Original Article

The maraviroc expanded access program — safety and efficacy data from an open-label study

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Purpose: The maraviroc (MVC) expanded access program (EAP) was initiated to increase MVC availability to patients with limited treatment options. Darunavir (DRV), raltegravir (RAL), and etravirine (ETV) were either recently approved or under regulatory review at study initiation and available for coadministration with MVC. Thus, the safety of MVC in combination with new antiretroviral therapies (ARVs) could be assessed. This open-label safety study of MVC was conducted at 262 sites worldwide in 1032 R5 HIV-positive treatment-experienced patients with limited/no therapeutic options.

Methods: Study visits included screening, baseline, end of study or early discontinuation, and follow-up 30 days after last dose. Interim visits for HIV-1 RNA and CD4 cell counts occurred according to local HIV infection management guidelines. Safety data were analyzed overall and by subgroup based on ARV combination [MVC + optimized background therapy (OBT), MVC ± OBT + DRV/r, MVC ± OBT + RAL, MVC ± OBT + RAL + DRV/r, MVC ± OBT + RAL + ETV ± DRV/r].

Results: Most (90.3%) adverse events (AEs) were of mild or moderate severity with few grade 3/4 events, discontinuations, or temporary discontinuations/dose reductions due to AEs or serious AEs. Similar results were observed across subgroups. Of treated patients, 79.9% and 50% had HIV-1 RNA <400 copies/ml and <50 copies/ml respectively, at the end of the study, early termination visits, or at last known status. Tropism changes and selection of MVC-resistant R5 virus, including high-level MVC dependence, were mechanisms of viral escape.

Conclusion: MVC was well tolerated with virologic suppression observed in most patients.

Keywords: HIV, Maraviroc, Darunavir, Raltegravir, Etravirine, Antiretroviral agents

Introduction

Maraviroc (MVC), a selective C–C chemokine receptor type-5 (CCR5) antagonist, is approved for use in treatment-experienced patients infected with CCR5-tropic human immunodeficiency virus subtype-1 (R5 HIV-1) at a dose of 300 mg twice daily (BID) or equivalent.[1,2] Approval was based on data from two identically designed, registrational phase IIb/III studies, A4001027 and A4001028 (known as MOTIVATE-1 and -2, for Maraviroc Plus Optimized Therapy in Viremic Antiretroviral Treatment Experienced Patients), which were conducted in the USA and Canada (MOTIVATE-1) and in the USA, Canada, Australia, and Europe (MOTIVATE-2). In these studies, MVC 300 mg (or 150 mg in combination with potent CYP3A4 inhibitors) administered BID or once daily (QD) demonstrated safety and efficacy when used as part of combination antiretroviral (ARV) regimens. Both MVC regimens were significantly superior to placebo in all primary and secondary virologic and immunologic efficacy endpoints.[3–5]

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A significant need remains for new drugs with novel mechanisms of action to be developed for treatment-experienced patients who have few or no remaining options due to multiclass drug resistance and/or intolerance to existing classes of ARV agents. Furthermore, several studies have demonstrated an association between the number of active drugs in the ARV regimen and virologic response rates.[4,6–8] It is therefore important that new drugs are combined with other active drugs in order to improve the likelihood of a sustained virologic response in heavily pretreated patients. In many cases, this would require the combination of two or more new drugs.

However, safety data are often limited for new drugs when used in a wider patient population. New combinations may result in unexpected side effects due to pharmacokinetic and/or pharmacodynamic interactions. Darunavir (DRV) was not permitted as part of optimized background therapy (OBT) in the MOTIVATE studies because it was not approved at the time the studies started and drug–drug interaction data were not available.[4,6] Raltegravir (RAL) and etravirine (ETV) were both still in development at the time the MOTIVATE studies were conducted and were only approved for use in patients with HIV infection after MVC received its marketing authorization.

Following completion of the MOTIVATE studies and while MVC was under regulatory review, an expanded access program (EAP) (Study A4001050) was initiated in February 2007 to make MVC available to patients with limited or no approved treatment options due to resistance or intolerance and who required MVC to create a viable treatment regimen. The key objectives of this study were to allow for collection of safety data in a larger patient population more representative of those who now receive the drug in countries where MVC has been approved for use compared with the patients included in the phase IIb/III clinical study and to evaluate the safety of MVC in combination with new ARVs (DRV, RAL, and ETV) that were not available for use in the MOTIVATE studies. A secondary objective of the EAP was to evaluate the effectiveness of MVC in treatment-experienced patients who were followed according to local medical practice. In this paper we describe the safety and efficacy of MVC in the EAP, including its use in combination with the newer ARVs.

Methods

Study design, population, and conduct

Study A4001050 was an open-label, non-comparative, international, phase IIIb safety study of MVC in treatment-experienced patients with R5 HIV who had limited or no therapeutic options with approved therapies. The study was conducted at 262 centers throughout the world (Argentina, Australia, Austria, Belgium, Canada, Chile, Costa Rica, France, Greece, Hong Kong, India, Ireland, Italy, Malaysia, Mexico, Portugal, Puerto Rico, Romania, Spain, Switzerland, Taiwan, UK, the Netherlands, and the USA).

Patients were eligible for the study if they were at least 16 years of age (or minimum adult age as determined by local regulatory authorities or as dictated by local law); had limited or no approved treatment options available to them owing to resistance or intolerance; had failed to achieve adequate virologic suppression on their current regimen and had HIV-1 RNA $\geq$1000 copies/ml; and had only R5 HIV as verified by the original Trofile™ tropism assay (Monogram Biosciences, Inc., South San Francisco, CA, USA). Patients receiving other investigational ARV compounds through pre-approval EAPs or participation in Phase III or IV clinical studies were eligible for inclusion provided the two investigational agents offered the patient a regimen with two or three active ARVs (i.e. one approved treatment or no approved treatments were available to the patient due to resistance or intolerance), neither protocol prohibited the use of the other ARV, and the dosing of the two agents when used together was known. Patients receiving MVC or another CCR5 antagonist in an ongoing study that was being terminated or in which the patient's active dosing portion of the study was completed could be enrolled if the patient had only R5 HIV at the time of screening for the other study, had achieved a virologic response ($>$0.5 $\log_{10}$ reduction from baseline HIV-1 RNA concentration), and had never met the definition of virologic failure.

Key exclusion criteria were: prior treatment failure with any CCR5 antagonist; participation in any ongoing CCR5 antagonist study; or previous premature discontinuation in an MVC study. Patients were also excluded if they had a potentially life-threatening (grade 4) laboratory abnormality or medical condition (according to the Division of AIDS table for grading the severity of adult adverse events) that was still under investigation, unless a diagnosis had been established and was felt not to affect the risk/benefit assessment or eventual interpretation of safety results. The recommended MVC dose was 300 mg BID or equivalent, with dose adjustments according to the combination of drugs in the OBT or used for treatment of other intercurrent conditions.

Patients could withdraw from the study at any time at their own request or could be withdrawn at any time at the discretion of the investigator or sponsor. Additionally, patients were discontinued from the study if they met the definition of virologic failure:

- failing to achieve a reduction from baseline in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/ml by the second viral load determination;
- experiencing a ≥ 0.5 $\log_{10}$ increase from nadir in HIV-1 RNA after achieving an HIV-1 RNA reduction from baseline of ≥ 0.5 $\log_{10}$ copies/ml;
- experiencing an HIV-1 RNA level of >1000 copies/ml after achieving an HIV-1 RNA level below the lower limit of quantification (LLOQ).

However, even if the definition of virologic failure was met, treatment could be continued if the investigator felt that the patient was benefiting from MVC.

Study visits included screening, baseline, end of study or early discontinuation, and a follow-up visit 30 days after last dose of MVC as well as interim visits (suggested schedule: weeks 2–4, 8, 12, and every 12 weeks thereafter) where HIV-1 RNA and CD4 cell count testing were conducted. Patients were managed according to local guidelines for HIV infection and HIV-1 RNA and CD4 count testing were performed in local laboratories. Laboratory testing for safety was performed in a designated central laboratory (Covance, Indianapolis, IN, USA; Geneva, Switzerland; and Singapore). Coreceptor tropism was tested using the Trofile assay and a subset of patients with virologic failure was tested for MVC susceptibility (PhenoSense Entry; Monogram Biosciences), at screening or day 1 and end of study visits. The cut-off for MVC susceptibility was set at 95% maximal percent inhibition (MPI).[9]

Safety was assessed by spontaneous reports, physical examinations, and laboratory test results in all patients who received at least one dose of study drug. Safety assessments were done at the screening, baseline, interim, and end of study or early discontinuation visits and included medical history (at screening only), complete or symptom-directed physical examination (at screening and end of study or early discontinuation visits only), vital signs and safety laboratory tests (e.g. hepatitis testing, pregnancy testing, hematology, and chemistry). Patients who met the following criteria were carefully evaluated:

- any patient (with normal baseline) who developed a grade 3 abnormality (with the exception of hypercholesterolemia; hypertriglyceridemia; asymptomatic creatine phosphokinase (CPK) elevations; aspartate aminotransferase (AST), or alanine aminotransferase (ALT) elevation in the absence of a total bilirubin elevation >2 times the upper limit of normal (ULN); or asymptomatic amylase or lipase elevations);
- any patient with abnormal baseline who developed a grade 3 abnormality and a level of ≥ 2 times baseline (with the exception of hypercholesterolemia; hypertriglyceridemia; asymptomatic CPK elevations; AST/ALT elevation in the absence of a total bilirubin elevation >2 times ULN; or asymptomatic amylase or lipase elevations);
- all patients who developed a grade 4 laboratory abnormality.

Study drug was discontinued immediately unless the medical monitor and investigator agreed that there was an adequate explanation for the abnormality and the patient could safely continue. If the decision was made to interrupt study drug treatment, patients remained in the study and re-challenge could occur if the abnormality had decreased to baseline within 14 days of stopping study drug. Longer treatment interruptions for the management of suspected drug toxicity or the recurrence of a grade 3 or 4 abnormality following re-challenge required permanent discontinuation of study drug. These patients remained "in-study off-drug" and were followed with appropriate medical management until there was a return to baseline values or a clinical diagnosis of an intercurrent illness had been established.

The study protocol was approved by the institutional review board or independent ethics committee at each study center. Written informed consent was obtained from all participants. The studies were performed in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and applicable local regulatory requirements and laws. An independent data and safety monitoring board was responsible for oversight of the progress of the study, the study data, and safety considerations.

Data analysis

The safety analysis population included any patient who was allocated into one of the analysis groups and received at least one dose of study medication. Efficacy analyses were performed on data for all treated patients, regardless of whether they had a post-baseline visit. Patients from the EAP were pooled into three main groups for analysis:

- all EAP patients;
- EAP patients who received OBT that did not include novel drugs (DRV, RAL, ETV, or combinations of these) at baseline;
- EAP patients who received MVC with OBT containing a novel drug or combination of novel drugs as defined above at baseline; within this group, patients were subdivided according to which new drugs, or combinations of these, they were taking:
    - ○ DRV/r only;
    - ○ RAL only;

- ○ RAL + DRV/r;
- ○ RAL + ETV (± DRV/r).

As this was an open-label study with no control arm, the data from the combined MOTIVATE studies[3,4] were used as a comparator cohort, as appropriate, to interpret any safety signals. The MOTIVATE studies were chosen primarily because patients in both the EAP and MOTIVATE had CCR5 tropic virus. Additionally, the study population included patients with similar treatment experience who received a similar number of background ARVs. There were no formal statistical comparisons between data from EAP and from the MOTIVATE studies.

All available data were included in the efficacy analyses. None of the efficacy analyses were based on the last observation carried forward. Endpoints included the following and were descriptive in nature:

- virologic response, determined by the proportions of patients with ≥ 0.5 $\log_{10}$ or ≥ 1.0 $\log_{10}$ reduction in HIV-1 RNA from baseline;
- proportions of patients who demonstrated a response to treatment in plasma HIV-1 RNA levels to <400 copies/ml or <50 copies/ml;
- change in CD4 count from baseline;
- proportions of patients with virologic failure and change in viral tropism from screening to end of study.

Results

Patient disposition, demographics, and baseline characteristics

Overall, 2584 patients were screened and 1047 patients assigned to MVC treatment. Of these, 1032 patients were treated with MVC BID. Overall, 916 patients (88.8%) completed the study and 116 patients (11.2%) discontinued (Table 1). The screening failure rate was 59.5% (1537/2584 patients), mainly due to the presence of CXCR4-using virus as determined by the original Trofile assay.

Of the 1032 patients assigned to treatment, 80.1% were male. Overall, 79.2% of patients were white, 10.3% were black, 5.2% were Asian, and 5.3% were of other race. Patients were aged between 16 and 80 years with a mean age of 45.6 years. The mean duration since first HIV diagnosis was 14.4 years (range: 0.3–27.0 years). The majority of patients (873; 84.6%) had R5 HIV recorded within the protocol-defined 42-day screening period. A further 2 patients had dual-mixed tropism recorded in this period, while 1 had a non-reportable tropism result. A further 156 patients had a screening tropism result recorded outside of the screening window. Of these patients, 151 had an R5 tropism result, 2 had dual-mixed tropism and 2 had a non-reportable tropism result. Therefore, a total of 1024 patients (99.2%) had an R5 tropism result recorded before study start. At baseline, mean HIV-1 RNA level was 4.3 $\log_{10}$ copies/ml and mean CD4 cell count was 259.6 cells/μl. Sixty patients (5.8%) tested positive for hepatitis B surface antigen and 158 patients (15.3%) were positive for hepatitis C antibody. A total of 1049 patients were included in the MOTIVATE studies of whom 414 received MVC QD, 426 received MVC BID, and 209 received placebo. Demographic characteristics were very similar to that of the EAP population; the mean baseline HIV-1 RNA level was 4.9 $\log_{10}$ copies/ml in the MVC QD, BID, and placebo groups. Mean baseline CD4 cell count [standard deviation (SD)] for patients in the combined MOTIVATE studies was 196.0 cells/μl (159.85) in the MVC QD group, 189.2 cells/μl (146.83) in the MVC BID group, and 186.4 cells/μl (133.52) in the placebo group.

In study A4001050, only 243/1032 (23.5%) of patients used MVC with an OBT that did not contain one of the newer ARVs. One hundred and fifty-eight (15.3%) included DRV as the only one of the newer drugs in their OBT, 155 (15.0%) RAL only, 263 (25.5%) DRV + RAL, and 213 (20.6%) ETV + RAL (± DRV).

Safety data

The median (range) duration of treatment was 174.0 (1–981) days (24.9 weeks) and was similar (169.0–181.0 days) for patients receiving each combination of novel ARVs. At least one all-causality AE was experienced by 70.4% of patients receiving MVC in the EAP. Overall, 2955 AEs were reported by 727 patients, of which 422 AEs experienced by 228 patients (22.1%) were considered related to the study drug. Table 2 summarizes treatment-emergent adverse events by combination of novel ARV treatment groups. There were no clinically important differences by combination of novel ARV treatment(s) in the proportion of patients with AEs, the number of AEs, or the severity of AEs (Table 2). The most frequently reported all-causality AEs (>5% of patients) were diarrhea (9.3%), bronchitis (6.5%), headache (6.4%), nausea (5.9%), and pyrexia (5.7%). By comparison, the overall percentages of patients reporting AEs in the MOTIVATE studies were 90.6%, 92.3%, and 84.7% for the groups treated with MVC QD, MVC BID, and placebo groups, respectively. The most commonly reported AEs in the MOTIVATE studies were diarrhea and nausea.

The majority of AEs (90.3%) were graded as mild or moderate in severity and there were few grade 3 or 4 events, discontinuations, or temporary discontinuations/dose reductions due to AEs (Table 3). The only grade 3 or 4 AEs that were reported by more than five patients were: hypertriglyceridemia (12

Table 1 Patient disposition overall and grouped by combination of novel ARVs

Patients	Total EAP	MVC ± OBT + DRV/r − RAL − ETV	MVC ± OBT + RAL	MVC ± OBT + DRV/r + RAL	MVC ± OBT + ETV ± DRV/r + RAL	MVC BT only
Screened, *N*	2584	...	...	...	...	...
Treated, *n*	1032	158	155	263	213	243
Completed, *n* (%)	916 (88.8)	140 (88.6)	141 (91.0)	242 (92.0)	203 (95.3)	190 (78.2)
Discontinued, *n* (%)	116 (11.2)	18 (11.4)	14 (9.0)	21 (8.0)	10 (4.7)	53 (21.8)

Note: ARV=antiretroviral treatment; EAP=expanded access program; DRV/r=darunavir/ritonavir; ETV=etravirine; MVC=maraviroc; OBT=optimized background therapy; RAL=raltegravir.

Table 2 Summary of treatment-emergent AEs (all causality) by combination of novel ARVs

AEs	Total EAP	MVC ± OBT + DRV/r − RAL − ETV	MVC ± OBT + RAL	MVC ± OBT + DRV/r + RAL	MVC ± OBT + ETV ± DRV/r + RAL	MVC OBT only
	(*n*=1032)	(*n*=158)	(*n*=155)	(*n*=263)	(*n*=213)	(*n*=243)
Patients with AEs, *n* (%)	727 (70.4)	107 (67.7)	122 (78.7)	176 (66.9)	159 (74.6)	163 (67.1)
Number of AEs	2955	395	447	658	712	743
Patients with grade 3 AEs, *n* (%)	136 (13.2)	21 (13.3)	21 (13.5)	39 (14.8)	27 (12.7)	28 (11.5)
Patients with grade 4 AEs, *n* (%)	65 (6.3)	10 (6.3)	9 (5.8)	14 (5.3)	11 (5.2)	21 (8.6)
Patients who discontinued due to AEs, *n* (%)	28 (2.7)	7 (4.4)	6 (3.9)	4 (1.5)	4 (1.9)	7 (2.9)
Patients with dose reduced or temporary discontinuation due to AEs, *n* (%)	47 (4.6)	5 (3.2)	7 (4.5)	12 (4.6)	13 (6.1)	10 (4.1)

Note: AE=adverse event; ARV=antiretroviral treatment; DRV/r=darunavir/ritonavir; ETV=etravirine; grade 3=severe; grade 4=very severe; MVC=maraviroc; OBT=optimized background therapy; RAL=raltegravir.

patients), pneumonia (9 patients), increased amylase (8 patients), increased gamma-glutamyl transferase (8 patients), chest pain (7 patients), increased lipase (7 patients), and nausea (6 patients).

A total of 182 patients (17.6%) experienced serious adverse events (SAEs), including 16 deaths. Two of the patients who died had completed the study prior to death; one died 31 days after the last dose of MVC and the other 328 days after the last dose. For 26 patients, the SAEs (including three deaths) were considered to be related or possibly related to treatment with MVC, by either the investigator or the sponsor (Table 3). SAEs occurred at a similar frequency across the subgroups based on the combination of novel ARV drugs used (Table 3). The proportion of patients experiencing SAEs in the MOTIVATE studies was 15.0%, 16.9%, and 16.7% for MVC QD, MVC BID, and placebo, respectively.

Twenty-three patients experienced a total of 28 Category C AIDS-defining conditions (Table 4). One event was categorized as DAIDS (Division of AIDS) grade 1, 14 as grade 2, 8 as grade 3, and 4 as grade 4. The grade 4 Category C AIDS-defining conditions were: AIDS-related encephalopathy, cryptococcal meningitis, meningitis tuberculosis, and *Mycobacterium kansasii* infection. The only

Table 3 Treatment-emergent, treatment-related (maraviroc) serious adverse events — EAP

Gender (M/F)/ age[a] (years)	Suspect drugs	MVC discontinued	Day of SAE[b]	SAE	Outcome[c]
MVC ± OBT + DRV/r − RAL − ETV (*N*=158)					
M/52	MVC, DRV/r	Yes	24	Liver function test abnormal	Resolved
M/18	MVC	Yes	59	Chest pain	Resolved
		Yes	59	Blood creatine phosphokinase increased	Resolved
M/43	MVC, DRV/r, simvastatin	Yes	188	Hepatotoxicity	Resolved
M/48	MVC	Yes	70	Blood glucose increased	Resolved
		Yes	70	Vision blurred	Resolved
MVC ± OBT + RAL (*N*=155)					
M/38	MVC	No	253	Rectal cancer	Ongoing
M/32	MVC	Temporarily	40	Abdominal pain	Resolved
M/55	MVC	NA[d]	644	Cardiac failure congestive	Resolved
M/42	MVC, RAL	No	170	Blood alkaline phosphatase increased	Improved
M/45	MVC, RTV, RAL, tipranavir	No[e]	25	Transaminases increased	Unknown
M/44	MVC, RAL	No	19	Immune reconstitution syndrome	Resolved
MVC ± OBT + DRV/r + RAL (*N*=263)					
F/42	MVC, sodium valproate	Temporarily	27	Neutropenia	Resolved
F/38	MVC, DRV/r, 3TC	Temporarily	26	Transaminases increased	Resolved
M/43	MVC, DRV/r, RAL, abacavir, enfuvirtide, 3TC	Yes	42	Abdominal pain	Death
F/23	MVC, DRV, RAL	No	1	Drug toxicity	Resolved
M/44	MVC, DRV/r, RAL	No	44	Hepatic failure	Resolved
M/48	MVC, DRV/r, RAL	No	21	Diarrhea	Resolved
		No	24	Hypokalemia	Resolved
MVC ± OBT + ETV ± DRV/r + RAL (*N*=213)					
M/31	MVC, DRV, ETV	Yes	20	Dermatitis allergic	Resolved
M/43	MVC, ETV	No	44	Rash	Resolved
M/54	MVC, RAL, amlodipine, ramipril, candesartan cilexitil	No	38	Hypertensive crisis	Resolved
		No	38	Drug interaction	Resolved
M/59	MVC	No	178	Ventricular tachycardia	Unresolved
MVC ± OBT only (*N*=243)					
M/39	MVC	Yes	41	Unknown cause of death	Death
M/42	MVC	Yes	25	Cardiac arrest	Death
M/50	MVC	Yes	7	Syncope	Resolved
F/39	MVC	No	107	Vertigo	Resolved
		Yes	110	Orthostatic hypotension	Resolved
M/59	MVC	No	70	Peptic ulcer	Resolved
M/48	MVC	No	144	Basal cell carcinoma	Resolved

Note: [a]Age at start of the study. [b]Relative to the start of treatment. [c]At last follow-up. [d]NA=not applicable as MVC discontinued >30 days before event. [e]Dose reduced to 150 mg twice daily.
DRV/r=darunavir/ritonavir; EAP=expanded access program; ETV=etravirine; MVC=maraviroc; OBT=optimized background therapy; RAL=raltegravir; RTV=ritonavir; SAE=serious adverse event; 3TC=lamivudine.

Table 4 Incidence of Category C AIDS-defining illnesses by combination of novel ARVs in the MVC EAP

	Total EAP	MVC ± OBT + DRV/r − RAL − ETV	MVC ± OBT + RAL	MVC ± OBT + DRV/r + RAL	MVC ± OBT + ETV ± DRV/r + RAL	MVC OBT only
	(*n*=1032)	(*n*=158)	(*n*=155)	(*n*=263)	(*n*=213)	(*n*=243)
Encephalopathy	2 (0.2)	0	1 (0.6)[a]	0	0	1 (0.4)[b]
Extra-pulmonary tuberculosis[c]	3 (0.3)	0	0	2 (0.8)[a, b]	1 (0.5)[a]	0
Cytomegalovirus infection	2 (0.2)	0	0	1 (0.4)[a]	1 (0.5)[d]	0
Cryptococcal meningitis	1 (0.1)	0	0	1 (0.4)[b]	0	0
Mycobacterium avium complex infection	1 (0.1)	0	0	0	0	1 (0.4)[a]
Mycobacterium kansasii infection	1 (0.1)	0	0	0	0	1 (0.4)[b]
Mycobacterial pancreatitis	1 (0.1)	1 (0.6)[a]	0	0	0	0
Esophageal candidiasis	6 (0.6)	0	0	3 (1.1)[d]	2 (0.9)[d]	1 (0.4)[d]
Pneumocystis jiroveci pneumonia	1 (0.1)	0		1 (0.4)[a]	0	0
Progressive multifocal leukoencephalopathy	1 (0.1)	0	0	0	0	1 (0.4)[d]
Pulmonary tuberculosis	5 (0.5)	0	0	0	0	5 (2.1)[e]
Toxoplasmosis	1 (0.1)	1 (0.6)[a]	0	0	0	0
AIDS-defining neoplasms						
B-cell lymphoma	1 (0.1)	0	0	0	0	1 (0.4)[d]
Kaposi's sarcoma	2 (0.2)	0	1 (0.6)[f]	1 (0.4)[d]	0	0

Note: Only treatment-emergent (all-causality) Category C AIDS-defining illnesses were considered. Patients were counted only once per treatment per row. Includes data up to 30 days after last dose.
[a]DAIDS grade 3=severe. [b]DAIDS grade 4=very severe. [c]Includes one case of tuberculous meningitis and one of bone tuberculosis. [d]DAIDS grade 2=moderate. [e]DAIDS grade 2 (4 patients) and grade 3 (1 patient). [f]DAIDS grade 1=mild.
AIDS=acquired immune deficiency syndrome; ARV=antiretroviral treatment; DAIDS=Division of AIDS; DRV/r=darunavir/ritonavir; EAP=expanded access program; ETV=etravirine; MVC=maraviroc; OBT=optimized background therapy; RAL=raltegravir.

Category C AIDS-defining illnesses reported in more than two patients were esophageal candidiasis and pulmonary tuberculosis. There were no clinically important differences in the frequencies of Category C AIDS-defining illnesses when categorized by combination of novel antiretroviral treatment(s) (Table 4). In the MOTIVATE studies, 29 (7.0%), 22 (5.2%), and 16 (7.7%) patients in the MVC QD, MVC BID, and placebo treatment groups, respectively, had Category C AIDS-defining illnesses.

Sixteen (1.6%) treatment-emergent non-AIDS-defining malignancies were reported. Only anal cancer (three patients), rectal cancer (three patients), basal cell carcinoma (two patients), and carcinoma in situ of penis (two patients) were reported in more than one patient (Table 5). There were no clinically relevant differences between the type and incidence of non-AIDS-defining malignancies between patients receiving each novel combination of ARV treatment(s). In the MOTIVATE studies, 11 (2.7%), 14 (3.3%), and 10 (4.8%) patients in the MVC QD, MVC BID, and placebo treatment groups, respectively, presented with treatment-emergent non-AIDS-defining malignancies.

Table 5 Incidence of treatment-emergent non-AIDS-defining malignancies in the MVC EAP

Number of subjects evaluable for AEs	MVC (*N*=1032)				
		DAIDS severity grade			
	n (%)	1	2	3	4
Anal cancer	3 (0.3)	0	0	2	1
Basal cell carcinoma	2 (0.2)	0	2	0	0
Bowen's disease	1 (0.1)	0	1	0	0
Carcinoma in situ of penis	2 (0.2)	0	1	1	0
Gastric cancer	1 (0.1)	0	0	1	0
Hodgkin's disease	1 (0.1)	0	0	1	0
Prostate cancer	1 (0.1)	0	0	0	1
Rectal cancer	3 (0.3)	0	1	1	1
Squamous cell carcinoma	1 (0.1)	0	1	0	0
Tongue neoplasm malignant stage unspecified	1 (0.1)	0	1	0	0

Note: Only treatment-emergent (all causality) malignancies were considered. If the same subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence was taken. Subjects were counted only once per treatment per row. Includes data up to 30 days before last dose.
DAIDS grades estimate severity as: grade 1=mild, grade 2=moderate, grade 3=severe, and grade 4=very severe.
AE=adverse event; DAIDS=Division of AIDS; EAP=expanded access program; MVC=maraviroc; *N* = total number of subjects receiving treatment; *n* = total number of subjects with at least one observation.

A total of 1014 patients receiving MVC in the EAP were evaluable for laboratory tests and no clinically significant median changes from baseline occurred in any laboratory test. The incidence of clinically significant grade 3 and 4 laboratory test abnormalities is summarized in Table 6. The incidence of grade 3 and 4 liver enzyme abnormalities was low and there were no cases of hepatotoxicity reported that met the criteria for Hy's Law.

Virologic and immunologic responses

There was a mean (SD) decrease from baseline in viral load by week 2 of 1.688 (0.8934) $\log_{10}$ copies/ml that was maintained to week 48 [(1.992 (1.1910) $\log_{10}$ copies/ml relative to baseline] and generally maintained up to the last assessment at week 144. At week 48, 89% (203/228) and 86% (197/228) of patients achieved >0.5 and >1 $\log_{10}$ reductions from baseline in HIV-1 RNA, respectively. Overall, 825/1032 (79.9%) and 516/1032 (50.0%) of treated patients achieved HIV-1 RNA <400 copies/ml and <50 copies/ml, respectively, at either end of study or early termination visits, or at last known status. The proportion of patients with viral load <400 copies/ml increased from baseline [66/979 (6.7%) patients] to week 4 [562/773 (72.7%) patients] and was maintained to week 48 (184/228 [80.7%] patients). Similar results were observed for the <50 copies/ml endpoint (Table 7). Mean (SD) CD4 cell count gradually increased from baseline [259.6 (186.29) cells/μl] to week 48 [393.7 (221.41) cells/μl].

One hundred and ninety-two patients reached a virologic failure endpoint. The most common virologic failure endpoint (recorded in 44% of cases) was failing to achieve a reduction in HIV-1 RNA from baseline of ≥ 0.5 $\log_{10}$ copies/ml by the second viral load determination. Overall, 269 patients (26.1%) had reportable tropism results at the end of study assessment; 653 patients (63.3%) had non-reportable tropism results at the end of study assessment, reflecting the high proportion of patients with viral load <400 copies/ml. Of the 227 patients with R5 HIV at screening and a valid tropism result at the end of study assessment, 71% (161/227) did not change tropism; the remainder changed from R5 to X4 (13 patients) or to dual mixed (53 patients).

Virologic failure and MVC susceptibility

The evaluable virologic failure (eVF) population included those patients with protocol-defined virologic failure with plasma HIV-1 RNA >1000 copies/ml at the last on-treatment time point and at baseline (day 1). A total of 75 patients met these criteria. Notably, eVF patients tended to have low CD4 cell count and high plasma HIV-1 RNA levels at baseline compared with either the total virologic failure population or the total trial population (CD4 <50 cells/mm^3: 37.3%, 21.9%, 12.5%, respectively; plasma HIV-1 RNA $\geq 100{,}000$ copies/ml: 34.7%, 28.1%, 22.7%, respectively). At day 1, 11 eVF patients (14.7%) had DM/X4 virus, 54 (73.0%) had R5 virus, and 10 (13.5%) did not have a tropism result. Of the 54 patients with R5 virus at day 1, 18 (33.3%) had a tropism that changed to DM/X4 on treatment; 14 (25.9%) had R5 virus resistant to MVC, 12 (22.2%) had R5 virus that remained susceptible to MVC, and 10 (18.5%) did not have a susceptibility result. Prolonged treatment on a failing

Table 6 Incidence of maximum grade 3 and 4 laboratory test abnormalities (Division of AIDS) without regard to baseline abnormalities in the MVC expanded access program

	MVC (*N*=1032)		
Abnormality	No. tested	Grade 3, *n* (%)	Grade 4, *n* (%)
Raised alanine aminotransferase	1013	22 (2.2)	8 (0.8)
Raised aspartate aminotransferase	1013	21 (2.1)	4 (0.4)
Decreased absolute neutrophil count	1004	7 (0.7)	2 (0.2)
Raised alkaline phosphatase	1014	4 (0.4)	0
Raised creatinine	1014	5 (0.5)	1 (0.1)
Raised gamma-glutamyl transferase	1014	48 (4.7)	15 (1.5)
Decreased hemoglobin	1005	2 (0.2)	1 (0.1)
Hyperbilirubinemia	1013	13 (1.3)	3 (0.3)
Hyperuricemia	1014	7 (0.7)	1 (0.1)
Hypophosphatemia	1014	2 (0.2)	0
Raised lipase	409	18 (4.4)	5 (1.2)
Decreased platelets	997	15 (1.5)	3 (0.3)
Hyperkalemia	1014	1 (0.1)	2 (0.2)
Raised serum amylase	1014	49 (4.8)	3 (0.3)
Hypernatremia	1014	1 (0.1)	2 (0.2)
Hypertriglyceridemia	1014	48 (4.7)	20 (1.9)

Note: Patients were counted once per laboratory test, per grade. MVC=maraviroc.

Table 7 Proportions of patients with HIV-1 RNA <400 and <50 copies/ml at weeks 24 and 48

Endpoint	Week	*N*[a]	%
Patients with HIV-1 RNA <400 copies/ml	24	557	84.4
	48	228	80.7
Patients with HIV-1 RNA <50 copies/ml	24	557	55.8
	48	228	54.8

Note: [a]Patients contributing to summary statistics.

regimen may have contributed to the development of resistance in a subgroup of patients ($n=6$ treated for ≥ 365 days). The virus from one patient treated with MVC on a failing regimen for 538 days (Fig. 1A) showed full susceptibility to MVC at day 1 (Fig. 1B), but was able to replicate efficiently only in the presence of MVC after treatment, as indicated by a highly negative MPI (–1230%; Fig. 1C). V3-loop amino acid sequence comparisons between day 1 and the last on-treatment time point were successfully completed with samples from 13 of the 14 patients. Although changes between the paired time points were observed for each sample, both the number and nature of the changes differed between patients and a consistent pattern of resistance was not observed (Fig. 2). This is consistent with observations from the MOTIVATE studies as well as the A4001026 (MERIT) study in treatment-naive patients, which demonstrated that although resistance was found to involve a common basic mechanism,[10] significant complexity of co-evolution at multiple sites, restricted commonality of sequence mutations, and divergent phenotypes prevent identification of any dependable pattern of mutations leading to resistance.[10–12]

Discussion

MVC demonstrated a favorable safety profile and was efficacious in the MOTIVATE studies.[3–5] Consistent with data from other studies,[7,8,13,14] subgroup analysis demonstrated that virologic response rates increased with the number of active drugs in the ARV regimen.[4,6] Current guidelines recommend the use of at least two, and preferably three, fully active agents in a new regimen in patients with evidence of virologic resistance.[15,16] In many heavily pre-treated patients, the combination of two or more new drugs would be required to increase the likelihood of a sustained virologic response.

Patients participating in the MVC EAP had the opportunity to receive a novel treatment regimen; that is, a combination of MVC and two or three new drugs (DRV, RAL, and ETV) that were either not commercially available, had only recently been approved or were under regulatory review at the time the study was initiated. More than 75% of patients in the EAP received at least one of the new ARVs as part of their OBT, and 46.1% received a combination of MVC plus at least two new ARVs. Therefore, and in spite of the limitations presented by the fact that this is an open-label study with no control group, the MVC EAP provided a unique opportunity for collection and analysis of safety data on new drug

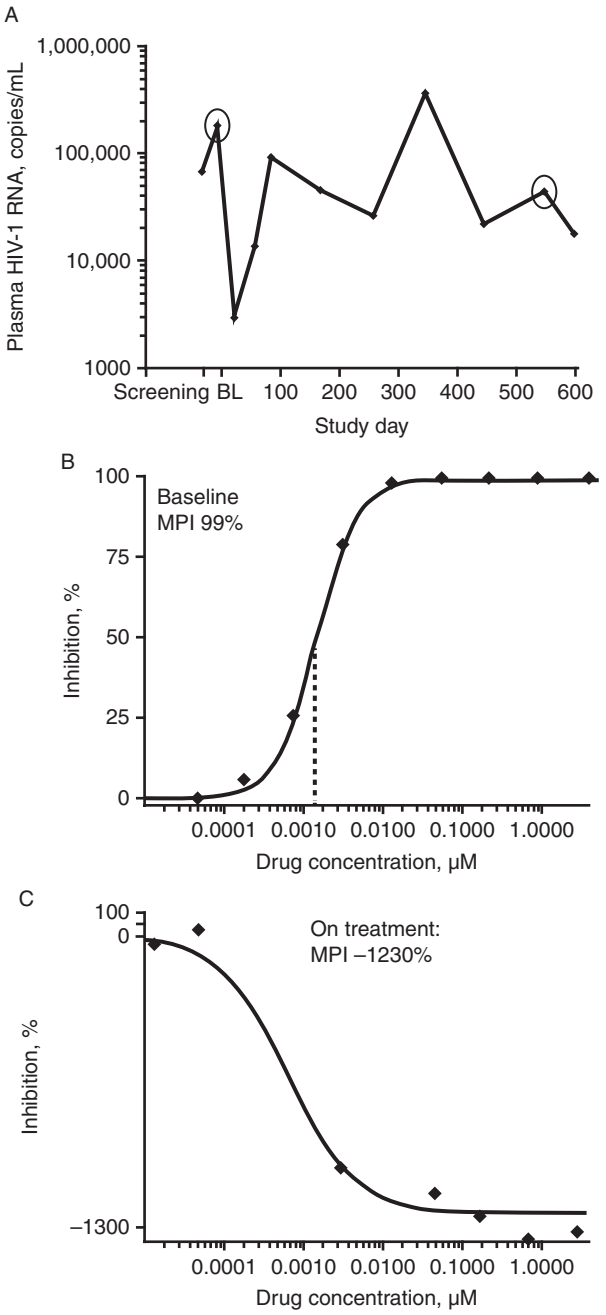

Figure 1 Analysis of (A) plasma HIV-1 RNA over time; (B) baseline MVC susceptibility; and (C) on-treatment MVC susceptibility in patient with virus showing strong MVC dependence. Circles show the time points used for the baseline and on-treatment analysis of MVC susceptibility. MPI = maximal percent inhibition; MVC = maraviroc.

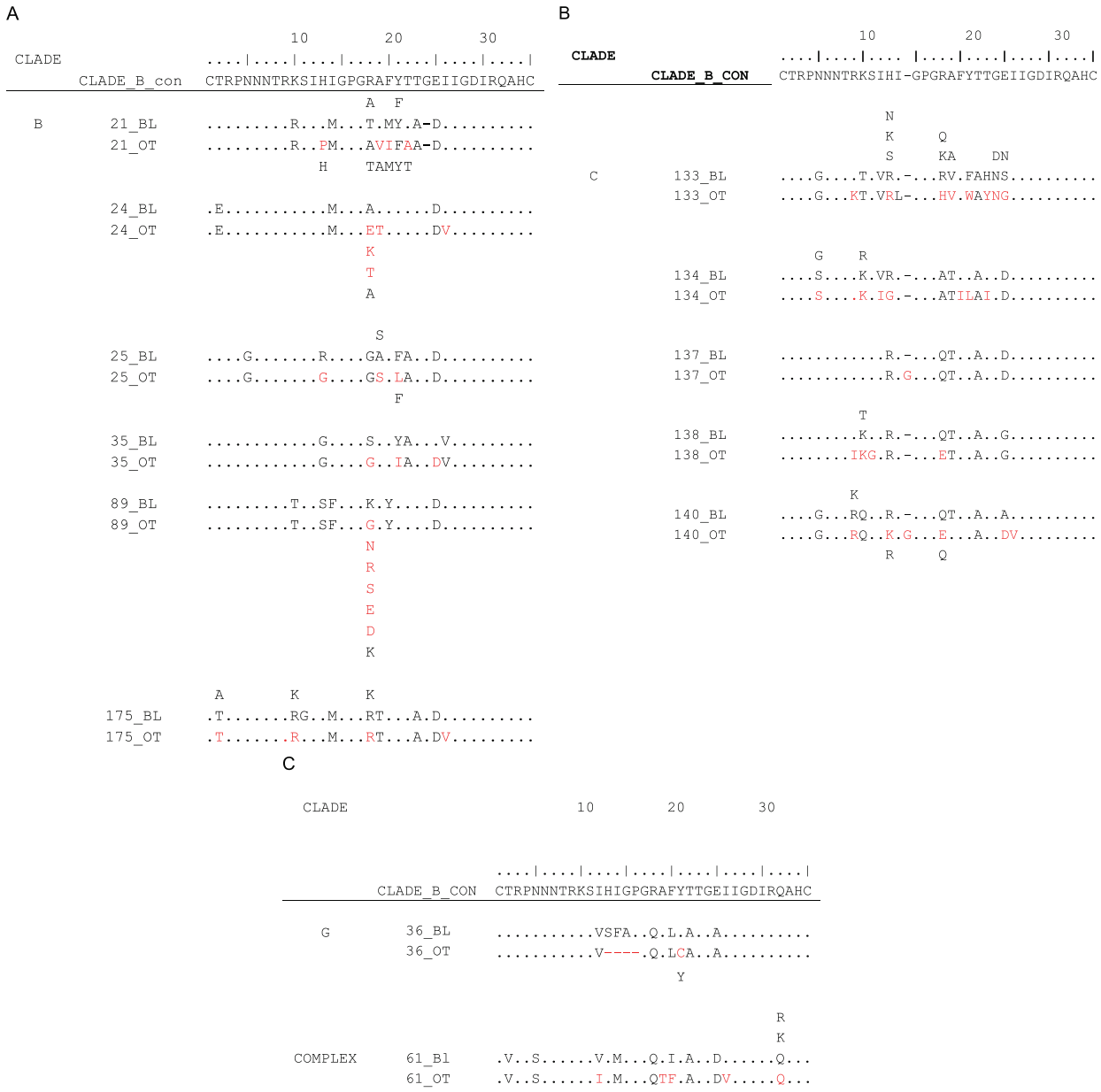

Figure 2 Insertions, deletions, and amino-acid changes between baseline and last on-treatment time point in the gp120 V3 loop of R5 virus from patients with evaluable virologic failure. Putative amino acids have been interpreted from the nucleotide sequence. Amino acids not seen in the baseline sequence are shown in red as are amino acids that have been selected from a mixture at baseline. The reference clade B sequence has been used for all three alignments. All amino acids that are identical to reference are shown with a dot. (A) Alignments of clade B sequences; (B) alignments of clade C sequences; (C) alignments of one pair of clade G and one pair of complex clade sequences.

combinations that had not been evaluated previously in a treatment-experienced population.

Overall, MVC was well tolerated in this population with rates of AEs, grade 3 and 4 AEs, discontinuations due to AEs, and SAEs similar to or lower than those reported in the MOTIVATE studies. The incidence of Category C AIDS-defining events and non-AIDS-defining malignancies was very low. This, together with data from the 96-week follow-up of the MOTIVATE studies[5] is reassuring in light of the lymphomas (and other cancers) reported in prior studies with another CCR5 antagonist.[17] Although individuals with the CCR5 delta 32 mutation are generally healthy, some immunological effects have been described,[18–20] raising concern at the time regarding the long-term safety of CCR5 antagonists.

Despite concerns regarding the hepatic safety of CCR5 antagonists,[21,22] an analysis of week 48 data from the MOTIVATE studies did not show a significant difference in severe hepatotoxic effects between MVC and placebo.[3] In the EAP, a very low rate of grade 3 and 4 liver enzyme abnormalities was

recorded, confirming the hepatic safety of MVC in a wider HIV patient population. Additionally, a separate analysis of the subpopulation of EAP patients co-infected with hepatitis B or C demonstrated no increased incidence of AEs or severe liver enzyme abnormalities.[23]

Comparison of the data from the EAP with that from the MOTIVATE studies demonstrated that MVC was equally well tolerated in this wider population and no additional safety concerns were highlighted. Finally, no significant differences were observed between the different subgroups based on the use of novel ARV combinations, demonstrating the safety of MVC as a component of each of the novel ARV regimens.

Patients eligible for the MVC EAP had very limited treatment options, but nonetheless the majority of patients (79.9%) achieved HIV-1 RNA <400 copies/ml. A significant immunologic response was also observed, with an increase in mean CD4 count from 259.6 cells/μl at baseline to 393.7 cells/μl at week 48. This is similar to the virologic and immunologic responses observed in patients who had received two or more active drugs in their OBT regimen (based on overall susceptibility scores) in the MOTIVATE studies.[4,6] Although the efficacy data from this open-label study should be interpreted with caution, the results indicate that even in a population of very treatment-experienced patients with limited treatment options remaining, the combination of MVC with one or more of the other new ARVs can elicit virologic suppression in the majority of patients.

The virologic findings in relation to mechanisms of viral escape were consistent with previous studies. As previously demonstrated, reduced maximal percent inhibition was the key observation of resistance to this inhibitor.[9] However, the data provide evidence not only of MVC resistance (i.e. the ability of the virus to replicate in the presence of MVC) but also of a rare case of MVC dependency (i.e. the need for MVC to be present for viral replication to occur efficiently) as indicated by negative values of percent inhibition in the presence of MVC seen in one patient. Altogether, these data further support the current hypothesis regarding the mechanism of resistance to CCR5 inhibitors.[9,10]

In summary, the data from the MVC EAP demonstrated that MVC was well tolerated in a population of patients managed according to local guidelines for the treatment of HIV, and in combination with other new ARVs to form novel combination regimens. Furthermore, the majority of patients participating in the EAP achieved an HIV-1 RNA level below the LLOQ, indicating the efficacy of MVC when used as a component of novel ARV combination regimens.

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Contributors

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Conflicts of interest

Adriano Lazzarin has received honoraria and given expert testimony for ViiV Healthcare, Bristol-Myers Squibb, Janssen Pharmaceuticals, Gilead, Abbvie, and Merck Sharp & Dohme. Jacques Reynes has received payments for development of education materials and travel grants and has worked as a consultant on advisory boards for Pfizer Inc. and ViiV Healthcare. Jean-Michel Molina has served on advisory boards for Merck Sharp & Dohme, Gilead, Bristol-Myers Squibb, and Janssen Pharmaceuticals, and has received research grants from Merck Sharp & Dohme and Gilead. Srinivas Valluri owns stock and holds stock options in Pfizer Inc. Geoffrey Mukwaya and Elna van der Ryst own stock in Pfizer Inc. Jayvant Heera owns stock and holds stock options in Pfizer, Inc. Charles Craig has worked as a consultant for Pfizer Inc, and ViiV Healthcare and owns stock in GlaxoSmithKline. Juan G. Sierra-Madero has received grants from Pfizer Inc, and Merck Sharp & Dohme, speaker fees from Merck Sharp & Dohme, Bristol-Myers Squibb, Gilead, Janssen Pharmaceuticals, and ViiV Healthcare, and worked as a consultant for Merck Sharp & Dohme. Elna van der Ryst was an employee of Pfizer Inc during the time this study was performed.

Ethical approval

The study protocol was approved by the institutional review board or independent ethics committee at each study center. Written informed consent was

obtained from all participants. The studies were performed in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and applicable local regulatory requirements and laws. An independent data and safety monitoring board was responsible for oversight of the progress of the study, the study data, and safety considerations. This manuscript is an honest, accurate, and transparent account of the study being reported; no aspects of the study have been omitted, and any discrepancies from the study as planned have been explained.

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