48th Annual ICAAC/IDSA 46th Meeting, Washington, DC, USA, October 25–28, 2008

Adverse Event Profile of Maraviroc in Treatment-experienced Patients Infected with R5 HIV-1

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Introduction

- Maraviroc (MVC; marketed as Celsentri®/Selzentry™) is a potent CCR5 antagonist approved for twice-daily (BID) administration as part of a combination antiretroviral (ARV) regimen in treatment-experienced (TE) patients infected with CCR5-tropic (R5) HIV-1.
- The efficacy and safety of MVC have been assessed in single- and multiple-dose studies in both healthy volunteers and HIV-infected patients, including the large Phase 2b/3 studies MERIT (MVC vs efavirenz, both with Combivir®, in treatment-naive patients), MOTIVATE 1 (USA and Canada), and MOTIVATE 2 (Europe, Australia and USA).
- In the MOTIVATE studies, adult TE patients with R5 HIV-1 infection, prior experience of or resistance to three ARV drug classes, and HIV-1 RNA ≥5,000 copies/mL, were randomized to receive placebo (PBO), MVC once daily (QD), or MVC BID, together with optimized background therapy (OBT) of 3–6 investigator-selected ARVs.[1]
- In both studies, patients who received MVC (BID or QD) plus OBT demonstrated significantly greater virologic suppression and CD4+ cell count increases than those receiving PBO plus OBT.[1]
  - The mean Week 48 change from baseline in HIV-1 RNA (ITT) in the pooled MOTIVATE 1 and 2 studies was –1.84 $\log_{10}$ copies/mL for MVC BID (46% <50 copies/mL) and –1.68 $\log_{10}$ for MVC QD (43% <50 copies/mL), vs –0.78 $\log_{10}$ for PBO (17% <50 copies/mL).
  - The mean change from baseline in CD4+ cell count (LOCF) in the pooled MOTIVATE 1 and 2 studies was +124 cells/mm^3 for MVC BID and +116 cells/mm^3 for MVC QD, vs +61 cells/mm^3 for PBO.
- We present here 48-week safety data from the combined MOTIVATE studies.

Methods

- Unadjusted and exposure-adjusted incidences of adverse events (AEs) of note were analyzed for 1,049 patients receiving MVC (QD or BID) or PBO over 48 weeks in the combined MOTIVATE 1 and 2 study datasets.
- AEs of interest included Category C infections, hepatotoxicity including liver abnormalities, hypersensitivity (HSR) including rash, malignancies and postural hypotension (postural hypotension was the dose-limiting AE in Phase 1/2a studies of MVC).[2]
- Subgroup analysis of AE data was performed by sex, age, race, CCR5Δ32 status, and co-infection with hepatitis B (HBV) or hepatitis C (HCV) virus.

Results

- A summary of AE frequencies at Week 48 is shown in Table 1. Despite the longer total exposure to MVC plus OBT, caused by the higher rate of discontinuations in patients receiving PBO, both all-cause and treatment-related AE rates on MVC BID or QD were similar to the PBO arm.
- Unadjusted incidences of serious AEs and grade 3/4 AEs were also similar between study arms, as was the proportion of AE-related discontinuations and deaths (Table 1).
- Exposure-adjusted incidence rates for AEs that occurred in at least 5% of any treatment arm are shown in Figure 1a (all-cause) and 1b (treatment-related). The majority of AEs noted were not considered to be related to study drug.
- Exposure-unadjusted rates of Category C events (Table 2) and non-Category C malignancies (Table 3) were low and similar between arms, other than a cluster of esophageal candidiasis events in the MVC QD arm that was not seen on MVC BID (Table 2).
- A slightly higher exposure-adjusted incidence of all malignancies (Category C and non-Category C combined) was noted in the PBO arm (Table 4). Exposure adjusted rates of all infections and infestations were similar between arms and postural hypotension was rare (Table 4).
- Overall, grade 3 and 4 elevations in liver function test results were uncommon (Table 5).
- Higher rates of grade 3/4 AST and ALT elevations were seen in HCV co-infected patients receiving MVC (Table 6). However, this does not take into account baseline values, which were unbalanced between arms. While this is an exposure-unadjusted analysis on a small sample, no effect on viral load or incidence or severity of adverse events was noted. Similarly, no effect on liver markers was seen for use of tipranavir in the OBT (Table 6).
- Time to onset (Table 7) and mean duration (Figure 2) of adverse events of interest were similar between arms.

Conclusions

- The safety profile of MVC in two large studies in treatment-experienced patients with few treatment options is similar to PBO.
- MVC was not associated with increased rates or severities of infections, malignancies, Category C events, orthostatic hypotension, or clinically significant abnormalities in markers of liver function.
- There were no differences in time to onset or duration of these AEs of interest between MVC and PBO arms, indicating no specific onset time and no effect of continued dosing on the incidence of such AEs.
- Similar results were observed in treatment-naive patients in MERIT[3] and in treatment-experienced patients with non-R5 infection in Study A4001029.[4]

Table 1. MOTIVATE 1 and 2 pooled 48-week safety summary

	Placebo + OBT N=209		MVC QD + OBT N=414		MVC BID + OBT N=426	
	All-cause n (%)	Tx-related n (%)	All-cause n (%)	Tx-related n (%)	All-cause n (%)	Tx-related n (%)
Total exposure, patient-years	111		300		309	
Patients with AEs	177 (84.7)	94 (45.0)	375 (90.6)	205 (49.5)	393 (92.3)	219 (51.4)
Patients discontinuing due to AEs	11 (5.3)	6 (2.9)	24 (5.8)	12 (2.9)	21 (4.9)	13 (3.1)
Patients with grade 3 AEs	46 (22.0)	7 (3.3)	84 (20.3)	24 (5.8)	104 (24.4)	22 (5.2)
Patients with grade 4 AEs	16 (7.7)	5 (2.4)	37 (8.9)	3 (0.7)	45 (10.6)	15 (3.5)
Patients with serious AEs	35 (16.7)	2 (1.0)	62 (15.0)	7 (1.7)	72 (16.9)	12 (2.8)
Patients with Category C events	16 (7.7)		29 (7.0)		23 (5.4)	
Deaths*	2 (1.0)	0	6 (1.4)	0	9 (2.1)	0

Includes all patients who received at least one dose of study medication

Tx, treatment

* Deaths reported up to 28 days after stopping study drug
No deaths were related to study drug according to the investigator

Figure 1. MOTIVATE 1 and 2 AEs occurring at a frequency ≥5% in any treatment arm
a) Exposure-adjusted frequency (all-cause, per 100 patient-years), and b) Exposure-adjusted frequency (treatment-related, per 100 patient-years)

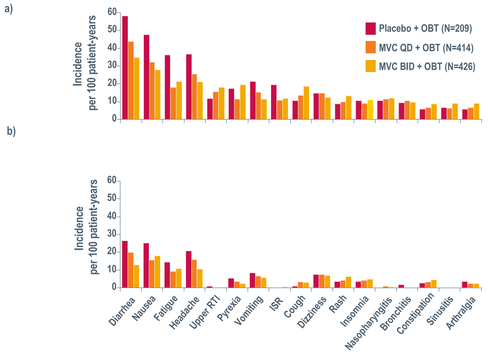


Table 2. MOTIVATE 1 and 2 pooled 48-week incidence of Category C events (unadjusted for exposure)

Event, n	Placebo + OBT N=209	MVC QD + OBT N=414	MVC BID + OBT N=426
Total exposure, patient-years	111	300	309
AIDS encephalopathy	0	1	0
Herpes virus infections*	4	11	7
Cryptosporidial gastroenteritis	1	1	0
Esophageal candidiasis	2	12	3
Cytomegalovirus infection†	1	1	2
Mycobacterium avium‡	2	0	3
Pneumonia§	3	3	1
Pneumocystis jiroveci pneumonia	0	0	2
Progressive multifocal leukoencephalopathy	1	0	1
Kaposi's sarcoma	3	1	2
Lymphoma‖	2	2	2
Total number of events	19	32	23
Number of patients affected (%)	16 (8%)	29 (7%)	23 (5%)

* Includes oral and genital herpes, unspecified herpes virus infection and herpes proctitis
† Includes CMV chorioretinitis, CMV gastrointestinal infection and cytomegaloviral pneumonia
‡ Includes both *M. avium* complex and mycobacterial infection terms
§ Includes lobar and bacterial pneumonia; excludes cytomegaloviral and *P. jiroveci* pneumonia
‖ Includes T-cell and large B-cell lymphoma

Table 3. MOTIVATE 1 and 2 pooled 48-week incidence of non-Category C malignancies (unadjusted for exposure)

All severities	Placebo + OBT N=209 Unadjusted n (%)	MVC QD + OBT N=414 Unadjusted n (%)	MVC BID + OBT N=426 Unadjusted n (%)
Total exposure, patient-years	111	300	309
Abdominal neoplasm	1	0	1
Anal cancer*	3	3	3
Basal cell carcinoma	0	1	1
Bile duct cancer	0	0	1
Bowen's disease	0	0	1
Bronchial carcinoma	0	0	1
Metastases to bone	0	0	1
Metastases to liver	0	1	1
Metastases to peritoneum	0	0	1
Neoplasm†	1	0	1
Esophageal carcinoma	0	1	0
Squamous cell carcinoma‡	1	2	1
Testicular neoplasm	0	1	0
Thyroid neoplasm	0	0	1
Tongue neoplasm (unspecified stage)	0	0	1
Total number of events	6	9	15
Number of patients affected (%)	5 (2.4)	8 (1.9)	10 (2.3)

* Includes terms "anal cancer" and "anal cancer stage 0"
† Not otherwise specified
‡ Includes terms "squamous cell carcinoma" and "squamous cell carcinoma of skin"

Only the most severe episode is listed for those patients with more than one occurrence of the same event

Table 4. MOTIVATE 1 and 2 pooled 48-week unadjusted and exposure-adjusted incidence of infections, malignancies, and postural hypotension (all-causes)

All severities, number of patients with at least one event	Placebo + OBT N=209		MVC QD + OBT N=414		MVC BID + OBT N=426	
	Unadjusted n (%)	Exposure-adjusted rate per 100 PY	Unadjusted n (%)	Exposure-adjusted rate per 100 PY	Unadjusted n (%)	Exposure-adjusted rate per 100 PY
All infections and infestations	84 (40.2)	132.9	214 (51.7)	123.7	233 (54.7)	133.2
Grade 1	35 (16.7)	55.4	104 (25.1)	60.1	107 (25.1)	61.2
Grade 2	35 (16.7)	55.4	86 (20.8)	49.7	98 (23.0)	56.0
Grade 3	7 (3.3)	11.1	14 (3.4)	8.1	19 (4.5)	10.9
Grade 4	7 (3.3)	11.1	10 (2.4)	5.8	9 (2.1)	5.1
All malignancies	10 (4.8)	13.3	11 (2.7)	9.3	14 (3.3)	8.8
Grade 1	2 (1.0)	3.8	3 (0.7)	6.2	4 (0.9)	3.4
Grade 2	4 (1.9)	5.7	3 (0.7)	1.4	3 (0.7)	2.4
Grade 3	3 (1.4)	2.9	1 (0.2)	0.3	2 (0.5)	1.0
Grade 4	1 (0.5)	1.0	4 (1.0)	1.4	5 (1.2)	2.0
Orthostatic hypotension	1 (0.5)	0.9	2 (0.5)	0.7	2 (0.5)	0.6
Grade 1	1 (0.5)	0.9	-	-	-	-
Grade 2	-	-	2 (0.5)	0.7	1 (0.2)	0.3
Grade 3	-	-	-	-	1 (0.2)	0.3
Grade 4	-	-	-	-	-	-

PY, patients-years

Only the most severe episode is listed for those patients with more than one occurrence of the same event

Table 5. MOTIVATE 1 and 2 pooled 48-week summary of unadjusted and exposure-adjusted maximum liver function test results irrespective of baseline

All causalities	Placebo + OBT N=207*		MVC QD + OBT N=408*		MVC BID + OBT N=421*	
	Unadjusted n (%)	Exposure-adjusted rate per 100 PY	Unadjusted n (%)	Exposure-adjusted rate per 100 PY	Unadjusted n (%)	Exposure-adjusted rate per 100 PY
AST:						
Grade 3 (5–10 x ULN)	6 (2.9)	5.6	15 (3.7)	5.1	18 (4.3)	6.0
Grade 4 (>10 x ULN)	0	0	4 (1.0)	1.3	6 (1.4)	2.0
ALT:						
Grade 3 (5–10 x ULN)	7 (3.4)	6.5	17 (4.2)	5.8	10 (2.4)	3.3
Grade 4 (>10 x ULN)	1 (0.5)	0.9	2 (0.5)	0.7	4 (1.0)	1.3
Total bilirubin:						
Grade 3 (>2.5–5 x ULN)	10 (4.8)	9.5	33 (8.1)	11.8	23 (5.5)	7.9
Grade 4 (>5 x ULN)	3 (1.4)	2.7	5 (1.2)	1.7	2 (0.5)	0.6

PY, patients-years; ULN, upper limit of normal, * Total patients evaluated for each laboratory parameter

Table 6. MOTIVATE 1 and 2 grade 3/4 liver function test results by hepatitis status or inclusion of tipranavir in the OBT (irrespective of baseline)

Grade 3/4 n/N (%)	HCV RNA (baseline)*		HBV surface antigen (screening)*		Tipranavir in OBT	
	negative	positive	negative	positive	No	Yes
AST						
PBO + OBT	6/187 (3.2)	0/19 (0)	6/188 (3.2)	0/17 (0)	5/178 (2.8)	1/29 (3.4)
MVC QD + OBT	14/392 (3.6)	2/15 (13.3)	15/382 (3.9)	0/20 (0)	13/342 (3.8)	3/66 (4.5)
MVC BID + OBT	14/391 (3.6)	6/29 (20.7)	19/392 (4.8)	1/27 (3.7)	15/358 (4.2)	5/63 (7.9)
ALT						
PBO + OBT	6/187 (3.2)	1/19 (5.3)	6/188 (3.2)	1/17 (5.9)	4/178 (2.2)	3/29 (10.3)
MVC QD + OBT	15/392 (3.8)	3/15 (20.0)	17/382 (4.5)	0/20 (0)	13/342 (3.8)	5/66 (7.6)
MVC BID + OBT	8/391 (2.0)	3/29 (10.3)	10/392 (2.6)	1/27 (3.7)	9/358 (2.5)	2/63 (3.2)
Bilirubin						
PBO + OBT	10/186 (5.4)	1/19 (5.3)	11/187 (5.9)	0/17 (0)	11/178 (6.2)	0/28 (0)
MVC QD + OBT	31/392 (7.9)	2/15 (13.3)	33/382 (8.6)	0/20 (0)	33/342 (9.6)	0/66 (0)
MVC BID + OBT	18/391 (4.6)	5/28 (17.9)	23/391 (5.9)	0/27 (0)	23/357 (6.4)	0/63 (0)

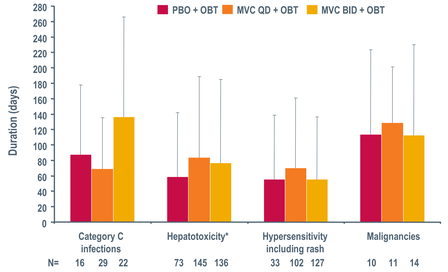
* Patients with missing HCV/HBV test results excluded

AST, aspartate aminotransferase; ALT, alanine aminotransferase
Includes only patients with both valid baseline and on-treatment values for parameters of interest

Table 7. MOTIVATE 1 and 2: Time-relatedness of adverse events of interest

		0–7 days n (%)	8 days–<1 month n (%)	1–<3 months n (%)	3–<6 months n (%)	≥6 months n (%)
Category C infections	PBO	1 (0.5)	4 (1.9)	4 (1.9)	3 (1.4)	4 (1.9)
	MVC QD	2 (0.5)	9 (2.2)	7 (1.7)	6 (1.4)	5 (1.2)
	MVC BID	4 (0.9)	4 (0.9)	6 (1.4)	4 (0.9)	4 (0.9)
Hepatotoxicity	PBO	28 (13.4)	16 (7.7)	13 (6.2)	11 (5.3)	5 (2.4)
	MVC QD	53 (12.8)	31 (7.5)	22 (5.3)	17 (4.1)	22 (5.3)
	MVC BID	60 (14.1)	29 (6.8)	17 (4.0)	19 (4.5)	11 (2.6)
Hypersensitivity including rash	PBO	4 (1.9)	10 (4.8)	5 (2.4)	9 (4.3)	5 (2.4)
	MVC QD	16 (3.9)	29 (7.0)	25 (6.0)	15 (3.6)	17 (4.1)
	MVC BID	22 (5.2)	30 (7.0)	26 (6.1)	20 (4.7)	29 (6.8)
Malignancies	PBO	1 (0.5)	2 (1.0)	4 (1.9)	2 (1.0)	1 (0.5)
	MVC QD	0	2 (0.5)	3 (0.7)	2 (0.5)	4 (1.0)
	MVC BID	1 (0.2)	2 (0.5)	1 (0.2)	4 (0.9)	6 (1.4)

Figure 2. MOTIVATE 1 and 2: Mean (SD) duration of AEs of interest



* Hepatotoxicity including liver abnormalities
† Duration = 1, SD = 0

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