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GENERIC DRUG NAME / COMPOUND NUMBER: Maraviroc / UK-427,857

PROTOCOL NO: A4001028

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of a Novel CCR5 Antagonist, UK-427,857, in Combination With Optimized Background Therapy Versus Optimized Background Therapy Alone for the Treatment of Antiretroviral-Experienced HIV-1 Infected Subjects

Study Centers: A total of 131 centers in 12 countries took part in the study and randomized subjects; 11 in Australia, 4 in Belgium, 12 in France, 19 in Germany, 9 in Italy, 2 in Netherlands, 3 in Poland, 13 in Spain, 1 in Sweden, 5 in Switzerland, 6 in United Kingdom and 46 in the United States of America.

Study Initiation Date, Primary Completion Date and Final Completion Date:
Study Initiation Date: 17 December 2004 (First Subject First Visit)
Primary Completion Date: 16 April 2007 (Final data collection date for primary outcome measure) and
Final Completion Date: 19 April 2011 (Last Subject Last Visit)

Phase of Development: Phase 2b/3

Study Objectives:

Primary Objective: To assess whether maraviroc (UK-427,857) added to optimized background therapy (OBT) provided an additional reduction in plasma human immunodeficiency virus type 1 ribonucleic acid (HIV-1 RNA; viral load) compared to OBT alone, as measured by the difference between each of the 2 maraviroc regimens versus the placebo regimen in the mean changes from baseline in plasma viral load at Week 48. This variable was also analyzed at Week 24.

Secondary Objectives:

- To compare the percentage of subjects with viral load <400 copies/mL at Weeks 24 and 48 for each of 2 maraviroc regimens versus the placebo regimen
- To compare the percentage of subjects with viral load <50 copies/mL at Weeks 24 and 48 for each of 2 maraviroc regimens versus the placebo regimen
- To compare the percentage of subjects who achieve <400 copies/mL or at least a 0.5 $\log_{10}$ reduction in viral load from baseline at Weeks 24 and 48 for each of 2 maraviroc regimens versus the placebo regimen

- To compare the percentage of subjects who achieve <400 copies/mL or at least a 1 $\log_{10}$ reduction in viral load from baseline at Weeks 24 and 48 for each of 2 maraviroc regimens versus the placebo regimen

- To compare the time to loss of virological response through Week 48 for each of 2 Maraviroc regimens versus the placebo regimen

- To compare the differences in the magnitude of changes in cluster of differentiation 4 (CD4) cell counts from baseline through Weeks 24 and 48 for each of 2 maraviroc regimens versus the placebo regimen

- To compare the differences in the magnitude of changes in cluster of differentiation 8 (CD8) cell counts from baseline through Weeks 24 and 48 for each of 2 maraviroc regimens versus the placebo regimen

- To compare the Time-Averaged Difference (TAD) in $\log_{10}$ viral load at Weeks 24 and 48 for each of 2 maraviroc regimens versus the placebo regimen

- To assess HIV-1 genotype and phenotype at baseline and at the time of failure (subjects with viral load >400 copies/mL at any visit after Week 4, or other reasons for treatment failure)

- To assess HIV-1 tropism at baseline and at the time of failure (subjects with viral load >400 copies/mL at any visit after Week 4, or other reasons for treatment failure)

- To assess the association between baseline resistance and virologic response

- To compare the safety and tolerability of each of 2 maraviroc regimens versus the placebo regimen.

METHODS:

Study Design: This was a randomized, multicenter Phase 2b/3 superiority study that consisted of 2 distinct and sequential phases: the active phase and the observational phase. The active phase also consisted of 2 distinct and sequential phases: the double-blind phase and the open-label (OL) phase. In the double-blind phase, subjects were randomized to 1 of 3 treatment groups (maraviroc 300 mg once daily [QD], maraviroc 300 mg twice daily [BID], or placebo) in a 2:2:1 ratio. The nominal length of this phase was 48 weeks. After the last subject to be enrolled completed their Week 48 visit, subjects were eligible to switch to OL maraviroc BID. Subjects who discontinued due to treatment failure or for another reason could be eligible to switch to OL maraviroc BID before their Week 48 visit. In the interim period between an individual subject's Week 48 visit and the start of the OL phase, subjects were to be maintained on their double-blind treatment. The duration of the OL phase was nominally 48 weeks; therefore, the nominal total length of the active phase was 96 weeks.

After completing their Week 96 visit, subjects were eligible to enter the observational phase to monitor long-term survival and selected endpoints. During this phase, subjects continued

OL maraviroc for a period extending to 5 years from their first dose of double-blind treatment. This study planned to enroll 400 subjects infected with Chemokine (C-C motif) Receptor 5 (CCR5) tropic HIV-1, ≥16 years of age, with no evidence of infection with chemokine (C-X-C motif) co-receptor (CXCR4) or dual/mixed-tropic virus. Subjects must have had ≥6 months of prior treatment with at least 1 agent from 3 of the 4 antiretroviral drug classes (at least 2 for protease inhibitors [PIs]) or documented multi-class resistance, and treatment failure to an existing regimen, defined by a plasma HIV-1 RNA ≥5000 copies/mL. Subjects visited the study centers for screening approximately 6 weeks before the start of scheduled dosing with study drug. After giving informed consent, an eligibility check was completed. If subjects were eligible for the study, screening evaluations were performed. Each subject returned to the study centers for a randomization visit between 4 and 7 days before the start of scheduled dosing with study drug. At this visit, the investigator selected/confirmed their open-label OBT regimen (which was sent to the sponsor for review) and they were randomized. Changes in OBT were only allowed after the baseline visit under circumstances specified in the protocol and after consultation with the sponsor. At baseline (Day 1), subjects underwent the study procedures for that day and then received their first dose of study drug. Subjects were required to bring their OBT medications to the baseline visit. Subjects remained on their assigned treatment unless they discontinued from the study for protocol-defined treatment failure or for other reasons such as adverse events (AEs), lost to follow-up, withdrawal of consent, or death. Subjects returned to the study centers at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 84, and 96. If a subject discontinued from the study before Week 96, he/she returned to the study centers for an early termination visit and remained, where possible, on protocol either in study, off drug (ISOD) or, if eligible, on OL maraviroc, and kept to the scheduled visits and procedures. After their Week 96 visit, subjects on OL maraviroc attended the clinic every 12 weeks until the last subject enrolled completed their Week 96 visit. Subjects could then enter the observational phase. Study procedures are summarized in Table 1.

Table 1. Timetable of Study Procedures

Procedures	Visits						
	Screening Day-42 to -28	Randomization Day-7 to -4	Baseline Day 1a	Week 2b	Weeks 4, 8, 12, 16, 20, 32, 40b,c	Weeks 24 and 48 or Early Terminationb,d	Observational Follow-Up (Every 6 Months)
Informed consent and eligibility check	•						•[e]
Medical history			•				
Physical examination/vital signs			•			•	
Targeted physical examination/vital signs					•		
Body weight/height[f]			•	•	•	•	
Selection/confirmation of OBT regimen		•					•
Adverse events			•	•	•	•	
Concomitant medications			•	•	•	•	
Laboratory safety tests (clinical chemistry/hematology)	•	•[g]	•	•	•	•	
Fasting metabolic assessment (total cholesterol, HDL/LDL, triglycerides, glucose, glycosylated hemoglobin)			•		•[h]	•	
12-lead ECG			•			•[i]	
Orthostatic blood pressure monitoring	•		•[j]	•		•	
Blood sample to measure plasma maraviroc concentration[k]				•	•	•	
Urinalysis			•			•	
Hepatitis screen (B core Ab, B sAg, B sAb, C Ab)	•						
Hepatitis C virus RNA[l]			•		•	•	
CD4/CD8 lymphocyte count determinations	•		•	•	•	•	
Plasma viral load	•	•	•	•	•	•	
Pregnancy test[e]	•		•		•	•	
Viral susceptibity to maraviroc (Plasma/ PBMC/proviral DNA storage)[f]			•		•	•	
Viral susceptibility (phenotype, genotype)[g]	•				•[h]	•[h,i]	
Co-receptor tropism (phenotype, genotype[j])	•		•		•[h,k]	•[h,i,k]	

Table 1. Timetable of Study Procedures

Procedures	Visits						
	Screening Day-42 to -28	Randomization Day-7 to -4	Baseline Day 1a	Week 2b	Weeks 4, 8, 12, 16, 20, 32, 40b,c	Weeks 24 and 48 or Early Terminationb,d	Observational Follow-Up (Every 6 Months)
Host genotyping			•[l]				
Free thyroxine 4, thyroid stimulating hormone			•			•	
Dispense study drug			•	•[m]	•	•[n]	•[o]
Assess dosing compliance				•	•	•	
LTS/SE							•

Ab = antibody; Ag = antigen; CD4 = cluster of differentiation 4; CD8 = cluster of differentiation 8; DNA = deoxyribonucleic acid; ECGs = electrocardiogram; HDL = high density lipoprotein; LDL = low density lipoprotein; LTS/SE = long-term survival and selected endpoints; OBT = optimized background therapy; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; RNA = ribonucleic acid; s = surface.

a. Day 1, prior to dosing.

b. All visits had to occur within ±4 days.

c. Also applicable for visits every 12 weeks post-Week 48 (ie, Week 60, 72, 84, 96, 108, 120, etc) until the last enrolled subject had reached the Week 96 visit (with the exception of PK sampling and ECGs).

d. Subjects who discontinued study drug due to treatment failure or for other reasons were followed per protocol until Week 48.

e. Test performed for women of child bearing potential. Serum pregnancy was performed at screening and urine tests at the following visits. A positive urine test was to be confirmed with a serum test.

f. Plasma aliquots (2 of 1 mL each) were obtained at all-time points. PBMCs and proviral DNA were stored at baseline and at Weeks 24 and 48, upon treatment failure, or at the Early Termination visit only.

g. Reverse transcriptase, protease, and fusion inhibitor resistance testing at screening was performed to determine background regimen, and performed at Week 24/48 if viral load >500 copies/mL or upon treatment failure.

h. Performed upon treatment failure. Sample was to be drawn when the confirmatory plasma viral load sample was collected.

i. Test was performed except at Early Termination if subject was a treatment failure (sample should have been drawn when confirmatory viral load was collected).

j. Genotype (V3 loop alone or as part of glycoprotein-160 sequencing) was performed at baseline, Weeks 24 and 48, and at treatment failure only.

k. Performed at Weeks 4, 8, 16, 32, 40, 48, treatment failure, or at Early Termination (if not treatment failure) only for subjects with a viral load of >500 copies/mL.

l. Host genotyping was performed unless prohibited by local regulations.

m. Container was from previous visit.

n. Performed at Week 48 or Early Termination; medication was dispensed to subjects who had completed 48 weeks of treatment, and for whom it was medically appropriate to continue or begin treatment with maraviroc.

o. Only those subjects who were already receiving OL maraviroc.

Number of Subjects (Planned and Analyzed): This study planned to enroll 400 subjects infected with CCR5 tropic HIV-1. Overall, 1428 subjects were screened and a total of 474 subjects (42 in Australia, 47 in Spain, 1 in Sweden, 25 in Belgium, 48 in France; 65 in Germany; 34 in Italy; 5 in Netherland, 13 in Poland, 11 in Switzerland, 33 in the United Kingdom and 150 in the United States of America) were randomized in the study. Among all subjects randomized to study treatment (N=474), 464 subjects were treated; 186 subjects received maraviroc QD, 194 subjects received maraviroc BID, and 94 subjects received placebo. A total of 205 subjects entered the observational phase on OL maraviroc, and 65 subjects entered as ISOD subjects.

Diagnosis and Main Criteria for Inclusion: Subjects were men or women ≥16 years of age, with an HIV-1 viral load of ≥5000 copies/mL and no evidence of infection with CXCR4-or dual/mixed-tropic virus. Subjects must have had greater than or equal 6 months of prior treatment with at least 1 agent from 3 of the 4 antiretroviral drug classes (at least 2 for PIs) or documented multi-class resistance, and treatment failure to an existing regimen, defined by a plasma viral load ≥5000 copies/mL.

Study Treatment: As maraviroc is a substrate for cytochrome P450 3A inhibition, the dose of maraviroc selected required adjustment based on the concomitant antiretroviral administered for OBT. OBT could consist of between 3 to 6 approved branded antiretroviral agents (excluding low-dose ritonavir and tipranavir) selected by investigators based on resistance testing at the screening visit, treatment history and safety considerations. OBT could include experimental antiretroviral agents available through pre-approval access programs or by other means if approved by the sponsor. Subjects with toxicity attributed to an OBT drug could, in consultation with the sponsor, replace it with another drug of the same class. If a subject was incorrectly assigned to an OBT due to documented human error, a substitution could be made within the first 2 weeks of treatment. Investigators were advised to consider adding a PI if efavirenz was used as part of the OBT. All subjects received their OBT in combination with maraviroc QD, maraviroc BID, or placebo until Week 48. Maraviroc was provided by the sponsor as a tablet for oral administration as 150 mg tablets and as 300 mg tablets (from September 2008 onwards). Study drug could have been taken with or without food, and subjects were to take missed doses only if it was not within 6 hours prior to the next planned dose.

Efficacy Endpoints:

Primary Endpoint:

- The primary efficacy variable was the change from baseline in $\log_{10}$ transformed viral load levels analyzed at 48 weeks. This analysis occurred after all randomized subjects had reached the end of 48 weeks or discontinued prior to reaching 48 weeks. The primary efficacy variable was also analyzed at Week 24.

Secondary Endpoints:

The following secondary efficacy variables were analyzed:

- Percentage of subjects with viral load levels <400 copies/mL

- Percentage of subjects with viral load levels <400 copies/mL or at least 0.5-log-transformed decrease from baseline
- Percentage of subjects with viral load levels <400 copies/mL or at least 1.0-log-transformed decrease from baseline
- Percentage of subjects with viral load levels <50 copies/mL
- Change from baseline in CD4 cell count
- Change from baseline in CD8 cell count
- Time to virologic failure
- Time-Averaged Difference (TAD) in $\log_{10}$ viral load
- Genotype and phenotype at baseline and at the time of failure
- Tropism at baseline and at the time of failure
- Association between baseline resistance and virological response

All secondary variables were analyzed at Week 24 and Week 48, apart from time to virological failure, which was only be analyzed at Week 48.

Safety Evaluations: Safety evaluations (including AEs, laboratory evaluations, physical examination, vital signs [blood pressure, heart rate], and electrocardiogram [ECG]) were performed during the double-blind phase of the study at specified time points up to and including Week 96. Any ECGs performed after Week 48 were done at the clinical discretion of the investigator and were not included in the safety data set.

Statistical Methods:

Full Analysis Set (FAS): Defined as all randomized subjects who received at least 1 dose of study medication. The FAS was separated into the following subsets:

FAS – As Randomized, where subjects were analysed according to the treatment they were randomized to receive, and

FAS – As Treated, where subjects were analysed according to the treatment they actually received

Per Protocol (PP) Analysis Set: Defined as all randomized subjects who met the following criteria:

- Received at least 1 dose of study medication
- Treated for at-least 14 days or discontinued before this time due to treatment failure

- More than 80% compliant with randomized treatment
- No Violation of any inclusion or exclusion criteria, which would affect efficacy (such as tropism status)

The PP analysis set was separated into the following subsets:

- PP-As Randomized, where subjects were analysed according to the treatment they were randomized to receive, and;
- PP-As Treated, where subjects were analysed according to the treatment they actually received

The primary endpoint was analysed using both populations, but the secondary endpoints were analyzed using FAS and PP–As Treated analysis set only.

Safety Analysis Set (SAS): Defined as all randomized subjects who received at least 1 dose of study medication. Subjects were reported in the dose group they actually received.

Primary Endpoint: Defined as the change from baseline in log_{10} viral load at Week 48 which was analyzed using Analysis of covariance and performed on both the FAS and PP populations. This was calculated for each subject as log_{10} viral load minus Baseline log_{10} viral load. If a decrease in viral load concentration was observed, a negative change from baseline was calculated per subject. This endpoint was analyzed at Weeks 24 and 48.

Secondary Endpoint: Analyses was performed using the FAS (and PP where indicated) analysis sets.

- Viral Load (copies/mL or log_{10} copies/mL): Where required, baseline was calculated as the mean of all 3 pre-dose assessments (Screening, Randomization and Day 1 pre-dose). If any of the 3 assessments were missing, an average of the remaining assessments was used. Baseline was only be missing if all 3 measurements are missing.
- Time-Averaged Difference (TAD): calculated as (AUC of viral load [log_{10} copies/mL] / time period) -Baseline viral load (log_{10} copies/mL). TAD was analyzed at Weeks 24 and 48.
- Time to Virologic Failure: calculated as the time from the first dose of study medication (Day 1) until the time of virologic failure. Time to virologic failure is defined using the following time to loss of virologic response algorithm. This analysis was performed only at Week 48.
- Time to Treatment Failure: calculated as the time from the first dose of study medication (Day 1) until the day on which treatment failure is defined. This analysis was performed at Weeks 24 and 48.
- Change in CD4 / CD8 cell count (Cells/uL) From Baseline: Baseline was defined for either CD4 or CD8 as the average of pre-dose measurements taken at screening and

pre-dose on Day 1. Baseline was missing only if both pre-dose measurements are missing.

- HIV-1 Tropism at Baseline and at the Time of Failure: Virus tropism was determined using the Monogram Biosciences (formally ViroLogic) PhenoSense™ Entry Assay.

- Genotypic and Phenotypic Susceptibility at Baseline and at Time of Failure: Phenotypic and genotypic resistance to PIs, nucleoside or nucleotide reverse transcriptase inhibitors, and non-nucleoside reverse transcriptase inhibitors were evaluated using the Monogram Biosciences (formally ViroLogic) PhenoSense GT™ assay.

RESULTS:

Subject Disposition and Demography: A total of 474 subjects were randomized in the study; of which 464 subjects had been treated with at least 1 dose of active study drug or placebo (182 subjects received maraviroc QD, 191 subjects received maraviroc BID, and 91 subjects received placebo). A total of 205 subjects entered the observational phase on OL maraviroc, and 65 subjects entered as ISOD subjects. There were 133 subjects who completed the observational phase on-treatment and 48 subjects who completed the observational phase as ISOD. Subject evaluation groups are provided in Table 2.

Table 2. Subject Disposition

Number of Subjects	Maraviroc QD	Maraviroc BID	Placebo	Total
Screened, 1428 subjects				
Number of subjects randomized	186	194	94	474
Entered double-blind therapy	182	191	91	464
Discontinued double-blind therapy	84	86	74	244
Completed double-blind therapy	98	105	17	220
Entered open-label therapya	114	115	43	272
Completed double-blind therapy and did not enter open-label therapy	4	3	11	18
Completed both double-blind and open-label therapy	83	90	4	177
Entered observational phase on treatment (OL maraviroc)	87	93	25	205
Entered observational phase as ISOD	18	28	19	65
Completed observational phase on treatment (OL maraviroc)	54	64	15	133
Completed observational phase as ISOD	13	21	14	48
With post-treatment date in observational phase (OL maraviroc)	15	13	8	36

Treatment columns represented the original randomized treatment group. Regardless of original therapy, subjects who remained in study long enough were switched to OL maraviroc BID. Each column included such subjects.
BID = twice daily; ISOD = in study, off drug; OL = open-label; QD = once daily.
a. Subjects did not have to complete double-blind therapy to enter open-label therapy.

Subject demographics are summarized in Table 3. Males accounted for slightly <90% of the study population. The majority of subjects were aged between 35 and 54 years and the mean ages were similar for all treatment groups. Most of the subjects recruited into the study were White, with a similar racial mix for the 3 treatment groups.

Table 3. Summary of Demographic Characteristics (Randomized Subjects)

	Maraviroc QD	Maraviroc BID	Placebo
	All	All	All
Number of subjects	182	191	91
Mean age (range)	45 (17-75)	47 (21-73)	45 (29-72)
Gender			
Male	153	170	79
Female	29	21	12
Race			
White	149 (81.9%)	166 (86.9%)	79 (86.8%)
Black	31 (17.0%)	18 (9.4%)	11 (12.1%)
Asian	0	3 (1.6%)	1 (1.1%)
Other	2 (1.1%)	4 (2.1%)	0

BID = twice daily; QD = once daily.

Efficacy Results:

Primary Endpoint:

Viral Load Change From Baseline to Weeks 24 and 48: The statistical analysis of the mean change from baseline in viral load at Weeks 24 and 48 (maraviroc versus placebo), based on the FAS-As Treated and As Randomized population is summarized in Table 4.

The statistical analysis showed that maraviroc QD and maraviroc BID were superior in comparison to placebo. Viral load decreased from baseline through to Weeks 24 and 48 in all 3 treatment groups. However, the decrease seen in the maraviroc treatment groups was greater than in the placebo treatment group at all-time points measured post-baseline.

Table 4. Summary of Statistical Analysis of Change From Baseline in Viral Load (log_{10} copies/mL) Through Weeks 24 and 48

Treatment Group	N	Adjusted Mean (SE)	Treatment Difference (Maraviroc – Placebo)	
			Estimate	97.5% CI
As Treated				
Week 24				
Maraviroc QD	182	-1.950 (0.1054)	-1.021	-1.426, -0.616
Maraviroc BID	191	-1.971 (0.1026)	-1.042	-1.444, -0.640
Placebo	91	-0.929 (0.1473)		
Week 48				
Maraviroc QD	182	-1.718 (0.1086)	-0.961	-1.379, -0.544
Maraviroc BID	191	-1.865 (0.1057)	-1.109	-1.523, -0.695
Placebo	91	-0.757 (0.1518)		
As Randomized				
Week 24				
Maraviroc QD	182	-1.949 (0.1053)	-1.034	-1.438, -0.630
Maraviroc BID	191	-1.976 (0.1024)	-1.062	-1.463, -0.661
Placebo	91	-0.915 (0.1472)		
Week 48				
Maraviroc QD	182	-1.717 (0.1085)	-0.968	-1.384, -0.551
Maraviroc BID	191	-1.868 (0.1055)	-1.119	-1.532, -0.705
Placebo	91	-0.749 (0.1517)		

BID = twice daily; CI = confidence interval; N = number of subjects in the treatment group in the indicated population; QD = once daily; SE = standard error

Secondary Endpoints:

Subjects with Viral Load <400 and <50 copies/mL at Weeks 24 and 48: The percentage of subjects with viral load <400 copies/mL, <50 copies/mL, <400 copies/mL or at least a 1.0 $\log_{10}$ decrease from baseline, and <400 copies/mL or at least a 0.5 $\log_{10}$ decrease from baseline at Weeks 24 and 48 for the FAS – As Treated population are summarized in Table 5 There was a higher percentage of subjects in the maraviroc treatment groups compared with the placebo treatment group with a viral load <400 copies/mL, <50 copies/mL, <400 copies/mL or at least a 1.0 $\log_{10}$ decrease from baseline, and <400 copies/mL or at least a 0.5 $\log_{10}$ decrease from baseline at Weeks 24 and 48.

Table 6 summarizes the statistical analyses performed at Weeks 24 and 48; difference in proportions and logistic regression of viral load <400 copies/mL, <50 copies/mL, viral load <400 copies/mL or ≥1.0 $\log_{10}$ decrease in viral load from baseline and <400 copies/mL or ≥0.5 $\log_{10}$ decrease in viral load from baseline based on the FAS - As Treated population.

Table 5. Subjects With Viral Load <400 and <50 Copies/mL at Weeks 24 and 48

Parameter	Maraviroc QD N=182	Maraviroc BID N=191	Placebo N=91
Week 24			
<400 copies/mL	55.5% (n=101)	61.3% (n=117)	23.1% (n=21)
<50 copies/mL	45.6% (n=83)	40.8% (n=78)	20.9% (n=19)
<400 copies/mL or ≥1.0 $\log_{10}$ viral load decrease from baseline	66.5% (n=121)	69.6% (n=133)	30.8% (n=28)
<400 copies/mL or ≥0.5 $\log_{10}$ viral load decrease from baseline	69.8% (n=127)	72.3% (n=138)	37.4% (n=34)
Week 48			
<400 copies/mL	52.8% (n=96)	55.0% (n=105)	23.1% (n=21)
<50 copies/mL	45.1% (n=82)	44.5% (n=85)	17.6% (n=16)
<400 copies/mL or ≥1.0 $\log_{10}$ viral load decrease from baseline	58.8% (n=107)	63.4% (n=121)	27.5% (n=25)
<400 copies/mL or ≥0.5 $\log_{10}$ viral load decrease from baseline	61.0% (n=111)	66.0% (n=126)	31.9% (n=29)

BID = twice daily; N = number of subjects in the treatment group in the indicated population; n = number of subjects contributing to the calculation of the percentage; QD = once daily.

Table 6. Summary of Statistical Analysis of Proportion of Subjects With Viral Load at Weeks 24 and 48

Comparison	Difference in Proportions[a]		Logistic Regression		
	Difference in Proportions	95% CI	Odds Ratio	95% CI	p-value
Week 24					
<400 copies/mL					
Maraviroc QD versus placebo	0.33	0.22, 0.44	4.59	2.56, 8.23	<0.0001
Maraviroc BID versus placebo	0.41	0.31, 0.52	6.01	3.35, 10.78	<0.0001
<50 copies/mL					
Maraviroc QD versus placebo	0.25	0.15, 0.35	3.55	1.95, 6.48	<0.0001
Maraviroc BID versus placebo	0.22	0.12, 0.33	2.88	1.59, 5.23	0.0005
<400 copies/mL or ≥1.0 $\log_{10}$ viral load decrease from baseline					
Maraviroc QD versus placebo	0.36	0.24, 0.47	4.58	2.64, 7.92	<0.0001
Maraviroc BID versus placebo	0.40	0.29, 0.52	5.42	3.13, 9.39	<0.0001
<400 copies/mL or ≥0.5 $\log_{10}$ viral load decrease from baseline					
Maraviroc QD versus placebo	0.36	0.24, 0.48	4.69	2.72, 8.10	<0.0001
Maraviroc BID versus placebo	0.38	0.27, 0.50	5.01	2.91, 8.62	<0.0001
Week 48					
<400 copies/mL					
Maraviroc QD versus placebo	0.30	0.19, 0.41	4.03	2.25, 7.20	<0.0001
Maraviroc BID versus placebo	0.34	0.23, 0.45	4.41	2.47, 7.85	<0.0001
<50 copies/mL					
Maraviroc QD versus placebo	0.28	0.18, 0.38	4.23	2.26, 7.92	<0.0001
Maraviroc BID versus placebo	0.30	0.20, 0.40	4.10	2.20, 7.64	<0.0001
<400 copies/mL or ≥1.0 $\log_{10}$ viral load decrease from baseline					
Maraviroc QD versus placebo	0.33	0.21, 0.44	4.01	2.29, 7.00	<0.0001
Maraviroc BID versus placebo	0.38	0.27, 0.50	5.08	2.91, 8.89	<0.0001
<400 copies/mL or ≥0.5 $\log_{10}$ viral load decrease from baseline					
Maraviroc QD versus placebo	0.31	0.20, 0.43	3.67	2.13, 6.32	<0.0001
Maraviroc BID versus placebo	0.36	0.25, 0.48	4.64	2.69, 8.02	<0.0001

An odds ratio >1 indicates a benefit of maraviroc over placebo.
BID = twice daily; CI = confidence interval; QD = once daily
a. Adjusted for randomization strata.

Change From Baseline in CD4 and CD8 Cell Count Through to Weeks 24 and 48: Table 7 summarizes the mean baseline values and the mean changes from baseline for CD4 cell count at each visit for the FAS – As Treated population. The mean increase from baseline in CD4 cell count was similar for both maraviroc treatment groups and was greater than the placebo treatment group (across all timepoints). At Weeks 24 and 48, the mean change in CD4 cell count (cells/μL) was substantially higher for the maraviroc treatment groups (Week 24: maraviroc QD 111.7 cells/μL and maraviroc BID 101.9 cells/μL; Week 48: maraviroc QD 121.5 cells/μL and maraviroc BID 127.8 cells/μL) than that observed in the placebo treatment group (Week 24: 63.8 cells/μL; Week 48: 69.3 cells/μL; Table 8).

Table 7. Change From Baseline in CD4 Cell Count at Weeks 24 and 48

Parameter	Maraviroc QD N=182	Maraviroc BID N=191	Placebo N=91
CD4 cell count at baseline (cells/μL)			
n	182	191	90
Mean (SD)	206.0 (171.99)	204.9 (149.21)	198.5 (140.39)
Change from baseline in CD4 cell count (cells/μL) at:			
Week 24			
n	128	135	37
Mean (SD)	133.8 (127.52)	110.5 (97.53)	100.9 (83.14)
Week 48			
n	110	128	27
Mean (SD)	149.3 (121.26)	147.3 (124.31)	136.9 (147.98)

The baseline value was the average of the values from screening and baseline (Day 1) visits.
BID = twice daily; CD4 = cluster of differentiation 4; N = number of subjects in the treatment group in the indicated population; n = number of subjects contributing to the summary statistics; QD = once daily; SD = standard deviation.

Table 8 summarizes the statistical analysis of change from baseline in CD4 cell count at Weeks 24 and 48 (maraviroc versus placebo), based on the FAS - As Treated population.

Table 8. Summary of Statistical Analysis of Change From Baseline in CD4 Cell Count at Weeks 24 and 48

Treatment Group	N	Adjusted Mean (SE)	Treatment Difference (Maraviroc – Placebo)	
			Estimate	95% CI
Week 24				
Maraviroc QD	180	111.7 (7.82)	47.9	21.6, 74.3
Maraviroc BID	185	101.9 (7.68)	38.1	12.0, 64.3
Placebo	90	63.8 (10.93)		
Week 48				
Maraviroc QD	180	121.5 (8.65)	52.2	23.1, 81.3
Maraviroc BID	185	127.8 (8.50)	58.5	29.5, 87.4
Placebo	90	69.3 (12.09)		

CI = confidence interval; CD4 = cluster of differentiation 4; N = number of subjects contributing to the summary statistics; SE = standard error.

At Weeks 24 and 48, the mean change in CD8 cell count (cells/μL) was substantially higher for the maraviroc treatment groups (Week 24: maraviroc QD 340.7 cells/μL and maraviroc BID 255.4 cells/μL; Week 48: maraviroc QD 241.4 cells/μL and maraviroc BID 244.8 cells/μL) than that observed in the placebo treatment group (Week 24: 122.2 cells/μL; Week 48: 104.5 cells/μL).

Table 9 summarizes the statistical analysis of the mean change from baseline in CD8 cell count at Week 24 and 48 (maraviroc versus placebo), based on the FAS - As Treated population.

Table 9. Summary of Statistical Analysis of Change From Baseline in CD8 Cell Count at Weeks 24 and 48

Treatment Group	N	Adjusted Mean (SE)	Treatment Difference (Maraviroc – Placebo)	
			Estimate	95% CI
Week 24				
Maraviroc QD	180	340.7 (41.6)	218.6	78.6, 358.5
Maraviroc BID	185	255.4 (40.9)	133.2	-6.0, 272.5
Placebo	90	122.2 (58.2)		
Week 48				
Maraviroc QD	180	241.4 (33.79)	136.9	23.2, 250.6
Maraviroc BID	185	244.8 (33.20)	140.3	27.2, 253.4
Placebo	90	104.5 (47.23)		

CI = confidence interval; CD8 = cluster of differentiation 8; N = number of subjects contributing to the summary statistics; SE = standard error.

At Week 48 there was an increase from baseline in CD4% (CD4 cell count as a percentage of the total lymphocyte count) of similar size in all the treatment groups (maraviroc QD 4.4%, maraviroc BID 4.3% and placebo 4.6%; Table 10), based on the FAS – As Treated Population. At Week 48, the decrease in CD8% (CD8 cell count as a percentage of the total lymphocyte count) from baseline was larger in the placebo group (-8.5%) compared with the maraviroc treatment groups (maraviroc QD -4.7% and maraviroc BID -5.8%). There was a similar increase from baseline in the CD4/CD8 ratios in all 3 treatment groups, summarized in Table 10 for subjects in the FAS - As Treated population.

Table 10. Change From Baseline in CD4% and CD8% at Week 48 and CD4/CD8 Ratios at Weeks 24 and 48

Parameter	Maraviroc QD N=182	Maraviroc BID N=191	Placebo N=91
CD4% at baseline (cells/μL)			
n	182	191	90
Mean (SD)	12.7 (7.43)	12.7 (7.35)	12.7 (7.49)
Change from baseline in CD4% at Week 48			
n	110	128	27
Mean (SD)	4.4 (3.76)	4.3 (3.81)	4.6 (3.87)
CD8% at baseline (cells/μL)			
n	182	191	90
Mean (SD)	62.2 (12.23)	62.0 (12.27)	61.2 (12.13)
Change from baseline in CD8% at Week 48			
n	110	128	27
Mean (SD)	-4.7 (8.41)	-5.8 (7.22)	-8.5 (7.98)
CD4/CD8 ratio at baseline			
N	182	191	90
Mean (SD)	0.2 (0.16)	0.2 (0.16)	0.2 (0.16)
Change from baseline in CD4/CD8 ratio at:			
Week 24			
n	128	135	37
Mean (SD)	0.1 (0.09)	0.1 (0.10)	0.1 (0.14)
Week 48			
n	110	128	27
Mean (SD)	0.1 (0.10)	0.1 (0.10)	0.1 (0.17)

The baseline value was the average of the values from screening and baseline (Day 1) visits.
BID = twice daily; CD4 = cluster of differentiation 4; CD8 = cluster of differentiation 8; N = number of subjects in the treatment group in the indicated population; n = number of subjects contributing to the summary statistics; QD = once daily; SD = standard deviation.

Time-Averaged Difference (TAD): The estimate of TAD in viral load from baseline up to Weeks 24 and 48 was similar in the 2 maraviroc treatment groups and greater than that observed in the placebo treatment group. Summary of the statistical analysis of TAD from baseline to Weeks 24 and 48 in viral load, based on the FAS - As Treated population is provided in Table 11.

Table 11. Summary of Statistical Analysis of TAD from Baseline to Week 24 and Week 48 in Viral Load (log_{10} Copies/mL)

Treatment Group	N	Adjusted Mean (SE)	Treatment Difference (Maraviroc – Placebo)	
			Estimate	95% CI
Week 24				
Maraviroc QD	182	-1.75 (0.09)	-0.88	-1.18, -0.58
Maraviroc BID	191	-1.76 (0.09)	-0.88	-1.18, -0.58
Placebo	91	-0.87 (0.13)		
Week 48				
Maraviroc QD	182	-1.60 (0.099)	-0.86	-1.19, -0.52
Maraviroc BID	191	-1.78 (0.097)	-1.03	-1.36, -0.70
Placebo	91	-0.75 (0.139)		

BID = twice daily; CI = confidence interval; N = number of subjects in the treatment group in the indicated population; QD = once daily; SE = standard error.

Time to Virologic Failure at Week 48: The time to protocol defined virologic failure was similar in the maraviroc treatment groups and was longer than that observed in the placebo

treatment group. The statistical analyses of time to virologic failure, using the log-rank test (controlling for randomization strata) and Cox's proportional hazard ratio modelling, based on the FAS - As Treated population are summarized in Table 12.

Table 12. Summary of Statistical Analysis of Time to Virologic Failure (Days)

Comparison	Log-Rank Test			Cox's Proportion Hazards	
	Log-Rank	χ^2	p-value	Hazard Ratio	95% CI
Maraviroc QD versus placebo	-46.27	16.32	<0.0001	0.40	0.29, 0.56
Maraviroc BID versus placebo	-27.56	25.19	<0.0001	0.33	0.23, 0.46

A hazard ratio <1 indicates a benefit of maraviroc over placebo.
BID = twice daily; CI = confidence interval; QD = once daily.

Time to Treatment Failure at Weeks 24 and 48: At Weeks 24 and 48, the time to protocol-defined treatment failure was similar in the maraviroc treatment groups and was longer than that observed in the placebo treatment group. The statistical analyses of time to treatment failure, using the log-rank test (controlling for randomization strata) and Cox's proportional hazard ratio modelling, based on the FAS - As Treated population are summarized in Table 13.

Table 13. Summary of Statistical Analysis of Time to Treatment Failure (Days)

Comparison	Log-Rank Test			Cox's Proportion Hazards	
	Log-Rank	χ^2	p-value	Hazard Ratio	95% CI
Week 24					
Maraviroc QD versus placebo	-52.51	40.03	<0.0001	0.25	0.16, 0.38
Maraviroc BID versus placebo	-25.96	37.87	<0.0001	0.29	0.19, 0.43
Week 48					
Maraviroc QD versus placebo	-52.43	34.55	<0.0001	0.31	0.21, 0.46
Maraviroc BID versus placebo	-28.25	42.47	<0.0001	0.28	0.19, 0.42

A hazard ratio <1 indicated a benefit of maraviroc over placebo.
BID = twice daily; CI = confidence interval; QD = once daily.

Change From Baseline in Viral Load at Weeks 24 and 48 by Overall Susceptibility Score (OSS) at Screening: As the OSS at screening increased, the mean change from baseline in viral load at Week 48 also increased across all treatment groups. However, the mean change was greater in the maraviroc treatment groups compared with the placebo treatment group at each OSS level.

Table 14 summarizes the mean and median changes from baseline in viral load at Weeks 24 and 48, by OSS at screening, for the FAS – As Treated population.

Table 14. Summary of Change from Baseline in Viral Load at Weeks 24 and 48 by OSS at Screening

OSS at Screening	Mean/Median	Maraviroc QD N=182	Maraviroc BID N=191	Placebo N=91
Week 24				
0	n	22	29	16
	Mean	-1.721	-1.231	-0.264
	Median	-1.622	-0.921	-0.056
1	n	54	48	23
	Mean	-1.822	-2.051	-0.651
	Median	-1.975	-2.308	-0.294
2	n	37	39	21
	Mean	-2.145	-2.515	-0.611
	Median	-2.388	-2.609	-0.401
≥3	n	64	68	29
	Mean	-2.655	-2.530	-2.109
	Median	-2.936	-2.807	-2.627
Missing	n	3	1	2
	Mean	-2.642	-0.544	-1.169
	Median	-2.229	-0.544	-1.169
		Week 48		
0	n	22	29	16
	Mean	-1.745	-1.290	-0.249
	Median	-1.717	-1.011	-0.056
1	n	54	48	23
	Mean	-1.678	-1.899	-0.594
	Median	-1.723	-2.097	-0.294
2	n	38	39	21
	Mean	-2.207	-2.565	-0.591
	Median	-2.500	-2.618	-0.407
≥3	n	63	68	29
	Mean	-2.448	-2.426	-1.942
	Median	-2.838	-2.716	-2.316
Missing	n	3	1	2
	Mean	-2.795	-0.833	-1.105
	Median	-2.948	-0.833	-1.105

LOCF has been used to impute missing values.
The baseline value was the average of the values from screening, randomization and baseline (Day 1) visits.
BID = twice daily; LOCF = Last observation carried forward; N = number of subjects in the treatment group in the indicated population; n = number of subjects contributing to the summary statistics; OSS = overall susceptibility score; QD = once daily.

Change in Phenotypic Susceptibility Score/Genotypic Susceptibility Score/OSS From Screening to Time of Treatment Failure at Weeks 24 and 48: Table 15 summarizes the change in susceptibility scores at time of treatment failure at Weeks 24 and 48.

Table 15. Summary of Change in Susceptibility Scores From Screening to Time of Treatment Failure at Weeks 24 and 48

Susceptibility Scores	Change in Susceptibility Score								
	≤3	-3	-2	-1	0	1	2	3	>3
Week 24									
Genotype									
Maraviroc QD (N=27) n=22	0	0	0	9	13	0	0	0	0
Maraviroc BID (N=31) n=25	1	0	0	6	15	3	0	0	0
Placebo (N=44) n=40	0	0	1	15	22	1	1	0	0
Phenotype									
Maraviroc QD (N=27) n=22	0	1	2	8	10	1	0	0	0
Maraviroc BID (N=31) n=24	0	0	3	8	13	0	0	0	0
Placebo (N=44) n=40	0	2	3	16	18	1	0	0	0
Overall									
Maraviroc QD (N=27) n=22	0	0	3	8	10	1	0	0	0
Maraviroc BID (N=31) n=24	0	1	1	9	11	2	0	0	0
Placebo (N=44) n=40	0	0	4	15	9	2	0	0	0
Week 48									
Genotype									
Maraviroc QD (N=41) n=35	0	0	0	12	23	0	0	0	0
Maraviroc BID (N=38) n=33	1	0	0	6	22	4	0	0	0
Placebo (N=49) n=46	0	0	2	17	24	2	1	0	0
Phenotype									
Maraviroc QD (N=41) n=35	0	1	3	13	16	2	0	0	0
Maraviroc BID (N=38) n=32	0	0	3	9	19	0	1	0	0
Placebo (N=49) n=46	0	3	4	18	19	2	0	0	0
Overall									
Maraviroc QD (N=41) n=35	0	0	3	14	17	1	0	0	0
Maraviroc BID (N=38) n=32	0	1	1	9	18	2	1	0	0
Placebo (N=49) n=46	0	0	5	17	21	3	0	0	0

BID = twice daily; N = number of subjects in the treatment group who have discontinued due to lack of efficacy; n = number of subjects contributing to the summary statistics; QD = once daily.

Virology-Viral Tropism:

The number of subjects with a change in tropism result between baseline and Weeks 24 and 48, for the FAS – As Treated population, are summarized in Table 16.

Four hundred and sixty two subjects with a CCR5 tropism result at screening were included in the study. Two subjects (1 in each maraviroc treatment group) were erroneously included

in the study as they did not have a CCR5 tropism result at screening; both subjects had a dual/mixed tropism result.

Of the 462 subjects with a CCR5-tropism result at screening, 36 (8%) subjects had a different tropism result at baseline; all of these were assigned a dual/mixed tropism result. This illustrates the background change in tropism result over a 4 to 6 week period in this heavily pre-treated population, prior to a change in antiretroviral regimen or administration of a CCR5 antagonist. The proportion of subjects with a dual/mixed tropism result at baseline was similar across the treatment groups.

Table 16. Change in Tropism Result Between Baseline and Weeks 24 and 48

Treatment Group	Tropism at Baseline[a]	Tropism[b]			
		CCR5	CXCR4	Dual/ Mixed	NR/NP
Week 24					
Total population	CCR5	29 (6.3%)	4 (0.9%)	8 (1.7%)	7 (1.5%)
N=462	Dual/mixed	2 (0.4%)	0	3 (0.7%)	0
n=55[c]					
Maraviroc QD	CCR5	11 (6.1%)	2 (1.1%)	1 (0.6%)	4 (2.2%)
N=180[d]	Dual/mixed	0	0	1 (0.6%)	0
n=22[e]					
Maraviroc BID	CCR5	6 (3.1%)	2 (1.1%)	6 (3.1%)	3 (1.6%)
N=191	Dual/mixed	0	0	0	0
n=17					
Placebo	CCR5	12 (13.2%)	0	1 (1.1%)	0
N=91	Dual/mixed	2 (2.2%)	0	2 (2.0%)	0
n=17					
Week 48					
Total population	CCR5	27 (5.8%)	3 (0.7%)	9 (1.9%)	4 (0.9%)
N=464	Dual/mixed	0	1 (0.2%)	2 (0.4%)	0
n=48[f]					
Maraviroc QD	CCR5	11 (6.0%)	0	1 (0.6%)	1 (0.6%)
N=182	Dual/mixed	0	1 (0.6%)	1 (0.6%)	0
n=17[f]					
Maraviroc BID	CCR5	11 (5.8%)	3 (1.6%)	7 (3.7%)	1 (0.5%)
N=191	Dual/mixed	0	0	0	0
n=22					
Placebo	CCR5	5 (5.5%)	0	1 (1.1%)	2 (2.2%)
N=91	Dual/mixed	0	0	1 (1.1%)	0
n=9					

BID = twice daily; CCR5 = chemokine (C-C motif) receptor 5; CXCR4 = chemokine (C-X-C motif) co-receptor; NR/NP = non-reportable/non-phenotypable; N = number of subjects in the treatment group in the indicated population; n = number of subjects contributing to the summary statistics; QD = once daily.

a. This table only included subjects with a CCR5 or dual/mixed result at baseline.
b. This table only included subjects with a CCR5, CXCR4, dual/mixed or NR/NP result at Week 24 and 48.
c. Two subjects who had a NR/NP tropism result at baseline.
d. N=180, because 2 subjects had a missing tropism result at baseline.
e. Two subjects who had a NR/NP tropism result at baseline and 1 subject who had a missing tropism result at baseline.
f. Two subjects who had a NR/NP tropism result at baseline.

Changes in Viral Tropism From Baseline and Time of Treatment Failure at Weeks 24 and 48: The number of subjects with a change in tropism result between baseline and time of treatment failure, for the FAS – As Treated population, are summarized in Table 17. Most subjects who responded had no tropism assignment at Weeks 24 and 48, and many had no on treatment tropism result as they had a viral load of <500 copies/mL at all visits from Week 4 onwards. Of the subjects in the study only a few had treatment failure due to insufficient

clinical response and had a change in tropism result, more of these subjects were in the maraviroc treatment groups compared with the placebo treatment group, summarized in Table 17.

Table 17. Change in Tropism Result Between Baseline and Time of Treatment Failure at Weeks 24 and 48

Treatment Group	Tropism at Baseline[a]	Tropism at Time of Treatment Failure[b,c]			
		CCR5	CXCR4	Dual/Mixed	NR/NP
Week 24					
Total population	CCR5	51 (11.0%)	4 (0.9%)	14 (3.0%)	13 (2.8%)
N=462	Dual/mixed	3 (0.6%)	2 (0.4%)	10 (2.2%)	1 (0.2%)
n=101[d]					
Maraviroc QD	CCR5	8 (4.4%)	2 (1.1%)	5 (2.8%)	6 (3.3%)
N=180[e]	Dual/mixed	1 (0.6%)	0	3 (1.7%)	0
n=26[f]					
Maraviroc BID	CCR5	7 (3.7%)	2 (1.0%)	6 (3.1%)	5 (2.6%)
N=191	Dual/mixed	0	2 (1.0%)	7 (3.7%)	1 (0.5%)
n=31[g]					
Placebo	CCR5	36 (39.6%)	0	3 (3.3%)	2 (2.2%)
N=91	Dual/mixed	2 (2.2%)	0	0	0
n=44[h]					
Week 48					
Total population	CCR5	66 (14.2%)	4 (0.9%)	21 (4.5%)	14 (3.0%)
N=464	Dual/mixed	4 (0.9%)	2 (0.4%)	10 (2.2%)	1 (0.2%)
n=128[i]					
Maraviroc QD	CCR5	17 (9.3%)	2 (1.1%)	8 (4.4%)	6 (3.3%)
N=182	Dual/mixed	1 (0.5%)	0	3 (1.6%)	0
n=41[j]					
Maraviroc BID	CCR5	9 (4.7%)	2 (1.0%)	10 (5.2%)	6 (3.1%)
N=191	Dual/mixed	0	2 (1.0%)	7 (3.7%)	1 (0.5%)
n=38[k]					
Placebo	CCR5	40 (44.0%)	0	3 (3.3%)	2 (2.2%)
N=91	Dual/mixed	3 (3.3%)	0	0	0
n=49[l]					

BID = twice daily; CCR5 = chemokine (C-C motif) receptor 5; CXCR4 = chemokine (C-X-C motif) co-receptor; NR/NP = non-reportable/non-phenotypable; N = number of subjects in the treatment group in the indicated population; n = number of subjects contributing to the summary statistics; QD = once daily.

a. This table only included subjects with a CCR5 or dual/mixed result at baseline.
b. This table only included subjects with a CCR5, CXCR4, dual/mixed or NR/NP result at time of treatment failure.
c. The assessment for time of treatment failure is defined as the last on treatment assessment.
d. Two subjects who had a NR/NP tropism result at baseline and 1 subject who had a CCR5 tropism result at baseline but had a viral load <500 copies/mL at time of treatment failure (tropism test either cancelled or censored).
e. N=180, because 2 subjects had a missing tropism result at baseline.
f. One subject who had a NR/NP tropism result at baseline.
g. One subject who had a CCR5 tropism result at baseline but had a viral load <500 copies/mL at time of treatment failure (tropism test either cancelled or censored).
h. One subject who had a NR/NP tropism result at baseline.
i. Four subjects who had a NR/NP tropism result at baseline and 2 subjects who had a CCR5 tropism result at baseline but had a viral load <500 copies/mL at time of treatment failure (tropism result either cancelled or censored).
j. Three subjects who had a NR/NP tropism result at baseline and 1 subject who had a CCR5 tropism result at baseline but had a viral load <500 copies/mL at time of treatment failure (tropism result either cancelled or censored).
k. One subject who had a CCR5 tropism result at baseline but had a viral load <500 copies/mL at time of treatment failure (tropism result either cancelled or censored).
l. One subject who had a NR/NP tropism result at baseline.

Safety Results: The number of subjects reporting treatment emergent adverse events (TEAEs) (all causality and treatment related) for Weeks 24 and 48 is summarized in

Table 18. The proportion of subjects reporting treatment related AEs was similar in the maraviroc BID and placebo treatment groups and slightly higher in the maraviroc QD group for Weeks 24 and 48. The proportion of subjects reporting all causality AEs was slightly higher in the maraviroc treatment groups (92%) compared with the placebo group (84%). Similarly, the proportion of subjects reporting treatment related AEs was slightly higher in the maraviroc treatment groups (QD 60%, BID, 55%) compared with the placebo group (50%) in Week 48.

Table 18. Summary of Adverse Events by Treatment Group for Weeks 24 and 48

Number (%) of Subjects	Maraviroc QD N=182		Maraviroc BID N=191		Placebo N=91
	24 Weeks	48 Weeks	24 Weeks	48 Weeks	24 and 48 Weeks
All Causality	162 (89.0%)	167 (91.8%)	170 (89.0%)	176 (92.1%)	76 (83.5%)
Treatment Related	110 (60.4%)	110 (60.4%)	99 (51.8%)	105 (55.0%)	45 (49.5%)

BID = twice daily; N = number of subjects in the treatment group in the indicated population; QD = once daily.

The number of subjects reporting TEAEs (all causality and treatment related) for Week 96 are summarized in Table 19. Percentages of subjects reporting AEs were approximately 95% and 97% for maraviroc double-blind QD and BID treatment switched to OL maraviroc, respectively. The maraviroc double-blind groups not switching to OL maraviroc and the placebo groups had similar but lower percentages of subjects with AEs. The group with the lowest number (81.4%) of subjects reporting AEs was the placebo to OL maraviroc, first phase group.

Table 19. Summary of Treatment-Emergent Adverse Events for Week 96

Initial Treatment	Maraviroc QD		Maraviroc BID		Placebo		
Treatment Switched to Maraviroc OL BID:	No N=69	Yes N=113	No N=78	Yes N=113	No N=48	Yes (First Phase)a N=43	Yes (Second Phase) a N=43
Number of AEs							
All causality	347	1100	431	971	286	188	208
Treatment related	127	357	140	276	111	78	38
Subjects with AEs, n (%)							
All causality	61 (88.4)	107 (94.7)	68 (87.2)	110 (97.3)	42 (87.5)	35 (81.4)	36
Treatment related	42 (60.9)	72 (63.7)	49 (62.8)	67 (59.3)	24 (50.0)	21 (48.8)	15
Subjects with SAEs, n (%)							
All causality	17 (24.6)	27 (23.9)	23 (29.5)	26 (23.0)	12 (25.0)	4 (9.3)	9
Treatment related	3 (4.3)	3 (2.7)	7 (9.0)	3 (2.7)	0	1 (2.3)	3
Subjects discontinued due to AEs, n (%)							
All causality	11 (15.9)	2 (1.8)	12 (15.4)	3 (2.7)	4 (8.3)	2 (4.7)	1
Treatment related	8 (11.6)	1 (0.9)	8 (10.3)	1 (0.9)	2 (4.2)	2 (4.7)	0
Subjects with dose reduced or temporary discontinuation due to AEs, n (%)							
All causality	7 (10.1)	6 (5.3)	6 (7.7)	8 (7.1)	5 (10.4)	3 (7.0)	2
Treatment related	2 (2.9)	1 (0.9)	4 (5.1)	4 (3.5)	0	2 (4.7)	0

AE = adverse event; BID = twice daily; n = number of subjects; N = number of subjects in the treatment group in the indicated population; OL = open-label; QD = once daily; SAE = serious adverse event.
a. Subjects in the placebo switched to OL maraviroc group had their data separated into 2 phases: The first phase includes data while the subject was taking placebo; the second phase summarizes data while the subject was taking maraviroc OL BID.

The numbers of subjects reporting TEAEs (all causality and treatment related) for OL are summarized in Table 20.

Table 20. Treatment-Emergent Adverse Events (All Causality and Treatment Related) for Subjects in the Open-Label Phase

	Open-Label Maraviroc BID N=272			
	All Causality		Treatment Related	
	n	%	n	%
Number of adverse events	721	-	105	-
Number of subjects:				
With adverse events	194	71.3	53	19.5
With serious adverse events	28	10.3	6	2.2
Discontinued due to adverse events	7	2.6	4	1.5
With dose reduced or temporary discontinuation due to adverse events	9	3.3	2	0.7

BID = twice daily; N = number of subjects evaluable for adverse events; n = number of subjects with observations; % = percentage of subjects with observations.

Incidence of AEs:

The results for TEAEs - All Causalities by System Organ Class (SOC) are summarized in Table 21. The most frequently reported all causality TEAEs in all 3 treatment groups were diarrhoea, nausea and headache. The most frequently reported (reported by ≥5% of subjects in any treatment group) AEs for Weeks 24 and 48 (all causality with treatment related in parentheses) are summarized in Table 22.

The most frequently reported treatment-emergent treatment-related AEs across all treatment groups (without adjustment for exposure to the study drug) were diarrhoea, nausea, vomiting, and headache. The most frequently reported (≥5% of subjects in any treatment group) AEs for Week 96 are summarized in Table 23.

Table 21. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5

Number (%) of Subjects With Adverse Events by System Organ Class and MedDRA (v13.0) Preferred Term	Maraviroc QD	Maraviroc BID	Placebo	Maraviroc BID, Open-Label
	n (%)	n (%)	n (%)	n (%)
Evaluable for adverse events	182	191	91	272
With adverse events	138 (75.8)	147 (77.0)	64 (70.3)	15 (5.5)
Gastrointestinal disorders	87 (47.8)	77 (40.3)	39 (42.9)	0
Abdominal pain	13 (7.1)	10 (5.2)	5 (5.5)	0
Abdominal pain upper	15 (8.2)	5 (2.6)	4 (4.4)	0
Constipation	10 (5.5)	12 (6.3)	6 (6.6)	0
Diarrhoea	49 (26.9)	39 (20.4)	19 (20.9)	15 (5.51%)
Flatulence	9 (4.9)	4 (2.1)	7 (7.7)	0
Nausea	39 (21.4)	33 (17.3)	17 (18.7)	0
Vomiting	24 (13.2)	20 (10.5)	9 (9.9)	0
General disorders and administration site conditions	50 (27.5)	57 (29.8)	25 (27.5)	0
Asthenia	11 (6.0)	8 (4.2)	3 (3.3)	0
Fatigue	25 (13.7)	22 (11.5)	13 (14.3)	0
Injection site reaction	12 (6.6)	13 (6.8)	5 (5.5)	0
Pyrexia	14 (7.7)	26 (13.6)	8 (8.8)	0
Infections and infestations	74 (40.7)	67 (35.1)	21 (23.1)	0
Bronchitis	18 (9.9)	18 (9.4)	7 (7.7)	0
Influenza	10 (5.5)	8 (4.2)	0	0
Nasopharyngitis	28 (15.4)	27 (14.1)	4 (4.4)	0
Oral candidiasis	15 (8.2)	8 (4.2)	7 (7.7)	0
Upper respiratory tract infection	20 (11.0)	26 (13.6)	5 (5.5)	0
Investigations	7 (3.8)	8 (4.2)	6 (6.6)	0
Weight decreased	7 (3.8)	8 (4.2)	6 (6.6)	0
Metabolism and nutrition disorders	14 (7.7)	15 (7.9)	9 (9.9)	0
Decreased appetite	14 (7.7)	15 (7.9)	9 (9.9)	0
Musculoskeletal and connective tissue disorders	38 (20.9)	37 (19.4)	10 (11.0)	0
Arthralgia	10 (5.5)	14 (7.3)	3 (3.3)	0
Back pain	13 (7.1)	10 (5.2)	3 (3.3)	0
Muscle spasms	10 (5.5)	7 (3.7)	4 (4.4)	0
Myalgia	17 (9.3)	11 (5.8)	1 (1.1)	0
Nervous system disorders	48 (26.4)	45 (23.6)	23 (25.3)	0
Dizziness	17 (9.3)	15 (7.9)	8 (8.8)	0
Headache	36 (19.8)	30 (15.7)	16 (17.6)	0
Neuropathy peripheral	6 (3.3)	11 (5.8)	3 (3.3)	0
Psychiatric disorders	17 (9.3)	28 (14.7)	8 (8.8)	0
Depression	10 (5.5)	14 (7.3)	4 (4.4)	0
Insomnia	10 (5.5)	16 (8.4)	4 (4.4)	0
Respiratory, thoracic and mediastinal disorders	17 (9.3)	28 (14.7)	5 (5.5)	0
Cough	17 (9.3)	28 (14.7)	5 (5.5)	0
Skin and subcutaneous tissue disorders	16 (8.8)	22 (11.5)	8 (8.8)	0
Pruritus	5 (2.7)	6 (3.1)	5 (5.5)	0
Rash	12 (6.6)	17 (8.9)	5 (5.5)	0

Subjects were only counted once per treatment for each row.
Included data up to 7 days after last dose of study drug.
MedDRA (v13.0) coding dictionary applied.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with observations.

Table 22. Percentage of Subjects Reporting Adverse Events-All Causality (Treatment Related), by ≥5% of Subjects in Any Treatment Group for Weeks 24 and 48

Percentage of Subjects	Maraviroc QD N=182		Maraviroc BID N=191		Placebo N=91	
All Causality (Treatment Related)	24 Week	48 Week	24 Week	48 Week	24 Week	48 Week
Diarrhoea	22.5 (17.0)	24.2 (17.6)	20.9 (9.4)	20.4 (9.4)	19.8 (16.5)	20.9 (16.5)
Flatulence	3.8 (2.2)	3.8 (2.2)	2.6 (2.1)	2.6 (2.1)	6.6 (5.5)	6.6 (5.5)
Nausea	20.3 (11.5)	22.0 (13.2)	14.7 (11.0)	14.7 (10.5)	16.5 (12.1)	18.7 (13.2)
Vomiting	11.5 (6.6)	12.1 (6.6)	8.4 (4.2)	8.9 (4.2)	9.9 (5.5)	11.0 (6.6)
Fatigue	9.9 (7.1)	11.5 (8.2)	10.5 (7.9)	11.0 (7.9)	14.3 (9.9)	14.3 (8.8)
Dizziness	8.2 (4.9)	8.8 (5.5)	6.3 (3.7)	6.3 (3.1)	8.8 (5.5)	8.8 (5.5)
Headache	15.4 (11.0)	17.0 (12.1)	13.1 (8.4)	14.7 (8.4)	14.3 (12.1)	16.5 (12.1)
Nasopharyngitis	12.6 (1.6)	13.7 (1.6)	8.9 (1.0)	11.0 (1.0)	2.2 (0)	4.4 (0)
Pyrexia	6.6 (2.2)	7.1 (2.7)	12.6 (2.1)	13.6 (2.1)	7.7 (3.3)	8.8 (3.3)
Upper respiratory tract infection	7.1 (0.5)	8.8 (0.5)	9.9 (0.5)	12.6 (0.5)	4.4 (1.1)	4.4 (1.1)
Cough	6.6 (2.7)	7.1 (3.3)	11.0 (4.2)	12.6 (4.7)	5.5 (1.1)	5.5 (1.1)
Bronchitis	6.0 (0)	8.2 (0)	5.2 (0)	7.3 (0)	3.3 (1.1)	4.4 (2.2)
Rash	4.4 (2.7)	4.9 (2.7)	7.9 (4.7)	8.9 (4.7)	3.3 (3.3)	4.4 (4.4)
Injection site reaction	4.9 (0)	6.0 (0)	5.8 (0)	6.8 (0%)	5.5 (0)	5.5 (0)
Oral candidiasis	5.5 (1.1)	7.1 (1.6)	3.1 (0)	3.7 (0)	6.6 (1.1)	7.7 (1.1)
Anorexia	4.9 (3.3)	4.9 (3.3	4.7 (3.7)	4.7 (3.7)	7.7 (4.4)	8.8 (4.4)
Constipation	5.5 (3.3)	5.5 (3.3)	4.7 (1.6)	5.2 (1.6)	6.6 (3.3)	6.6 (3.3)
Abdominal pain upper	7.7 (4.4)	8.2 (4.9)	2.6 (1.0)	2.6 (1.0)	4.4 (3.3)	4.4(3.3)
Back pain	7.1 (1.6)	7.7 (1.6)	3.1 (1.6)	3.7 (1.6)	2.2 (0)	3.3 (0)
Insomnia	3.3 (1.1)	3.8 (1.6)	5.8 (3.7)	6.8 (4.2)	4.4 (2.2)	4.4 (2.2)
Myalgia	6.6 (3.3)	7.7 (3.3)	3.1 (1.0)	3.7 (1.0)	1.1 (0)	1.1 (0)
Asthenia	5.5 (2.7)	6.0 (2.7)	2.6 (2.1)	3.1 (2.1)	3.3 (1.1)	3.3 (1.1)
Abdominal pain	0	5.5 (3.8)	0	4.7 (3.1)	0	5.5 (3.3)
Arthralgia	0	3.3 (1.1)	0	5.2 (2.1)	0	4.4 (2.2)
Weight decreased	0	3.3 (0.5)	0	4.7 (1.6)	0	5.5 (1.1)

AE/SAEs are not separated out.
BID = twice daily; N = number of subjects in the treatment group in the indicated population; QD = once daily.

Table 23. Percentage of Subjects Reporting Incidence of Treatment-Emergent Adverse Events-All Causality (Treatment Related) Events Reported by ≥5% of Subjects in Any Treatment Group for Week 96

Initial Treatment	Maraviroc QD		Maraviroc BID		Placebo		
Treatment Switched to Maraviroc OL BID:	No N=69	Yes N=113	No N=78	Yes N=113	No N=48	Yes (First Phase)[a] N=43	Yes (Second Phase)[a] N=43
Percentage of Subjects - All Causality % (Treatment Related %)[b]							
Diarrhoea	18.8 (11.6)	37.2 (23.9)	20.5 (9.0)	24.8 (11.5)	22.9 (16.7)	20.9 (16.3)	3 (0)
Nausea	18.8 (11.6)	26.5 (17.7)	21.8 (16.7)	18.6 (6.2)	20.8 (14.6)	16.3 (11.6)	3 (1)
Vomiting	13.0 (4.3)	18.6 (8.8)	14.1 (6.4)	11.5 (2.7)	12.5 (6.3)	9.3 (7.0)	1(0)
Headache	13.0 (7.2)	23.9 (15.9)	14.1 (9.0)	17.7 (8.0)	18.8 (12.5)	16.3 (11.6)	5 (2)
Oral candidiasis	10.1 (1.4)	7.1 (1.8)	3.8 (0)	7.1 (0)	8.3 (0)	7.0 (2.3)	3 (0)
Cough	7.2 (1.4)	15.0 (4.4)	14.1 (3.8)	17.7 (6.2)	6.3 (2.1)	4.7 (0)	1 (0)
Myalgia	7.2 (4.3)	10.6 (4.4)	3.8 (0)	6.2 (1.8)	2.1 (0)	2.3 (0)	1 (0)
Nasopharyngitis	7.2 (0)	21.2 (2.7)	9.0 (0)	20.4 (2.7)	6.3 (0)	2.3 (0)	4 (0)
Fatigue	5.8 (4.3)	19.5 (13.3)	14.1 (7.7)	12.4 (8.0)	14.6 (8.3)	14.0 (9.3)	3 (2)
Abdominal pain upper	4.3 (4.3)	11.5 (6.2)	1.3 (1.3)	4.4 (0.9)	4.2 (2.1)	4.7 (4.7)	0
Anorexia	4.3 (2.9)	7.1 (3.5)	7.7 (6.4)	3.5 (1.8)	12.5 (4.2)	7.0 (4.7)	4 (0)
Dizziness	4.3 (2.9)	13.3 (7.1)	1.3 (0)	12.4 (6.2)	12.5 (6.3)	4.7 (4.7)	0
Rash	4.3 (1.4)	8.8 (4.4)	6.4 (1.3)	13.3 (8.0)	8.3 (6.3)	2.3 (2.3)	2 (0)
Pyrexia	2.9 (1.4)	11.5 (3.5)	15.4 (2.6)	16.8 (1.8)	10.4 (4.2)	11.6 (2.3)	1 (0)
Bronchitis	2.9 (0)	14.2 (0.9)	6.4 (0)	15.9 (0.9)	12.5 (2.1)	2.3 (2.3)	3 (0)
Back pain	2.9 (0)	10.6 (2.7)	3.8 (1.3)	7.1 (1.8)	2.1 (0)	7.0 (2.3)	2 (1)
Muscle spasms	2.9 (2.9)	10.6 (6.2)	2.6 (1.3)	4.4 (2.7)	2.1 (0)	7.0 (4.7)	0
Insomnia	2.9 (1.4)	9.7 (3.5)	12.8 (5.1)	6.2 (3.5)	6.3 (4.2)	2.3 (0)	3 (2)
Influenza	1.4 (1.4)	8.0 (0)	1.3 (0)	9.7 (0)	0	0	4 (0)
Upper respiratory tract infection	1.4 (1.4)	17.7 (0)	10.3 (0)	17.7 (0.9)	10.4 (2.1)	2.3 (0)	3 (0)
Arthralgia	1.4 (1.4)	7.1 (2.7)	1.3 (0)	11.5 (3.5)	4.2 (2.1)	4.7 (2.3)	2 (0)
Depression	0	10.6 (1.8)	3.8 (0)	13.3 (1.8)	4.2 (2.1)	4.7 (0)	4 (0)

AE/SAEs are not separated out.
BID = twice daily; N = number of subjects in the treatment group in the indicated population; n = number of subjects with observations; OL = open-label; QD = once daily.
a. Subjects in the placebo switched to OL maraviroc group had their data separated into 2 phases: The first phase includes data while the subject was taking placebo; the second phase summarizes data while the subject was taking maraviroc OL BID.
b. Number of subjects – all causality (treatment related). No percentages were generated for the Second Phase data.

The results for treatment-emergent serious adverse events-All Causalities by SOC are summarized in Table 24.

Table 24. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥0

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v13.0) Preferred Term	Maraviroc QD n (%)	Maraviroc BID n (%)	Placebo n (%)	Open-Label Maraviroc BID n (%)
Blood and lymphatic system disorders	4 (2.2)	6 (3.1)	0	2 (0.7)
Anaemia	1 (0.5)	0	0	2 (0.7)
Febrile neutropenia	1 (0.5)	1 (0.5)	0	0
Haemolytic anaemia	0	1 (0.5)	0	0
Lymphadenopathy	1 (0.5)	1 (0.5)	0	0
Neutropenia	1 (0.5)	2 (1.0)	0	0
Pancytopenia	0	2 (1.0)	0	0
Thrombocytopenia	0	0	0	1 (0.4)
Cardiac disorders	3 (1.6)	2 (1.0)	2 (2.2)	1 (0.4)
Aortic valve disease	0	0	1 (1.1)	0
Arrhythmia	0	1 (0.5)	0	0
Cardiac failure acute	1 (0.5)	0	0	0
Cardio-respiratory arrest	0	1 (0.5)	0	0
Coronary artery occlusion	1 (0.5)	0	0	0
Myocardial infarction	1 (0.5)	0	0	1 (0.4)
Supraventricular tachyarrhythmia	0	0	1 (1.1)	0
Endocrine disorders	1 (0.5)	0	0	0
Hypothyroidism	1 (0.5)	0	0	0
Eye Disorders	1 (0.5)	0	0	0
Retinal detachment	1 (0.5)	0	0	0
Gastrointestinal disorders	6 (3.3)	8 (4.2)	3 (3.3)	3 (1.1)
Abdominal pain	0	1 (0.5)	0	0
Diarrhoea	2 (1.1)	2 (1.0)	1 (1.1)	1 (0.4)
Dysphagia	0	1 (0.5)	0	0
Inguinal hernia	0	1 (0.5)	0	1 (0.4)
Nausea	3 (1.6)	2 (1.0)	1 (1.1)	0
Proctitis	1 (0.5)	0	0	0
Rectal ulcer	1 (0.5)	0	0	0
Vomiting	3 (1.6)	3 (1.6)	2 (2.2)	0
Reflux oesophagitis	0	0	0	1 (0.4)
General disorders and administration site conditions	4 (2.2)	5 (2.6)	3 (3.3)	4 (1.5)
Chest pain	1 (0.5)	1 (0.5)	0	1 (0.4)
Fatigue	1 (0.5)	1 (0.5)	0	0
Hyperthermia	0	1 (0.5)	0	0
Oedema peripheral	1 (0.5)	0	0	0
Pyrexia	1 (0.5)	2 (1.0)	3 (3.3)	1 (0.4)
Sudden death	0	0	0	1 (0.4)
Mucosal erosion	0	0	0	1 (0.4)
Hepatobiliary disorders	1 (0.5)	3 (1.6)	0	0
Bile duct stone	1 (0.5)	0	0	0
Cholecystitis	1 (0.5)	0	0	0
Hepatic failure	0	2 (1.0)	0	0
Jaundice cholestatic	0	1 (0.5)	0	0
Immune system disorders	1 (0.5)	2 (1.0)	1 (1.1)	0
Drug hypersensitivity	1 (0.5)	1 (0.5)	1 (1.1)	0
Immune reconstitution syndrome	0	1 (0.5)	0	0
Infections and infestations	13 (7.1)	21 (11.0)	8 (8.8)	9 (3.3)
Anogenital warts	2 (1.1)	0	0	0
Appendicitis	0	1 (0.5)	0	1 (0.4)
Aspergillosis	1 (0.5)	0	0	0
Bronchitis	0	1 (0.5)	0	0

Table 24. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥0

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v13.0) Preferred Term	Maraviroc QD n (%)	Maraviroc BID n (%)	Placebo n (%)	Open-Label Maraviroc BID n (%)
Bronchopneumonia	0	1 (0.5)	0	0
Cellulitis	1 (0.5)	0	0	0
Cystitis	0	1 (0.5)	0	0
Endocarditis	0	1 (0.5)	0	0
Gastroenteritis	1 (0.5)	1 (0.5)	0	0
Genital herpes	0	0	1 (1.1)	0
Genitourinary tract infection	0	1 (0.5)	0	0
Herpes simplex	1 (0.5)	0	0	0
Herpes virus infection	0	1 (0.5)	0	0
Herpes zoster	0	1 (0.5)	0	
Herpes zoster disseminated	0	0	0	1 (0.4)
Lung infection	0	0	0	1 (0.4)
Klebsiella sepsis	1 (0.5)	0	0	0
Laryngitis	0	1 (0.5)	0	0
Liver abscess	1 (0.5)	0	0	0
Lobar pneumonia	1 (0.5)	0	1 (1.1)	0
Malaria	1 (0.5)	0	0	0
Mycobacterial infection	0	1 (0.5)	0	0
Mycobacterium avium complex infection	0	1 (0.5)	1 (1.1)	1 (0.4)
Mycoplasma infection	0	1 (0.5)	0	0
Neurosyphilis	0	1 (0.5)	0	0
Oesophageal candidiasis	1 (0.5)	1 (0.5)	1 (1.1)	0
Oral candidiasis	1 (0.5)	0	0	0
Pneumococcal sepsis	0	1 (0.5)	0	0
Pneumocystis jiroveci pneumonia	0	1 (0.5)	0	0
Pneumonia	2 (1.1)	5 (2.6)	1 (1.1)	3 (1.1)
Pneumonia bacterial	1 (0.5)	0	1 (1.1)	0
Pneumonia cytomegaloviral	0	0	1 (1.1)	0
Progressive multifocal leukoencephalopathy	0	0	1 (1.1)	0
Pyothorax	0	0	1 (1.1)	0
Respiratory tract infection	0	0	1 (1.1)	1 (0.4)
Sepsis	0	0	1 (1.1)	0
Septic shock	1 (0.5)	0	0	0
Sinusitis	1 (0.5)	0	0	0
Syphilis	1 (0.5)	1 (0.5)	0	0
Upper respiratory tract infection	0	0	1 (1.1)	0
Urinary tract infection	1 (0.5)	0	0	0
Tuberculosis	0	0	0	1 (0.4)
Injury, poisoning and procedural complications	1 (0.5)	0	0	0
Post procedural discomfort	1 (0.5)	0	0	0
Investigations	4 (2.2)	4 (2.1)	0	1 (0.4)
Alanine aminotransferase increased	0	1 (0.5)	0	0
Aspartate aminotransferase increased	0	1 (0.5)	0	1 (0.4)
Blood creatine phosphokinase increased	0	0	0	1 (0.4)
Blood bilirubin increased	1 (0.5)	0	0	0
Hepatic enzyme increased	0	1 (0.5)	0	0
Liver function test abnormal	2 (1.1)	0	0	0
Weight decreased	1 (0.5)	2 (1.0)	0	0
Metabolism and nutrition disorders	2 (1.1)	3 (1.6)	1 (1.1)	0
Decreased appetite	1 (0.5)	0	1 (1.1)	0

Table 24. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥0

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v13.0) Preferred Term	Maraviroc QD n (%)	Maraviroc BID n (%)	Placebo n (%)	Open-Label Maraviroc BID n (%)
Dehydration	0	2 (1.0)	0	0
Diabetes mellitus	1 (0.5)	0	0	0
Gout	0	1 (0.5)	0	0
Musculoskeletal and connective tissue disorders	5 (2.7)	3 (1.6)	1 (1.1)	1 (0.4)
Osteonecrosis	0	0	0	1 (0.4)
Back pain	2 (1.1)	1 (0.5)	1 (1.1)	0
Costochondritis	1 (0.5)	0	0	0
Flank pain	0	1 (0.5)	0	0
Intervertebral disc protrusion	0	1 (0.5)	0	0
Myositis	1 (0.5)	0	0	0
Osteoporotic fracture	1 (0.5)	0	0	0
Neoplasms benign, malignant and unspecified (inclusive cysts and polyps)	6 (3.3)	4 (2.1)	0	5 (1.8)
Hodgkin's disease	0	0	0	2 (0.7)
Anal cancer	2 (1.1)	1 (0.5)	0	
Metastatic salivary gland cancer	0	0	0	1 (0.4)
Bile duct cancer	0	1 (0.5)	0	0
Bronchial carcinoma	0	1 (0.5)	0	0
Kaposi's sarcoma	1 (0.5)	0	0	0
Lymphoma	1 (0.5)	1 (0.5)	0	0
Metastases to bone	0	1 (0.5)	0	0
Metastases to liver	0	1 (0.5)	0	0
Metastases to peritoneum	0	1 (0.5)	0	0
Prostate cancer	1 (0.5)	0	0	0
Metastatic squamous cell carcinoma	0	0	0	1 (0.4)
Paraganglion neoplasm	0	0	0	1 (0.4)
Squamous cell carcinoma	0	0	0	1 (0.4)
Squamous cell carcinoma of skin	1 (0.5)	0	0	0
Tongue neoplasm malignant stage unspecified	0	1 (0.5)	0	0
Nervous system disorders	4 (2.2)	4 (2.1)	3 (3.3)	2 (0.7)
Demyelination	0	0	0	1 (0.4)
Lumbar radiculopathy	0	0	0	1 (0.4)
Cerebral haemorrhage	1 (0.5)	0	0	0
Convulsion	1 (0.5)	0	0	0
Encephalitis	0	1 (0.5)	0	0
Epilepsy	0	1 (0.5)	0	0
IIIrd nerve disorder	0	0	1 (1.1)	0
Polyneuropathy	1 (0.5)	0	0	0
Syncope	0	2 (1.0)	1 (1.1)	0
Transient ischaemic attack	1 (0.5)	0	1 (1.1)	0
Pregnancy, puerperium and perinatal conditions	1 (0.5)	1 (0.5)	0	0
Pregnancy	1 (0.5)	1 (0.5)	0	0
Psychiatric disorders	2 (1.1)	3 (1.6)	0	0
Abnormal behaviour	0	1 (0.5)	0	0
Depression	2 (1.1)	1 (0.5)	0	0
Schizophrenia	0	1 (0.5)	0	0
Suicidal ideation	1 (0.5)	0	0	0
Renal and urinary disorders	3 (1.6)	3 (1.6)	2 (2.2)	0
Proteinuria	1 (0.5)	0	0	0
Renal colic	1 (0.5)	0	0	0
Renal failure	0	2 (1.0)	0	0

Table 24. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥0

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v13.0) Preferred Term	Maraviroc QD n (%)	Maraviroc BID n (%)	Placebo n (%)	Open-Label Maraviroc BID n (%)
Renal failure acute	1 (0.5)	1 (0.5)	2 (2.2)	0
Respiratory, thoracic and mediastinal disorders	1 (0.5)	3 (1.6)	2 (2.2)	4 (1.5)
Asthma	0	0	0	2 (0.7)
Acute respiratory failure	0	0	1 (1.1)	0
Chronic obstructive pulmonary disease	0	1 (0.5)	1 (1.1)	0
Lung disorder	0	0	0	1 (0.4)
Dyspnoea	0	0	1 (1.1)	1 (0.4)
Pulmonary embolism	0	1 (0.5)	0	0
Pulmonary hypertension	1 (0.5)	0	0	0
Respiratory arrest	0	1 (0.5)	0	0
Skin and subcutaneous tissue disorders	2 (1.1)	0	0	0
Lipohypertrophy	1 (0.5)	0	0	0
Purpura	1 (0.5)	0	0	0
Urticaria	1 (0.5)	0	0	0
Surgical and medical procedures	0	1 (0.5)	0	1 (0.4)
Osteotomy	0	0	0	1 (0.4)
Arterial bypass operation	0	1 (0.5)	0	0
Vascular disorders	1 (0.5)	3 (1.6)	1 (1.1)	0
Aortic arteriosclerosis	0	0	1 (1.1)	0
Arterial occlusive disease	0	1 (0.5)	0	0
Haematoma	0	1 (0.5)	0	0
Hypertension	1 (0.5)	0	0	0
Iliac artery stenosis	0	0	1 (1.1)	0
Orthostatic hypotension	0	1 (0.5)	0	0

Subjects were only counted once per treatment for each row.
Included data up to 7 days after last dose of study drug.
MedDRA (v13.0) coding dictionary applied.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the treatment group in the indicated population; n = number of subjects with observations.

The SAEs were considered treatment related by the investigator for 3/69 (4.3%) subjects receiving maraviroc QD not to OL maraviroc, 3/113 (2.7%) subjects receiving maraviroc QD to OL maraviroc, 7/78 (9.0%) subjects receiving maraviroc BID not to OL maraviroc, 3/113 (2.7%) subjects receiving maraviroc BID to OL maraviroc, 0 subjects receiving placebo not to OL maraviroc, 1/43 (2.3%) subjects receiving placebo to OL maraviroc (first phase), and 3/43 (no percentage calculated) subjects receiving placebo to OL maraviroc (second phase). These treatment related events are summarized in Table 25.

Table 25. Treatment Emergent Treatment Related Serious Adverse Events

Subjects	Serious Adverse Events
Maraviroc QD to OL Maraviroc BID	
1	Proteinuria
2	Polyneuropathy[a]
3	Osteoporotic fracture
Maraviroc QD not to OL Maraviroc BID	
4	Myositis
5	Liver function test abnormal[b]
6	Aplasitc anaemia[b]
Maraviroc BID to OL Maraviroc BID	
7	Hodgkin's disease[a,c]
8	Demyelination[a,b]
9	Diarrhoea[c]
Maraviroc BID not to OL Maraviroc BID	
10	Pneumonia (2 events) [a,b]
	Respiratory arrest (2 events) [a,b]
11	Hepatic failure[b]
12	Alanine amino transferase increased[b]
13	Hepatic enzymes increased[c]
14	Syncope[,b]
	Pancytopenia[b]
15	Bile duct cancer[b,d]
	Metastases to liver[b,d]
	Metastases to bone[b,d]
	Metastases to peritoneum[b,d]
16	Orthostatic hypotension[b]
	Syncope[b]
Placebo BID to OL Maraviroc BID	
17	Renal failure acute[c]
18	Myocardial infarction[a]
Placebo BID not to OL Maraviroc BID	
None	

BID = twice daily; OL = open-label; QD = once daily.
a. Events reported since the Week 48 report.
b. Subject permanently discontinued due to this adverse event.
c. Subject temporarily discontinued due to this adverse event.
d. This subject died from this event.

Permanent Discontinuations Due to AEs: The AEs leading to discontinuation were considered treatment related by the investigator for 8 (11.6%) subjects receiving maraviroc QD not to OL maraviroc, 1 (0.9%) subject receiving maraviroc QD to OL maraviroc, 8 (10.3%) subjects receiving maraviroc BID not to OL maraviroc, 1 (0.9%) subject receiving maraviroc BID to OL maraviroc, 2 (4.2%) subjects receiving placebo not to OL maraviroc, 2 (4.7%) subjects receiving placebo to OL maraviroc first phase, and 0 subjects receiving placebo to OL maraviroc second phase. The results are summarized in Table 26.

Table 26. Permanent Discontinuations Due to Adverse Events

Subject	Adverse Events Leading to Discontinuation (Severity)	Causality
Maraviroc QD not to OL Maraviroc BID		
1	Muscular weakness (Grade 3)	Study drug
2	Septic shock (Grade 4)[a,b]	Other - lymphoma
3	ALT increased (Grade 2)	Study drug
	AST increased (Grade 2)	Study drug
4	Pregnancy (Grade 1)[a,b]	Other-contraception failure
5	Liver function test abnormal (Grade 4)[a,b]	Study drug
6	Raynaud's phenomenon (Grade 1)	Study drug
7	Anaemia (Grade 3) [a]	Study drug
8	Myalgia (Grade 3)	Study drug
9	Myalgia (Grade 1)	Study drug
10	Diarrhoea (Grade 2)	Study drug
11	Hepatic enzyme increased (Grade 4)	Other-liver mets
Maraviroc QD to OL Maraviroc BID		
12	Somatoform disorder pregnancy (Grade 3) [b]	Study drug
13	Mycobacterium avium complex infection (Grade 3)[a,b]	Other-illness
Maraviroc BID not to OL Maraviroc BID		
14	Respiratory arrest (Grade 4)[a,b]	Study drug
	Respiratory arrest (Grade 4)[a,b]	Study drug
15	Viral load increased (Grade 1)	Study drug
16	ALT increased (Grade 2)[b]	Study drug
	AST increased (Grade 2)[b]	Study drug
	GGT increased (Grade 2)[b]	Study drug
	GGT increased (Grade 3)[b]	Disease under study
17	Hepatic failure (Grade 4)[a]	Study drug
18	ALT increased (Grade 4)[a]	Study drug
	AST increased (Grade 4)[a]	Study drug
19	Endocarditis (Grade 4)[a,b]	Other-Streptococcus pneumonia
	Pneumonia (Grade 4)[a,b]	Disease under study
20	Syncope (Grade 4)[a]	Study drug
21	Bile duct cancer (Grade 4)[a]	Study drug
22	Renal failure (Grade 4)[a,b]	Concomitant treatment-tenofovir
23	Orthostatic hypotension (Grade 3)[a]	Study drug
24	Tongue neoplasm malignant stage unspecified (Grade 3)[a]	Other-squamous cell carcinoma of the left tongue base
25	Gastrointestinal infection (Grade 2)	Other-norovirus infection
Maraviroc BID to OL Maraviroc BID		
26	Pregnancy (Grade 1)	Other-unknown
27	Demyelination (Grade 4)	Study drug
28	Syncope vasovagal (Grade 1)[b]	Disease under study
Placebo not to OL Maraviroc BID		
29	Depression (Grade 2)[b]	Study drug
30	Dizziness (Grade 2)	Study drug
31	Injection site pruritis (Grade 2)[b]	Concomitant treatment-enfuvirtide
32	Sepsis (Grade 4)[a]	Other-illness
	Renal failure acute (Grade 4)[a]	Other-illness
Placebo to OL Maraviroc BID, First Phase		
33	Cytolytic hepatitis (Grade 3)	Study drug
34	Hepatic enzyme increased (Grade 4)	Study drug
Placebo to OL Maraviroc BID, Second Phase		

Table 26. Permanent Discontinuations Due to Adverse Events

Subject	Adverse Events Leading to Discontinuation (Severity)	Causality
35	AST and ALT increased (Grade 3)[b]	Other-HCV infection

ALT = alanine transferase; AST = aspartate transferase; BID = twice daily; GGT = gamma glutamyl transpeptidase; HCV = hepatitis C virus OL = open-label; QD = once daily.
a. Serious adverse event.
b. Events reported since the Week 48.

Deaths: Of the 474 subjects who were randomized to treatment, a total of 33 subjects died during the study. Cumulative study results were generally similar between the original treatment assignments, with deaths experienced by 8 maraviroc BID subjects, 7 maraviroc OL subjects, 4 maraviroc QD subjects, 8 subjects who were never treated, 1 placebo subject, 3 post-maraviroc BID subjects, 1 post-maraviroc OL subject, and 1 post-maraviroc QD subject. The 33 deaths were due to a variety of causes across all treatment groups. As a clarifying note, in the maraviroc BID group, there were 8 subjects who died. Three subjects in the maraviroc BID group, who died, had 6 causal events in the Neoplasms SOC; 2 subjects had 1 event each (metastatic bronchial carcinoma, central nervous system lymphoma) and 1 subject had 4 events (cholangiocarcinoma, bone metastases, liver metastases, and peritoneal metastases). The results for death are summarized in Table 27.

Table 27. Summary of Death

MedDRA System Organ Class\ Preferred Event Term	Number of Events							
	Maraviroc BID	Maraviroc OL	Maraviroc QD	Never Treated	Placebo	Post/ Maraviroc BID	Post/ Maraviroc OL	Post/ Maraviroc QD
Cardiac disorders								
Acute myocardial infarction	0	0	0	0	0	0	1	0
Arteriosclerosis coronary artery	0	0	1	0	0	0	1	0
Cardiac arrest	0	0	0	0	0	2	0	0
Cardiac failure acute	0	0	1	0	0	0	0	0
Cardiac failure congestive	0	1	0	0	0	0	0	0
Cardio-respiratory arrest	1	0	0	0	0	0	0	0
Myocardial infarction	0	0	1	0	0	0	0	0
Gastrointestinal disorders								
Gastrointestinal haemorrhage	0	0	0	2	0	0	0	0
Haematemesis	0	0	0	1	0	0	0	0
General disorders and administration site conditions								
Asthenia	0	0	0	1	0	0	0	0
Death	1	0	0	0	0	0	0	0
Disease progression	0	0	0	1	0	0	0	0
Multi-organ failure	1	0	0	0	0	0	0	0
Sudden death	0	1	0	0	0	0	0	0
Infections and infestations								
HIV infection	1	0	0	0	0	0	0	0
Pneumonia	0	0	0	1	0	0	0	0
Pneumonia bacterial	0	0	1	0	0	0	0	0
Pneumonia legionella	0	1	0	0	0	0	0	0
Pneumonia primary atypical	0	1	0	0	0	0	0	0
Progressive multifocal leukoencephalopathy	0	0	0	1	1	0	0	0
Septic shock	0	1	1	0	0	0	0	0
Injury, poisoning and procedural complications								
Drug exposure during pregnancy	0	0	0	1	0	0	0	0

Table 27. Summary of Death

MedDRA System Organ Class\ Preferred Event Term	Number of Events							
	Maraviroc BID	Maraviroc OL	Maraviroc QD	Never Treated	Placebo	Post/ Maraviroc BID	Post/ Maraviroc OL	Post/ Maraviroc QD
Metabolism and nutrition disorders								
Decreased appetite	0	0	1	1	0	0	0	0
Dehydration	0	0	0	1	0	0	0	0
Neoplasms benign, malignant and unspecified (include cysts and polyps)								
Bile duct cancer	1	0	0	0	0	0	0	0
Central nervous system lymphoma	1	0	0	0	0	0	0	0
Colon cancer	0	0	0	0	0	0	0	1
Lung cancer metastatic	0	0	0	0	0	1	0	0
Metastases to bone	1	0	0	0	0	0	0	0
Metastases to liver	1	0	0	0	0	0	0	0
Metastases to peritoneum	1	0	0	0	0	0	0	0
Metastatic bronchial carcinoma	1	0	0	0	0	0	0	0
Squamous cell carcinoma	0	1	0	0	0	0	0	0
Nervous system disorder								
Hemiplegia	0	0	0	1	0	0	0	0
Renal and urinary disorders								
Renal failure	0	0	0	1	0	0	0	0
Respiratory, thoracic and mediastinal disorders								
Chronic obstructive pulmonary disease	1	0	0	0	0	0	0	0
Interstitial lung disease	0	1	0	0	0	0	0	0
Pulmonary hypertension	0	1	0	0	0	0	0	0
Respiratory arrest	0	0	0	1	0	0	0	0
Respiratory failure	0	1	0	1	0	0	0	0
Total preferred term events	11	9	6	14	1	3	2	1
Total number of cases	8	7	4	8	1	3	1	1
Total number of subjects with SAEs	8	7	4	8	1	3	1	1

BID = twice daily; OL = open-label; QD = once daily; SAE = serious adverse event.

There were no clinically significant median changes from baseline in any laboratory test for all subjects. There were no clinically significant mean changes from baseline to last observation in any treatment group for standing or supine systolic blood pressure, diastolic blood pressure and pulse rate. ECG measurements were small and clinically insignificant in all treatment groups.

CONCLUSIONS:

Analysis of the primary endpoint change from baseline through to Week 48 in viral load (log_{10} copies/mL) has shown that maraviroc QD and maraviroc BID added to OBT are superior in comparison with OBT alone.

In addition, all the secondary endpoint results at Week 48 were consistent with the primary endpoint and support the superior efficacy of both maraviroc treatment groups over placebo.

Maraviroc, dosed either QD or BID, was well tolerated. There were no clinically relevant differences in the safety profile between the maraviroc and placebo treatment groups in this highly treatment experienced HIV population.

Maraviroc, when added to OBT, was efficacious, safe and well tolerated in a heavily treatment experienced population infected with CCR5-tropic HIV-1 after 48 weeks of treatment.