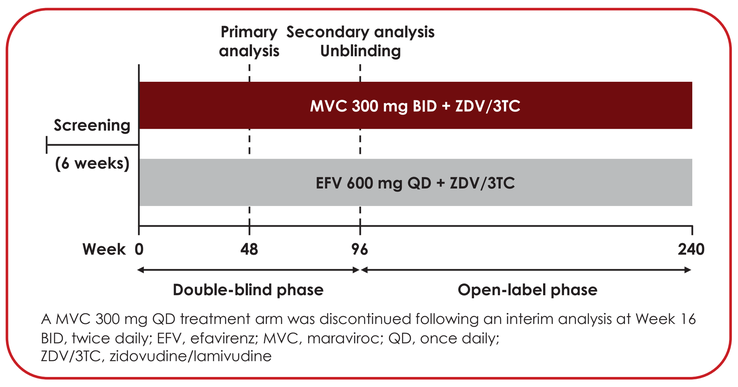
- Maraviroc (MVC) is a first-in-class, selective chemokine co-receptor type-5 (CCR5) antagonist indicated for the treatment of CCR5-tropic (R5) HIV-1 infection.[1,2] MVC has a unique mechanism of action among approved antiretrovirals in that it binds to a host receptor rather than a viral target.
- The efficacy and safety of MVC versus efavirenz (EFV), both in combination with zidovudine/lamivudine, in treatment-naïve patients with R5 HIV-1 was evaluated in the Phase IIB/III Maraviroc versus Efavirenz Regimens as Initial Therapy (MERIT) study.[3,4]
- Here we report findings from an open-label phase extending to 5 years.

Methods

Study design and treatment

- MERIT was a randomized, double-blind, multicenter Phase IIB/III study that included treatment-naïve patients (aged ≥16 years) with R5 HIV-1 (initially determined using the original Trofile assay), and screening viral load (plasma HIV-1 RNA) ≥2000 copies/mL.
- Patients were assigned to treatment with MVC 300 mg once daily (QD), MVC 300 mg twice daily (BID), or EFV 600 mg QD, each in combination with zidovudine/lamivudine 300 mg/150 mg BID for 96 weeks. Following an interim analysis at Week 16, the MVC QD treatment arm was discontinued and the study continued with two arms (Figure 1).
- The study was unblinded after the last patient's Week 96 visit, and patients could enter the nominal, 3-year, open-label phase.

Figure 1. Study design



A MVC 300 mg QD treatment arm was discontinued following an interim analysis at Week 16
BID, twice daily; EFV, efavirenz; MVC, maraviroc; QD, once daily;
ZDV/3TC, zidovudine/lamivudine

Study assessments

- Blood samples (10 mL) were collected throughout the study, including at 12-weekly visits during the open-label phase, and were analyzed by a third party for viral load and immunological status.
- Efficacy endpoints included proportion of patients with viral load <50 and <400 copies/mL, and change from baseline in CD4+ cell count.
- Safety assessments included adverse events (AEs) monitoring, laboratory evaluations, and vital signs measurement.
- Additionally, reports of hepatoxicity and malignancies with investigational CCR5 antagonists plus other theoretical safety concerns prompted a retrospective identification of the following sponsor-defined long-term survival and selected endpoints: hepatic failure; myocardial infarction/cardiac ischemia; malignancies; category C AIDS-defining events, serious infectious events, and rhabdomyolysis.

Statistical analysis

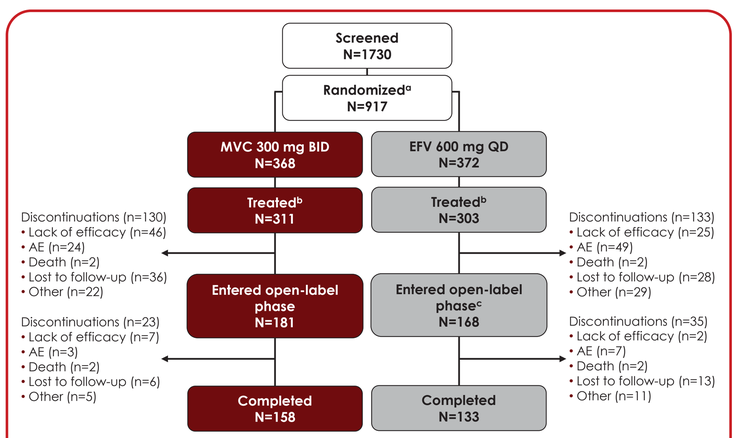
- Efficacy analyses were based on the cohort of patients who received ≥1 dose of study medication and were confirmed as having R5 HIV-1 following re-testing of screening samples using the enhanced sensitivity Trofile assay (R5 Trofile ES cohort), which replaced the original Trofile assay. All treated patients were included in safety analyses.
- Efficacy and safety variables were summarized descriptively by treatment group.

Results

Study population

- Study disposition is summarized in Figure 2. Of 917 patients randomized, 311 and 303 patients who were treated with MVC BID and EFV QD, respectively, had confirmed R5 HIV-1 (Trofile ES) and were included in the efficacy analysis.

Figure 2. Patient disposition



[a]In total, 177 patients were randomized to the MVC QD arm, which was subsequently discontinued; [b]patients with confirmed R5 HIV-1 treated in the double-blind phase; [c]two patients who completed double-blind EFV treatment did not enter the open-label phase
AE, adverse event; BID, twice daily; EFV, efavirenz; HIV, human immunodeficiency virus; MVC, maraviroc; QD, once daily; R5, chemokine co-receptor type-5

- Total duration of therapy was 1243.3 years in the MVC BID arm and 1204.1 years in the EFV QD arm.
- In the R5 Trofile ES cohort, patient demographics and baseline characteristics were similar among treatment groups, as summarized in Table 1.

Table 1. Patient demographics and baseline characteristics

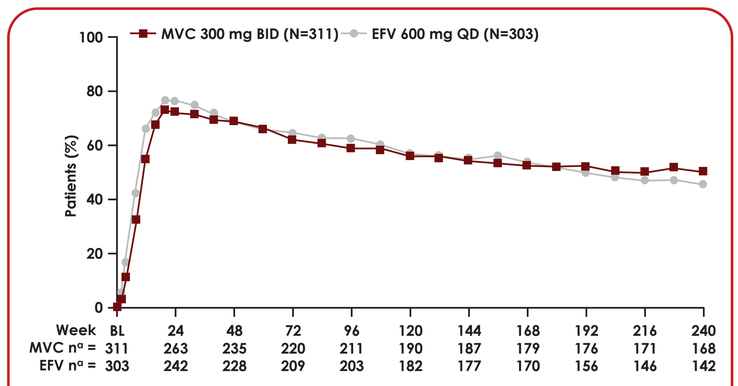
	MVC 300 mg BID (N=311)	EFV 600 mg QD (N=303)
Gender, n (%)		
Male	220 (70.7)	213 (70.3)
Age (years), mean (range)	36.4 (20-69)	37.3 (18-77)
Race, n (%)		
White	167 (53.7)	161 (53.1)
Black	114 (36.7)	118 (38.9)
Other	30 (9.6)	24 (7.9)
Viral load (HIV-1 RNA $\log_{10}$ copies/mL), mean (SD)[a]	4.9 (0.6)	4.8 (0.6)
CD4+ cell count (cells/µL), mean (SD)	261.2 (140.9)	276.8 (132.0)

[a]Baseline values were the average of pre-dose measurements collected at screening and baseline visits
BID, twice daily; EFV, efavirenz; HIV, human immunodeficiency virus; MVC, maraviroc; QD, once daily; SD, standard deviation; RNA, ribonucleic acid

Viral load response

- The proportion of patients achieving viral load <50 copies/mL peaked at approximately Week 20 and decreased gradually through to Week 240 in both treatment groups (Figure 3). Viral load <50 and <400 copies/mL was achieved by a similar proportion of patients in each group at Weeks 48, 96 and 240 (Table 2).

Figure 3. Patients with viral load <50 copies/mL throughout the study



R5 Trofile ES cohort
[a]Number of patients with available data at each time point; missing data=failure
BID, twice daily; BL, baseline; EFV, efavirenz; MVC, maraviroc; QD, once daily;
R5, chemokine co-receptor type 5; Trofile ES, enhanced sensitivity Trofile

Table 2. Patients with viral load <50 and <400 copies/mL at Week 48, 96 and 240

	MVC 300 mg BID (N=311)	EFV 600mg QD (N=303)
Viral load <50 copies/mL, n (%)		
Week 48	213 (68.5)	207 (68.3)
Week 96	183 (58.8)	190 (62.7)
Week 240	158 (50.8)	139 (45.9)
Viral load <400 copies/mL, n (%)		
Week 48	228 (73.3)	219 (72.3)
Week 96	199 (64.0)	195 (64.4)
Week 240	163 (52.4)	140 (46.2)

R5 Trofile ES cohort. Missing data=failures
BID, twice daily; EFV, efavirenz; MVC, maraviroc; QD, once daily; R5, chemokine co-receptor type-5; Trofile ES, enhanced sensitivity Trofile assay

- A numerically greater proportion of Week 96 responders (viral load <50 copies/mL) maintained their response at Week 240 in the MVC BID group (n=152/182, 83.5%) versus the EFV QD group (n=136/187, 72.7%).
- A similar proportion of Week 96 non-responders went on to respond at Week 240 in the MVC BID group (n=6/20, 30.0%) and EFV QD group (n=3/9, 33.3%). Consequently, the numerical advantage of EFV (n=187/196, 95.4%) over MVC (n=182/202, 90.1%) at Week 96 reversed to a numerical advantage of MVC (n=158/202, 78.2%) over EFV (n=139/196, 70.9%) at Week 240.

CD4+ cell response

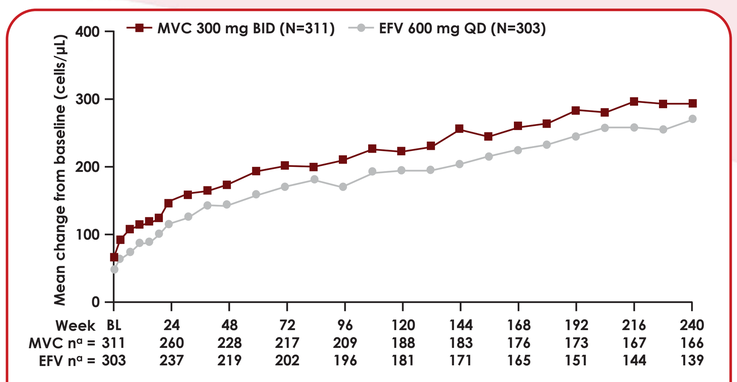
- Mean change from baseline in CD4+ cell count was numerically greater in the MVC BID group versus the EFV QD group from Week 2, and this difference was maintained throughout the study (Figure 4). At Week 240, mean increase from baseline was 292.9 cells/µL versus 270.6 cells/µL, respectively (Table 3).

Table 3. Mean change from baseline in CD4+ cell count (cells/µL) at Weeks 48, 96 and 240

	MVC 300 mg BID (N=311)	EFV 600mg QD (N=303)
Week 48	172.8 (131.6)	144.3 (123.5)
Week 96	211.3 (151.4)	171.1 (149.4)
Week 240	292.9 (229.9)	270.6 (230.3)

R5 Trofile ES cohort
Data shown as mean (SD). Missing data imputed using last observation carried forward
BID, twice daily; EFV, efavirenz; MVC, maraviroc; QD, once daily; R5, chemokine co-receptor type-5; SD, standard deviation; Trofile ES, enhanced sensitivity Trofile

Figure 4. Mean change from baseline in CD4+ cell count throughout the study



R5 Trofile ES cohort
[a]Number of patients with available data at each time point; missing data imputed using last observation carried forward
BID, twice daily; BL, baseline; EFV, efavirenz; MVC, maraviroc; QD, once daily;
R5, chemokine co-receptor type-5; Trofile ES, enhanced sensitivity Trofile

Safety

- Overall AE incidence (all causality) was 95.3% in the MVC BID group and 96.1% in EFV QD group. Grade 3 and 4 AE incidence was 27.5% and 12.2%, respectively, in the MVC BID group, and 29.4% and 12.5%, respectively, in the EFV QD group.
- Nausea was the most common AE, reported by 38.6% and 36.6% of patients, respectively. Other commonly-reported AEs (≥20% of patients, either group) included dizziness (MVC 11.9% versus EFV 28.0%), and headache (MVC 30.3% versus EFV 29.1%).
- A numerically greater proportion of patients in the EFV QD versus MVC BID group experienced treatment-related AEs (81.7% versus 68.9%), and discontinued due to all causality AEs (21.3% versus 10.6%) and treatment-related AEs (14.1% versus 5.3%). No individual AE (all causality) led to the discontinuation of >8 patients in either treatment group.
- Serious AEs occurred in 21.4% of patients in the MVC BID group and 22.7% in the EFV QD group. Treatment-related serious AEs were recorded for 3.3% of MVC-BID-treated patients and 4.4% of EFV QD-treated patients. There were few deaths in either group (MVC BID: n=8; EFV QD: n=9).

Table 4. Summary of retrospectively-identified long-term survival and selected endpoints

	MVC 300 mg BID (N=360) PY=1243.3			EFV 600 mg QD (N=361) PY=1204.1		
	n (%)	Raw rate[a]	Exposure-adjusted rate[b]	n (%)	Raw rate[a]	Exposure-adjusted rate[b]
Any event	38 (10.6)	4.0	3.3	45 (12.5)	5.1	4.0
Hepatic failure	0 (0.0)	0.0	0.0	0 (0.0)	0.0	0.0
MI/cardiac ischemia	5 (1.4)	0.5	0.4	6 (1.7)	0.5	0.5
Malignancies	7 (1.9)	0.6	0.6	13 (3.6)	1.2	1.1
Category C AIDS defining events	11 (3.1)	1.0	0.9	14 (3.9)	1.3	1.2
Infections reported as SAEs	24 (6.7)	2.3	2.0	25 (6.9)	2.9	2.2
Rhabdomyolysis	0 (0.0)	0.0	0.0	0 (0.0)	0.0	0.0

[a]Total number of events/100 PY; [b]events/100 PY based on time to first event
BID, twice daily; EFV, efavirenz; MI, myocardial infarction; MVC, maraviroc; PY, patient-years; QD, once daily; SAE, serious adverse event

- The incidence of clinically significant laboratory abnormalities was similar across treatment groups. Grade 3 or 4 ALT elevations were observed in 8 patients in the MVC BID group (2.2%) and 5 patients in the EFV QD group (1.4%).

Discussion

- MVC demonstrated comparable efficacy to EFV over 48 and 96 weeks in the MERIT study.[3,4] Findings from the open-label extension phase demonstrate long-term efficacy maintained throughout 5 years of follow-up. Safety findings were consistent with those observed at Week 96.
- This is the first report of the long-term safety of MVC in treatment-naïve patients. The findings are comparable with other long-term studies of combinations that included EFV in terms of CD4+ cell response,[5-7] although greater virologic response has been observed previously with tenofovir DF or stavudine plus EFV and lamivudine over 3 years[6] and over 288 weeks.[7] Variation across studies may be attributable to procedural and population differences.

Conclusions

- **MVC maintained similar long-term antiviral efficacy to EFV over 5 years in treatment-naïve patients with R5 HIV-1.**
- **MVC was generally well-tolerated: there were no unexpected safety findings.**

Disclosure

This study was conducted by Pfizer Inc., and was sponsored by ViiV Healthcare. Technical support was provided by Simon Portsmouth of Pfizer Inc. Editorial support was provided by Lynsey Stevenson of Complete Medical Communications Limited, and funded by ViiV Healthcare.

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