Section 2.7.3 Appendix Table A1: Description of Maraviroc Clinical Efficacy Studies.

Protocol No. Study Design, Patient Population and Status	Treatment Groups	No. of Subjects, by Treatment Arm	Demographics, by Treatment Group	Efficacy Endpoints	Study Report Location
A4001027 A multicentre, randomised, double-blind, placebo-controlled trial of maraviroc in combination with OBT versus OBT alone for the treatment of antiretroviral-experienced patients infected with CCR5 tropic HIV-1. Patients with a non-CCR5 tropism result at screening (dual/mixed, CXCR4-tropic or non-phenotypable) were excluded from the study. The study was conducted in North America and endpoints formally evaluated at 24 weeks. The study is ongoing to 48 weeks.	Maraviroc (Once daily [QD] Oral tablet) plus Optimised Background Therapy (OBT)	Treated: N= 232 Reached 24 weeks: N= 149 (64%)	Sex: 210 M / 22 F Mean Age (min/max): 46 (19/75) years	<u>1° efficacy endpoints:</u> • Change from Baseline in $\log_{10}$ HIV-1 RNA level at Week 24. <u>2° efficacy endpoints:</u> • Percentage of patients with an HIV-1 RNA <400 copies/mL at Week 24; • Percentage of patients with an HIV-1 RAN <50 copies/mL at Week 24; • Percentage of patients who achieved at least a 0.5 $\log_{10}$ reduction in HIV-1 RNA from baseline or <400 copies/mL; • Percentage of patients who achieved at least a 1.0 $\log_{10}$ reduction in HIV-1 RNA from baseline or <400 copies/mL at Week 24; • Differences in the magnitude of change in CD4 cell count from baseline to Week 24; • Differences in the magnitude of change in CD8 cell count from baseline to Week 24; • Time Averaged Difference (TAD) in $\log_{10}$ HIV-1 RNA at Week 24; • Assess HIV-1 genotype and phenotype at baseline and at time of failure.	Module 5.3.5.1

Maraviroc: Submission for Treatment-Experienced Patients Infected with CCR5 Tropic HIV-1.
Module 2.7.3 Summary of Clinical Efficacy Appendix Table A1

Protocol No. Study Design, Patient Population and Status	Treatment Groups	No. of Subjects, by Treatment Arm	Demographics, by Treatment Group	Efficacy Endpoints	Study Report Location
	Maraviroc (Twice daily [BID] Oral tablet) plus Optimised Background Therapy (OBT)	Treated: N= 235 Reached 24 weeks: N= 155 (66%)	Sex: 212 M / 23 F Mean Age (min/max): 46 (25/69) years	As above	As Above
	Matched Placebo (Twice daily [BID] Oral tablet) plus Optimised Background Therapy (OBT)	Treated: N= 118 Reached 24 weeks: N= 44 (37%)	Sex: 106 M / 12 F Mean Age (min/max): 46 (31/71) years	As above	As Above

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Protocol No. Study Design, Patient Population and Status	Treatment Groups	No. of Subjects, by Treatment Arm	Demographics, by Treatment Group	Efficacy Endpoints	Study Report Location
A4001028 A multicentre, randomised, double-blind, placebo-controlled trial of maraviroc in combination with OBT versus OBT alone for the treatment of antiretroviral-experienced patients infected with CCR5 tropic HIV-1. Patients with a non-CCR5 tropism result at screening (dual/mixed, CXCR4-tropic or non-phenotypable) were excluded from the study. The study was conducted in Europe, Australia and North America and endpoints formally evaluated at 24 weeks. The study is ongoing to 48 weeks.	Maraviroc (Once daily [QD] Oral tablet) plus Optimised Background Therapy (OBT)	Treated: N= 182 Reached 24 weeks: N= 122 (67%)	Sex: 153 M / 29 F Mean Age (min/max): 45 (17/75) years	1° efficacy endpoints: • Change from Baseline in log_{10} HIV-1 RNA level at Week 24. 2° efficacy endpoints: • Percentage of patients with an HIV-1 RNA <400 copies/mL at Week 24; • Percentage of patients with an HIV-1 RAN <50 copies/mL at Week 24; • Percentage of patients who achieved at least a 0.5 log_{10} reduction in HIV-1 RNA from baseline or <400 copies/mL; • Percentage of patients who achieved at least a 1.0 log_{10} reduction in HIV-1 RNA from baseline or <400 copies/mL at Week 24; • Differences in the magnitude of change in CD4 cell count from baseline to Week 24; • Differences in the magnitude of change in CD8 cell count from baseline to Week 24; • Time Averaged Difference (TAD) in log_{10} HIV-1 RNA at Week 24; • Assess HIV-1 genotype and phenotype at baseline and at time of failure.	Module 5.3.5.1

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Protocol No. Study Design, Patient Population and Status	Treatment Groups	No. of Subjects, by Treatment Arm	Demographics, by Treatment Group	Efficacy Endpoints	Study Report Location
	Maraviroc (Twice daily [BID] Oral tablet) plus Optimised Background Therapy (OBT)	Treated: N= 191 Reached 24 weeks: N= 133 (70%)	Sex: 170 M / 21 F Mean Age (min/max): 47 (21/73) years		As above
	Matched Placebo (Twice daily [BID] Oral tablet) plus Optimised Background Therapy (OBT)	Treated: N= 91 Reached 24 weeks: N= 32 (35%)	Sex: 79 M / 12 F Mean Age (min/max): 45 (29/72) years		As above

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Protocol No. Study Design, Patient Population and Status	Treatment Groups	No. of Subjects, by Treatment Arm	Demographics, by Treatment Group	Efficacy Endpoints	Study Report Location
A4001029 A multicentre, randomised, double-blind, placebo-controlled trial of maraviroc in combination with OBT versus OBT alone for the treatment of antiretroviral-experienced patients infected with non-CCR5 tropic (CCR5/CXCR4, CXCR4-using or non-phenotypable) HIV-1. Patients with a CCR5 tropism result at screening were excluded from study. The study was conducted in Europe, Australia and North America and endpoints formally evaluated at 24 weeks. The study is ongoing to 48 weeks.	Maraviroc (Once daily [QD] Oral tablet) plus Optimised Background Therapy (OBT)	Treated: N= 63 Reached 24 weeks: N= 25 (40%)	Sex: 53 M / 10 F Mean Age (min/max): 43 (16/59) years	1° efficacy endpoints: • Change from Baseline in $\log_{10}$ HIV-1 RNA level at Week 24. 2° efficacy endpoints: • Percentage of patients with an HIV-1 RNA <400 copies/mL at Week 24; • Percentage of patients with an HIV-1 RAN <50 copies/mL at Week 24; • Percentage of patients who achieved at least a 0.5 $\log_{10}$ reduction in HIV-1 RNA from baseline or <400 copies/mL; • Percentage of patients who achieved at least a 1.0 $\log_{10}$ reduction in HIV-1 RNA from baseline or <400 copies/mL at Week 24; • Differences in the magnitude of change in CD4 cell count from baseline to Week 24; • Differences in the magnitude of change in CD8 cell count from baseline to Week 24; • Time Averaged Difference (TAD) in $\log_{10}$ HIV-1 RNA at Week 24; • Assess HIV-1 genotype and phenotype at baseline and at time of failure.	Module 5.3.5.1

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Protocol No. Study Design, Patient Population and Status	Treatment Groups	No. of Subjects, by Treatment Arm	Demographics, by Treatment Group	Efficacy Endpoints	Study Report Location
	Maraviroc (Twice daily [BID] Oral tablet) plus Optimised Background Therapy (OBT)	Treated: N= 61 Reached 24 weeks: N= 29 (48%)	Sex: 55 M / 6 F Mean Age (min/max): 43 (16/62) years	As Above	As above
	Matched Placebo (Twice daily [BID] Oral tablet) plus Optimised Background Therapy (OBT)	Treated: N= 62 Reached 24 weeks: N= 24 (39%)	Sex: 53 M / 9 F Mean Age (min/max): 45 (23/65) years	As Above	As above

Maraviroc: Submission for Treatment-Experienced Patients Infected with CCR5 Tropic HIV-1.
Module 2.7.3 Appendix Table A2

Section 2.7.3 Appendix Table A2 Results of Maraviroc Efficacy Studies

Protocol No. (Country) Title	Treatment Groups	No. of Subjects by Treatment Group	Efficacy Results	Study Report Location
A4001027 (North America). A Multicentre, Randomised, Double-Blind, Placebo-Controlled Trial of a Novel CCR5 Antagonist, Maraviroc (UK-427,857), in Combination with Optimised Background Therapy versus Optimised Background Therapy alone for the Treatment of Antiretroviral-Experienced HIV-1 Infected Subjects. Total Patients Screened: N= 1816 Total Patients Randomised: N= 601	Maraviroc 300 mg QD + OBT	Treated: N= 232 Reached 24 weeks: N= 149 (64%)	*Primary Endpoint Analysis:* There was a greater mean decrease in HIV-1 RNA from baseline to Week 24 in both maraviroc treatment groups compared with placebo; -1.818 and -1.952 versus -1.030 $\log_{10}$ copies/mL for maraviroc QD, BID and placebo respectively. The treatment difference from placebo was -0.788 (97.5% CI -1.141, -0.435) and -0.922 (-1.275, -0.570) $\log_{10}$ copies/mL for maraviroc QD and BID respectively. *Selected Secondary Endpoint Analysis:* There was a higher proportion of patients with an HIV-1 RNA <50 and <400 copies/mL at Week 24 in the maraviroc treatment groups compared with placebo; 98 (42%), 114 (49%) and 29 (25%) for maraviroc QD, BID and placebo [<50 copies/mL] and 127 (55%), 142 (60%) and 37 (31%) for maraviroc QD, BID and placebo [<400 copies/mL]. There was a higher proportion of patients achieving a ≥1.0 and ≥0.5 $\log_{10}$ reduction in HIV-1 RNA from baseline to Week 24 in the maraviroc treatment groups compared with placebo; 159 (69%), 166 (71%) and 55 (47%) for maraviroc QD, BID and placebo [≥1.0 $\log_{10}$ reduction] and 151 (65%), 161 (69%) and 46 (39%) for maraviroc QD, BID and placebo [≥0.5 $\log_{10}$ reduction]. There was a greater mean increase from baseline to Week 24 in CD4 cell count for both maraviroc treatment groups than placebo; +106.6, +111.1 and +52.1 cells/μL for maraviroc QD, BID and placebo. The difference from placebo was 54.5 cells/μL (95% CI 30.1, 78.9) for maraviroc QD and 58.9 cells/μL (95% CI 34.6, 83.3) for maraviroc BID.	Module 5.3.5.1
	Maraviroc 300 mg BID + OBT	Treated: N= 235 Reached 24 weeks: N= 155 (66%)	Included above.	

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Protocol No. (Country) Title	Treatment Groups	No. of Subjects by Treatment Group	Efficacy Results	Study Report Location
	Placebo + OBT	Treated: N= 118 Reached 24 weeks: N= 44 (37%)	Included above.	
A4001028 (EU, Australia and North America) A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of A Novel CCR5 Antagonist, Maraviroc (UK-427,857), In Combination with Optimized Background Therapy versus Optimized Background Therapy Alone For the Treatment of Antiretroviral-Experienced HIV-1 Infected Subjects. Total Patients Screened: N= 1428 Total Patients Randomised: N= 475	Maraviroc 300 mg QD + OBT	Treated: N= 182 Reached 24 weeks: N= 122 (67%)	*Primary Endpoint Analysis:* There was a greater mean decrease in HIV-1 RNA from baseline to Week 24 in both maraviroc treatment groups compared with placebo; -1.950 and -1.971 versus -0.929 $\log_{10}$ copies/mL for maraviroc QD, BID and placebo respectively. The treatment difference from placebo was -1.021 (97.5% CI -1.426, -0.616) and -1.042 (-1.444, -0.640) $\log_{10}$ copies/mL for maraviroc QD and BID respectively. *Selected Secondary Endpoint Analysis:* There was a higher proportion of patients with an HIV-1 RNA <50 and <400 copies/mL at Week 24 in the maraviroc treatment groups compared with placebo; 84 (46%), 79 (41%) and 19 (21%) for maraviroc QD, BID and placebo [<50 copies/mL] and 101 (56%), 118 (62%) and 21 (23%) for maraviroc QD, BID and placebo [<400 copies/mL]. There was a higher proportion of patients achieving a ≥1.0 and ≥0.5 $\log_{10}$ reduction in HIV-1 RNA from baseline to Week 24 in the maraviroc treatment groups compared with placebo; 128 (70%), 137 (72%) and 32 (35%) for maraviroc QD, BID and placebo [≥1.0 $\log_{10}$ reduction] and 121 (67%), 134 (70%) and 29 (32%) for maraviroc QD, BID and placebo [≥0.5 $\log_{10}$ reduction]. There was a greater mean increase from baseline to Week 24 in CD4 cell count for both maraviroc treatment groups than placebo; +111.7, +101.9 and +63.8 cells/μL for maraviroc QD, BID and placebo. The difference from placebo was 47.9 cells/μL (95% CI 21.6, 74.3) maraviroc QD and 38.1 cells/μL (95% CI 12.0, 64.3) for maraviroc BID.	Module 5.3.5.1

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Protocol No. (Country) Title	Treatment Groups	No. of Subjects by Treatment Group		Efficacy Results	Study Report Location
	Maraviroc 300 mg BID + OBT	Treated: N= 191 Reached 24 weeks: N= 133 (70%)	Included above.		
	Placebo + OBT	Treated: N= 91 Reached 24 weeks: N= 32 (35%)	Included above.		

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Protocol No. (Country) Title	Treatment Groups	No. of Subjects by Treatment Group	Efficacy Results	Study Report Location
A4001029 (EU, Australia, North America)) A multicentre, randomised, double-blind, placebo controlled trial of a novel CCR5 antagonist, maraviroc, in combination with optimized background therapy v optimized background therapy alone for the treatment of antiretroviral-experienced, non CCR5 tropic HIV-1 infected subjects. Total Patients Screened: N= 1816 Total Patients Randomised: N= 601	Maraviroc 300 mg QD + OBT	Treated: N= 63 Reached 24 weeks: N= 25 (40%)	*Primary Endpoint Analysis:* Neither dose of maraviroc demonstrated superiority nor non-inferiority to placebo treatment as the point estimates for the mean change from baseline to Week 24 in HIV-1 RNA were similar for all 3 treatment groups and the upper limit of each 97.5% CI was >0.25 $\log_{10}$ copies/mL (pre-defined non-inferiority margin); mean change from baseline was -0.913, -1.200 and -0.968 $\log_{10}$ copies/mL for maraviroc QD, BID and placebo respectively and the difference from placebo was 0.055 $\log_{10}$ copies/mL (97.5% CI -0.528, 0.638) for maraviroc QD and -0.232 $\log_{10}$ copies/mL (97.5 CI -0.829, 0.364) for maraviroc BID. *Selected Secondary Endpoint Analysis:* There was a slightly higher proportion of patients receiving maraviroc BID who achieved an HIV-1 RNA <50 and <400 copies/mL at Week 24 compared with maraviroc QD and placebo; 12 (21%), 14 (27%) and 9 (16%) for maraviroc QD, BID and placebo [<50 copies/mL] and 14 (25%), 16 (31%) and 14 (24%) for maraviroc QD, BID and placebo [<400 copies/mL]. Similarly, there was a slightly higher proportion of patients receiving maraviroc BID who achieved a ≥1.0 and ≥0.5 $\log_{10}$ reduction in HIV-1 RNA from baseline to Week 24 compared with maraviroc QD and placebo; 18 (32%), 23 (44%) and 21 (36%) for maraviroc QD, BID and placebo [≥1.0 $\log_{10}$ reduction] and 24 (42%), 25 (48%) and 23 (40%) for maraviroc QD, BID and placebo [≥0.5 $\log_{10}$ reduction]. Change in CD4 cell count from baseline was higher for both doses of maraviroc compared with placebo; +59.6, +62.4 and +35.7 cells/μL for maraviroc QD, BID and placebo. The difference from placebo was 23.9 (95% CI -1.4, 49.2, p= 0.064) for maraviroc QD and 26.7 (95% CI 0.9, 52.5, p= 0.043).	Module 5.3.5.1

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Protocol No. (Country) Title	Treatment Groups	No. of Subjects by Treatment Group	Efficacy Results	Study Report Location
	Maraviroc 300 mg BID + OBT	Treated: N= 61 Reached 24 weeks: N= 29 (48%)	Included above.	
	Placebo + OBT	Treated: N= 62 Reached 24 weeks: N= 24 (39%)	Included above.	

OBT = Optimised Background Therapy; QD = Once daily dosing; BID = Twice daily dosing; CIs = Confidence intervals.

Table 13.4.3.1.1
Maraviroc Summary of Clinical Efficacy
Summary of HIV-1 RNA (log10 copies/mL) by Visit
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Baseline	N**	414	426	209
	Mean (s.d.)	4.863 (0.6508)	4.852 (0.6163)	4.860 (0.6197)
	Median (Min, Max)	4.885 (2.490, 6.753)	4.855 (2.955, 6.878)	4.892 (3.460, 7.068)
Week 2	N**	386	407	202
	Mean (s.d.)	3.201 (0.9682)	3.203 (0.9467)	3.669 (1.1101)
	Median (Min, Max)	3.070 (1.690, 6.906)	3.037 (1.690, 7.009)	3.544 (1.690, 6.196)
Week 4	N**	399	402	205
	Mean (s.d.)	3.009 (1.1545)	2.969 (1.1173)	3.639 (1.2819)
	Median (Min, Max)	2.744 (1.690, 7.013)	2.680 (1.690, 7.107)	3.556 (1.690, 5.957)
Week 8	N**	390	398	193
	Mean (s.d.)	2.791 (1.2510)	2.744 (1.2146)	3.596 (1.3994)
	Median (Min, Max)	2.304 (1.690, 6.655)	2.273 (1.690, 6.462)	3.725 (1.690, 6.210)
Week 12	N**	368	379	172
	Mean (s.d.)	2.663 (1.2578)	2.555 (1.1660)	3.442 (1.4418)
	Median (Min, Max)	2.051 (1.690, 6.496)	1.982 (1.690, 6.104)	3.670 (1.690, 6.262)
Week 16	N**	331	341	128
	Mean (s.d.)	2.424 (1.1266)	2.306 (1.0351)	2.982 (1.3338)
	Median (Min, Max)	1.690 (1.690, 5.985)	1.690 (1.690, 5.486)	2.484 (1.690, 6.238)
Week 20	N**	312	318	108
	Mean (s.d.)	2.318 (1.0335)	2.182 (0.8960)	2.892 (1.3434)
	Median (Min, Max)	1.690 (1.690, 6.246)	1.690 (1.690, 5.718)	2.102 (1.690, 6.167)
Week 24	N**	294	313	99
	Mean (s.d.)	2.232 (0.9340)	2.126 (0.8365)	2.763 (1.2938)
	Median (Min, Max)	1.690 (1.690, 5.526)	1.690 (1.690, 5.560)	1.771 (1.690, 5.422)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
Blinded therapy data only is summarized.
Each individual subjects baseline value is calculated as the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.
Early Termination visits included within normal visits as per visit windowing.

Table 13.4.4.1
Maraviroc Summary of Clinical Efficacy
Summary of CD4 Cell Count (cells/uL) by Visit
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Baseline	N**	413	426	208
	Mean (s.d.)	195.7 (160.06)	189.2 (146.83)	187.2 (133.05)
	Median (Min, Max)	171.0 (0.5, 965.5)	166.8 (2.0, 820.0)	171.3 (1.0, 675.0)
Week 2	N**	363	386	187
	Mean (s.d.)	250.3 (183.21)	248.9 (167.92)	220.2 (141.13)
	Median (Min, Max)	225.0 (3.0, 1113.0)	233.0 (2.0, 905.0)	200.0 (2.0, 608.0)
Week 4	N**	380	388	192
	Mean (s.d.)	267.2 (181.24)	265.7 (167.86)	225.0 (154.03)
	Median (Min, Max)	236.0 (3.0, 1055.0)	243.0 (1.0, 973.0)	201.0 (1.0, 647.0)
Week 8	N**	373	384	188
	Mean (s.d.)	287.5 (193.76)	285.0 (176.47)	231.8 (165.18)
	Median (Min, Max)	256.0 (3.0, 1572.0)	265.5 (1.0, 1031.0)	200.0 (1.0, 802.0)
Week 12	N**	353	356	165
	Mean (s.d.)	302.9 (202.20)	297.8 (180.00)	259.3 (165.92)
	Median (Min, Max)	278.0 (1.0, 1124.0)	273.0 (2.0, 1097.0)	238.0 (2.0, 734.0)
Week 16	N**	312	330	123
	Mean (s.d.)	324.2 (199.05)	319.5 (180.82)	281.1 (157.92)
	Median (Min, Max)	295.0 (7.0, 1560.0)	292.5 (2.0, 1034.0)	267.0 (4.0, 728.0)
Week 20	N**	301	303	105
	Mean (s.d.)	331.2 (189.65)	324.5 (186.24)	286.4 (156.70)
	Median (Min, Max)	310.0 (4.0, 1084.0)	285.0 (2.0, 1251.0)	257.0 (7.0, 832.0)
Week 24	N**	284	295	95
	Mean (s.d.)	350.5 (210.58)	331.0 (175.96)	300.1 (183.22)
	Median (Min, Max)	307.0 (2.0, 1279.0)	301.0 (3.0, 974.0)	263.0 (11.0, 922.0)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
Blinded therapy data only is summarized.
Each individual subjects baseline value is calculated as the average of the pre-dose measurements collected at the screening visit and baseline visit.
Early Termination visits included within normal visits as per visit windowing.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Change from Baseline through Week 24 in Log10 Transformed HIV-1 RNA (Log10 copies/mL)
Full Analysis Set - As Randomized

		Change from Baseline through Week 24			Treatment difference maraviroc - Placebo	
		Raw Mean		Adjusted Mean	Estimate	
Treatment	N	(s.e.)	Median	(s.e.)	(s.e.)	97.5% CI
maraviroc QD	414	-1.868 (0.0689)	-2.274	-1.875 (0.0691)	-0.894 (0.1181)	(-1.159, -0.629)
maraviroc BID	426	-1.960 (0.0688)	-2.424	-1.963 (0.0680)	-0.982 (0.1175)	(-1.246, -0.718)
Placebo	209	-0.980 (0.0910)	0.000	-0.981 (0.0968)		

Missing values have been imputed as the baseline value for subjects who discontinued from blinded therapy.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Change from Baseline through Week 24 in Log10 Transformed HIV-1 RNA (Log10 copies/mL)
Full Analysis Set - As Randomized

		Change from Baseline through Week 24			Treatment difference maraviroc (BID - QD)	
		Raw Mean		Adjusted Mean	Estimate	
Treatment	N	(s.e.)	Median	(s.e.)	(s.e.)	95% CI
maraviroc BID	426	-1.960 (0.0688)	-2.424	-1.963 (0.0680)	-0.088 (0.0961)	(-0.276, 0.101)
maraviroc QD	414	-1.868 (0.0689)	-2.274	-1.875 (0.0691)		

Missing values have been imputed as the baseline value for subjects who discontinued from blinded therapy.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Change from Baseline through Week 24 in Log10 Transformed HIV-1 RNA (Log10 copies/mL)
Full Analysis Set - As Treated

		Change from Baseline through Week 24			Treatment difference maraviroc - Placebo	
		Raw Mean		Adjusted Mean	Estimate	
Treatment	N	(s.e.)	Median	(s.e.)	(s.e.)	97.5% CI
maraviroc QD	414	-1.868 (0.0689)	-2.274	-1.876 (0.0692)	-0.888 (0.1182)	(-1.153, -0.623)
maraviroc BID	426	-1.957 (0.0690)	-2.424	-1.960 (0.0680)	-0.973 (0.1176)	(-1.237, -0.709)
Placebo	209	-0.987 (0.0909)	0.000	-0.987 (0.0968)		

Missing values have been imputed as the baseline value for subjects who discontinued from blinded therapy.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Change from Baseline through Week 24 in Log10 Transformed HIV-1 RNA (Log10 copies/mL)
Full Analysis Set - As Treated

		Change from Baseline through Week 24			Treatment difference maraviroc (BID - QD)	
Treatment	N	Raw Mean (s.e.)	Median	Adjusted Mean (s.e.)	Estimate (s.e.)	95% CI
maraviroc BID	426	-1.957 (0.0690)	-2.424	-1.960 (0.0680)	-0.085 (0.0961)	(-0.274, 0.104)
maraviroc QD	414	-1.868 (0.0689)	-2.274	-1.876 (0.0692)		

Missing values have been imputed as the baseline value for subjects who discontinued from blinded therapy.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Time Averaged Difference from Baseline through Week 24 in Log10 Transformed HIV-1 RNA (Log10 copies/mL)
Full Analysis Set - As Treated

		Change from Baseline through Week 24			Treatment difference maraviroc - Placebo	
Treatment	N	Raw Mean (s.e.)	Median	Adjusted Mean (s.e.)	Estimate (s.e.)	95% CI
maraviroc QD	414	-1.683 (0.0591)	-2.105	-1.686 (0.0591)	-0.775 (0.1010)	(-0.973, -0.576)
maraviroc BID	426	-1.748 (0.0581)	-2.197	-1.748 (0.0581)	-0.836 (0.1005)	(-1.033, -0.639)
Placebo	209	-0.915 (0.0801)	0.000	-0.911 (0.0827)		

Discontinuations prior to the time point of analysis have been imputed as 0 for the purpose of analysis.
The baseline value used in the calculation of time averaged difference from baseline is the average
of the pre-dose measurements collected at the screening visit, randomization visit and the baseline visit.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Time Averaged Difference from Baseline through Week 24 in Log10 Transformed HIV-1 RNA (Log10 copies/mL)
Full Analysis Set - As Treated

		Change from Baseline through Week 24			Treatment difference maraviroc (BID - QD)	
		Raw Mean		Adjusted Mean	Estimate	
Treatment	N	(s.e.)	Median	(s.e.)	(s.e.)	95% CI
maraviroc BID	426	-1.748 (0.0581)	-2.197	-1.748 (0.0581)	-0.062 (0.0821)	(-0.223, 0.099)
maraviroc QD	414	-1.683 (0.0591)	-2.105	-1.686 (0.0591)		

Discontinuations prior to the time point of analysis have been imputed as 0 for the purpose of analysis.
The baseline value used in the calculation of time averaged difference from baseline is the average
of the pre-dose measurements collected at the screening visit, randomization visit and the baseline visit.

Table 13.4.6.11
Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Change from Baseline through Week 24 in CD4 Cell Count (cells/uL)
Full Analysis Set - As Treated

		Change from Baseline through Week 24			Treatment difference maraviroc - Placebo	
Treatment	N	Raw Mean (s.e.)	Median	Adjusted Mean (s.e.)	Estimate (s.e.)	95% CI
maraviroc QD	407	108.72 (5.983)	86.00	108.60 (5.345)	51.23 (9.158)	(33.26, 69.20)
maraviroc BID	418	105.81 (4.886)	88.25	106.34 (5.259)	48.97 (9.114)	(31.08, 66.85)
Placebo	206	56.54 (6.710)	30.75	57.37 (7.476)		

LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit and baseline visit.

		Change from Baseline through Week 24			Treatment difference maraviroc (BID - QD)	
Treatment	N	Raw Mean (s.e.)	Median	Adjusted Mean (s.e.)	Estimate (s.e.)	95% CI
maraviroc BID	418	105.81 (4.886)	88.25	106.34 (5.259)	-2.26 (7.458)	(-16.90, 12.38)
maraviroc QD	407	108.72 (5.983)	86.00	108.60 (5.345)		

LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Change from Baseline through Week 24 in CD8 Cell Count (cells/uL)
Full Analysis Set - As Treated

		Change from Baseline through Week 24			Treatment difference maraviroc - Placebo	
Treatment	N	Raw Mean (s.e.)	Median	Adjusted Mean (s.e.)	Estimate (s.e.)	95% CI
maraviroc QD	407	295.87 (29.020)	211.00	305.51 (25.008)	251.22 (42.861)	(167.11, 335.32)
maraviroc BID	418	274.08 (22.103)	208.50	278.85 (24.597)	224.56 (42.639)	(140.89, 308.23)
Placebo	206	51.67 (29.627)	9.25	54.29 (34.978)		

LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit and baseline visit.

		Change from Baseline through Week 24			Treatment difference maraviroc (BID - QD)	
Treatment	N	Raw Mean (s.e.)	Median	Adjusted Mean (s.e.)	Estimate (s.e.)	95% CI
maraviroc BID	418	274.08 (22.103)	208.50	278.85 (24.597)	-26.65 (34.896)	(-95.13, 41.82)
maraviroc QD	407	295.87 (29.020)	211.00	305.51 (25.008)		

LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Difference in Proportion of Subjects with HIV-1 RNA <400 copies/mL at Week 24
Full Analysis Set - As Treated

Comparison*	Difference in Proportions	95% CI
maraviroc QD vs Placebo	0.28	(0.21,0.35)
maraviroc BID vs Placebo	0.35	(0.27,0.42)
maraviroc BID vs maraviroc QD	0.06	(-0.01,0.12)

Missing values at Week 24 are defined as responders if they are a responder at both Weeks 20 and 32.
If their Week 20 or 32 value is missing, or they have discontinued prior to Week 32 then they are defined as a non-responder.
* The estimate of the difference in proportions has been adjusted for the randomization strata as described below:
Stratum 1: Screening HIV-1 RNA level: <100,000 copies/mL, Enfuvirtide use: Yes
Stratum 2: Screening HIV-1 RNA level: <100,000 copies/mL, Enfuvirtide use: No
Stratum 3: Screening HIV-1 RNA level: >=100,000 copies/mL, Enfuvirtide use: Yes
Stratum 4: Screening HIV-1 RNA level: >=100,000 copies/mL, Enfuvirtide use: No

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Proportion of Subjects with HIV-1 RNA < 400 copies/mL at Week 24 (Logistic Regression)
Full Analysis Set - As Treated

Odds Ratio for Treatment Difference

			Treatment Comparison maraviroc - Placebo		
Treatment	N	Positive Response (%)	Odds Ratio	95% CI for Odds Ratio	P-value
maraviroc QD	414	55.1	3.48	(2.41, 5.04)	<0.0001
maraviroc BID	426	61.0	4.49	(3.10, 6.51)	<0.0001
Placebo	209	27.8			

Missing values at Week 24 are defined as responders if they are responders at both Weeks 20 and 32.
If their Week 20 or 32 value is missing, or they have discontinued prior to Week 32 then they are defined as a non-responder.
An odds ratio greater than 1 indicates a beneficial response for subjects on test treatment compared to reference treatment.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Proportion of Subjects with HIV-1 RNA < 400 copies/mL at Week 24 (Logistic Regression)
Full Analysis Set - As Treated

Odds Ratio for Treatment Difference

			Treatment Comparison maraviroc (BID - QD)		
Treatment	N	Positive Response (%)	Odds Ratio	95% CI for Odds Ratio	P-value
maraviroc BID	426	61.0	1.29	(0.97, 1.71)	0.0782
maraviroc QD	414	55.1			

Missing values at Week 24 are defined as responders if they are responders at both Weeks 20 and 32.
If their Week 20 or 32 value is missing, or they have discontinued prior to Week 32 then they are defined as a non-responder.
An odds ratio greater than 1 indicates a beneficial response for subjects on test treatment compared to reference treatment.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Difference in Proportion of Subjects with HIV-1 RNA <50 copies/mL at Week 24
Full Analysis Set - As Treated

Comparison*	Difference in Proportions	95% CI
maraviroc QD vs Placebo	0.21	(0.14,0.27)
maraviroc BID vs Placebo	0.23	(0.16,0.30)
maraviroc BID vs maraviroc QD	0.02	(-0.05,0.08)

Missing values at Week 24 are defined as responders if they are a responder at both Weeks 20 and 32.
If their Week 20 or 32 value is missing, or they have discontinued prior to Week 32 then they are defined as a non-responder.
* The estimate of the difference in proportions has been adjusted for the randomization strata as described below:
Stratum 1: Screening HIV-1 RNA level: <100,000 copies/mL, Enfuvirtide use: Yes
Stratum 2: Screening HIV-1 RNA level: <100,000 copies/mL, Enfuvirtide use: No
Stratum 3: Screening HIV-1 RNA level: >=100,000 copies/mL, Enfuvirtide use: Yes
Stratum 4: Screening HIV-1 RNA level: >=100,000 copies/mL, Enfuvirtide use: No

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Proportion of Subjects with HIV-1 RNA < 50 copies/mL at Week 24 (Logistic Regression)
Full Analysis Set - As Treated

Odds Ratio for Treatment Difference

			Treatment Comparison maraviroc - Placebo		
Treatment	N	Positive Response (%)	Odds Ratio	95% CI for Odds Ratio	P-value
maraviroc QD	414	44.0	2.87	(1.95, 4.22)	<0.0001
maraviroc BID	426	45.3	3.02	(2.05, 4.44)	<0.0001
Placebo	209	23.0			

Missing values at Week 24 are defined as responders if they are responders at both Weeks 20 and 32.
If their Week 20 or 32 value is missing, or they have discontinued prior to Week 32 then they are defined as a non-responder.
An odds ratio greater than 1 indicates a beneficial response for subjects on test treatment compared to reference treatment.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Proportion of Subjects with HIV-1 RNA < 50 copies/mL at Week 24 (Logistic Regression)
Full Analysis Set - As Treated

Odds Ratio for Treatment Difference

			Treatment Comparison maraviroc (BID - QD)		
Treatment	N	Positive Response (%)	Odds Ratio	95% CI for Odds Ratio	P-value
maraviroc BID	426	45.3	1.05	(0.79, 1.40)	0.7204
maraviroc QD	414	44.0			

Missing values at Week 24 are defined as responders if they are responders at both Weeks 20 and 32.
If their Week 20 or 32 value is missing, or they have discontinued prior to Week 32 then they are defined as a non-responder.
An odds ratio greater than 1 indicates a beneficial response for subjects on test treatment compared to reference treatment.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Difference in Proportion of Subjects with HIV-1 RNA < 400 copies/mL or at least 1.0 log10 Decrease from Baseline at Week 24
Full Analysis Set - As Treated

Comparison*	Difference in Proportions	95% CI
maraviroc QD vs Placebo	0.30	(0.22,0.38)
maraviroc BID vs Placebo	0.34	(0.26,0.42)
maraviroc BID vs maraviroc QD	0.03	(-0.03,0.10)

Missing values at Week 24 are defined as responders if they are a responder at both Weeks 20 and 32.
If their Week 20 or 32 value is missing, or they have discontinued prior to Week 32 then they are defined as a non-responder.
* The estimate of the difference in proportions has been adjusted for the randomization strata as described below:
Stratum 1: Screening HIV-1 RNA level: <100,000 copies/mL, Enfuvirtide use: Yes
Stratum 2: Screening HIV-1 RNA level: <100,000 copies/mL, Enfuvirtide use: No
Stratum 3: Screening HIV-1 RNA level: >=100,000 copies/mL, Enfuvirtide use: Yes
Stratum 4: Screening HIV-1 RNA level: >=100,000 copies/mL, Enfuvirtide use: No
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Table 13.4.6.7
Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Proportion of Subjects with HIV-1 RNA < 400 copies/mL or at least 1.0 log10 Decrease from Baseline at Week 24 (Logistic Regression)
Full Analysis Set - As Treated

Odds Ratio for Treatment Difference

			Treatment Comparison maraviroc - Placebo		
Treatment	N	Positive Response (%)	Odds Ratio	95% CI for Odds Ratio	P-value
maraviroc QD	414	65.7	3.63	(2.55, 5.17)	<0.0001
maraviroc BID	426	69.2	4.25	(2.98, 6.07)	<0.0001
Placebo	209	35.9			

Missing values at Week 24 are defined as responders if they are a responder at both Weeks 20 and 32.
If their Week 20 or 32 value is missing, or they have discontinued prior to Week 32 then they are defined as a non-responder.
An odds ratio greater than 1 indicates a beneficial response for subjects on test treatment compared to reference treatment.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Table 13.4.6.7
Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Proportion of Subjects with HIV-1 RNA < 400 copies/mL or at least 1.0 log10 Decrease from Baseline at Week 24 (Logistic Regression)
Full Analysis Set - As Treated

Odds Ratio for Treatment Difference

			Treatment Comparison maraviroc (BID - QD)		
Treatment	N	Positive Response (%)	Odds Ratio	95% CI for Odds Ratio	P-value
maraviroc BID	426	69.2	1.17	(0.87, 1.57)	0.2895
maraviroc QD	414	65.7			

Missing values at Week 24 are defined as responders if they are a responder at both Weeks 20 and 32.
If their Week 20 or 32 value is missing, or they have discontinued prior to Week 32 then they are defined as a non-responder.
An odds ratio greater than 1 indicates a beneficial response for subjects on test treatment compared to reference treatment.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Maraviroc Summary of Clinical Efficacy

Summary of Statistical Analysis: Difference in Proportion of Subjects with HIV-1 RNA < 400 copies/mL or at least 0.5 log10 Decrease from Baseline at Week 24

Full Analysis Set - As Treated

Comparison*	Difference in Proportions	95% CI
maraviroc QD vs Placebo	0.28	(0.20,0.36)
maraviroc BID vs Placebo	0.30	(0.22,0.38)
maraviroc BID vs maraviroc QD	0.02	(-0.04,0.08)

Missing values at Week 24 are defined as responders if they are a responder at both Weeks 20 and 32.
If their Week 20 or 32 value is missing, or they have discontinued prior to Week 32 then they are defined as a non-responder.
* The estimate of the difference in proportions has been adjusted for the randomization strata as described below:
Stratum 1: Screening HIV-1 RNA level: <100,000 copies/mL, Enfuvirtide use: Yes
Stratum 2: Screening HIV-1 RNA level: <100,000 copies/mL, Enfuvirtide use: No
Stratum 3: Screening HIV-1 RNA level: >=100,000 copies/mL, Enfuvirtide use: Yes
Stratum 4: Screening HIV-1 RNA level: >=100,000 copies/mL, Enfuvirtide use: No
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Table 13.4.6.9
Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Proportion of Subjects with HIV-1 RNA < 400 copies/mL or at least 0.5 log10 Decrease from Baseline at Week 24 (Logistic Regression)
Full Analysis Set - As Treated

Odds Ratio for Treatment Difference

			Treatment Comparison maraviroc - Placebo		
Treatment	N	Positive Response (%)	Odds Ratio	95% CI for Odds Ratio	P-value
maraviroc QD	414	69.3	3.34	(2.35, 4.74)	<0.0001
maraviroc BID	426	71.1	3.62	(2.55, 5.14)	<0.0001
Placebo	209	41.6			

Missing values at Week 24 are defined as responders if they are a responder at both Weeks 20 and 32.
If their Week 20 or 32 value is missing, or they have discontinued prior to Week 32 then they are defined as a non-responder.
An odds ratio greater than 1 indicates a beneficial response for subjects on test treatment compared to reference treatment.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Table 13.4.6.9
Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Proportion of Subjects with HIV-1 RNA < 400 copies/mL or at least 0.5 log10 Decrease from Baseline at Week 24 (Logistic Regression)
Full Analysis Set - As Treated

Odds Ratio for Treatment Difference

			Treatment Comparison maraviroc (BID - QD)		
Treatment	N	Positive Response (%)	Odds Ratio	95% CI for Odds Ratio	P-value
maraviroc BID	426	71.1	1.08	(0.80, 1.46)	0.5939
maraviroc QD	414	69.3			

Missing values at Week 24 are defined as responders if they are a responder at both Weeks 20 and 32.
If their Week 20 or 32 value is missing, or they have discontinued prior to Week 32 then they are defined as a non-responder.
An odds ratio greater than 1 indicates a beneficial response for subjects on test treatment compared to reference treatment.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Table 13.4.9.1.1
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by HIV-1 RNA at Screening
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
<100,000 copies/mL	N**	238	243	123
	Mean (s.d.)	-2.067 (1.0949)	-2.129 (1.0666)	-1.247 (1.2858)
	Median (Min, Max)	-2.385 (-3.597, 2.039)	-2.442 (-3.513, 0.780)	-0.688 (-3.428, 0.965)
>=100,000 copies/mL	N**	170	176	84
	Mean (s.d.)	-2.127 (1.4871)	-2.197 (1.5263)	-1.032 (1.3011)
	Median (Min, Max)	-2.394 (-4.492, 0.822)	-2.797 (-4.547, 1.317)	-0.395 (-4.148, 0.619)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Maraviroc Summary of Clinical Efficacy

Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by Enfuvirtide Usage in OBT

Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
Yes	N**	165	180	90
	Mean (s.d.)	-2.136 (1.2838)	-2.228 (1.3305)	-1.155 (1.2754)
	Median (Min, Max)	-2.405 (-4.492, 1.080)	-2.587 (-4.547, 1.317)	-0.744 (-3.650, 0.965)
No	N**	243	239	117
	Mean (s.d.)	-2.062 (1.2653)	-2.105 (1.2384)	-1.164 (1.3122)
	Median (Min, Max)	-2.382 (-4.428, 2.039)	-2.453 (-4.407, 1.200)	-0.598 (-4.148, 0.619)

* This is the number of subjects in the treatment group in the indicated population.

** This is the number of subjects contributing to the summary statistics.

LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.

The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Table 13.4.9.1.3
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by CD4 Cell Count at Baseline
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
<50 cells/uL	N**	85	85	37
	Mean (s.d.)	-1.311 (1.4495)	-1.351 (1.6320)	-0.632 (0.9581)
	Median (Min, Max)	-0.734 (-4.492, 0.505)	-0.632 (-4.407, 1.317)	-0.309 (-3.510, 0.483)
50-100 cells/uL	N**	51	55	25
	Mean (s.d.)	-2.181 (1.3058)	-2.258 (1.3962)	-0.943 (1.2855)
	Median (Min, Max)	-2.599 (-3.872, 0.822)	-2.645 (-4.547, 0.021)	-0.396 (-3.588, 0.472)
101-200 cells/uL	N**	93	104	56
	Mean (s.d.)	-2.229 (1.1455)	-2.360 (1.0688)	-1.157 (1.4312)
	Median (Min, Max)	-2.540 (-4.428, 0.450)	-2.613 (-4.504, 0.532)	-0.474 (-4.148, 0.965)
201-350 cells/uL	N**	116	116	62
	Mean (s.d.)	-2.400 (1.0987)	-2.336 (1.0164)	-1.439 (1.3153)
	Median (Min, Max)	-2.582 (-4.303, 2.039)	-2.571 (-3.871, 0.602)	-1.014 (-3.665, 0.641)
>350 cells/uL	N**	62	59	26
	Mean (s.d.)	-2.290 (1.0590)	-2.520 (0.8946)	-1.397 (1.1509)
	Median (Min, Max)	-2.465 (-3.834, 1.080)	-2.620 (-4.068, 0.647)	-1.306 (-3.519, 0.300)
Missing	N**	1	0	1
	Mean (s.d.)	-3.156 (.)		-2.817 (.)
	Median (Min, Max)	-3.156 (-3.156, -3.156)		-2.817 (-2.817, -2.817)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline in HIV-1 RNA is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.
The baseline CD4 Cell Count value is calculated as the average of the pre-dose measurements collected at the screening visit and baseline visit.

Table 13.4.9.1.4
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by Age in Years
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
<45	N**	202	193	98
	Mean (s.d.)	-2.066 (1.3302)	-1.937 (1.3646)	-1.250 (1.3745)
	Median (Min, Max)	-2.235 (-4.428, 2.039)	-2.314 (-4.410, 1.317)	-0.583 (-3.588, 0.965)
45 to 64	N**	196	221	106
	Mean (s.d.)	-2.105 (1.2338)	-2.351 (1.1745)	-1.088 (1.2252)
	Median (Min, Max)	-2.442 (-4.492, 0.822)	-2.719 (-4.547, 1.200)	-0.619 (-4.148, 0.641)
>=65	N**	10	5	3
	Mean (s.d.)	-2.372 (0.7302)	-2.118 (1.0968)	-0.753 (0.9500)
	Median (Min, Max)	-2.547 (-3.342, -0.799)	-2.557 (-3.188, -0.332)	-0.598 (-1.770, 0.111)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Table 13.4.9.1.5
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by Sex
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
MALE	N**	357	376	184
	Mean (s.d.)	-2.051 (1.2759)	-2.144 (1.2755)	-1.118 (1.2813)
	Median (Min, Max)	-2.351 (-4.492, 2.039)	-2.454 (-4.547, 1.200)	-0.549 (-4.148, 0.641)
FEMALE	N**	51	43	23
	Mean (s.d.)	-2.378 (1.2160)	-2.282 (1.3152)	-1.493 (1.3688)
	Median (Min, Max)	-2.634 (-4.231, 0.295)	-2.719 (-3.890, 1.317)	-1.666 (-3.519, 0.965)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by Race
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
WHITE	N**	333	357	178
	Mean (s.d.)	-2.137 (1.2487)	-2.212 (1.2858)	-1.132 (1.2831)
	Median (Min, Max)	-2.437 (-4.492, 1.080)	-2.571 (-4.547, 1.317)	-0.537 (-4.148, 0.965)
BLACK	N**	67	50	25
	Mean (s.d.)	-1.799 (1.3730)	-1.704 (1.1929)	-1.515 (1.3766)
	Median (Min, Max)	-2.170 (-4.231, 2.039)	-1.858 (-3.890, 0.532)	-0.801 (-3.519, 0.512)
ASIAN	N**	3	5	1
	Mean (s.d.)	-2.424 (0.4579)	-2.729 (0.6660)	0.101 (.)
	Median (Min, Max)	-2.271 (-2.939, -2.062)	-2.972 (-3.485, -1.821)	0.101 (0.101, 0.101)
OTHER	N**	4	7	3
	Mean (s.d.)	-2.690 (1.4337)	-2.227 (1.3159)	-0.261 (0.3966)
	Median (Min, Max)	-2.886 (-4.224, -0.763)	-2.842 (-3.389, -0.292)	-0.131 (-0.706, 0.055)
Missing	N**	1	0	0
	Mean (s.d.)	-3.266 (.)		
	Median (Min, Max)	-3.266 (-3.266, -3.266)		

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Table 13.4.9.1.7
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by Overall Susceptibility Score at Screening
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
0	N**	51	56	35
	Mean (s.d.)	-1.280 (1.0347)	-1.372 (1.3075)	-0.166 (0.6943)
	Median (Min, Max)	-0.989 (-3.395, 0.080)	-1.057 (-3.524, 1.317)	-0.045 (-2.817, 0.641)
1	N**	130	134	44
	Mean (s.d.)	-1.874 (1.2148)	-1.951 (1.3213)	-0.507 (0.8920)
	Median (Min, Max)	-2.124 (-3.907, 1.080)	-2.325 (-4.504, 0.780)	-0.272 (-3.428, 0.512)
2	N**	88	104	59
	Mean (s.d.)	-2.115 (1.3602)	-2.331 (1.0038)	-1.023 (1.0798)
	Median (Min, Max)	-2.411 (-4.295, 2.039)	-2.580 (-4.547, -0.030)	-0.629 (-3.181, 0.965)
>=3	N**	132	121	64
	Mean (s.d.)	-2.594 (1.1457)	-2.592 (1.2295)	-2.307 (1.1398)
	Median (Min, Max)	-2.954 (-4.492, 0.822)	-2.907 (-4.410, 1.200)	-2.641 (-4.148, 0.442)
Missing	N**	7	4	5
	Mean (s.d.)	-2.315 (1.1563)	-2.442 (1.3488)	-0.785 (1.1301)
	Median (Min, Max)	-2.336 (-3.705, -0.042)	-2.823 (-3.579, -0.544)	-0.521 (-2.679, 0.341)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Table 13.4.9.1.8
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by CCR5 Delta32 Genotype
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
WT/WT	N**	351	368	174
	Mean (s.d.)	-2.090 (1.2864)	-2.155 (1.2794)	-1.171 (1.2847)
	Median (Min, Max)	-2.388 (-4.492, 2.039)	-2.472 (-4.547, 1.317)	-0.639 (-3.665, 0.965)
Deletion/WT	N**	32	27	16
	Mean (s.d.)	-2.206 (1.0315)	-2.491 (1.0492)	-1.352 (1.5943)
	Median (Min, Max)	-2.267 (-4.295, 0.080)	-2.738 (-3.956, -0.279)	-0.348 (-4.148, 0.111)
Missing	N**	25	24	17
	Mean (s.d.)	-1.973 (1.3734)	-1.830 (1.4523)	-0.868 (1.0837)
	Median (Min, Max)	-2.509 (-3.907, 0.224)	-2.101 (-4.504, 0.313)	-0.437 (-3.109, 0.341)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by Inferred Promoter Haplotype
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
P1	N**	192	186	98
	Mean (s.d.)	-2.154 (1.2383)	-2.216 (1.1972)	-1.309 (1.3995)
	Median (Min, Max)	-2.383 (-4.428, 2.039)	-2.476 (-4.410, 0.647)	-0.661 (-4.148, 0.571)
P4	N**	53	58	22
	Mean (s.d.)	-2.047 (1.3873)	-2.305 (1.2820)	-1.184 (1.2972)
	Median (Min, Max)	-2.202 (-4.492, 0.822)	-2.515 (-4.407, 0.390)	-0.807 (-3.549, 0.337)
P1/P4	N**	127	141	65
	Mean (s.d.)	-2.051 (1.2704)	-2.119 (1.3400)	-1.042 (1.1967)
	Median (Min, Max)	-2.351 (-4.303, 0.450)	-2.555 (-4.547, 1.317)	-0.537 (-3.359, 0.965)
Other	N**	11	10	5
	Mean (s.d.)	-1.965 (1.2277)	-1.552 (1.3499)	-0.639 (0.8447)
	Median (Min, Max)	-2.481 (-3.762, -0.187)	-1.295 (-3.761, -0.051)	-0.396 (-1.479, 0.512)
Missing	N**	25	24	17
	Mean (s.d.)	-1.973 (1.3734)	-1.830 (1.4523)	-0.868 (1.0837)
	Median (Min, Max)	-2.509 (-3.907, 0.224)	-2.101 (-4.504, 0.313)	-0.437 (-3.109, 0.341)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by Protease Inhibitor and/or Delavirdine Usage in OBT
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
Yes	N**	316	329	169
	Mean (s.d.)	-2.100 (1.3006)	-2.169 (1.2928)	-1.191 (1.2876)
	Median (Min, Max)	-2.419 (-4.428, 2.039)	-2.476 (-4.547, 1.317)	-0.649 (-4.148, 0.619)
No	N**	92	90	38
	Mean (s.d.)	-2.065 (1.1735)	-2.118 (1.2319)	-1.021 (1.3264)
	Median (Min, Max)	-2.327 (-4.492, 0.822)	-2.452 (-3.793, 0.780)	-0.463 (-3.650, 0.965)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.
Subjects using tipranavir are included under the No group.

Maraviroc Summary of Clinical Efficacy

Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by Virus Subtype(B, Non B or not Determined)

Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
B	N**	385	400	197
	Mean (s.d.)	-2.081 (1.2770)	-2.154 (1.2805)	-1.170 (1.2939)
	Median (Min, Max)	-2.388 (-4.492, 2.039)	-2.467 (-4.547, 1.317)	-0.629 (-4.148, 0.965)
Non B	N**	19	15	7
	Mean (s.d.)	-2.264 (1.3013)	-2.305 (1.2132)	-1.279 (1.4688)
	Median (Min, Max)	-2.268 (-4.231, 0.259)	-2.557 (-3.890, -0.218)	-0.346 (-3.398, 0.218)
Undetermined	N**	4	4	3
	Mean (s.d.)	-2.318 (0.4863)	-1.999 (1.6545)	-0.181 (0.4585)
	Median (Min, Max)	-2.240 (-2.974, -1.819)	-2.554 (-3.199, 0.313)	-0.361 (-0.521, 0.341)

* This is the number of subjects in the treatment group in the indicated population.

** This is the number of subjects contributing to the summary statistics.

LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.

The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Percentage of Subjects with HIV-1 RNA < 400 copies/mL at Week 24 by HIV-1 RNA at Screening
Full Analysis Set - As Treated

	Treatment	N**	n	Percentage (%)
Total Population	maraviroc QD (N=414)*	408	248	60.78
	maraviroc BID (N=426)*	419	273	65.16
	Placebo (N=209)*	207	63	30.43
<100,000 copies/mL	maraviroc QD (N=414)*	238	172	72.27
	maraviroc BID (N=426)*	243	182	74.90
	Placebo (N=209)*	123	50	40.65
>=100,000 copies/mL	maraviroc QD (N=414)*	170	76	44.71
	maraviroc BID (N=426)*	176	91	51.70
	Placebo (N=209)*	84	13	15.48

* This is the number of subjects in the treatment group in the indicated population.
** For each subgroup, this is the number of subjects with a post baseline observation used to calculate the percentage.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.

Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Percentage of Subjects with HIV-1 RNA < 400 copies/mL at Week 24 by Enfuvirtide Usage in OBT
Full Analysis Set - As Treated

	Treatment	N**	n	Percentage (%)
Total Population	maraviroc QD (N=414)*	408	248	60.78
	maraviroc BID (N=426)*	419	273	65.16
	Placebo (N=209)*	207	63	30.43
Yes	maraviroc QD (N=414)*	165	97	58.79
	maraviroc BID (N=426)*	180	117	65.00
	Placebo (N=209)*	90	26	28.89
No	maraviroc QD (N=414)*	243	151	62.14
	maraviroc BID (N=426)*	239	156	65.27
	Placebo (N=209)*	117	37	31.62

* This is the number of subjects in the treatment group in the indicated population.
** For each subgroup, this is the number of subjects with a post baseline observation used to calculate the percentage.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.

Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Percentage of Subjects with HIV-1 RNA < 400 copies/mL at Week 24 by Overall Susceptibility Score
Full Analysis Set - As Treated

	Treatment	N**	n	Percentage (%)
Total Population	maraviroc QD (N=414)*	408	248	60.78
	maraviroc BID (N=426)*	419	273	65.16
	Placebo (N=209)*	207	63	30.43
0	maraviroc QD (N=414)*	51	13	25.49
	maraviroc BID (N=426)*	56	23	41.07
	Placebo (N=209)*	35	2	5.71
1	maraviroc QD (N=414)*	130	74	56.92
	maraviroc BID (N=426)*	134	77	57.46
	Placebo (N=209)*	44	5	11.36
2	maraviroc QD (N=414)*	88	55	62.50
	maraviroc BID (N=426)*	104	75	72.12
	Placebo (N=209)*	59	14	23.73
>=3	maraviroc QD (N=414)*	132	102	77.27
	maraviroc BID (N=426)*	121	95	78.51
	Placebo (N=209)*	64	41	64.06
Missing	maraviroc QD (N=414)*	7	4	57.14
	maraviroc BID (N=426)*	4	3	75.00
	Placebo (N=209)*	5	1	20.00

* This is the number of subjects in the treatment group in the indicated population.
** For each subgroup, this is the number of subjects with a post baseline observation used to calculate the percentage.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.

Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Percentage of Subjects with HIV-1 RNA < 50 copies/mL at Week 24 by HIV-1 RNA at Screening
Full Analysis Set - As Treated

	Treatment	N**	n	Percentage (%)
Total Population	maraviroc QD (N=414)*	408	194	47.55
	maraviroc BID (N=426)*	419	201	47.97
	Placebo (N=209)*	207	51	24.64
<100,000 copies/mL	maraviroc QD (N=414)*	238	146	61.34
	maraviroc BID (N=426)*	243	140	57.61
	Placebo (N=209)*	123	42	34.15
>=100,000 copies/mL	maraviroc QD (N=414)*	170	48	28.24
	maraviroc BID (N=426)*	176	61	34.66
	Placebo (N=209)*	84	9	10.71

* This is the number of subjects in the treatment group in the indicated population.
** For each subgroup, this is the number of subjects with a post baseline observation used to calculate the percentage.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.

Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Percentage of Subjects with HIV-1 RNA < 50 copies/mL at Week 24 by Enfuvirtide Usage in OBT
Full Analysis Set - As Treated

	Treatment	N**	n	Percentage (%)
Total Population	maraviroc QD (N=414)*	408	194	47.55
	maraviroc BID (N=426)*	419	201	47.97
	Placebo (N=209)*	207	51	24.64
Yes	maraviroc QD (N=414)*	165	81	49.09
	maraviroc BID (N=426)*	180	82	45.56
	Placebo (N=209)*	90	23	25.56
No	maraviroc QD (N=414)*	243	113	46.50
	maraviroc BID (N=426)*	239	119	49.79
	Placebo (N=209)*	117	28	23.93

* This is the number of subjects in the treatment group in the indicated population.
** For each subgroup, this is the number of subjects with a post baseline observation used to calculate the percentage.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.

Maraviroc Summary of Clinical Efficacy

Subgroup Analyses: Percentage of Subjects with HIV-1 RNA < 50 copies/mL at Week 24 by Overall Susceptibility Score

Full Analysis Set - As Treated

	Treatment	N**	n	Percentage (%)
Total Population	maraviroc QD (N=414)*	408	194	47.55
	maraviroc BID (N=426)*	419	201	47.97
	Placebo (N=209)*	207	51	24.64
0	maraviroc QD (N=414)*	51	9	17.65
	maraviroc BID (N=426)*	56	16	28.57
	Placebo (N=209)*	35	1	2.86
1	maraviroc QD (N=414)*	130	56	43.08
	maraviroc BID (N=426)*	134	58	43.28
	Placebo (N=209)*	44	4	9.09
2	maraviroc QD (N=414)*	88	46	52.27
	maraviroc BID (N=426)*	104	55	52.88
	Placebo (N=209)*	59	11	18.64
>=3	maraviroc QD (N=414)*	132	81	61.36
	maraviroc BID (N=426)*	121	70	57.85
	Placebo (N=209)*	64	35	54.69
Missing	maraviroc QD (N=414)*	7	2	28.57
	maraviroc BID (N=426)*	4	2	50.00
	Placebo (N=209)*	5	0	0.00

* This is the number of subjects in the treatment group in the indicated population.

** For each subgroup, this is the number of subjects with a post baseline observation used to calculate the percentage. LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.

Table 13.4.9.4.1
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in CD4 Cell Counts (cell/uL) at Week 24 by HIV-1 RNA at Screening
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	407	418	206
	Mean (s.d.)	108.72 (120.694)	105.81 (99.898)	56.54 (96.302)
	Median (Min, Max)	86.00 (-263.50, 834.50)	88.25 (-277.00, 561.00)	30.75 (-301.00, 452.50)
<100,000 copies/mL	N**	238	242	122
	Mean (s.d.)	94.82 (105.954)	99.76 (99.751)	58.62 (100.214)
	Median (Min, Max)	74.25 (-193.00, 585.00)	88.25 (-277.00, 536.50)	34.25 (-184.50, 452.50)
>=100,000 copies/mL	N**	169	176	84
	Mean (s.d.)	128.29 (136.777)	114.12 (99.785)	53.52 (90.826)
	Median (Min, Max)	106.50 (-263.50, 834.50)	89.00 (-93.50, 561.00)	19.25 (-301.00, 298.50)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit and baseline visit.

Table 13.4.9.4.2
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in CD4 Cell Counts (cell/uL) at Week 24 by Enfuvirtide Usage in OBT
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	407	418	206
	Mean (s.d.)	108.72 (120.694)	105.81 (99.898)	56.54 (96.302)
	Median (Min, Max)	86.00 (-263.50, 834.50)	88.25 (-277.00, 561.00)	30.75 (-301.00, 452.50)
Yes	N**	165	180	89
	Mean (s.d.)	101.62 (106.456)	111.42 (100.776)	53.25 (78.351)
	Median (Min, Max)	84.50 (-263.50, 588.00)	85.25 (-131.00, 561.00)	31.50 (-184.50, 264.50)
No	N**	242	238	117
	Mean (s.d.)	113.56 (129.500)	101.57 (99.231)	59.05 (108.249)
	Median (Min, Max)	86.50 (-193.00, 834.50)	92.50 (-277.00, 536.50)	29.50 (-301.00, 452.50)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Virology Analysis: Summary of Genotypic, Phenotypic and Overall Susceptibility Scores at Screening
Full Analysis Set - As Treated

Susceptibility Scores		maraviroc QD (N=414)*	(%)	maraviroc BID (N=426)*	(%)	Placebo (N=209)*	(%)
Genotypic	0	91	(22.0)	102	(23.9)	51	(24.4)
	1	146	(35.3)	138	(32.4)	53	(25.4)
	2	63	(15.2)	80	(18.8)	41	(19.6)
	>=3	109	(26.3)	104	(24.4)	59	(28.2)
	N**	409		424		204	
	Median	1.0		1.0		1.0	
	Mean	1.6		1.6		1.7	
	Missing	5		2		5	
Phenotypic	0	45	(10.9)	50	(11.7)	29	(13.9)
	1	116	(28.0)	115	(27.0)	38	(18.2)
	2	93	(22.5)	107	(25.1)	58	(27.8)
	>=3	154	(37.2)	150	(35.2)	79	(37.8)
	N**	408		422		204	
	Median	2.0		2.0		2.0	
	Mean	2.0		2.0		2.1	
	Missing	6		4		5	
Overall	0	52	(12.6)	57	(13.4)	35	(16.7)
	1	133	(32.1)	136	(31.9)	44	(21.1)
	2	88	(21.3)	104	(24.4)	59	(28.2)
	>=3	134	(32.4)	125	(29.3)	66	(31.6)
	N**	407		422		204	
	Median	2.0		2.0		2.0	
	Mean	1.9		1.8		1.9	
	Missing	7		4		5	

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.

Table 13.5.4.2
Maraviroc Summary of Clinical Efficacy
Virology Analysis: Shift Table of Tropism between Baseline and Time of Treatment Failure, Overall and by Treatment
Full Analysis Set - As Treated

Treatment Group: All Subjects (N=242)

	Time of Treatment Failure Tropism Status					
Baseline Tropism Status	R5	X4	Dual Mixed	NR/NP	BLQ	Missing
R5	115 (47.52%)	15 (6.20%)	52 (21.49%)	20 (8.26%)	2 (0.83%)	0
X4	0	0	0	0	0	0
Dual Mixed	4 (1.65%)	8 (3.31%)	18 (7.44%)	3 (1.24%)	0	0
NR/NP	2 (0.83%)	0	1 (0.41%)	2 (0.83%)	0	0
BLQ	0	0	0	0	0	0

N = Number of subjects with treatment failure due to insufficient clinical response and who have a tropism assessment at baseline.
R5=CCR5, X4=CXCR4.
NR/NP = Non-Reportable/Non-Phenotypable.
BLQ = Below lower limit of quantification due to HIV-1 RNA viral load less than 500 copies/mL.
Missing = No tropism assessment or subject discontinued from blinded therapy.
The assessment for time of treatment failure is defined as the last on treatment assessment.
Baseline refers to the baseline visit.

Table 13.5.4.2
Maraviroc Summary of Clinical Efficacy
Virology Analysis: Shift Table of Tropism between Baseline and Time of Treatment Failure, Overall and by Treatment
Full Analysis Set - As Treated

Treatment Group: maraviroc QD (N=68)

	Time of Treatment Failure Tropism Status					
Baseline Tropism Status	R5	X4	Dual Mixed	NR/NP	BLQ	Missing
R5	18 (26.47%)	8 (11.76%)	23 (33.82%)	7 (10.29%)	1 (1.47%)	0
X4	0	0	0	0	0	0
Dual Mixed	1 (1.47%)	1 (1.47%)	6 (8.82%)	1 (1.47%)	0	0
NR/NP	0	0	1 (1.47%)	1 (1.47%)	0	0
BLQ	0	0	0	0	0	0

N = Number of subjects with treatment failure due to insufficient clinical response and who have a tropism assessment at baseline.
R5=CCR5, X4=CXCR4.
NR/NP = Non-Reportable/Non-Phenotypable.
BLQ = Below lower limit of quantification due to HIV-1 RNA viral load less than 500 copies/mL.
Missing = No tropism assessment or subject discontinued from blinded therapy.
The assessment for time of treatment failure is defined as the last on treatment assessment.
Baseline refers to the baseline visit.

Table 13.5.4.2
Maraviroc Summary of Clinical Efficacy
Virology Analysis: Shift Table of Tropism between Baseline and Time of Treatment Failure, Overall and by Treatment
Full Analysis Set - As Treated

Treatment Group: maraviroc BID (N=77)

	Time of Treatment Failure Tropism Status					
Baseline Tropism Status	R5	X4	Dual Mixed	NR/NP	BLQ	Missing
R5	17 (22.08%)	7 (9.09%)	25 (32.47%)	8 (10.39%)	1 (1.30%)	0
X4	0	0	0	0	0	0
Dual Mixed	0	6 (7.79%)	11 (14.29%)	2 (2.60%)	0	0
NR/NP	0	0	0	0	0	0
BLQ	0	0	0	0	0	0

N = Number of subjects with treatment failure due to insufficient clinical response and who have a tropism assessment at baseline.
R5=CCR5, X4=CXCR4.
NR/NP = Non-Reportable/Non-Phenotypable.
BLQ = Below lower limit of quantification due to HIV-1 RNA viral load less than 500 copies/mL.
Missing = No tropism assessment or subject discontinued from blinded therapy.
The assessment for time of treatment failure is defined as the last on treatment assessment.
Baseline refers to the baseline visit.

Table 13.5.4.2
Maraviroc Summary of Clinical Efficacy
Virology Analysis: Shift Table of Tropism between Baseline and Time of Treatment Failure, Overall and by Treatment
Full Analysis Set - As Treated

Treatment Group: Placebo (N=97)

	Time of Treatment Failure Tropism Status					
Baseline Tropism Status	R5	X4	Dual Mixed	NR/NP	BLQ	Missing
R5	80 (82.47%)	0	4 (4.12%)	5 (5.15%)	0	0
X4	0	0	0	0	0	0
Dual Mixed	3 (3.09%)	1 (1.03%)	1 (1.03%)	0	0	0
NR/NP	2 (2.06%)	0	0	1 (1.03%)	0	0
BLQ	0	0	0	0	0	0

N = Number of subjects with treatment failure due to insufficient clinical response and who have a tropism assessment at baseline.
R5=CCR5, X4=CXCR4.
NR/NP = Non-Reportable/Non-Phenotypable.
BLQ = Below lower limit of quantification due to HIV-1 RNA viral load less than 500 copies/mL.
Missing = No tropism assessment or subject discontinued from blinded therapy.
The assessment for time of treatment failure is defined as the last on treatment assessment.
Baseline refers to the baseline visit.

Table 13.5.6.1
Maraviroc Summary of Clinical Efficacy
Virology Analysis: Percentage of Subjects who Switched from R5 Tropic to X4 or Dual Mixed between Screening and Baseline
Full Analysis Set - As Treated

	maraviroc QD (N=402)*	maraviroc BID (N=415)*	Placebo (N=206)*
n(%)**	31 (7.7%)	31 (7.5%)	17 (8.3%)
Difference***	14 (-0.5%)	14 (-0.8%)	N/A
95% CI	(-5.1, 4.0)	(-5.3, 3.7)	N/A

* Number of subjects with CCR5 virus at Screening.
** Number of subjects who have switched from CCR5 tropic to CXCR4 or Dual Mixed Tropic.
*** Difference between active treatment and control.
R5=CCR5, X4=CXCR4.
Only subjects with both screening and baseline tropism result are considered.
Baseline refers to the baseline visit.

Table 13.5.6.3
Maraviroc (UK-427,857) Protocol OCS5
Virology Analysis: Percentage of Subjects who Switched from R5 Tropic to X4 or Dual Mixed between Baseline and Time of Treatment Failure
Full Analysis Set - As Treated

	maraviroc QD (N=57)*	maraviroc BID (N=57)*	Placebo (N=89)*
n(%)**	33 (57.9%)	35 (61.4%)	4 (4.5%)
Difference***	29 (53.4%)	31 (56.9%)	N/A
95% CI	(39.9, 66.9)	(43.6, 70.3)	N/A

* Number of subjects with treatment failure due to insufficient clinical response and who have a R5 virus at screening.
** Number of subjects who have switched from CCR5 tropic to CXCR4 or Dual Mixed Tropic.
*** Difference between active treatment and control.
R5=CCR5, X4=CXCR4.
Only subjects with both baseline and on treatment tropism result are considered.
The last on treatment result is used to detect a change in tropism status.
If the last on-treatment assessment is recorded as NR/NP, the previous on-treatment assessment will be used to assess if a switch in tropism occurred.

Maraviroc (UK-427,857) Protocol OCS5
Virology Analysis: Percentage of Subjects who Switched from R5 Tropic to X4 or Dual Mixed between Baseline and Time of Treatment Failure (not using LOCF)
Full Analysis Set - As Treated

	maraviroc QD (N=57)*	maraviroc BID (N=58)*	Placebo (N=89)*
n(%)**	31 (54.4%)	32 (55.2%)	4 (4.5%)
Difference***	27 (49.9%)	28 (50.7%)	N/A
95% CI	(36.3, 63.5)	(37.2, 64.2)	N/A

* Number of subjects with treatment failure due to insufficient clinical response and who have a R5 virus at screening.
** Number of subjects who have switched from CCR5 tropic to CXCR4 or Dual Mixed Tropic.
*** Difference between active treatment and control.
R5=CCR5, X4=CXCR4.
Only subjects with both baseline and on treatment tropism result are considered.
If the last on-treatment assessment is recorded as NR/NP, these subjects will not be included in n(%)**.
The last on-treatment result is used to detect a change in tropism status.
Baseline refers to the baseline visit.

Table 15.1.1
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by PSS at Baseline
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
0	N**	44	49	29
	Mean (s.d.)	-1.277 (1.0375)	-1.310 (1.2961)	-0.134 (0.6843)
	Median (Min, Max)	-0.966 (-3.395, 0.080)	-1.029 (-3.511, 1.317)	-0.039 (-2.817, 0.641)
1	N**	113	114	38
	Mean (s.d.)	-1.835 (1.2207)	-1.883 (1.3322)	-0.402 (0.8223)
	Median (Min, Max)	-2.103 (-3.780, 1.080)	-2.256 (-3.956, 0.780)	-0.158 (-3.428, 0.571)
2	N**	93	107	58
	Mean (s.d.)	-2.062 (1.2504)	-2.252 (1.0727)	-0.899 (1.1016)
	Median (Min, Max)	-2.337 (-4.199, 2.039)	-2.582 (-4.547, -0.030)	-0.508 (-3.181, 0.965)
>=3	N**	152	145	77
	Mean (s.d.)	-2.529 (1.2265)	-2.583 (1.1888)	-2.141 (1.1530)
	Median (Min, Max)	-2.932 (-4.492, 0.822)	-2.852 (-4.504, 1.200)	-2.316 (-4.148, 0.442)
Missing	N**	6	4	5
	Mean (s.d.)	-2.312 (1.2667)	-2.442 (1.3488)	-0.785 (1.1301)
	Median (Min, Max)	-2.579 (-3.705, -0.042)	-2.823 (-3.579, -0.544)	-0.521 (-2.679, 0.341)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Table 15.1.2
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by GSS at Baseline
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
0	N**	88	101	51
	Mean (s.d.)	-1.497 (1.1432)	-1.682 (1.3233)	-0.214 (0.7047)
	Median (Min, Max)	-1.481 (-3.525, 1.080)	-1.862 (-4.547, 1.317)	-0.045 (-2.915, 0.619)
1	N**	145	137	53
	Mean (s.d.)	-2.055 (1.2573)	-2.040 (1.2398)	-0.597 (0.8644)
	Median (Min, Max)	-2.337 (-4.492, 0.597)	-2.372 (-4.504, 0.780)	-0.351 (-3.198, 0.641)
2	N**	63	79	41
	Mean (s.d.)	-2.062 (1.4206)	-2.434 (1.1253)	-1.529 (1.1666)
	Median (Min, Max)	-2.384 (-4.295, 2.039)	-2.658 (-3.978, 0.532)	-1.772 (-3.344, 0.965)
>=3	N**	107	100	57
	Mean (s.d.)	-2.642 (1.0654)	-2.587 (1.2212)	-2.296 (1.1879)
	Median (Min, Max)	-2.967 (-4.428, 0.822)	-2.826 (-4.410, 1.200)	-2.676 (-4.148, 0.442)
Missing	N**	5	2	5
	Mean (s.d.)	-2.257 (1.3714)	-1.867 (1.8719)	-0.785 (1.1301)
	Median (Min, Max)	-2.336 (-3.705, -0.042)	-1.867 (-3.191, -0.544)	-0.521 (-2.679, 0.341)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by Protease Inhibitor Usage in OBT
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
Yes	N**	373	385	193
	Mean (s.d.)	-2.102 (1.2733)	-2.163 (1.2789)	-1.174 (1.2980)
	Median (Min, Max)	-2.405 (-4.428, 2.039)	-2.476 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
No	N**	35	34	14
	Mean (s.d.)	-1.988 (1.2680)	-2.098 (1.2940)	-0.959 (1.2539)
	Median (Min, Max)	-2.113 (-4.492, 0.822)	-2.454 (-3.793, 0.313)	-0.493 (-3.650, 0.381)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Table 15.1.4
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by Tipranavir Usage in OBT
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	408	419	207
	Mean (s.d.)	-2.092 (1.2717)	-2.158 (1.2787)	-1.160 (1.2932)
	Median (Min, Max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
Yes	N**	65	62	29
	Mean (s.d.)	-2.137 (1.1422)	-2.143 (1.2428)	-0.985 (1.3727)
	Median (Min, Max)	-2.439 (-3.977, 0.505)	-2.518 (-4.273, 0.780)	-0.404 (-3.428, 0.965)
No	N**	343	357	178
	Mean (s.d.)	-2.084 (1.2962)	-2.160 (1.2865)	-1.188 (1.2816)
	Median (Min, Max)	-2.382 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.661 (-4.148, 0.619)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Table 15.1.5
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in HIV-1 RNA (log10 copies/mL) at Week 24 by Tropism Status at Baseline
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	406	417	207
	Mean (s.d.)	-2.099 (1.2712)	-2.162 (1.2736)	-1.160 (1.2932)
	Median (Min, Max)	-2.387 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
R5	N**	362	377	187
	Mean (s.d.)	-2.168 (1.2382)	-2.254 (1.2413)	-1.149 (1.2904)
	Median (Min, Max)	-2.484 (-4.492, 2.039)	-2.571 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
X4	N**	0	1	0
	Mean (s.d.)		-2.289 (.)	
	Median (Min, Max)		-2.289 (-2.289, -2.289)	
Dual Mixed	N**	33	33	17
	Mean (s.d.)	-1.510 (1.5400)	-1.073 (1.2551)	-1.450 (1.3745)
	Median (Min, Max)	-1.002 (-4.303, 0.597)	-0.392 (-4.504, 0.326)	-1.176 (-3.398, 0.483)
NR/NP	N**	8	5	3
	Mean (s.d.)	-1.741 (1.0625)	-2.563 (0.5040)	-0.169 (0.3059)
	Median (Min, Max)	-1.705 (-3.326, -0.179)	-2.618 (-3.047, -1.732)	-0.012 (-0.521, 0.027)
BLQ	N**	3	1	0
	Mean (s.d.)	-1.148 (0.3430)	-1.265 (.)	
	Median (Min, Max)	-1.158 (-1.485, -0.799)	-1.265 (-1.265, -1.265)	

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Table 15.2.1
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Percentage of Subjects with HIV-1 RNA < 400 copies/mL at Week 24 by PSS at Baseline
Full Analysis Set - As Treated

	Treatment	N**	n	Percentage (%)
Total Population	maraviroc QD (N=414)*	408	248	60.78
	maraviroc BID (N=426)*	419	273	65.16
	Placebo (N=209)*	207	63	30.43
0	maraviroc QD (N=414)*	44	10	22.73
	maraviroc BID (N=426)*	49	19	38.78
	Placebo (N=209)*	29	2	6.90
1	maraviroc QD (N=414)*	113	66	58.41
	maraviroc BID (N=426)*	114	66	57.89
	Placebo (N=209)*	38	3	7.89
2	maraviroc QD (N=414)*	93	56	60.22
	maraviroc BID (N=426)*	107	75	70.09
	Placebo (N=209)*	58	14	24.14
>=3	maraviroc QD (N=414)*	152	112	73.68
	maraviroc BID (N=426)*	145	110	75.86
	Placebo (N=209)*	77	43	55.84
Missing	maraviroc QD (N=414)*	6	4	66.67
	maraviroc BID (N=426)*	4	3	75.00
	Placebo (N=209)*	5	1	20.00

* This is the number of subjects in the treatment group in the indicated population.
** For each subgroup, this is the number of subjects with a post baseline observation used to calculate the percentage.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.

Table 15.2.2
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Percentage of Subjects with HIV-1 RNA < 400 copies/mL at Week 24 by GSS at Baseline
Full Analysis Set - As Treated

	Treatment	N**	n	Percentage (%)
Total Population	maraviroc QD (N=414)*	408	248	60.78
	maraviroc BID (N=426)*	419	273	65.16
	Placebo (N=209)*	207	63	30.43
0	maraviroc QD (N=414)*	88	34	38.64
	maraviroc BID (N=426)*	101	50	49.50
	Placebo (N=209)*	51	3	5.88
1	maraviroc QD (N=414)*	145	87	60.00
	maraviroc BID (N=426)*	137	83	60.58
	Placebo (N=209)*	53	7	13.21
2	maraviroc QD (N=414)*	63	42	66.67
	maraviroc BID (N=426)*	79	60	75.95
	Placebo (N=209)*	41	18	43.90
>=3	maraviroc QD (N=414)*	107	82	76.64
	maraviroc BID (N=426)*	100	79	79.00
	Placebo (N=209)*	57	34	59.65
Missing	maraviroc QD (N=414)*	5	3	60.00
	maraviroc BID (N=426)*	2	1	50.00
	Placebo (N=209)*	5	1	20.00

* This is the number of subjects in the treatment group in the indicated population.
** For each subgroup, this is the number of subjects with a post baseline observation used to calculate the percentage.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.

Table 15.2.3
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Percentage of Subjects with HIV RNA < 400 copies/mL at Week 24 by CD4 Cell Count at Baseline
Full Analysis Set - As Treated

	Treatment	N**	n	Percentage (%)
Total Population	maraviroc QD (N=414)*	408	248	60.78
	maraviroc BID (N=426)*	419	273	65.16
	Placebo (N=209)*	207	63	30.43
<50 cells/uL	maraviroc QD (N=414)*	85	17	20.00
	maraviroc BID (N=426)*	85	26	30.59
	Placebo (N=209)*	37	2	5.41
50-100 cells/uL	maraviroc QD (N=414)*	51	29	56.86
	maraviroc BID (N=426)*	55	29	52.73
	Placebo (N=209)*	25	6	24.00
101-200 cells/uL	maraviroc QD (N=414)*	93	61	65.59
	maraviroc BID (N=426)*	104	77	74.04
	Placebo (N=209)*	56	19	33.93
201-350 cells/uL	maraviroc QD (N=414)*	116	92	79.31
	maraviroc BID (N=426)*	116	89	76.72
	Placebo (N=209)*	62	23	37.10
>350 cells/uL	maraviroc QD (N=414)*	62	48	77.42
	maraviroc BID (N=426)*	59	52	88.14
	Placebo (N=209)*	26	12	46.15
Missing	maraviroc QD (N=414)*	1	1	100.00
	maraviroc BID (N=426)*	0	0	
	Placebo (N=209)*	1	1	100.00

* This is the number of subjects in the treatment group in the indicated population.
** For each subgroup, this is the number of subjects with a post baseline observation used to calculate the percentage.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline CD4 Cell Count value is calculated as the average of the pre-dose measurements collected at the screening visit and baseline visit.

Table 15.3.1
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Percentage of Subjects with HIV-1 RNA < 50 copies/mL at Week 24 by PSS at Baseline
Full Analysis Set - As Treated

	Treatment	N**	n	Percentage (%)
Total Population	maraviroc QD (N=414)*	408	194	47.55
	maraviroc BID (N=426)*	419	201	47.97
	Placebo (N=209)*	207	51	24.64
0	maraviroc QD (N=414)*	44	8	18.18
	maraviroc BID (N=426)*	49	12	24.49
	Placebo (N=209)*	29	1	3.45
1	maraviroc QD (N=414)*	113	49	43.36
	maraviroc BID (N=426)*	114	50	43.86
	Placebo (N=209)*	38	3	7.89
2	maraviroc QD (N=414)*	93	45	48.39
	maraviroc BID (N=426)*	107	57	53.27
	Placebo (N=209)*	58	10	17.24
>=3	maraviroc QD (N=414)*	152	90	59.21
	maraviroc BID (N=426)*	145	80	55.17
	Placebo (N=209)*	77	37	48.05
Missing	maraviroc QD (N=414)*	6	2	33.33
	maraviroc BID (N=426)*	4	2	50.00
	Placebo (N=209)*	5	0	0.00

* This is the number of subjects in the treatment group in the indicated population.
** For each subgroup, this is the number of subjects with a post baseline observation used to calculate the percentage.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.

Table 15.3.2
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Percentage of Subjects with HIV-1 RNA < 50 copies/mL at Week 24 by GSS at Baseline
Full Analysis Set - As Treated

	Treatment	N**	n	Percentage (%)
Total Population	maraviroc QD (N=414)*	408	194	47.55
	maraviroc BID (N=426)*	419	201	47.97
	Placebo (N=209)*	207	51	24.64
0	maraviroc QD (N=414)*	88	25	28.41
	maraviroc BID (N=426)*	101	33	32.67
	Placebo (N=209)*	51	1	1.96
1	maraviroc QD (N=414)*	145	68	46.90
	maraviroc BID (N=426)*	137	64	46.72
	Placebo (N=209)*	53	6	11.32
2	maraviroc QD (N=414)*	63	34	53.97
	maraviroc BID (N=426)*	79	44	55.70
	Placebo (N=209)*	41	15	36.59
>=3	maraviroc QD (N=414)*	107	66	61.68
	maraviroc BID (N=426)*	100	59	59.00
	Placebo (N=209)*	57	29	50.88
Missing	maraviroc QD (N=414)*	5	1	20.00
	maraviroc BID (N=426)*	2	1	50.00
	Placebo (N=209)*	5	0	0.00

* This is the number of subjects in the treatment group in the indicated population.
** For each subgroup, this is the number of subjects with a post baseline observation used to calculate the percentage.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.

Table 15.3.3
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Percentage of Subjects with HIV-1 RNA < 50 copies/mL at Week 24 by CD4 Cell Count at Baseline
Full Analysis Set - As Treated

	Treatment	N**	n	Percentage (%)
Total Population	maraviroc QD (N=414)*	408	194	47.55
	maraviroc BID (N=426)*	419	201	47.97
	Placebo (N=209)*	207	51	24.64
<50 cells/uL	maraviroc QD (N=414)*	85	9	10.59
	maraviroc BID (N=426)*	85	17	20.00
	Placebo (N=209)*	37	1	2.70
50-100 cells/uL	maraviroc QD (N=414)*	51	23	45.10
	maraviroc BID (N=426)*	55	22	40.00
	Placebo (N=209)*	25	4	16.00
101-200 cells/uL	maraviroc QD (N=414)*	93	47	50.54
	maraviroc BID (N=426)*	104	51	49.04
	Placebo (N=209)*	56	16	28.57
201-350 cells/uL	maraviroc QD (N=414)*	116	74	63.79
	maraviroc BID (N=426)*	116	73	62.93
	Placebo (N=209)*	62	18	29.03
>350 cells/uL	maraviroc QD (N=414)*	62	41	66.13
	maraviroc BID (N=426)*	59	38	64.41
	Placebo (N=209)*	26	11	42.31
Missing	maraviroc QD (N=414)*	1	0	0.00
	maraviroc BID (N=426)*	0	0	
	Placebo (N=209)*	1	1	100.00

* This is the number of subjects in the treatment group in the indicated population.
** For each subgroup, this is the number of subjects with a post baseline observation used to calculate the percentage.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline CD4 Cell Count value is calculated as the average of the pre-dose measurements collected at the screening visit and baseline visit.

Table 15.4.1
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in CD4 Cell Counts(cells/uL) at Week 24 by CD4 Cell Count at Baseline
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	407	418	206
	Mean (s.d.)	108.72 (120.694)	105.81 (99.898)	56.54 (96.302)
	Median (Min, Max)	86.00 (-263.50, 834.50)	88.25 (-277.00, 561.00)	30.75 (-301.00, 452.50)
<50 cells/uL	N**	85	85	37
	Mean (s.d.)	73.71 (82.118)	73.58 (75.480)	25.34 (48.937)
	Median (Min, Max)	45.00 (-31.00, 431.00)	59.00 (-29.00, 307.00)	6.50 (-13.00, 172.00)
50-100 cells/uL	N**	51	55	25
	Mean (s.d.)	102.86 (69.968)	111.07 (74.453)	42.94 (61.322)
	Median (Min, Max)	86.00 (-11.50, 270.00)	89.00 (8.00, 322.00)	25.50 (-47.50, 191.50)
101-200 cells/uL	N**	93	103	56
	Mean (s.d.)	111.83 (93.657)	115.81 (95.048)	47.43 (76.614)
	Median (Min, Max)	90.00 (-52.00, 476.50)	103.50 (-77.00, 561.00)	31.50 (-65.00, 265.00)
201-350 cells/uL	N**	116	116	62
	Mean (s.d.)	120.81 (137.033)	110.30 (103.392)	73.10 (113.683)
	Median (Min, Max)	102.75 (-193.00, 588.00)	102.25 (-174.00, 428.00)	58.00 (-184.50, 440.50)
>350 cells/uL	N**	62	59	26
	Mean (s.d.)	134.25 (179.817)	121.03 (138.754)	94.17 (143.443)
	Median (Min, Max)	99.25 (-263.50, 834.50)	109.50 (-277.00, 536.50)	95.50 (-301.00, 452.50)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit and baseline visit.
The baseline CD4 Cell Count value is calculated as the average of the pre-dose measurements collected at the screening visit and baseline visit.

Table 15.4.2
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in CD4 Cell Counts (cell/uL) at Week 24 by Tropism Status at Baseline and Failure
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	68	77	97
	Mean (s.d.)	49.35 (72.038)	71.06 (86.130)	13.78 (69.259)
	Median (Min, Max)	32.75 (-193.00, 263.50)	47.00 (-131.00, 319.50)	3.00 (-301.00, 187.00)
R5 -> R5	N**	18	17	80
	Mean (s.d.)	60.78 (106.322)	137.56 (85.494)	14.53 (67.232)
	Median (Min, Max)	35.25 (-193.00, 263.50)	164.50 (0.50, 319.50)	2.50 (-301.00, 187.00)
R5 -> DM/X4	N**	31	32	4
	Mean (s.d.)	37.00 (42.787)	56.02 (81.880)	67.13 (78.529)
	Median (Min, Max)	25.00 (-49.00, 122.00)	36.25 (-131.00, 317.00)	54.25 (-11.00, 171.00)
R5 -> NR/NP/BLQ/missing	N**	8	9	5
	Mean (s.d.)	65.44 (98.951)	94.94 (79.642)	-42.00 (84.565)
	Median (Min, Max)	29.75 (-63.50, 205.50)	123.50 (-1.00, 227.50)	-24.00 (-184.50, 41.50)
non-R5 -> all	N**	11	19	8
	Mean (s.d.)	53.77 (47.638)	25.58 (58.412)	14.50 (64.704)
	Median (Min, Max)	63.00 (-31.00, 116.00)	15.50 (-93.50, 178.00)	13.25 (-76.00, 149.00)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit and baseline visit.

Table 15.5.1
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in CD8 Cell Counts (cell/uL) at Week 24 by Enfuvirtide Usage in OBT
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	407	418	206
	Mean (s.d.)	295.87 (585.457)	274.08 (451.888)	51.67 (425.222)
	Median (Min, Max)	211.00 (-994.00, 6247.50)	208.50 (-2885.00, 2110.50)	9.25 (-1910.50, 2379.00)
Yes	N**	165	180	89
	Mean (s.d.)	361.56 (707.272)	343.36 (438.682)	35.80 (529.772)
	Median (Min, Max)	256.50 (-901.50, 6247.50)	276.75 (-572.50, 2110.50)	2.00 (-1910.50, 2379.00)
No	N**	242	238	117
	Mean (s.d.)	251.08 (481.718)	221.69 (455.571)	63.74 (326.019)
	Median (Min, Max)	191.75 (-994.00, 2450.00)	169.50 (-2885.00, 1924.50)	21.00 (-684.50, 1134.00)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit and baseline visit.

Table 15.5.2
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in CD8 Cell Counts(cells/ uL) at Week 24 by CD4 Cell Count at Baseline
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	407	418	206
	Mean (s.d.)	295.87 (585.457)	274.08 (451.888)	51.67 (425.222)
	Median (Min, Max)	211.00 (-994.00, 6247.50)	208.50 (-2885.00, 2110.50)	9.25 (-1910.50, 2379.00)
<50 cells/uL	N**	85	85	37
	Mean (s.d.)	446.65 (510.026)	381.36 (381.248)	154.12 (362.083)
	Median (Min, Max)	345.50 (-493.50, 2185.00)	291.00 (-201.00, 1376.50)	28.00 (-631.50, 1176.00)
50-100 cells/uL	N**	51	55	25
	Mean (s.d.)	441.51 (523.541)	386.93 (453.061)	28.58 (259.818)
	Median (Min, Max)	288.00 (-403.50, 2131.00)	334.50 (-398.00, 2110.50)	5.50 (-394.00, 639.00)
101-200 cells/uL	N**	93	103	56
	Mean (s.d.)	357.97 (780.740)	349.41 (422.839)	80.83 (315.935)
	Median (Min, Max)	263.00 (-728.00, 6247.50)	255.50 (-378.50, 1924.50)	45.25 (-495.00, 1054.00)
201-350 cells/uL	N**	116	116	62
	Mean (s.d.)	161.05 (458.335)	202.91 (425.493)	-14.16 (580.333)
	Median (Min, Max)	152.75 (-917.00, 1958.00)	128.50 (-573.00, 1650.50)	-32.50 (-1910.50, 2379.00)
>350 cells/uL	N**	62	59	26
	Mean (s.d.)	128.44 (514.522)	22.77 (528.901)	22.23 (397.621)
	Median (Min, Max)	129.25 (-994.00, 1672.50)	53.00 (-2885.00, 1449.00)	-46.25 (-684.50, 1074.00)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit and baseline visit.

Table 15.5.3
Maraviroc Summary of Clinical Efficacy
Subgroup Analyses: Summary of Change from Baseline in CD8 Cell Counts (cell/uL) at Week 24 by HIV-1 RNA at Screening
Full Analysis Set - As Treated

		maraviroc QD (N=414)*	maraviroc BID (N=426)*	Placebo (N=209)*
Total Population	N**	407	418	206
	Mean (s.d.)	295.87 (585.457)	274.08 (451.888)	51.67 (425.222)
	Median (Min, Max)	211.00 (-994.00, 6247.50)	208.50 (-2885.00, 2110.50)	9.25 (-1910.50, 2379.00)
<100,000 copies/mL	N**	238	242	122
	Mean (s.d.)	182.22 (388.353)	242.98 (381.280)	45.51 (457.758)
	Median (Min, Max)	153.75 (-917.00, 1432.00)	164.00 (-568.50, 1612.50)	13.75 (-1910.50, 2379.00)
>=100,000 copies/mL	N**	169	176	84
	Mean (s.d.)	455.91 (755.986)	316.84 (532.172)	60.61 (375.464)
	Median (Min, Max)	294.50 (-994.00, 6247.50)	271.75 (-2885.00, 2110.50)	8.50 (-1527.00, 1147.50)

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects contributing to the summary statistics.
LOCF has been used to impute missing values. Blinded therapy values only have been carried forward.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Change from Baseline through Week 24 in Log10 Transformed HIV-1 RNA (Log10 copies/mL) - Subjects Receiving a PI and/or Delavirdine in OBT
Full Analysis Set - As Randomized

		Change from Baseline through Week 24			Treatment difference maraviroc - Placebo	
Treatment	N	Raw Mean (s.e.)	Median	Adjusted Mean (s.e.)	Estimate (s.e.)	97.5% CI
maraviroc QD	320	-1.869 (0.0798)	-2.274	-1.889 (0.0796)	-0.891 (0.1332)	(-1.191, -0.592)
maraviroc BID	335	-1.979 (0.0780)	-2.437	-1.993 (0.0778)	-0.996 (0.1320)	(-1.292, -0.699)
Placebo	171	-0.990 (0.1010)	0.000	-0.997 (0.1080)		

Missing values have been imputed as the baseline value for subjects who discontinued from blinded therapy.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Change from Baseline through Week 24 in Log10 Transformed HIV-1 RNA (Log10 copies/mL) - Subjects Receiving a PI and/or Delavirdine in OBT
Full Analysis Set - As Randomized

		Change from Baseline through Week 24			Treatment difference maraviroc (BID - QD)	
Treatment	N	Raw Mean (s.e.)	Median	Adjusted Mean (s.e.)	Estimate (s.e.)	95% CI
maraviroc BID	335	-1.979 (0.0780)	-2.437	-1.993 (0.0778)	-0.104 (0.1098)	(-0.320, 0.112)
maraviroc QD	320	-1.869 (0.0798)	-2.274	-1.889 (0.0796)		

Missing values have been imputed as the baseline value for subjects who discontinued from blinded therapy.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Change from Baseline through Week 24 in Log10 Transformed HIV-1 RNA (Log10 copies/mL) - Subjects Receiving a PI and/or Delavirdine in OBT
Full Analysis Set - As Treated

		Change from Baseline through Week 24			Treatment difference maraviroc - Placebo	
Treatment	N	Raw Mean (s.e.)	Median	Adjusted Mean (s.e.)	Estimate (s.e.)	97.5% CI
maraviroc QD	320	-1.869 (0.0798)	-2.274	-1.889 (0.0797)	-0.885 (0.1333)	(-1.184, -0.585)
maraviroc BID	335	-1.974 (0.0782)	-2.437	-1.990 (0.0779)	-0.985 (0.1322)	(-1.282, -0.688)
Placebo	171	-0.998 (0.1009)	0.000	-1.005 (0.1080)		

Missing values have been imputed as the baseline value for subjects who discontinued from blinded therapy.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Summary of Statistical Analysis: Change from Baseline through Week 24 in Log10 Transformed HIV-1 RNA (Log10 copies/mL) - Subjects Receiving a PI and/or Delavirdine in OBT
Full Analysis Set - As Treated

		Change from Baseline through Week 24			Treatment difference maraviroc (BID - QD)	
Treatment	N	Raw Mean (s.e.)	Median	Adjusted Mean (s.e.)	Estimate (s.e.)	95% CI
maraviroc BID	335	-1.974 (0.0782)	-2.437	-1.990 (0.0779)	-0.100 (0.1099)	(-0.316, 0.116)
maraviroc QD	320	-1.869 (0.0798)	-2.274	-1.889 (0.0797)		

Missing values have been imputed as the baseline value for subjects who discontinued from blinded therapy.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

	maraviroc QD N=414	maraviroc BID N=426	Placebo N=209
	n (%)	n (%)	n (%)
Screening Viral Load			
<100,000 copies/mL	239 (57.7)	247 (58.0)	125 (59.8)
>=100,000 copies/mL	175 (42.3)	179 (42.0)	84 (40.2)

Table 15.8.2
Maraviroc Summary of Clinical Efficacy
Summary of CD4 Cell Count at Baseline

	maraviroc QD N=414		maraviroc BID N=426		Placebo N=209	
	n	(%)	n	(%)	n	(%)
Baseline CD4 Cell Count						
<=200 cells/uL	235	(56.8)	250	(58.7)	118	(56.5)
>200 cells/uL	178	(43.0)	176	(41.3)	90	(43.1)
Missing	1	(0.2)	0		1	(0.5)

Each individual subjects baseline value is calculated as the average of the pre-dose measurements collected at the screening visit and baseline visit.

Maraviroc Summary of Clinical Efficacy
Summary of Resistance Associated PI, NNRTI and NRTI Mutations at Screening
Full Analysis Set - As Treated

	Treatment	N**	Median	Minimum	Maximum
PI Resistance Mutations at Screening	maraviroc QD (N=414)*	412	10	0	18
	maraviroc BID (N=426)*	425	10	0	17
	Placebo (N=209)*	206	10	0	17
NNRTI Resistance Mutations at Screening	maraviroc QD (N=414)*	412	1	0	5
	maraviroc BID (N=426)*	425	1	0	5
	Placebo (N=209)*	206	1	0	5
NRTI Resistance Mutations at Screening	maraviroc QD (N=414)*	412	6	0	11
	maraviroc BID (N=426)*	425	6	0	11
	Placebo (N=209)*	206	6	0	13

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects with a valid assessment at screening that have contributed to the summary statistics.

Maraviroc Summary of Clinical Efficacy
Summary of Subjects with Enfuvirtide Resistance Mutations at Screening
Full Analysis Set - As Treated

	Treatment	N**	n	Percentage (%)
Subjects without Enfuvirtide Mutations at Screening	maraviroc QD (N=414)*	411	333	81.02
	maraviroc BID (N=426)*	424	334	78.77
	Placebo (N=209)*	209	164	78.47
Subjects with Enfuvirtide Mutations at Screening	maraviroc QD (N=414)*	411	78	18.98
	maraviroc BID (N=426)*	424	90	21.23
	Placebo (N=209)*	209	45	21.53

* This is the number of subjects in the treatment group in the indicated population.
** This is the number of subjects with a valid assessment at screening used to calculate the percentages.

Maraviroc Summary of Clinical Efficacy
Statistical Analysis of Change from Baseline through Week 24 in Log10 Transformed HIV-1 RNA (Log10 copies/mL) -
Sensitivity Analysis (Treatment Failure Classification, No Change)
Full Analysis Set - As Treated

		Change from Baseline through Week 24			Treatment difference maraviroc - Placebo		
Treatment	N	Raw Mean (s.e.)	Median	Adjusted Mean (s.e.)	Estimate (s.e.)	97.5% CI	P-value
maraviroc QD	414	-1.856 (0.0695)	-2.274	-1.862 (0.0696)	-0.901 (0.1189)	(-1.168, -0.634)	<0.0001
maraviroc BID	426	-1.953 (0.0691)	-2.424	-1.956 (0.0685)	-0.995 (0.1183)	(-1.260, -0.729)	<0.0001
Placebo	209	-0.962 (0.0917)	0.000	-0.961 (0.0974)			

		Change from Baseline through Week 24			Treatment difference maraviroc (BID - QD)	
Treatment	N	Raw Mean (s.e.)	Median	Adjusted Mean (s.e.)	Estimate (s.e.)	95% CI
maraviroc BID	426	-1.953 (0.0691)	-2.424	-1.956 (0.0685)	-0.094 (0.0967)	(-0.284, 0.096)
maraviroc QD	414	-1.856 (0.0695)	-2.274	-1.862 (0.0696)		

Significance of Main Effect Terms

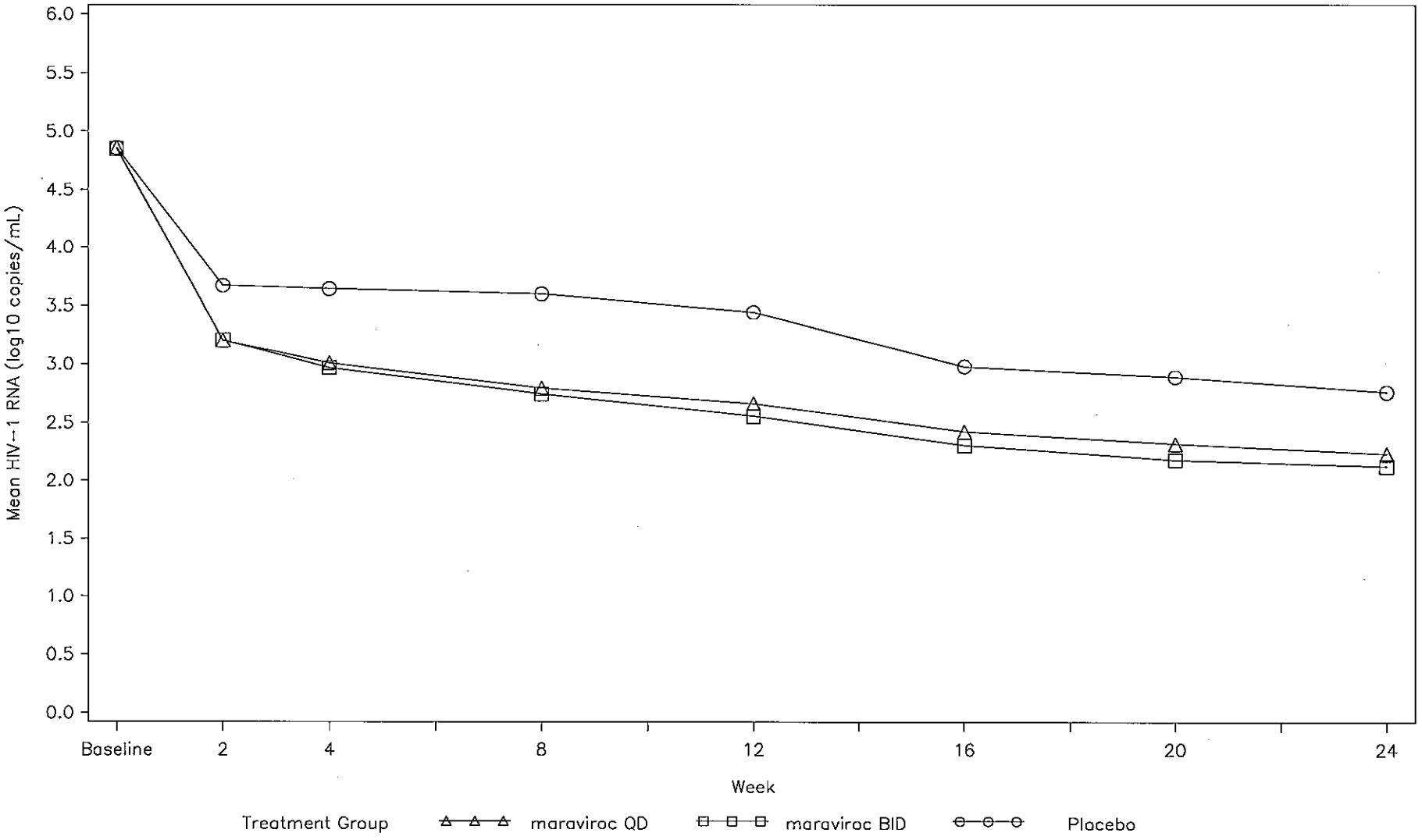
Parameter	df	Type III SS	Mean Square	F-value	P-value
Treatment	2	152.27	76.13	38.79	<0.0001
Screening HIV-1 RNA	1	3.18	3.18	1.62	0.2030
Enfuvirtide use	1	6.01	6.01	3.06	0.0805
Residual Error	1044	2048.90	1.96		

Parameter Estimate for the Main Effect Terms

Parameter	Level	df	Parameter Estimate	s.e.	T-value	P-value
Intercept		1044	-0.827	0.1191	-6.95	<0.0001
Treatment	maraviroc QD	1044	-0.901	0.1189	-7.57	<0.0001
	maraviroc BID	1044	-0.995	0.1183	-8.41	<0.0001
	Placebo		0.000			
Screening HIV-1 RNA	<100,000 copies/mL	1044	-0.113	0.0884	-1.27	0.2030
	>=100,000 copies/mL		0.000			
Enfuvirtide use	Yes	1044	-0.155	0.0883	-1.75	0.0805
	No		0.000			

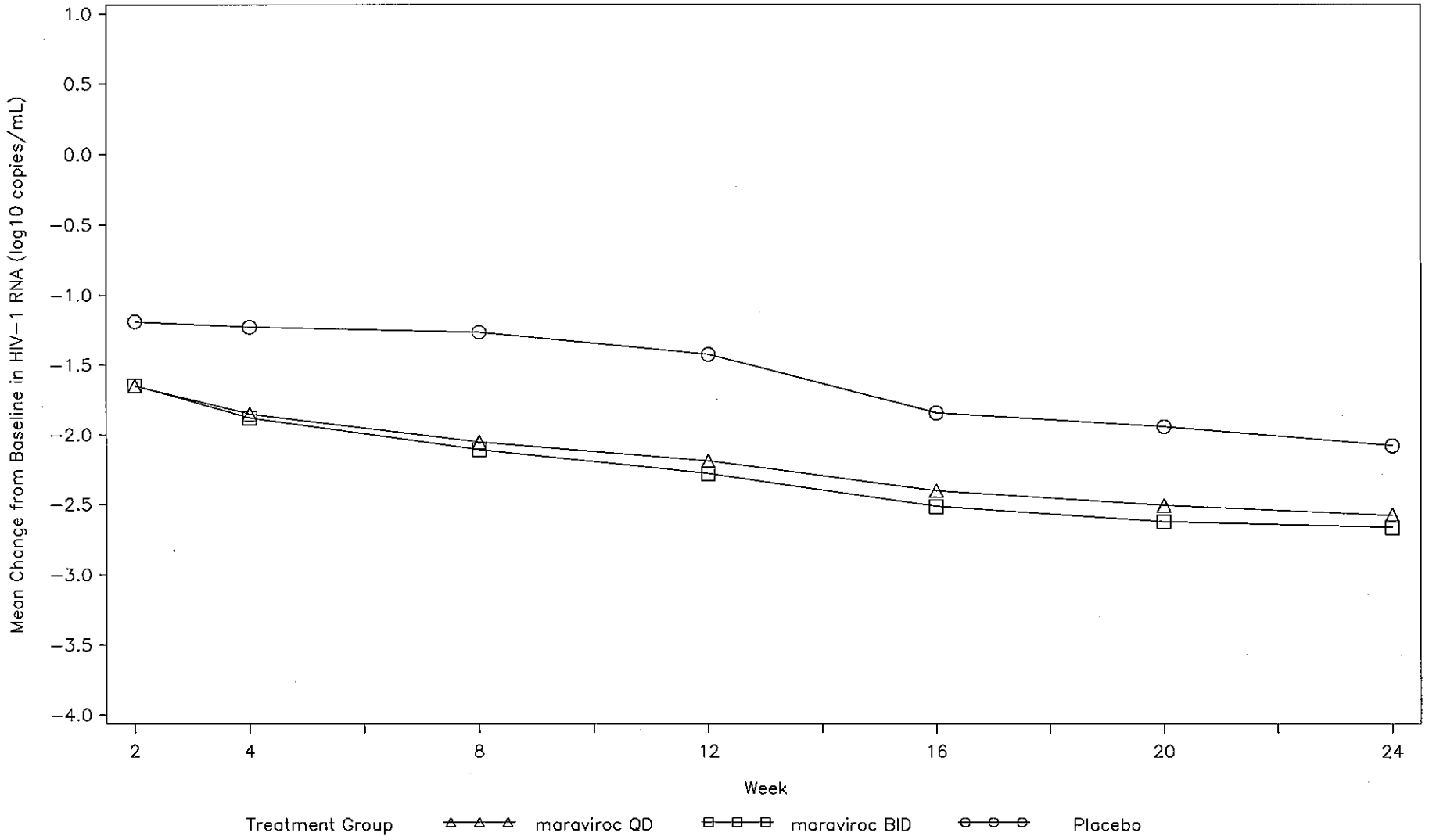
Missing values have been imputed as the baseline value for subjects who discontinued from blinded therapy or those patients who have met at least 1 of the treatment failure criteria but have not been discontinued by the investigator.
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit,randomization visit and baseline visit.

Figure 14.1.1
Maraviroc Summary of Clinical Efficacy
Line Plot of Mean HIV-1 RNA (log10 copies/mL) by Visit
Full Analysis Set – As Treated



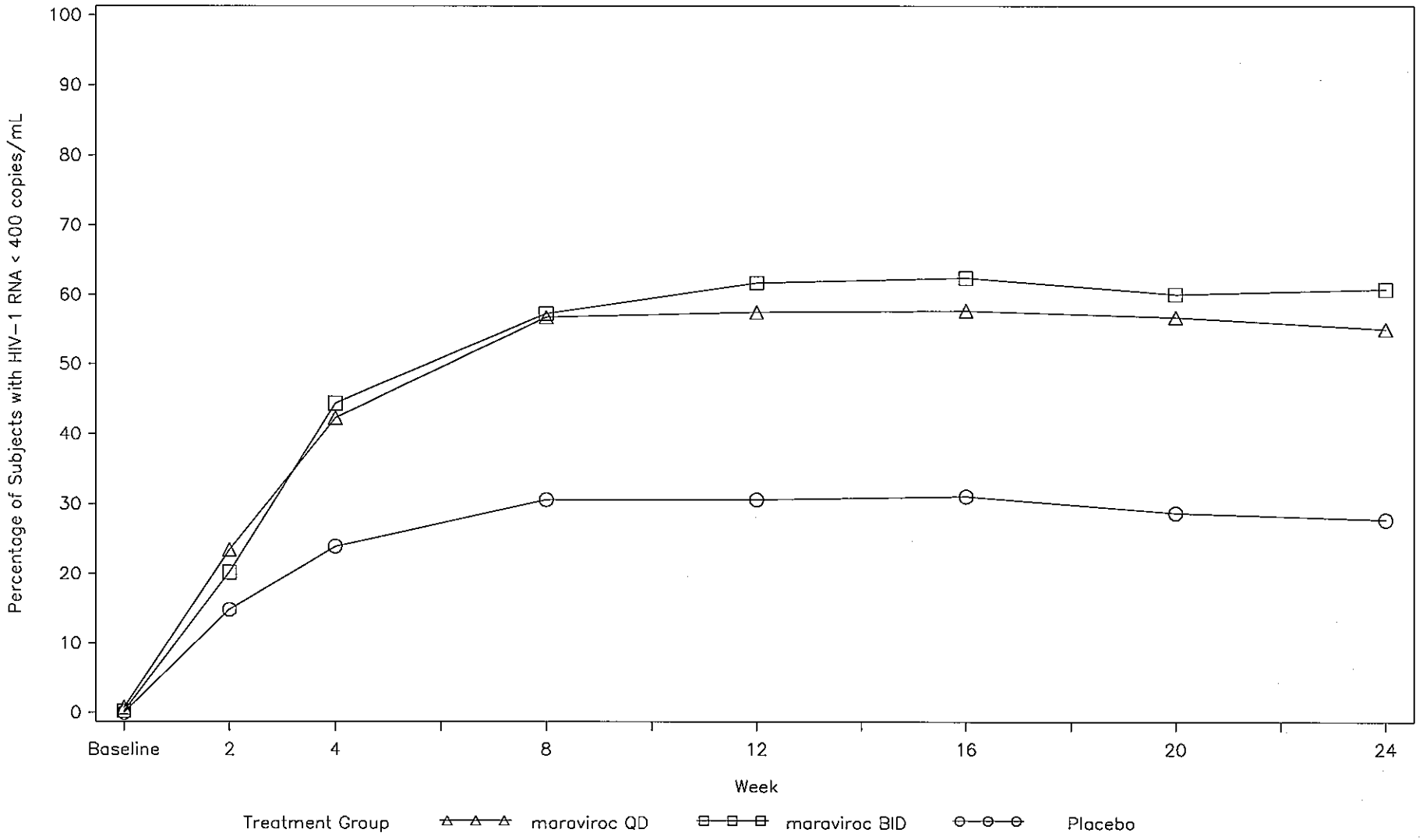
Each individual subjects baseline value is calculated as the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.

Figure 14.2.1
Maraviroc Summary of Clinical Efficacy
Line Plot of Mean Change from Baseline in HIV−1 RNA (log10 copies/mL) by Visit
Full Analysis Set − As Treated



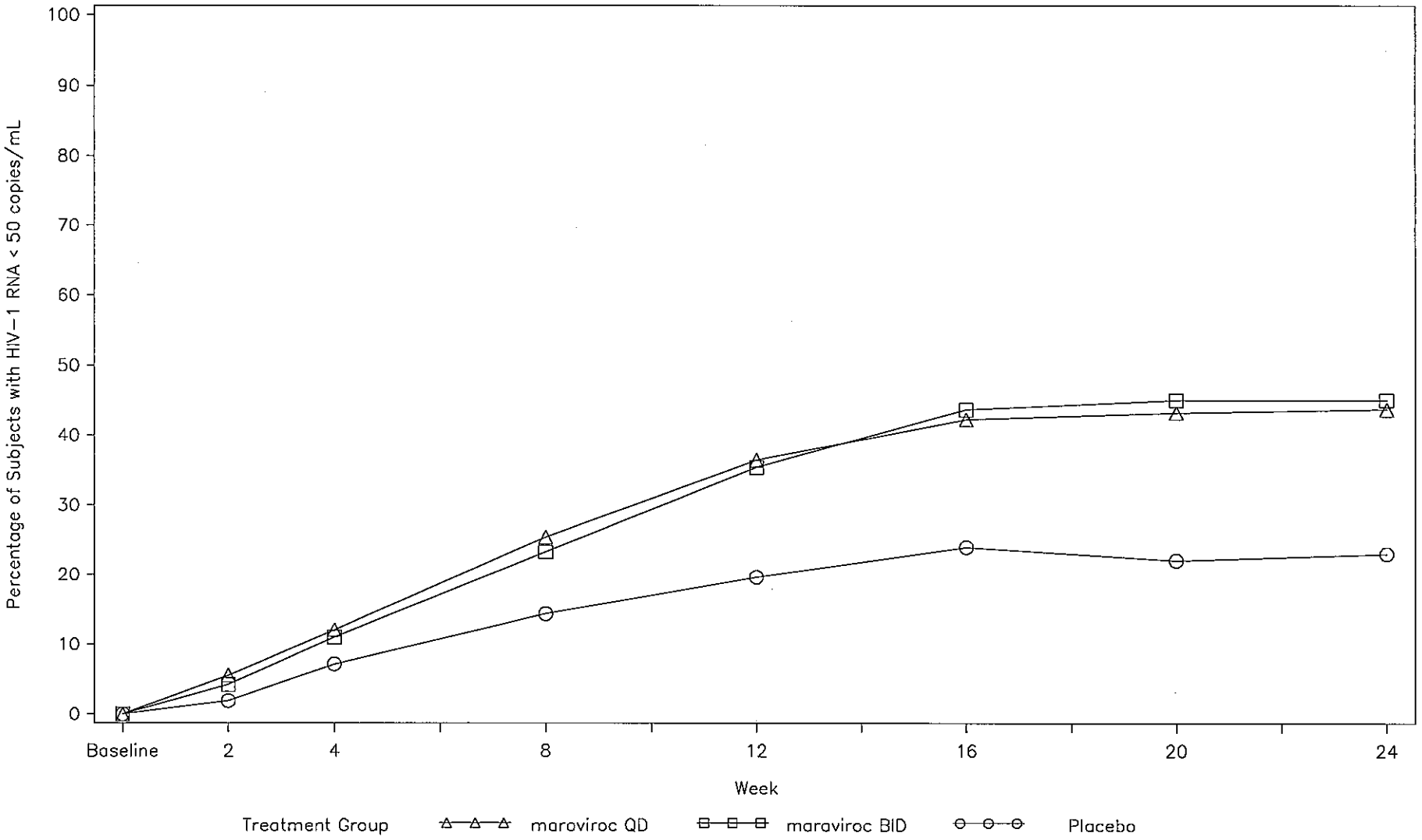
The baseline value used in the calculation of change from baseline is the average of the pre−dose measurements collected at the screening visit, randomization visit and baseline visit.

Figure 14.3.1
Maraviroc Summary of Clinical Efficacy
Percentage of Subjects with HIV−1 RNA < 400 copies/mL by Visit
Full Analysis Set − As Treated



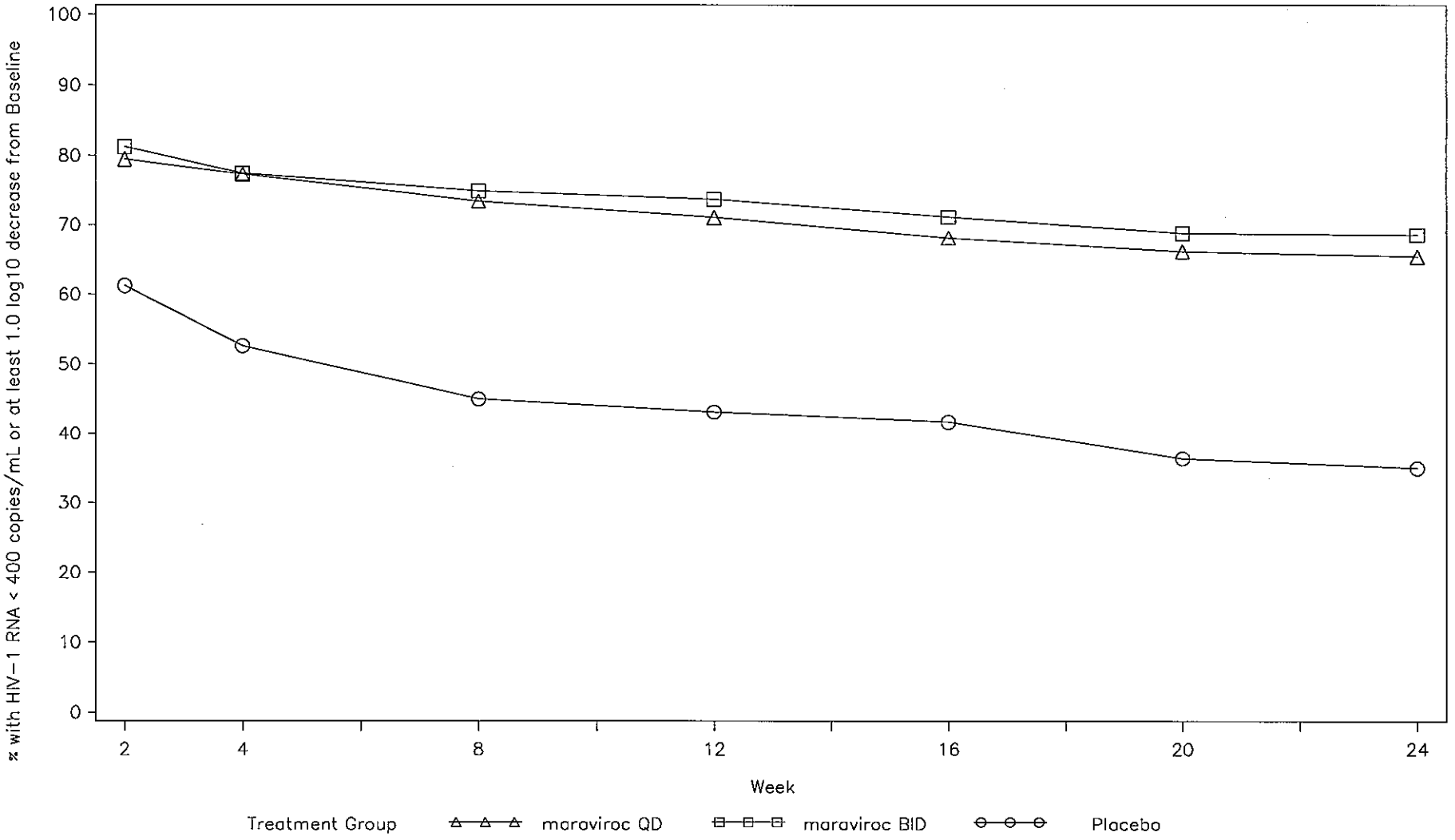
Baseline refers to the Baseline visit.
Discontinuations and failures are included at all time points.

Figure 14.4.1
Maraviroc Summary of Clinical Efficacy
Percentage of Subjects with HIV−1 RNA < 50 copies/mL by Visit
Full Analysis Set − As Treated



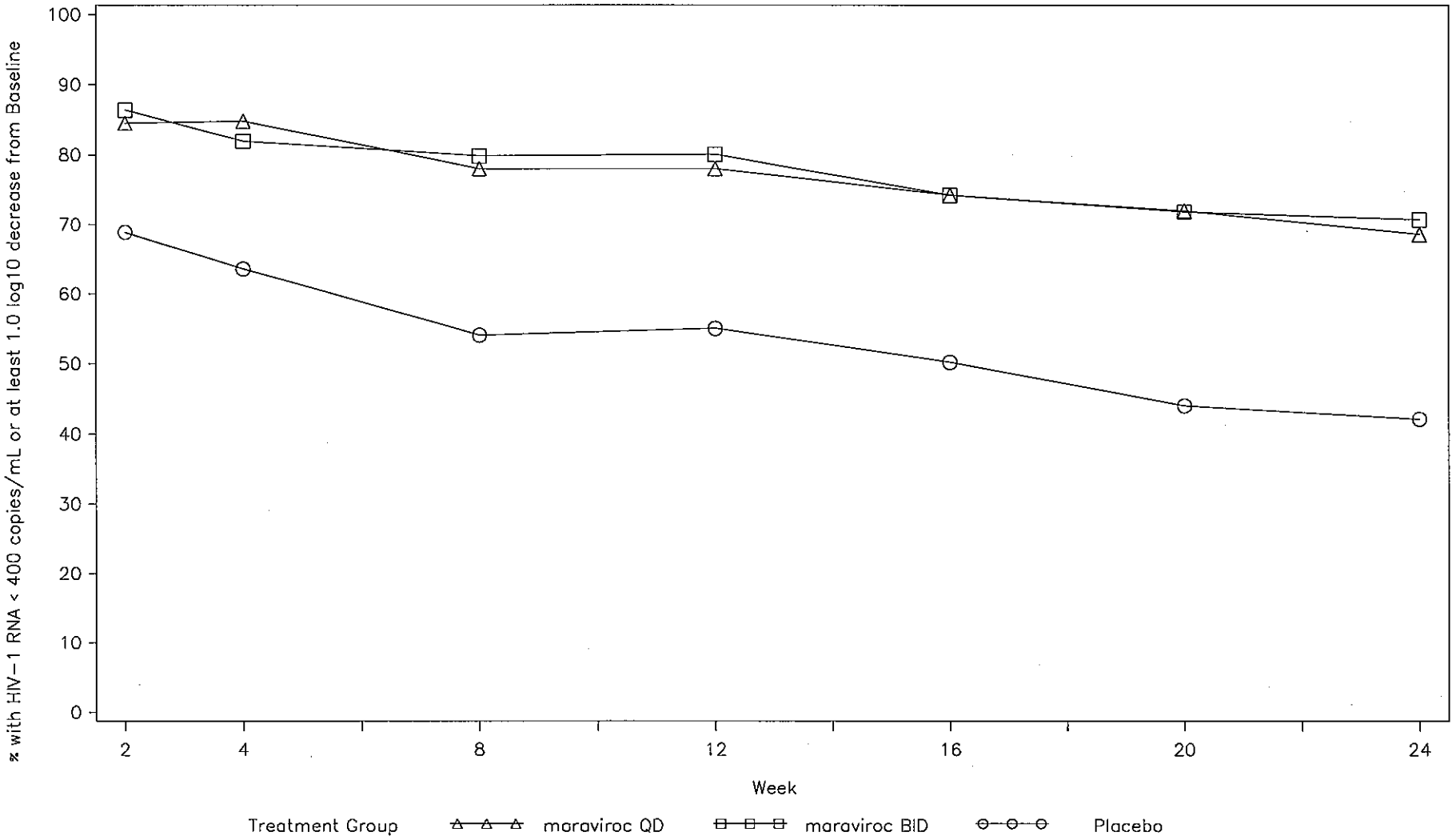
Baseline refers to the Baseline visit.
Discontinuations and failures are included at all time points.

Figure 14.5
Maraviroc Summary of Clinical Efficacy
Percentage of Subjects with HIV−1 RNA < 400 copies/mL or at least 1.0 log10 decrease from Baseline by Visit
Full Analysis Set − As Treated



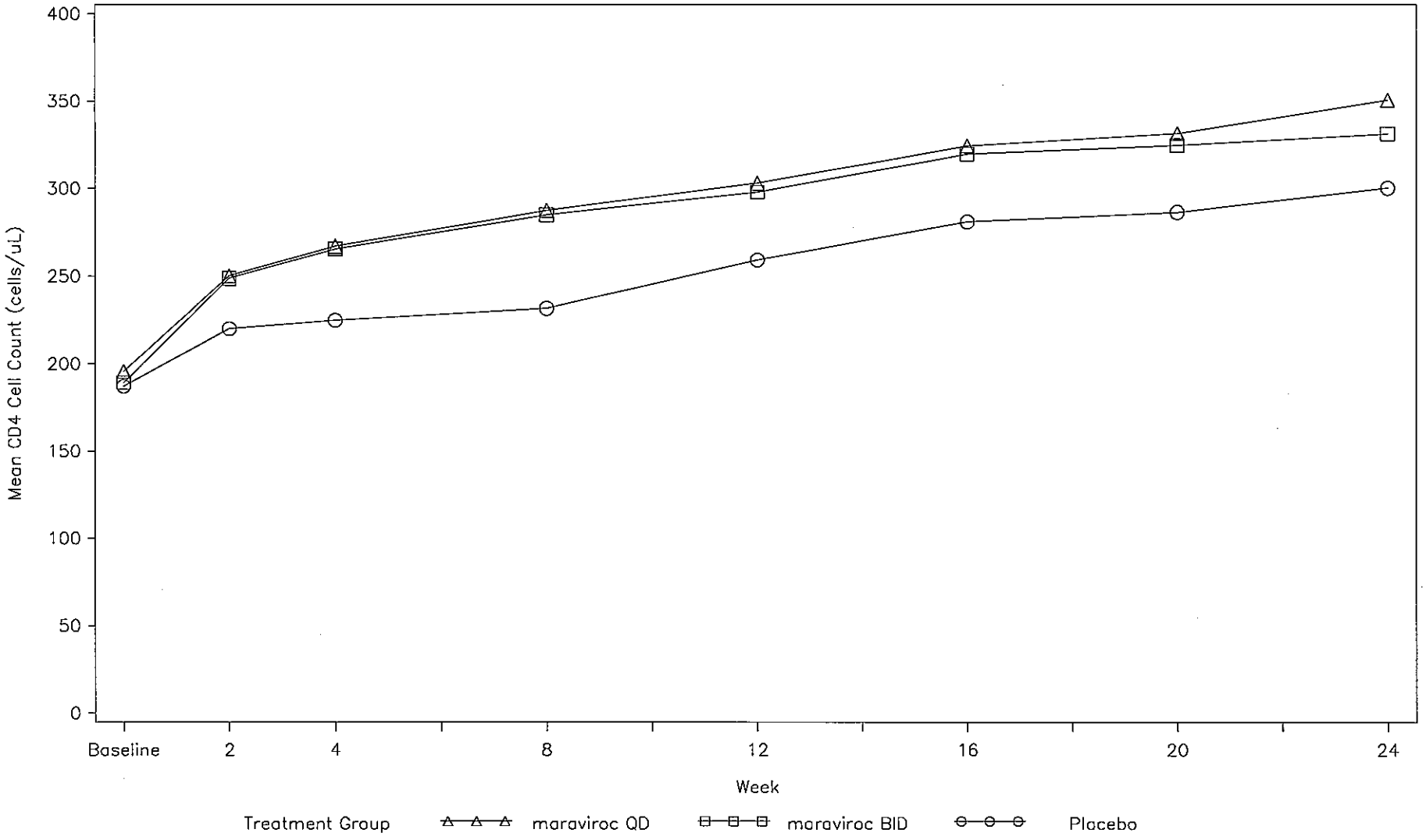
The baseline value used in the calculation of change from baseline is the average of the pre−dose measurements collected at the screening visit, randomization visit and baseline visit.
Discontinuations and failures are included at all time points.

Figure 14.6
Maraviroc Summary of Clinical Efficacy
Percentage of Subjects with HIV-1 RNA < 400 copies/mL or at least 0.5 log10 decrease from Baseline by Visit
Full Analysis Set – As Treated



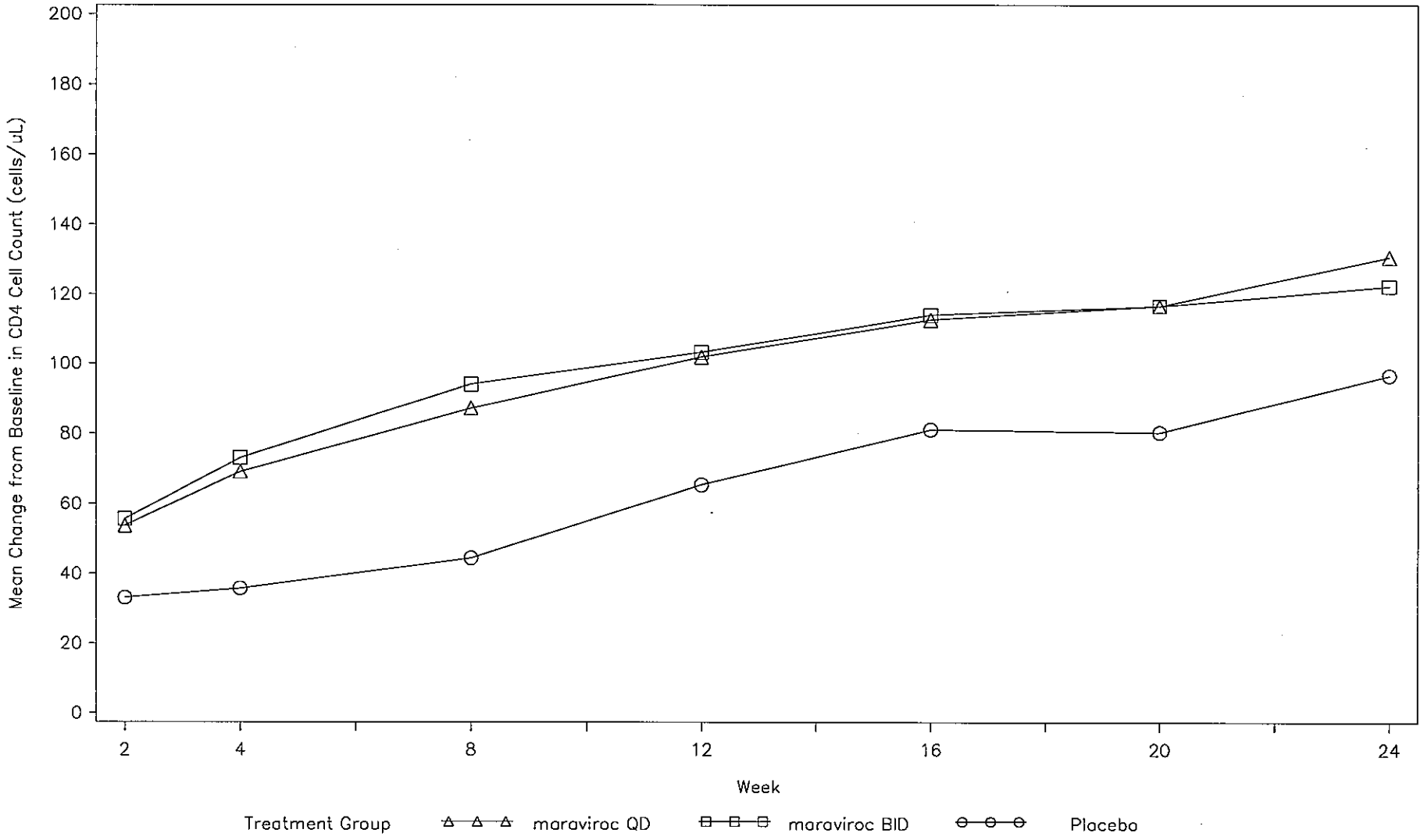
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit, randomization visit and baseline visit.
Discontinuations and failures are included at all time points.

Figure 14.7
Maraviroc Summary of Clinical Efficacy
Line Plot of Mean CD4 Cell Count (cells/uL) by Visit
Full Analysis Set – As Treated



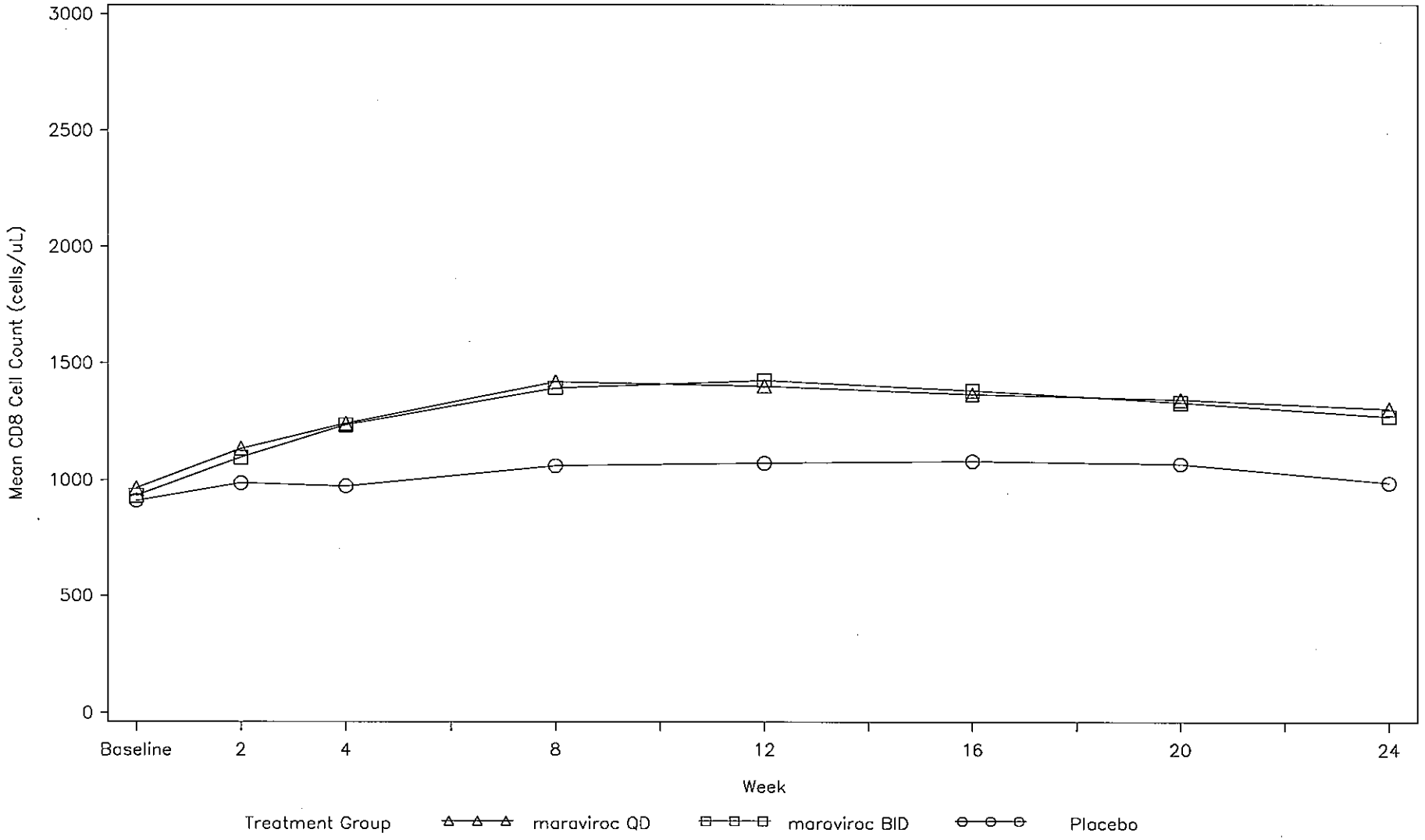
Each individual subjects baseline value is calculated as the average of the pre-dose measurements collected at the screening visit and baseline visit.

Figure 14.8
Maraviroc Summary of Clinical Efficacy
Line Plot of Mean Change from Baseline in CD4 Cell Count (cells/uL) by Visit
Full Analysis Set – As Treated



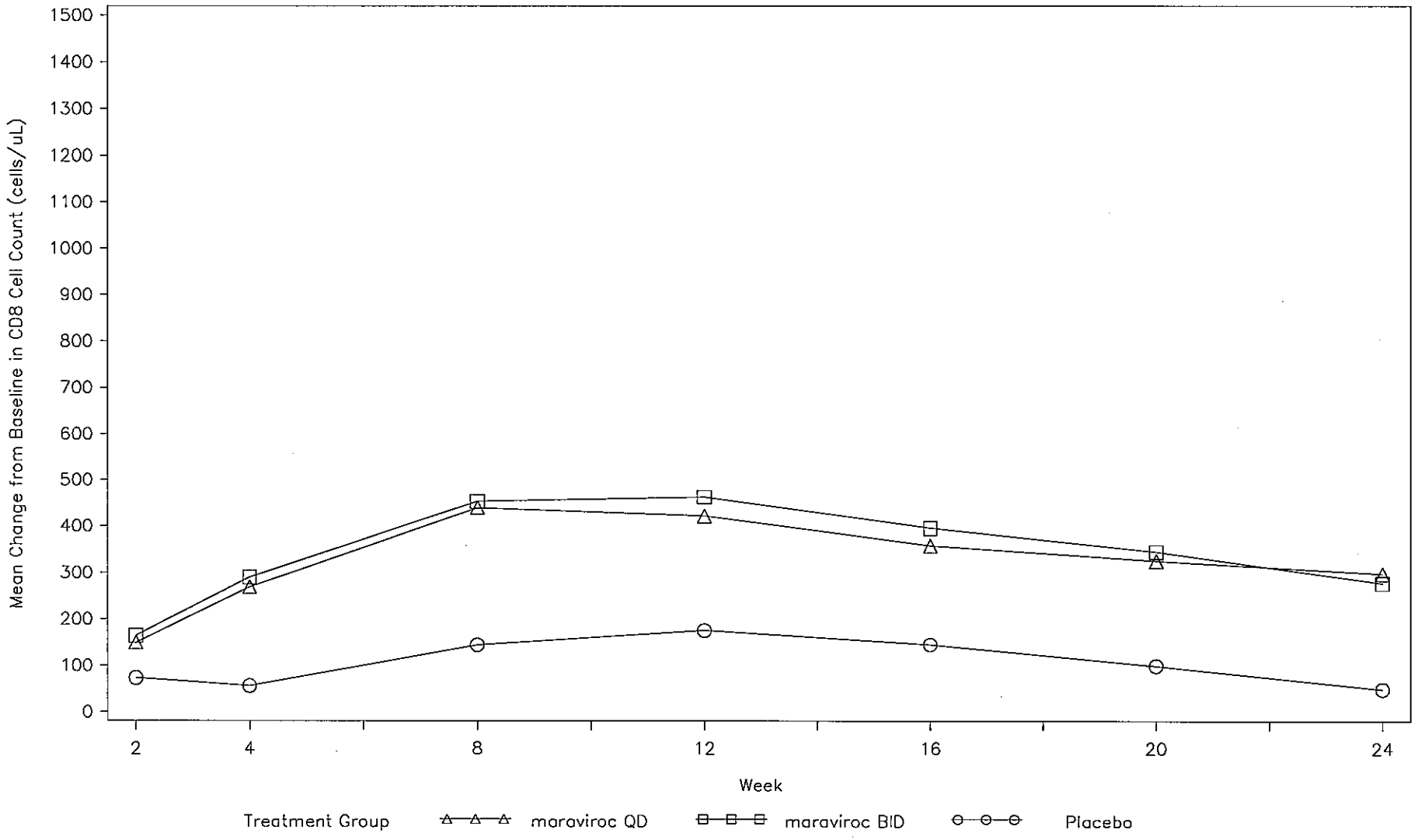
The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit and baseline visit.

Figure 14.9
Maraviroc Summary of Clinical Efficacy
Line Plot of Mean CD8 Cell Count (cells/uL) by Visit
Full Analysis Set – As Treated



Each individual subjects baseline value is calculated as the average of the pre-dose measurements collected at the screening visit and baseline visit.

Figure 14.10
Maraviroc Summary of Clinical Efficacy
Line Plot of Mean Change from Baseline in CD8 Cell Count (cells/uL) by Visit
Full Analysis Set -- As Treated



The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening visit and baseline visit.

Figure 14.11.1
Maraviroc Summary of Clinical Efficacy
Kaplan Meier Plot of Time to Discontinuation
Full Analysis Set – As Treated

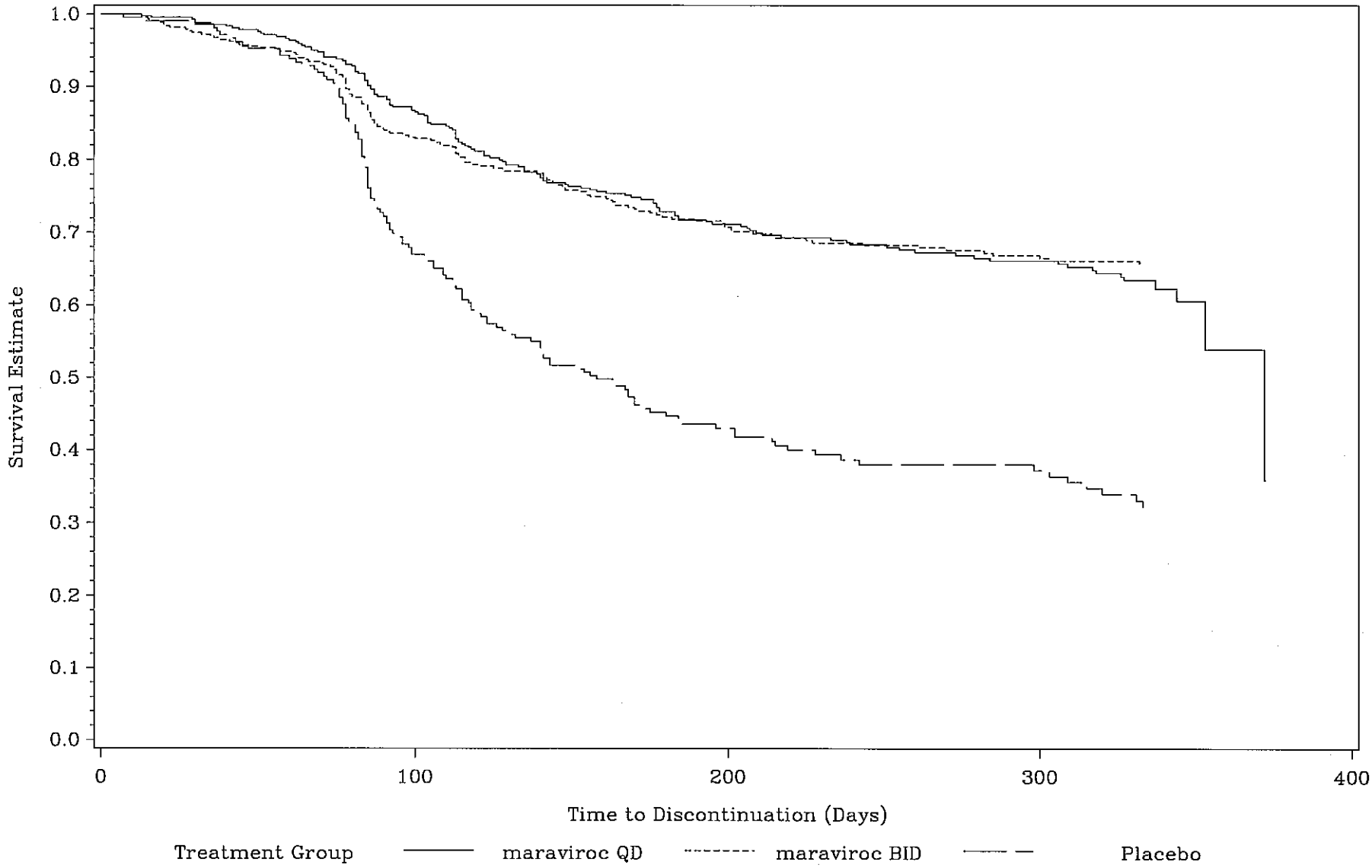
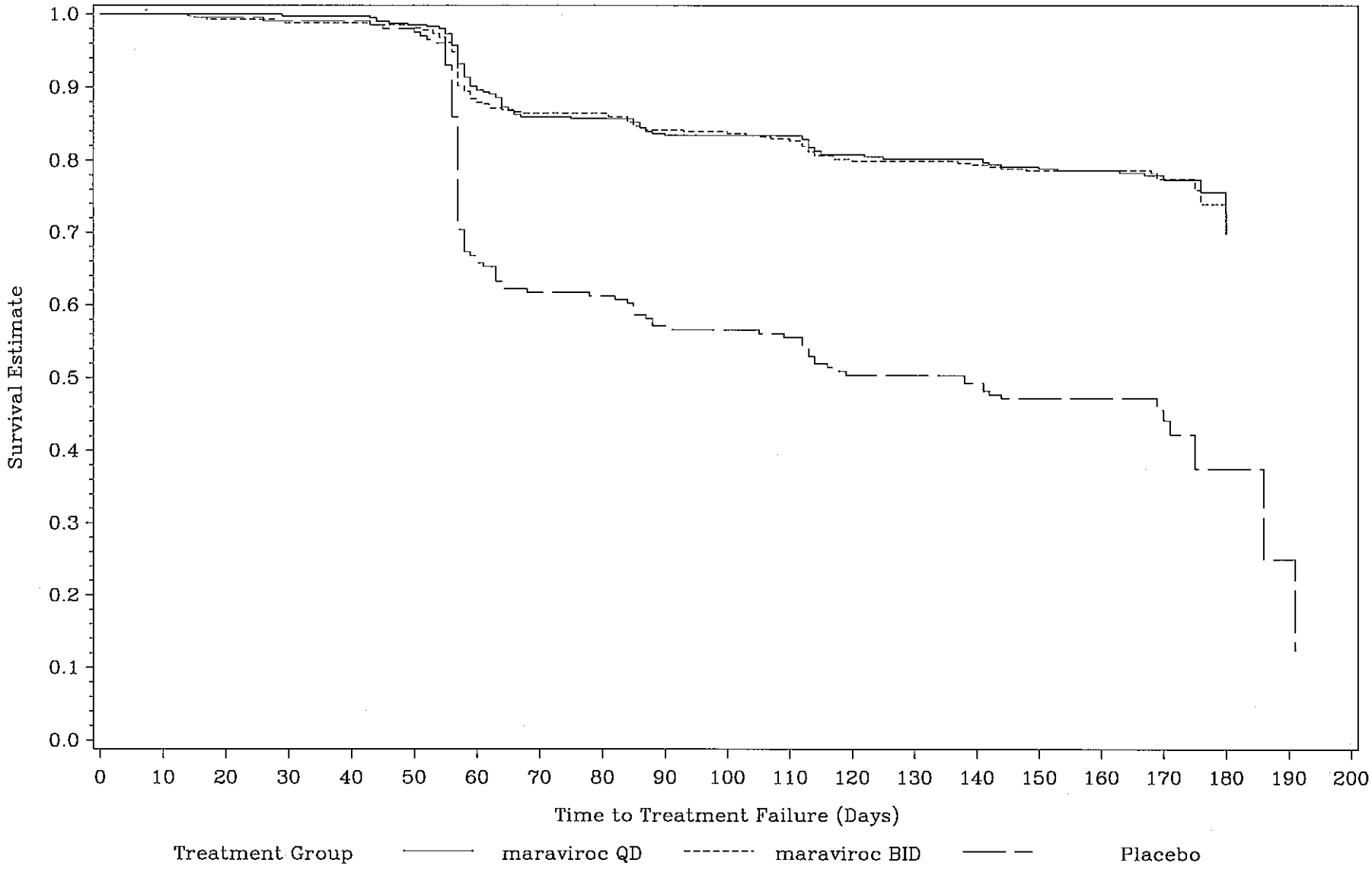


Figure 14.11.3
Maraviroc Summary of Clinical Efficacy
Kaplan Meier Plot of Time to Treatment Failure
Full Analysis Set – As Treated



2.7.4 SUMMARY OF CLINICAL SAFETY

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACTG	AIDS clinical trial group
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
APD	Action potential duration
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
BID	Twice daily
bpm	Beats per minute
CCR5	CC chemokine receptor 5
CCR5Δ32	32 basepair deletion of CCR5
CI	Confidence interval
CSR	Clinical study report
CXCR4	Chemokine (C-X-C motif) receptor 4
DBP	Diastolic blood pressure
DSMB	Data safety monitoring board
ECG	Electrocardiogram
GSS	Genotype susceptibility score
GTN	Glyceryl trinitrate
HAART	Highly active antiretroviral therapies
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High density lipoprotein
hERG	Human ether-a-go-go-related gene
HIV-1	Human immunodeficiency virus subtype 1
ICG	Impedence cardiography
ICH	International Conference on Harmonization
IR	Immediate release
ISOD	In study off drug
i.v.	Intravenous
LDL	Low density lipoprotein
LFT	Liver function test
MAI	*Mycobacterium avium-intracellulare*
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MR	Modified release
msec	Milliseconds
NNRTI	Non nucleotide/nucleoside reverse transcriptase inhibitor
Non-R5	Non-CC chemokine receptor tropic (dual/mixed, CXCR4-tropic or non-phenotypable) HIV-1
NRTI	Nucleotide/nucleoside reverse transcriptase inhibitor
OBT	Optimised background therapy
OL	Open label
OSS	Overall susceptibility score
PI	Protease inhibitor
PK	Pharmacokinetic
PSS	Phenotype susceptibility score
PY	Patient years
QD	Once daily
QT	Time from the beginning of the QRS complex to the end of the T wave in the electrocardiogram
QTc	QT interval, corrected for heart rate.
QTcB	QTc interval with Bazett's correction
QTcF	QTc interval with Fridericia's correction
QTcI	QTc interval, calculate using an individual correction factor

QTcP	Qt interval calculated using specific population correction factor
R5	CC chemokine receptor 5 tropic HIV-1
RMP	Risk management plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SOC	System organ class
TdP	Torsade de pointes
TE	Treatment-experienced
TFT	Thyroid function tests
Tmax	Time of occurrence of Cmax
US	United States
wt	Wild type

2.7.4. SUMMARY OF CLINICAL SAFETY

Acquired immune deficiency syndrome (AIDS) has caused the death of more than 25 million people since it was first recognized in 1981, making it one of the most destructive epidemics in recorded history. Despite recent improved access to antiretroviral treatment and care in many regions of the world, the AIDS epidemic is estimated to have claimed 3.1 million (2.8 to 3.6 million) lives in 2005. The vast majority of these deaths occurred in sub-Saharan Africa and more than half a million were children.

Maraviroc is a selective, slowly reversible CC chemokine receptor 5 (CCR5) co-receptor antagonist, which has been shown to be active in vitro against a wide range of clinical isolates, including those resistant to existing drug classes. The Sponsor is seeking marketing authorisation for maraviroc administered twice daily (BID) at a dose of 300 mg (adjusted as appropriate for interacting drugs) in combination with other antiretroviral agents for the treatment of CCR5-tropic human immunodeficiency virus subtype 1 (HIV-1) in treatment-experienced (TE) patients. This Summary of Clinical Safety provides the integrated safety analyses performed for TE patients infected with CCR5 tropic HIV-1. It includes additional safety analyses on data from TE infected patients infected with non-CCR5 tropic (dual/mixed, CXCR4-tropic and non-phenotypable) HIV-1, treatment-naïve patients infected with CCR5 tropic HIV-1 and healthy volunteers.

The 2 Phase 3 registrational studies include a population of TE patients infected with CCR5-tropic HIV-1 with resistance to 3 of the 4 antiretroviral classes, as measured by phenotypic and genotypic resistance testing or by a history of usage of drugs from 3 of 4 antiretroviral classes for at least 6 months, including at least 2 protease inhibitors (PIs). The population recruited into both studies was predominantly male and white with a median time after HIV-1 infection of 14 years, reflecting the demographics of the epidemic in the early 1990s. The Phase 2b/3 clinical studies were conducted with the oversight of an independent external Data Safety Monitoring Board (DSMB).

Although maraviroc is the first CCR5 antagonist to be submitted for marketing authorisation, other experimental agents in this new class of antiretroviral agents have undergone clinical development and have been associated with significant safety issues. Aplaviroc (Glaxo-Smith-Kline) was discontinued from Phase 2b/3 development for severe hepatic toxicity. In a recent placebo-controlled clinical trial with another CCR5 antagonist, vicriviroc (Schering Plough), 4 cases of lymphoma and 1 of gastric adenocarcinoma were reported in patients treated with active drug. There was no clear evidence that these malignancies were linked to drug. Small numbers in the study (90/118 received vicriviroc) confound assessment of a causal relationship between vicriviroc and development of malignancies. The data presented in this dossier do not indicate that maraviroc is associated with hepatotoxicity or carcinogenicity relative to placebo.

Safety concerns raised by pre-clinical models and the Phase 1

/2a studies include postural hypotension and QT prolongation. Theoretical concerns based on the drug's mechanism of action include an increased risk for infection and development of malignancy. However, there is no evidence from the Phase 2b/3 studies that maraviroc

administered at a dose equivalent of 300 mg (QD or BID) is associated with an increased frequency relative to placebo of symptomatic postural hypotension, QTc interval prolongation, infections or tumours (see Section 2.7.4.2.1.5).

The adverse event (AE) profile of maraviroc is similar for both the QD and BID dosing arms in TE patients up to and beyond 24 weeks of treatment. The most commonly reported all-causality AEs during the Phase 3 studies (A4001027 and A4001028) were pyrexia, cough, upper respiratory tract infection, rash, herpes simplex, myalgia, dysuria, dyspnoea, ALT increased, AST increased, blood creatine phosphokinase increased and influenza. Most treatment-related AEs associated with maraviroc occurred at similar incidences with placebo. There are no age-, gender- or race-related differences in the safety profile of the maraviroc treatment groups versus placebo. There is no significant difference in the safety profile of maraviroc plus optimised background therapy (OBT) compared with placebo plus OBT.

2.7.4.1. Exposure to Maraviroc

2.7.4.1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

2.7.4.1.1.1. Introduction/ General Overview

To date, 28 Phase 1 clinical studies have been completed, including 14 single-dose studies (2 conducted in males infected with HIV-1) and 14 multiple-dose studies. Ongoing Phase 1 studies are listed in the Risk Management Plan.

In the Phase 1 studies, a total of 595 healthy subjects and 37 patients infected with HIV-1 have been exposed to maraviroc. Table 1 and Table 2 present a summary of the single- and multiple-dose studies and give an overview of any safety concerns raised; any safety issues highlighted there are described further in Section 2.7.4.2.1.4. Narrative summaries for those studies that were designed to address specific safety concerns are presented in Section 2.7.4.1.1.4

Potential safety issues addressed in this summary document include those arising from the pre-clinical/toxicology programme, the Phase 1/2a clinical programme, the Phase 2b/3 clinical programme and concerns from other CCR5 antagonists in development. Each of these is described in detail in the following sections and, where appropriate, any longer-term pharmacovigilance follow-up proposed by the Sponsor is described in the Risk Management Plan.

Table 1. Overview of Completed Phase 1 Single-Dose Studies Design and Safety Outcome

Study Number Dose	Study Design	Safety Outcome
A4001001 (Solution) Maraviroc: between 1 mg and 1200 mg Placebo	A double-blind, dose escalating, crossover study to investigate the safety, tolerability and pharmacokinetics of single oral doses of maraviroc in healthy male volunteers in the fed and fasted states (N=24).	1) Maraviroc was tolerated up to 900 mg. 2) At 1200 mg the dose limiting AE was postural hypotension. 3) There was a mean increase in QTcF at 2 hours post-dose of 10.7 msec, and in QTcP of 7.8 msec, at 1200 mg
A4001003 (Tablet/Solution) Maraviroc: Tablet: 50 mg and 100 mg (fasted), 600 mg (fed/fasted) Solution: 100 mg (fasted)	An open, randomized crossover study in healthy male volunteers to investigate the pharmacokinetics of single oral doses of maraviroc (N=15).	There were no clinically significant safety concerns.
A4001004 (Tablet) Maraviroc: 100 mg at varying times of food intake (1 hour prior to 4 hours post)	An open randomized crossover study in fed and fasted healthy volunteers to investigate the effects of timing of food intake on the pharmacokinetics of maraviroc (N=15).	There were no clinically significant safety concerns.
A4001009 (Solution/Tablet) Maraviroc: i.v. doses between 3 mg and 30 mg (solution) vs. 100 mg oral tablet Placebo	A randomized double-blind third party open crossover study to investigate the pharmacokinetics, safety and tolerability of escalating i.v. doses of maraviroc, and to determine the absolute bioavailability after oral dose (N=12).	There were no clinically significant safety concerns.
A4001010 (Solution) Maraviroc: 300 mg	An open study to investigate the absorption, metabolism and excretion of [^{14}C] -maraviroc in healthy male subjects (N=3).	There were no clinically significant safety concerns.
A4001016 (Tablet) Maraviroc: 100, 300 and 900 mg Moxifloxacin Placebo	A placebo- and active-controlled double-blind crossover study to investigate the effect of escalating single doses of maraviroc on QTc interval in healthy subjects (N=59).	1) At 900 mg maraviroc did not have any clinically relevant effect on QTcI (mean difference from placebo was less than 4 msec, 90% upper CI <7 msec). 2) There were no additional clinically significant safety concerns.
A4001017 (Tablet) Maraviroc 300 mg +: Cohort 1: Efavirenz and TM1* Cohort 2: Efavirenz, didanosine and tenofovir Cohort 3: Nevirapine, lamivudine and tenofovir Cohort 4: TM2*, stavudine and lamivudine	An open probe study to investigate the effect of selected antiretroviral combinations on the pharmacokinetics of a single oral dose of maraviroc in HIV-infected subjects (N=29).	1) Maraviroc was tolerated in HIV-positive subjects when co-administered with 1 of 4 different ART regimens. 2) Although exposure to maraviroc was higher in subjects who received TM2*, the safety profile, in particular in AE incidence, did not appear to be different to that observed in the other 3 cohorts.
A4001032 (Solution) Part 1: 4 taste-masked maraviroc formulations and 2 comparator formulations, *rinse and spit* method Part 2: 1 of the 4 taste masked maraviroc formulations, *swallowed*	A single-blind study to investigate and compare the taste characteristics of selected paediatric formulations of maraviroc compared with marketed comparators in healthy adult volunteers (N=18).	There were no clinically significant safety concerns.

*:新薬承認情報提供時に置換えた。
TM1*はzidovudine/lamivudineを,
TM2*はlopinavir/ritonavirを示す。

Table 1. Overview of Completed Phase 1 Single-Dose Studies Design and Safety Outcome

Study Number Dose	Study Design	Safety Outcome
A4001033 (Tablet) Maraviroc 900 mg GTN Placebo	A crossover study to investigate the haemodynamic effects of oral maraviroc (N=16).	1) Maraviroc acted as a mild vasodilator with a fully compensated haemodynamic response maintaining supine blood pressure. 2) The 3/16 subjects experiencing postural hypotension implying that there was not always complete compensation for orthostatic changes. 3) There was no apparent relationship between % change from baseline in ICG parameters or change from baseline in supine blood pressure and pulse rate compared with maraviroc plasma concentration. 4) There were no other clinically significant safety concerns.
A4001038 (Tablet) Maraviroc: 300 mg	An open, 2-centre study, to compare the pharmacokinetics of a single oral dose of maraviroc in Asian and Caucasian healthy male subjects (N=24).	1) There were no differences in safety profile between Asian and Caucasian subjects. 2) There were no clinically significant safety concerns overall. 3) PK was similar between Caucasians and Asians.
A4001040 (Tablet) Maraviroc: 1x 300 mg commercial tablet 2x 150 mg research tablet	An open crossover study to confirm bioequivalence of maraviroc research and commercial tablets (N=44).	There were no clinically significant safety concerns.
A4001043 (Tablet) Maraviroc: 300 mg commercial tablet Fed and fasted	An open crossover study to confirm the effect of food on the pharmacokinetics of the maraviroc commercial tablet (N=12).	There were no clinically significant safety concerns.
A4001046 (Tablet) Maraviroc: 150 mg Saquinavir	An open study to investigate the range of maraviroc exposures following a single dose in HIV positive patients receiving antiretroviral therapy containing boosted saquinavir (N=8).	There were no clinically significant safety concerns.
A4001047 (Tablet) Maraviroc: 600 mg IR fasted MR 4, 6 9 hour fasted and 6 h fed	An open crossover study to investigate the pharmacokinetics and effect of food on modified release maraviroc (N=10).	There were no clinically significant safety concerns.

AE = adverse event; GTN = glyceryl trinitrate; ICG = impedence cardiography; IR = immediate release; MR = modified release; PK = pharmacokinetic; QTcI = Individually-corrected QT.

Table 2. Overview of Completed Phase 1 Multiple-Dose Studies Design and Safety Outcome

Study Number Dose	Study Design	Safety Outcome
A4001002 (Tablet) Maraviroc: Cohort 6: 3 & 10 mg BID Cohort 4: 25 mg BID Cohort 1: 100 mg BID Cohort 2: 300 mg BID Cohort 3: 600 mg QD Cohort 5: 600 mg QD Placebo	A double-blind parallel group, single dose and multiple escalating oral dose study to investigate the safety, toleration and pharmacokinetics of maraviroc in healthy male subjects (N=72).	1) At doses up to 300 mg BID, there were few adverse effects. 2) At 600 mg QD, there was severe symptomatic postural hypotension (2/9 subjects on 600 mg QD and 1/3 subjects on placebo in Cohort 3). A second cohort was successfully dosed at 600 mg without this degree of postural events. 3) Minor effects on blood pressure and pulse rate occurred more frequently at 600 mg QD. 4) One subject discontinued due to a laboratory test abnormality: a severe increase in transaminase levels, concurrent with food poisoning. 5) Eight maraviroc subjects had transaminase levels above the ULN which tended to increase up until the last day of treatment and decrease thereafter. These events were sporadic, not dose-related and were not associated with an elevation in bilirubin. 6) There were apparent dose-related increases in total cholesterol and LDL-cholesterol.
A4001005 (Tablet) Maraviroc: 100 mg Ethinyloestradiol and levonorgestrel Placebo	A double-blind, placebo-controlled, crossover study to investigate the effects of maraviroc on the pharmacokinetics of oral contraceptive steroids in young women (N=15).	There were no clinically significant safety concerns.
A4001006 (Tablet) Maraviroc: 100 mg BID Ketoconazole Saquinavir Placebo	An open crossover study to investigate the effect of ketoconazole and saquinavir on the steady state pharmacokinetics, safety and tolerability of maraviroc in healthy volunteers (N=12).	There were no clinically significant safety concerns.
A4001008 (Tablet) Maraviroc: 100 or 300 mg BID Placebo	A double-blind, multiple dose study to investigate the safety of maraviroc BID for 28 days in healthy subjects (N=54).	There were no clinically significant safety concerns.
A4001011 (Tablet) Maraviroc: 100 or 200 mg BID Rifampicin Efavirenz	An open parallel group study to investigate the effect of rifampicin and efavirenz on the steady-state pharmacokinetics of maraviroc in healthy volunteers (N=36).	There were no clinically significant safety concerns.
A4001012 (Tablet) Maraviroc 300 mg BID + midazolam Placebo + midazolam	A double-blind, 2-period crossover study to investigate the effects of steady-state maraviroc on the pharmacokinetics of a single oral dose of midazolam (N=12).	There were no clinically significant safety concerns.
A4001013 Maraviroc 25, 50 or 100 mg BID + Ritonavir, Saquinavir + ritonavir Lopinavir + ritonavir Placebo	An open, 4-treatment, parallel group study to explore the steady-state pharmacokinetics of maraviroc when co-administered with ritonavir, saquinavir plus ritonavir or lopinavir plus ritonavir ([redacted]TM) (N=32).	There were no clinically significant safety concerns.

Table 2. Overview of Completed Phase 1 Multiple-Dose Studies Design and Safety Outcome

Study Number Dose	Study Design	Safety Outcome
A4001018 Maraviroc 300 mg BID + TM13* Placebo	An open 2-period crossover study to investigate the effects of TM13* on the steady-state pharmacokinetics of maraviroc in healthy volunteers (N=16).	There were no clinically significant safety concerns.
A4001019 (Tablet) Maraviroc: 300, 600 and 900 mg BID 900 and 1200 mg QD Placebo	A double-blind, parallel group study to investigate the safety, tolerability and pharmacokinetics of multiple escalating oral doses of maraviroc in healthy subjects (N=36).	1) Two subjects permanently discontinued: 1 due to treatment related rash and 1 to infectious mononucleosis (Epstein Barr Virus). 2) Four subjects had severe treatment-related AEs: 3 had postural hypotension (900 mg QD or 1200 mg QD), and 1 had dizziness (600 mg BID). 3) Postural hypotension and conjunctivitis were more common at doses of 900 mg and above. Blurred vision was more common at 600 mg and above 4) 7/9 subjects on 1200 mg QD and 1/2 subject on placebo had increased plasma creatinine. 5) There was no increase in QTc in this study.
A4001020 (Tablet) Maraviroc 300 mg BID + TM1* Placebo + TM1*	A double-blind 2-period crossover study to investigate the effects of steady-state maraviroc on the steady-state pharmacokinetics of TM1* in healthy subjects (N=12).	There were no clinically significant safety concerns.
A4001021 (Tablet) Maraviroc 100 or 300 mg BID + efavirenz with TM2* efavirenz with boosted saquinavir efavirenz with both TM2* and saquinavir Placebo	An open 2-way crossover study to investigate the effect of co-administration of efavirenz with TM2*, efavirenz with boosted saquinavir and efavirenz with both TM2* and saquinavir on the pharmacokinetics of maraviroc in healthy subjects (N=36).	1) Maraviroc 100 mg BID in combination with boosted saquinavir or boosted saquinavir and efavirenz was tolerated with all AEs being mild to moderate. 2) Maraviroc 100 mg BID in combination with TM2* plus boosted saquinavir and efavirenz was discontinued due to treatment-related gastrointestinal AEs.
A4001022 (Tablet) Maraviroc 300 mg BID + Tenofovir Placebo	An open 2-way crossover study to investigate the effect of co-administration of tenofovir on the pharmacokinetics of maraviroc in healthy subjects (N=12).	There were no clinically significant safety concerns.
A4001025 (Tablet) Maraviroc 300 mg BID + Atazanavir Placebo	An open, placebo-controlled, randomised, 2-way crossover study to investigate the effect of co-administration of atazanavir alone and boosted with ritonavir on the pharmacokinetics of maraviroc in healthy subjects (N=12).	1) There was 1 severe AE of postural hypotension. 2) There were no other clinically significant safety concerns.
A4001042(Tablet) Maraviroc 150 mg BID + Tipranavir/ritonavir Placebo	An open 2-way crossover study to investigate the effect of tipranavir/ritonavir on the pharmacokinetics of maraviroc in healthy subjects (N=12).	There were no clinically significant safety concerns, other than tipranavir-related LFT elevations.

BID = Twice daily dosing; QD = once daily dosing; ULN = upper limit of normal.

*:新薬承認情報提供時に置換えた。
TM1*はzidovudine/lamivudineを,
TM2*はlopinavir/ritonavirを,
TM13*はtrimethoprim/sulfamethoxazoleを示す。

Two multiple-dose Phase 2a studies were conducted in patients infected with CCR5-tropic HIV-1 (A4001007 and A4001015). In these studies a total of 66 patients were exposed to maraviroc. No safety concerns were identified during these studies (Table 3).

Table 3. Overview of Phase 2a Studies (A4001007 and A4001015) Design and Safety Outcome

Study Number Dose	Study Design	Safety Outcome
A4001007 (Tablet) *Cohort 1*: Maraviroc 25 mg QD: 100 mg BID: Placebo. (1:1:1) *Cohort 2*: Maraviroc 50 mg BID: 300 mg BID: Placebo. (2:2:1)	A double-blind, multicentre study of maraviroc in asymptomatic patients infected with CCR5-tropic HIV-1 to investigate pharmacodynamics, pharmacokinetics, safety and tolerability (N=45)	There were no clinically significant safety concerns.
A4001015 (Tablet) Maraviroc 150 mg BID (fed & fasted): 100 mg and 300 mg QD (fasted): Placebo (fed & fasted). (4:4:4:4:1:1)	A double-blind investigation into the effects of food and dose regimen on viral load response in patients infected with CCR5-tropic HIV-1 on short-term monotherapy with maraviroc (N=37).	There were no clinically significant safety concerns.

The Phase 2b/3 clinical programme consists of 4 global studies: 3 conducted in TE patients receiving maraviroc in combination with other anti-retroviral drugs, the fourth in treatment-naïve patients receiving either maraviroc or efavirenz in combination with zidovudine/lamivudine ([redacted]™).

Two of these studies (A4001027 and A4001028) are ongoing Phase 3 studies conducted in TE patients infected with CCR5-tropic HIV-1 (who for the purposes of this document will be referred to as 'R5 TE patients'). These 2 studies provide the pivotal information for the target population supporting this submission. One smaller ongoing Phase 2b study (A4001029) is being conducted in TE patients infected with dual/mixed (CCR5/CXCR4) tropic, CXCR4-tropic or non-phenotypable HIV-1 (who for the purposes of this document will be referred to as 'non-R5 TE patients'). All 3 of these studies in TE patients compared 2 maraviroc dosing regimens (QD and BID, at dose equivalents of 300 mg; see Section 2.7.4.1.3.3.1) with placebo, and all were administered in combination with OBT selected on the basis of resistance testing, history of prior use and safety of combinations.

Study A4001026 is being conducted in treatment-naïve patients and is included in this submission to provide supportive safety data only. In January 2006, the independent DSMB recommended discontinuation of this study's maraviroc 300 mg QD treatment group after it failed to meet protocol-defined non-inferiority criteria at a predefined interim analysis (described in Section 2.7.3.1.3 Module 2.7.3 Summary of Clinical Efficacy). The DSMB further recommended rolling over these patients into an open label (OL) maraviroc BID arm. This study is still ongoing, and the unblinded data from the discontinued treatment group are presented in this submission to support an assessment of significant AEs across the Phase 2b/3 programme.

As of 15 September 2006, a total of 964 TE patients (840 R5 and 124 non-R5) have been exposed to maraviroc in the Phase 2b/3 studies, and 271 patients have received placebo (209 R5 and 62 non-R5 TE patients). Safety data are also available for 109 patients from Studies A4001028 and A4001029 who were discontinued for treatment failure and permitted to begin OL maraviroc BID. These patients were infected with CCR5 tropic HIV-1 at the time of starting OL maraviroc treatment. Safety data from 174 patients exposed to maraviroc in the discontinued QD arm from treatment-naïve Study A4001026 are also presented as supportive data.

Table 4. Overview of the Design and Safety Outcome of the Ongoing Phase 2b/3 Studies (Studies A4001027, A4001028, A4001029 and A4001026)

Study Number Dose	Study Design	Safety Outcome
A4001027 **Maraviroc 300 mg QD: 300 mg BID: Placebo. (2:2:1)**	A double-blind, placebo-controlled study of maraviroc in combination with OBT versus OBT alone in treatment-experienced CCR5-tropic HIV-1 infected individuals (US and Canada) (N=585).	There were no clinically significant safety concerns.
A4001028 **Maraviroc 300 mg QD: 300 mg BID: Placebo. (2:2:1)**	A double-blind, placebo-controlled study of maraviroc in combination with OBT versus OBT alone in treatment-experienced CCR5-tropic HIV-1 infected individuals (EU, Australia and North America) (N=464).	1) There was a slight imbalance in the number of deaths but a significant number of deaths were noted in the pre-randomisation period. 2) There were no clinically significant safety concerns.
A4001029 **Maraviroc 300 mg QD: 300 mg BID: Placebo. (1:1:1)**	A double-blind, placebo-controlled study of maraviroc in combination with OBT versus OBT alone in treatment-experienced patients with non CCR5-tropic HIV-1 (Global) (N=190).	There were no clinically significant safety concerns.
A4001026 **Maraviroc 300 mg QD: or 300 mg BID: Efavirenz (1:1:1) with Zidovudine/lamivudine**	A global, double-blind, comparative trial of maraviroc and efavirenz in combination with zidovudine/lamivudine in treatment-naïve CCR5 tropic HIV-1 infected individuals.	1) The 300 mg QD treatment group was discontinued after review by the DSMB, following failure to meet protocol defined non-inferiority criteria at a predefined interim analysis. The DSMB recommended rolling over the subjects in the maraviroc QD arm into an open label maraviroc BID arm. 2) There were no clinically significant safety concerns.

Individual summaries of the study designs and key safety results for these studies are provided in Appendix Table A1 of this document.

2.7.4.1.1.2. Pooling Strategy for Presentation of Integrated Safety Information

In order to investigate any safety issues arising from various stages of the maraviroc clinical programme, an integrated safety review was completed for the following subject populations:

- Phase 1 single-dose studies and Phase 1 multiple-dose studies

The Phase 1 population (represented by A in Figure 1) is comprised mainly of healthy HIV-1 negative volunteers, although 2 pharmacokinetic single-dose studies (A4001017 and

A4001046) were conducted in HIV-1 infected patients. This population has been pooled separately from the Phase 2b/3 population as subjects are less likely to have confounding AEs, serious co-morbidity or be taking concomitant medications. In addition, in many of these studies (i.e., in the non-interaction studies), maraviroc was administered alone, whereas in the Phase 2b/3 studies maraviroc is always administered with other antiretroviral therapy, and often other concomitant medications as well. The Phase 1 single-dose studies and Phase 1 multiple-dose studies have been analysed separately.

- Phase 2a studies (A4001007 and A4001015)

Data from Phase 2a Studies A4001007 and A4001015 (represented by B in Figure 1) have not been pooled with the Phase 2b/3 studies, since patients in these studies received maraviroc as short-term monotherapy only, were treatment-naïve (or off-treatment for at least 8 weeks prior to enrolment), were asymptomatic and had CD4 counts >250 cell/μL.

- Phase 2b/3 studies - all patients

This pool (represented by C in Figure 1) includes all HIV-1 infected patients in the Phase 2b/3 programme who have received at least 1 dose of maraviroc (Studies A4001026, A4001027, A4001028 and A4001029), including open label maraviroc. The purpose of this 'high-level' pool is to describe the safety experience and overall adverse event profile of maraviroc across the whole Phase 2b/3 clinical programme and to check for any differences in frequency and type of events compared with the target population of R5 TE patients.

- Phase 2b/3 studies

In November 2004, the 4 global Phase 2b/3 studies of maraviroc in combination with other antiretroviral therapy were initiated (Table 4). The safety data for these studies are pooled into the following populations:

- Phase 3 studies in TE patients infected with CCR5-tropic HIV-1 (Studies A4001027 and A4001028)

This analysis pool (represented by E in Figure 1) consists of the 2 registrational Phase 3 studies conducted in TE patients infected with CCR5-tropic HIV-1 (Studies A4001027 and A4001028).

- Phase 2b study in TE patients with non CCR5-tropic HIV-1 (Study A4001029)

This population (represented as F in Figure 1) provides safety data for patients infected with dual/mixed, CXCR4-tropic and non-phenotypable HIV-1 (Study A4001029). These safety data provide reassurance that there are no safety implications in patients who are infected with non-CCR5 tropic virus.

- Phase 2b/3 studies in TE patients infected with HIV-1 (Studies A4001027, A4001028 and A4001029)

This analysis (represented by D in Figure 1) includes all TE patients in the Phase 2b/3 clinical programme irrespective of viral tropism result, and thus includes patients from Studies A4001027, A4001028 and A4001029. This pool will provide larger numbers of TE patients from which to describe the overall AE profile of this population and to evaluate systematically collected parameters related to QTc and postural hypotension likely to be independent of maraviroc effects on HIV-1.

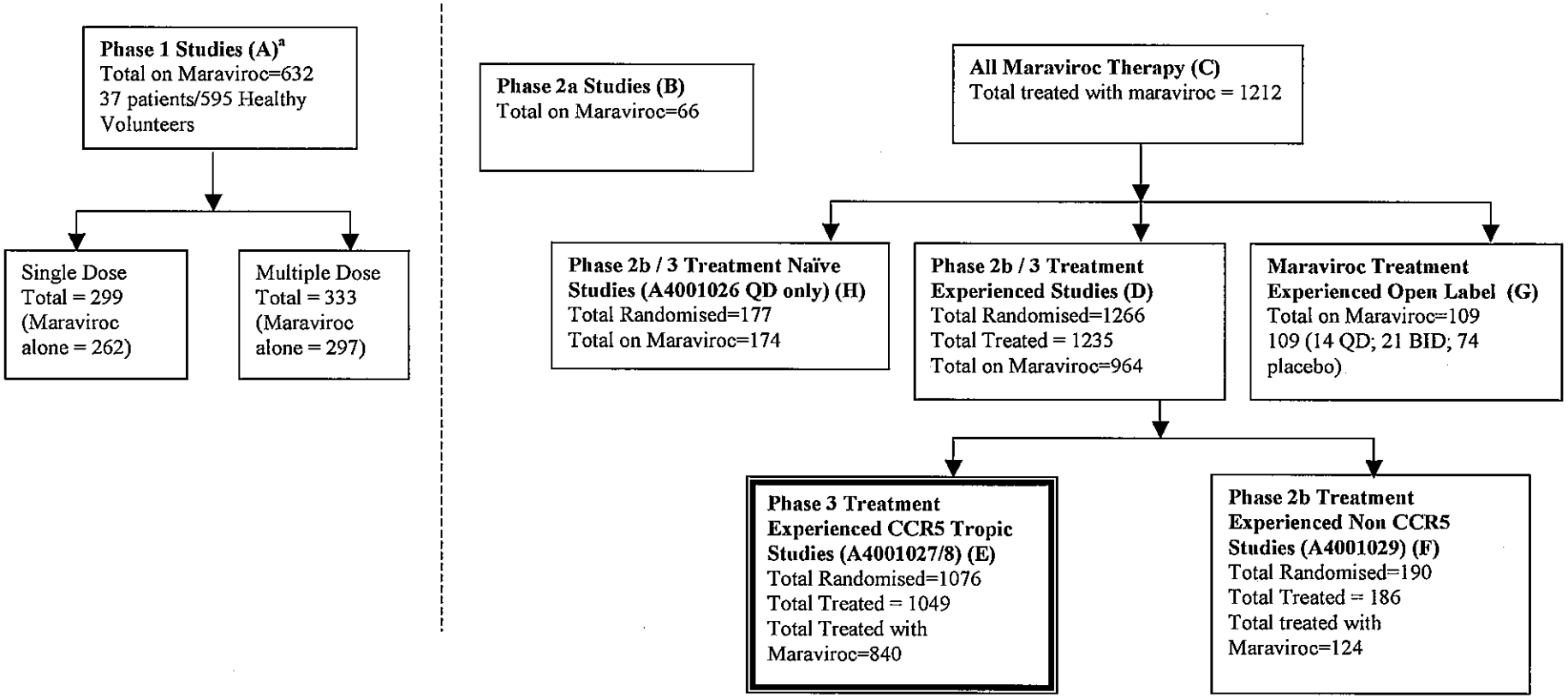
- Open label Phase 3 Studies in TE patients with CCR5-tropic HIV-1 (Studies A4001027 and A4001028)

This population pool (represented by G in Figure 1) includes data for patients in Studies A4001027 and A4001028 who discontinued from blinded therapy, irrespective of randomised treatment, for reasons other than for safety, but remained CCR5-tropic and continued in study on OL maraviroc.

- Phase 2b/3 study in treatment-naïve patients (Study A4001026)

This treatment-naïve population (represented by H in Figure 1) is included to provide supportive safety data only. In January 2006 the DSMB recommended that this study's maraviroc 300 mg QD treatment arm be discontinued for failure to meet pre-defined non-inferiority criteria, but that patients who were responding to treatment could be switched to maraviroc 300 mg BID. The unblinded data from the discontinued treatment arm and its OL follow-on phase are included to support assessment of AEs of interest (e.g., hepatotoxicity) across the Phase 2b/3 programme. Patients in this study are receiving a fixed combination of maraviroc and zidovudine/lamivudine.

Figure 1. Overall Reporting Strategy for Maraviroc Safety Data



Notes: [a] Includes 26 Studies in Healthy Volunteers plus 2 PK Studies in HIV-1 infected patients
Total Randomised = Total number of subjects randomised
Total on Maraviroc = Total number of subjects randomised to and received at least 1 dose of Maraviroc
Source: Summary of Clinical Safety Tables 1.1.1, 2.1, 3.1.2 and 3.4.7.1 and Individual Clinical Study Reports for A4001029 and A4001026 QD

2.7.4.1.1.3. Reporting definitions

The safety analysis population is defined as all subjects randomised who received at least one dose of study medication. Subjects are reported under the treatment they actually received.

AEs and laboratory values were analysed using the AIDS Clinical Trial Group (ACTG) Grade 1-4 severity scale.

In accordance with the International Conference of Harmonization Topic E2A[i], a serious adverse event (SAE) was defined as any event that was 1) life-threatening or resulted in death, 2) required or prolonged hospitalisation, 3) resulted in a persistent or significant disability or incapacity, 4) was a congenital anomaly or birth defect, or 5) was a medically significant event (defined as the event that jeopardised the subject or required medical or surgical intervention to prevent 1 of the outcomes listed herein). Any such event was reported on the Sponsor's SAE database (ARISg).

2.7.4.1.1.3.1. Databases

Integrated safety data (AEs, discontinuations due to AEs and laboratory abnormalities) are reported from the clinical database (Oracle Clinical). SAEs (including serious laboratory abnormalities) are reported from the Sponsor's SAE database (ARISg).

There are differences between the 2 databases with respect to safety data reporting. For example, ARISg references local laboratory data and specialist investigations; such data cannot always be merged into Oracle Clinical. Likewise, different terminology may be used to report the same event to the 2 databases, and the numbers of events reported may differ because of the different lag times used (see below).

2.7.4.1.1.3.2. Patients In-Study-Off-Drug

In Studies A4001027, A4001028 and A4001029, patients were encouraged to remain in the study for long term follow-up following discontinuation of study drug, either on OL maraviroc (if appropriate) or on another treatment regimen without maraviroc. When reporting SAEs or deaths that occurred more than 28 days after cessation of study drug in patients who did not go on to receive OL maraviroc, these subjects are designated as belonging to an 'In-Study-Off-Drug' (ISOD) treatment group.

A total of 50/414, 59/426 and 25/209 patients randomised to maraviroc QD, maraviroc BID, and placebo, respectively, discontinued therapy but remained in Studies A4001027 and A4001028. A further 79, 58 and 34 discontinued from each treatment group, respectively, in these 2 studies.

2.7.4.1.1.3.3. Safety Data Cut-Off Dates

Adverse Events and Laboratory Abnormalities Reported from Oracle Clinical

All safety data are included from the completed Phase 1 and Phase 2a clinical studies.

For the ongoing Phase 3 Studies A4001027 and A4001028, all safety data on all patients to Week 24 are reported to 15 September 2[redacted] All other safety data beyond Week 24 are reported to the Week 48 visit or 11 September 2[redacted] whichever occurred earlier.

All data are reported for the Week 24 primary analysis endpoint from the Phase 2b Study A4001029 (Last Patient Last Visit included from 8 December 2[redacted].

For the ongoing Phase 2b/3 Study A4001026, data for the discontinued 300 mg QD arm are included only to support data for AEs of significance (see Section 2.7.4.2.1.5.3).

Serious Adverse Events (SAEs) and Deaths Reported from ARISg

SAEs and deaths are reported up to the 15 September 2[redacted] for all studies, including OL data for Studies A4001027, A4001028 and A4001029 and for the discontinued 300 mg QD treatment group of Study A4001026. Blinded SAE data only are provided for the ongoing maraviroc BID and efavirenz treatment groups of Study A4001026, except patients who have died or where unblinding was necessary for patient management.

2.7.4.1.1.3.4. Lag Time for Reporting of Data

Adverse Events and Laboratory Abnormalities Reported from Oracle Clinical

A lag time of 7 days was used, specifically:

- An AE occurring or laboratory data recorded up to 7 days after cessation of dosing are classified as treatment-emergent in the summary tables. Any subsequent AE or laboratory abnormality is not (but is reported in individual report data listings).

Lag Time Phase 2b/3

For the purposes of the Phase 2b/3 studies, a lag of either 7 days or the time from end of blinded therapy to start of OL maraviroc, whichever is shorter, is used to process AEs and laboratory data. For the purpose of reporting, Blinded Therapy and OL are reported as separate treatment periods. Specifically:

- If the same AE occurs on Blinded Therapy, resolves before starting OL and then recurs on OL, the AE is reported as treatment-emergent on both.

- If an AE starts on Blinded Therapy (or within the lag period before starting OL) and continues into OL at same severity, the AE is reported as treatment emergent for Blinded Therapy only. Duration is reported in Blinded Therapy from the start to the stop date of the AE.

- If an AE starts after commencement of OL, and this is within the 7 day lag of Blinded Therapy, the AE is attributed to OL only.

- When combining Blinded Therapy and OL into single maraviroc exposure, only the most severe AE is reported. (A footnote is included in the tables to highlight that incidences

from separate summary tables of Blinded Therapy and OL do not add up to incidences presented for combined Blinded and OL therapy.)

Serious Adverse Events and Deaths Reported from ARISg

For all serious AEs and deaths, a lag time of 28 days was used, specifically:

- A SAE or death occurring up to 28 days after cessation of dosing is classified as treatment-emergent in the summary tables. Any subsequent event is not, except:
  - Treatment-related SAEs and deaths are reported irrespective of time post-dose and are reported against the last active study treatment.
  - For ISOD patients, any unrelated SAEs or deaths that occur ≤28 days are reported against the last active study treatment. All unrelated SAEs or deaths occurring >28 days post discontinuation of study therapy are assigned to ISOD.

2.7.4.1.1.3.5. MedDRA Coding

All AEs and SAEs are summarised by Medical Dictionary for Regulatory Activities (MedDRA) terms. All AEs and SAEs are reported using MedDRA Version 9.0 and are summarised by system organ class (SOC) and preferred term.

Note: Some of the clinical study reports (CSRs) have been reported using other versions of MedDRA, so AEs reported in this submission may differ slightly from those reported in the individual study reports.

2.7.4.1.1.4. Study Narratives

Brief narrative summaries of single-dose Studies A4001001, A4001016, and A4001033 and multiple-dose Studies A4001002, A4001008 and A4001019 are included below, because these studies were specifically designed to address the safety of maraviroc. Many of the remaining Phase 1 Studies were designed to study maraviroc pharmacokinetics and are discussed in Module 2.7.2. Summary of Clinical Pharmacology. Study narratives are not provided for the Phase 2a Studies A4001007 and A4001015 as no safety issues were identified. Efficacy data for the Phase 2/3 clinical programme are described in Module 2.7.3 Summary of Clinical Efficacy. For full details of all studies, refer to the individual CSRs in Module 5.3.

2.7.4.1.1.4.1. Phase 1 Single-Dose Studies

Study A4001001

This first-in-human study was a double-blind, dose escalating, placebo-controlled study with the primary objective of determining the safety and tolerability of single oral doses of maraviroc in healthy male volunteers, in both fed and fasted states.

Two separate cohorts were dosed alternately to ensure safe escalation of doses Cohort A (N=12): 1 mg, 10 mg, 100 mg, 900 mg and 100 mg (fed), and placebo; Cohort B(N=12):

3 mg, 30 mg, 300 mg and 1200 mg, and placebo). There was a washout period of at least 7 days between doses.

There were no SAEs, deaths or discontinuations. Most AEs were reported at the 1200 mg dose, and very few were reported at doses below 900 mg. Postural hypotension was the dose-limiting AE, occurring in 4 of 9 subjects (44.4%) at 1200 mg. Five subjects had severe treatment-related AEs (4 of postural hypotension at 1200 mg, and asthenia at 300 mg). Seven subjects had laboratory abnormalities (all in Cohort B, and most commonly in the placebo group).

Maraviroc 1200 mg was associated with a mean increase in QTcF (QTc interval with Fridericia's correction) of 10.7 msec and a mean increase in QTcB (QTc interval with Bazett's correction) interval of 20.3 msec at 2 hours post-dose. However, neither of these 2 correction factors adequately corrected for the increase in heart rate seen with this dose, which was confounded by haemodynamic changes related to postural hypotension. Further analysis of ECG data using a population correction factor gave a mean change from baseline in the population-corrected QTc (QTcP) interval of 7.8 msec. These data demonstrate the sensitivity of the QT interval to changes in heart rate and the importance of an appropriate correction factor. No subjects experienced a post-dose QTcB ≥450 msec or change from baseline of ≥60 msec.

Study A4001016

This was a double-blind placebo- and active-controlled crossover study designed to investigate the effect of 3 single oral doses of maraviroc (100, 300 and 900 mg) and an active comparator (oral moxifloxacin 400 mg) on the individually corrected QT interval (QTcI), and to evaluate its safety and tolerability in healthy subjects (N=60).

There were no SAEs or deaths, and most AEs were mild or moderate in severity. Three subjects discontinued due to AEs, none of which was considered treatment-related. Three subjects reported severe AEs, of which 2 [nausea (maraviroc 300 mg) and postural hypotension (maraviroc 300 mg)] were considered treatment related. Postural hypotension was reported as an AE following all treatments except maraviroc 100 mg. Thirty-six subjects had laboratory test result abnormalities, but these were distributed evenly between treatment groups.

Maraviroc, at single doses up to and including 900 mg, had no clinically relevant effect on QTcI. The mean difference from placebo in QTcI for all the primary endpoints was less than 4 msec for all 3 doses of maraviroc (100, 300 and 900 mg); for the active comparator, moxifloxacin, the mean difference in QTcI was between 12 and 14 msec. No subjects in the maraviroc treatment groups had a maximum QTcI value ≥ 450 msec (males) or ≥ 470 msec (females) or increases from baseline ≥ 60 msec at any timepoint, though such values were observed after moxifloxacin. There did not appear to be any differences in the magnitude of the effects of maraviroc and moxifloxacin between male and female subjects. A post hoc exposure-response analysis (Module 5.3.4.1, Exposure-Response Modelling Report for Maraviroc Exposure on QT interval Corrected for Heart rate Phase 1 Data [Protocol A4001016]) concluded that there was a small (less than 3 msec) increase in mean QTcI at

1 and 2 hours post-dose for subjects who received 900 mg maraviroc but not for those who received 100 mg and 300 mg.. A post hoc exposure-response analysis of PR interval data concluded that maraviroc has no effect on this parameter. The data are further discussed in Section 2.7.2.1.3.3 Module 2.7.2 Summary of Clinical Pharmacology and below in Section 2.7.4.2.1.4.1, 'Cardiovascular Safety'.

Study A4001033

This crossover study was specifically designed to investigate the effect of maraviroc on the cardiovascular function of healthy male subjects aged 18 to 45 years. In part 1, a single sublingual spray of 0.4 mg glyceryl trinitrate (GTN) was compared to GTN placebo. In part 2, a single oral dose of maraviroc 900 mg was compared with maraviroc placebo. Systemic vascular resistance, stroke index and cardiac index was measured during both parts of the study using non-invasive impedance cardiography (ICG), as was blood pressure and pulse rate (N=16).

There were no SAEs, deaths or discontinuations. The most common treatment-related AE after maraviroc administration was postural hypotension, occurring in 3 of the 16 subjects. There were no clinically significant effects on blood pressure, pulse rate or ECG data.

Maraviroc 900 mg did not cause a clinically significant change in supine systolic or diastolic blood pressure but did, to a lesser extent than GTN, decrease systemic vascular resistance (largest mean decrease –3.9%) and stroke index (largest mean decrease –5.6%). It also increased cardiac index (largest mean increase 6.8%) and pulse rate. These results are consistent with a mild vasodilator with a fully compensated haemodynamic response for supine blood pressure, with the observed postural hypotension suggesting partial or incomplete compensation for orthostatic changes.

There were no other clinically relevant safety concerns.

2.7.4.1.1.4.2. Phase 1 Multiple-Dose Studies

Study A4001002

This first multiple-dose study with maraviroc was a double-blind, placebo-controlled study designed to investigate the safety, tolerability and pharmacokinetics of multiple oral doses of maraviroc in 72 healthy male subjects, administered BID as a solution for 3, 10, 25, 100 and 300 mg, and QD as a tablet for 600 mg.

Six separate cohorts were dosed: Cohort 1: 100 mg BID maraviroc or placebo (ratio 3:1), Cohort 2: 300 mg BID maraviroc of placebo (ratio 3:1), Cohort 3: 600 mg QD maraviroc or placebo (ratio 3:1), Cohort 4: 25 mg BID maraviroc or placebo (ratio 3:1), Cohort 5: 600 mg QD maraviroc or placebo (ratio 3:1) and Cohort 6: 3 mg BID, 10 mg BID maraviroc or placebo (ratio 5:5:2).

There were no SAEs or deaths. One subject discontinued because of a laboratory test abnormality, a severe increase in transaminase levels (maximum ALT 300 IU/mL, maximum AST 233 IU/mL), concurrent with food poisoning. There were 8 subjects (all on maraviroc)

with transaminase levels above the upper limit of normal (ULN); these values tended to increase up until the last day of treatment and then decrease thereafter. These events did not show a dose relationship. There were apparent dose-related increases in total cholesterol and low density lipoprotein (LDL) cholesterol, but not in high density lipoprotein (HDL) cholesterol.

At doses up to 300 mg BID, there were few AEs, most of which were mild or moderate. Cohort 3 reported a higher incidence of AEs than any other cohort and dosing was terminated for this cohort because 3 subjects had severe symptomatic postural hypotension at 4 hours post-dose on Day 7 (2 after 600 mg of maraviroc and 1 after placebo). After review of the blood pressure and pulse rate data from Cohort 3, this dose was repeated in Cohort 5 and was tolerated in all subjects, with no severe AEs reported and just 1 episode of mild transient postural hypotension.

There were dose-related effects on the mean maximum decrease from baseline for standing systolic blood pressure at 300 mg BID and 600 mg QD and for standing diastolic blood pressure at 600 mg QD. There were no dose-related increases in the mean maximum decreases from baseline compared to placebo for supine systolic or diastolic blood pressure. There was an increase in the maximum change from baseline for standing pulse rate at 600 mg QD (21.2 bpm, cohort 3, Day 7). There was no effect on supine pulse rate (apart from 1 subject in cohort 3 on Day 7 who received 600 mg QD). At 600 mg QD the mean postural drop in systolic blood pressure (SBP) (-16.0 mmHg, cohort 5, Day 7) and in diastolic blood pressure (DBP) (-8.0 mmHg, cohort 3, Day 7) was greater than that on placebo (-9.3 mmHg SBP, -0.5 mmHg DBP, Day 7), but only Cohort 3 at 600 mg QD on Day 7 experienced postural changes outside the range of values observed on placebo. There was an increase in the mean postural change in pulse rate compared to placebo at 600 mg QD, although all individual values lay within the ranges seen on placebo (A4001002 Clinical Study Report Section 8.2.4).

There was no obvious clinically relevant dose-related or concentration-related effect on the QTc interval over the dose/concentration range studied.

Study A4001008

This double-blind, placebo-controlled study was designed to investigate the longer term safety (28 days) of multiple oral doses of maraviroc (100 or 300 mg administered BID) in healthy subjects aged 18 to 55 years inclusive (N=16).

No SAEs, deaths or severe AEs were reported during this study. Three subjects discontinued due to AEs, none of which was considered treatment-related. The incidence of AEs was similar across treatment groups.

One subject discontinued due to laboratory abnormalities during the placebo run-in phase. No trend of increasing liver enzymes over time was seen during the study, and no liver enzyme value was more than 2 times the ULN or 3 times the baseline value in any treatment group. There was no evidence of an effect of maraviroc on lipid parameters, on blood pressure, pulse rate or ECG, including QTcF.

Study A4001019

This double-blind, placebo-controlled, parallel group study was designed to investigate the safety, tolerability and pharmacokinetics of high multiple oral doses of maraviroc, and the effect of dose escalation on tolerability.

Three separate cohorts were dosed: Cohort 1 (N=9): Days 1 to 7 - maraviroc 300 mg BID or placebo, Days 8 to 14 - maraviroc 600 mg BID or placebo, Cohort 2 (N=9): Days 1 to 7 - maraviroc 600 mg BID or placebo, Days 8 to 14 - maraviroc 900 mg BID or placebo, Cohort 3 (N=9) - Days 1 to 7 - maraviroc 900 mg QD or placebo, Days 8 to 14 - maraviroc 1200 mg QD or placebo.

There were no SAEs or deaths in this study. One subject permanently discontinued from the study because of treatment-related rash and another permanently discontinued because of infectious mononucleosis (Epstein Barr virus infection).

The study concluded that in general dose titration did not lead to improved tolerability of higher doses. Dizziness was more frequent than placebo at doses above 600 mg BID, and more subjects whose dose escalated from 600 mg BID to 900 mg BID (Cohort 2) reported dizziness than those whose dose escalated from 900 mg QD to 1200 mg QD (Cohort 3). Postural hypotension was confined to the 900 mg QD→1200 mg QD escalation cohort, and conjunctivitis and related terms were reported only in the higher dose groups (900 mg QD and BID, and 1200 mg QD). Four subjects had severe treatment-related AEs, of whom 3 had severe postural hypotension (after 900 mg QD or 1200 mg QD), and 1 had dizziness (after 600 mg). The incidence and type of all-causality AEs were similar to the treatment-related AEs.

There were no discontinuations due to laboratory abnormalities. There were 36 subjects with laboratory test result abnormalities. The number of subjects with an abnormal laboratory test result was similar in each treatment group and there was no evidence of a dose effect. There were no clinically significant median changes from baseline in any laboratory parameter measured for any maraviroc dose or for placebo. However, 7 of 9 subjects who received maraviroc 1200 mg and 1 of 2 placebo subjects had abnormal creatinine measured at 1 time point. This was thought to be explained by a batch analysis difference (See A4001019 Clinical Study Report Module 5).

For the 1200 mg QD dose, the QTcF profile was similar to that seen with placebo. There were 6 subjects with at least 1 ECG that was considered more abnormal than that taken at screening, 1 in each group except the 900 mg QD group. None of these abnormalities was considered clinically significant, although there was 1 subject who had a QTcF >450 msec after 600 mg BID and QTcF increases ≥60 msec after 900 mg BID.

This study is discussed further in Section 2.7.4.2.1.5.1, 'Cardiovascular Safety'.

2.7.4.1.1.4.3. Phase 2a Studies

No safety concerns were identified by Studies A4001007 and A4001015 (refer to the individual Clinical Study Reports Module 5.3.4.2, Patient PD and PK/PD Study Reports for further details). Of note, approximately 40 months after the end of the 10-day maraviroc treatment in Study A4001007, 1 patient (PID 1[redacted]1301, a 4[redacted]year old male) reported a B cell lymphoma that was judged by the Investigator as treatment-related.

2.7.4.1.1.4.4. Phase 2b/3 Studies

In each of the Phase 2b/3 Studies in TE patients, 3 treatment groups received OBT (3-6 drugs prescribed by the Investigator based on treatment history and resistance testing excluding low-dose ritonavir) plus either maraviroc QD, maraviroc BID or placebo as blinded therapy. For both maraviroc treatment groups, patients whose OBT included a PI (other than tipranavir/ritonavir) or delavirdine received a maraviroc unit dose of 150 mg (see Section 2.7.4.1.3.3.1).

Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

Two multicentre, randomised, double-blind, placebo-controlled registrational Phase 3 superiority studies (Studies A4001027 and A4001028) were conducted to support this application in R5 TE patients. The study design was identical for both studies and the patient populations were similar between studies and between treatment groups. Therefore these 2 studies are described together in this section of the document.

Objectives: The primary objective of these studies was to confirm the hypothesis that maraviroc in combination with OBT provides an additional reduction in plasma HIV-1 RNA compared with placebo in combination with OBT, as measured by the difference between each of the 2 maraviroc regimens versus placebo in the mean change from baseline in plasma HIV-1 RNA at Weeks 24 and 48.

Methods of Study: Patients (585 in A4001027 and 464 in A4001028) received a maraviroc 300 mg QD or 300 mg BID dose equivalent or placebo (all in combination with open-label OBT) in a double-blind manner, with a 2:2:1 randomisation. No food restrictions were recommended for these studies. Most of these patients were receiving at least 1 PI (other than tipranavir/ritonavir) or delavirdine in their OBT, and therefore received a dose adjustment to 150 mg maraviroc.

Subjects who experienced treatment failure while on blinded therapy and whose infecting virus remained CCR5-tropic were given the option of switching to OL maraviroc BID therapy. These subjects continued to follow protocol-defined visit schedules and procedures. Any subject whose viral load increased to more than 3 times the value at early termination was considered a treatment failure during the OL phase (CSRs Section 5.2.5).

Safety Summary The data presented are from a pre-planned interim analysis for efficacy at Week 24, and include all safety data from all patients to Week 24, and all further available safety data up to the Week 48 visit or the date of database cut, whichever was sooner.

The study population for both studies consisted predominantly of white males. The distribution of age, gender and racial groups was similar for all treatment groups.

Maraviroc appeared to be well tolerated. Little difference in the safety profile was observed between the maraviroc and placebo treatment groups, despite the longer duration of therapy for both maraviroc treatment groups compared with the placebo treatment group.

In Study A4001027, deaths were evenly distributed, with 2 occurring in each maraviroc dosing arm and 1 on placebo. In Study A4001028, 4 deaths occurred in each of the maraviroc treatment groups, but none on placebo in patients on treatment or within 28 days of discontinuing study drug and 5 deaths occurred in each of the maraviroc treatment groups, but none in placebo irrespective of time on or off study drug. This should be seen in the context of the 2:2:1 randomisation schedule and the increased treatment duration in the maraviroc treatment groups relative to placebo. No deaths were reported as treatment-related. Eleven other subjects died in the 5 to 6 weeks between screening and randomisation for these 2 studies, reflecting the advanced state of disease in this subject population.

The AE profile was similar between the treatment groups. The numbers of treatment-related SAEs were low, though a slight preponderance of treatment-related SAEs occurred in the maraviroc treatment groups. There was a higher incidence of malignancies in the placebo treatment group. No important differences in the incidence of Grade 3/4 laboratory test abnormalities were noted between the treatment groups. There was no clinically relevant effect on liver enzymes. There were no clinically relevant effects on blood pressure or pulse rate, and the incidence of postural hypotension was low and similar in all treatment groups. There was no evidence of a mean increase from baseline in QTcF at Week 24 for either maraviroc treatment group relative to placebo.

Detailed analyses of the merged datasets from these 2 studies form the majority of the presentations discussed below.

Phase 2b Study in non-R5 TE patients (Study A4001029)

Although similar in design to Studies A4001027 and A4001028, the primary objective of Study A40001029 was to assess safety of maraviroc usage in non-CCR5 tropic HIV-1 infected patients with otherwise optimised therapy. This study recruited 186 subjects who underwent a 1:1:1 randomisation to maraviroc QD, maraviroc BID or placebo, all in combination with OBT.

There were 7 deaths (2 maraviroc QD, 2 maraviroc BID and 3 placebo) in this study, but none was considered treatment-related. Another death occurred in the pre-randomisation period. Thirty patients reported an SAE (10 maraviroc QD, 9 maraviroc BID and 11 placebo) but none was considered treatment-related. Although 2 subjects experienced SAEs that resulted in discontinuation, in neither case were the events considered treatment-related. Six patients permanently discontinued from the study due to AEs (2 maraviroc BID, 4 placebo). For 3 of these patients, an event was considered treatment-related: 1 subject on maraviroc BID (neutropaenia) and 2 on placebo (1 with nausea, vomiting, malaise, pyrexia, and oral paraesthesia and 1 with diarrhoea, nausea and lethargy).

There were 7 category C infections in the maraviroc QD group, 3 in the maraviroc BID and 3 in the placebo groups. There were no category C malignancies during the period of observation.

Approximately 90% of patients in each group reported at least 1 all-causality AE, and approximately 50% reported treatment-related AEs.

There were no important differences in the incidence of Grade 3/4 laboratory test abnormalities between the treatment groups. Overall, the incidence of liver function test (LFT) abnormalities was low and similar between groups. One patient in the maraviroc BID group had a significant (Grade 3) increase in creatinine concentration. There was some evidence of a higher incidence of Grade 3/4 increases in serum amylase and lipase in the maraviroc groups compared to placebo, and more Grade 4 amylase and lipase abnormalities were observed in the maraviroc BID group. However, the number of patients was small and none of these abnormalities was associated with clinical pancreatitis. There was a Grade 3/4 increase in ALT in the maraviroc QD group and 2 in the placebo group, but none in the BID group.

The incidence of increase in total cholesterol, LDL cholesterol and triglyceride concentration was low and similar between treatment groups. However, there was some evidence of an increase in HDL cholesterol in the maraviroc groups compared to placebo. There were no clinically significant median changes from baseline in any laboratory parameter measured for any treatment group.

Mean blood pressure and pulse rate were similar between treatment groups at baseline and were not changed significantly at the last observation. There was some evidence of a higher incidence of postural hypotension at Week 2 for patients on maraviroc than for those on placebo, but this was no longer the case at Week 24 (though the number of patients was small).

There were no permanent or temporary discontinuations due to syncope, dizziness or postural hypotension.

Mean baseline ECG parameters were similar between treatment groups and there were no significant mean changes from baseline in any treatment group. Two male patients, both in the placebo group, had a QTcF ≥450 msec. No female patient had a QTcF ≥470 msec. No patient had a QTcF change from baseline ≥60 msec.

Phase 2b/3 study in R5 treatment-naïve patients (Study A4001026)

This double-blind, comparator-controlled non-inferiority Phase 2b/3 study in treatment-naïve patients infected with CCR5-tropic HIV-1 was designed to determine the safety and efficacy of maraviroc with zidovudine/lamivudine compared to efavirenz with zidovudine/lamivudine.

The 300 mg QD arm of this study was discontinued in January 20[redacted] based on recommendation from the DSMB. Only unblinded safety data from this discontinued QD arm and from ongoing OL treatment are presented in this Safety Summary. Listings for SAEs are

also provided in this submission for the blinded treatment arms (maraviroc 300 mg BID versus efavirenz); the Sponsor, however, remains blinded for these and therefore no comparator data are available.

Five patients who enrolled in Study A4001026 are known to have died as of September 15th. Two died within 28 days of discontinuing their double-blind therapy, 1 from Castleman's Disease (efavirenz) and the other by suicide (maraviroc QD). Three other patients have been reported to have died, all more than 90 days following discontinuation of therapy, with causes of death reported as Hodgkin's disease (efavirenz), Non Hodgkin's lymphoma (maraviroc QD) and pneumonia/liver failure (maraviroc BID).

Twenty-one patients experienced SAEs during treatment in the QD arm of this study, in 4 of whom the SAEs were considered treatment-related. SAEs for the ongoing blinded treatment are presented in Table 3.8.1.4 Summary of Clinical Safety.

Thirteen patients in the maraviroc 300 mg QD treatment group permanently discontinued from the study due to AEs; 8 of these were considered treatment-related. AEs in 6 patients were considered serious; in 3 patients these were assessed by the Investigator as treatment-related and led to permanent discontinuation of study drug (arthralgia, rash, pyrexia, myalgia and asthaenia; rash and toxic hepatitis; and Stevens-Johnson syndrome). The event of toxic hepatitis resulted in the patient requiring orthotopic liver transplantation. (See narrative case description in the Clinical Study Report, Module 5.3.5.4 Other Study Reports).

Six Category C AIDS-defining illnesses were reported in the maraviroc 300 mg QD treatment group (2 cases of tuberculosis, 3 cases of *Pneumocystis* pneumonia and 1 case of Kaposi's sarcoma).

AEs (all-causality) were reported by 85% of patients in the maraviroc 300 mg QD treatment group. Most were mild to moderate in severity.

Few patients had laboratory abnormalities with maximum on-treatment values of Grade 3/4 in the 300 mg QD or the OL treatment groups.

In the OL maraviroc 300 mg BID period, 1 patient discontinued due to a Grade 3 abnormality in ALT, which was considered related to study drug. Nine patients experienced SAEs during treatment with OL maraviroc 300 mg BID, none of which was considered treatment-related. No patients died in the OL maraviroc 300 mg BID group.

AEs (all causality) were reported by 64% of patients in the OL maraviroc 300 mg BID group. No single AE was reported in >5% of patients. Most AEs reported were mild to moderate in severity.

2.7.4.1.2. Overall Extent of Exposure

2.7.4.1.2.1. Phase 1 Studies – Overall Extent of Exposure

A total of 674 subjects were evaluated for safety in the Phase 1 clinical programme, 632 of whom received maraviroc alone. During the Phase 1 studies subjects received single doses of

maraviroc ranging from 1 to 1200 mg, or multiple doses of maraviroc ranging from 3 to 900 mg BID and 1200 mg QD, for periods ranging from 7 to 28 days.

Phase 1 Single-Dose Studies

In total, 299 subjects (including 37 HIV-1 infected patients) received single doses of maraviroc in Phase 1 single-dose studies.

Phase 1 Multiple-Dose Studies

In total, 333 healthy volunteers received maraviroc, with a mean duration of 11 days (range 1 to 28 days, Table 5).

Table 5. Duration of Therapy (Days) for the Phase 1 Multiple-Dose Studies

Duration of Therapy	Placebo	Maraviroc Dose (mg)									Maraviroc only[a]
		<100	100 BID	150 BID	300 BID	600 QD	600 BID	900 QD	900 BID	1200 QD	
N	57	19	149	12	81	18	17	9	8	9	297
Mean (Days)	13.4	11.6	11.4	8.0	14.4	9.5	6.6	7.0	7.0	7.0	11.3
Minimum	1	5	1	8	3	7	1	7	7	7	1
Maximum	28	12	28	8	28	12	7	7	7	7	28

Source: SCS Table 1.2.2
[a] Subjects who received one or more doses of maraviroc without interactant for a period of the study
Includes Studies A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042

2.7.4.1.2.2. Phase 2a Studies – Overall Extent of Exposure

During the Phase 2a Studies (A4001007 and A4001015) a total of 66 HIV-1 infected patients received maraviroc as monotherapy for 10 days in doses ranging from 50 to 300 mg BID or 25 to 300 mg QD, except 2 patients who discontinued (1 male in Study A4001007 who decided not to participate further in the study 3 days after starting maraviroc 25 mg QD, and 1 patient receiving maraviroc 100 mg QD in Study A4001015 who discontinued prior to dosing on day 3 due to a moderate headache that was not considered treatment-related) (see Section 2.7.4.2.1.4.1.1).

2.7.4.1.2.3. Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029) - Overall Extent of Exposure

A total of 964 TE patients received at least 1 dose of maraviroc (QD or BID) in the Phase 2b/3 studies (Table 6), including 840 R5 TE patients in the pivotal Studies A4001027 and A4001028.

The duration of treatment with maraviroc QD and BID is much greater than that with placebo in studies in the Phase 3 R5 TE population (Studies A4001027 and A4001028). In contrast, the duration of exposure for the non-R5 TE population (Study A4001029) was similar for the 3 treatment groups (Table 6).

Table 6. Exposure to Maraviroc during the Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

Duration Categories (Days)	Maraviroc QD		Maraviroc mg BID		Placebo	
	R5[a]	Non-R5[b]	R5[a]	Non-R5[b]	R5[a]	Non-R5[b]
N	**414**	**63**	**426**	**61**	**209**	**62**
<1	0	0	1	0	0	1
2-14	5	0	5	1	2	2
15-28	1	0	11	2	2	1
29-90	51	19	53	12	64	20
91-180	104	19	92	17	60	14
181-364	248	25	262	29	80	24
≥365	5	0	2	0	1	0
Median (Days)	235.5	119.0	238.5	176.0	145	127.0
Range (Days)	2-381	64-317	1-366	11-326	7-427	1-318
Total Exposure (patient-years)[c]	**258.7**	**26.4**	**266.8**	**27.9**	**99.3**	**25.0**

Source: Tables 3.2.1.1 and 3.2.1.2 Summary of Clinical Saftey, A4001029 Week 24 Clinical Study Report Table 13.3.1.1 and Risk Management Plan Tables 0.1.1 and Table 0.1.2.
[a] R5 Tropic = Patients included in Studies A4001027 and A4001028
[b] Non R5 = Patients included in Study A4001029
[a] The sum of all subjects' duration of treatment, expressed in years.

Between 80 and 90% of patients dosed with maraviroc in these studies received unit doses of 150 mg, because their OBT included a PI (other than tipranavir/ritonavir) or delavirdine (see Section 2.7.4.1.3.3.1). The calculation of duration of therapy represents data collected to the patient's Week 24 visit and any subsequent exposure to a maximum of 48 weeks for each individual (see Section 2.7.4.1.1.3.3). This therefore, is an under-representation of exposure when considering the SAE and death data, but is accurate for the AE and laboratory data presented.

2.7.4.1.3. Demographic and Other Characteristics of Study Population

The demographic characteristics were recorded at the screening visit in all studies; refer to the individual clinical study reports (CSRs) for further details.

Maraviroc studies have not been conducted in children or adolescents ≤16 years.

2.7.4.1.3.1. Phase 1 Studies – Demography

Of the 674 subjects exposed to treatment in these studies, 529 were male and 145 were female.

Phase 1 Single-Dose Studies

The demographic characteristics of the single-dose studies were comparable between treatment groups and were similar to those of the multiple-dose studies (Table 1.3.1 Summary of Clinical Safety). A total of 241 males and 58 females were evaluated in these studies, of which 205 males and 57 females received maraviroc alone.

Phase 1 Multiple-Dose Studies

During the multiple-dose studies, 288 males and 87 females were evaluated. Of these subjects, 230 males and 67 females received maraviroc alone for a period of the study. Most subjects in these studies were aged 18-44 years and were white (Table 7). The demographic characteristics were comparable between treatment groups.

Table 7. Demographics for the Phase 1 Multiple-Dose Studies

Characteristic	Placebo	MVC Dose (mg)									MVC only[a]
		<100 BID	100 BID	150 BID	300 BID	600 QD	600 BID	900 QD	900 BID	1200 QD	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
N	**57**	**19**	**149**	**12**	**81**	**18**	**17**	**9**	**8**	**9**	**297**
Sex											
Male	34 (59.6)	19 (100)	117 (78.5)	6 (50.0)	60 (74.1)	18 (100)	9 (52.9)	5 (55.6)	4 (50.0)	5 (55.6)	230 (77.4)
Age											
18-44	55 (96.5)	19 (100)	144 (96.6)	12 (100)	81 (100)	18 (100)	17 (100)	9 (100)	8 (100)	9 (100)	292 (98.3)
Race											
White	55 (96.5)	17 (89.5)	138 (92.6)	11 (91.7)	52 (64.2)	17 (94.4)	17 (100)	9 (100)	8 (100)	9 (100)	253 (85.2)
Black	1 (1.8)	2 (10.5)	6 (4.0)	0	5 (6.2)	1 (5.6)	0	0	0	0	14 (4.7)
Asian	0	0	3 (2.0)	0	23 (28.4)	0	0	0	0	0	26 (8.8)
Other	1 (1.8)	0	2 (1.3)	1 (8.3)	1 (1.2)	0	0	0	0	0	4 (1.3)

Source: Table 1.3.2 Summary of Clinical Safety
Key: MVC – maraviroc
[a] Subjects who received one or more doses of maraviroc without interactant for a period of the study.
Includes Studies A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042

2.7.4.1.3.2. Phase 2a Studies – Demography

A total of 80 males and 2 females were evaluated in Studies A4001007 and A4001015 (SCS Table 2.3.1). The baseline demographics and disease characteristics were similar across all treatment groups, with a mean baseline viral load of 4.62 $\log_{10}$ HIV-1 RNA copies/mL (range 3.56-5.64 $\log_{10}$ copies/mL) and a mean CD4 cell count of 544 cells/μL (range 205-1137 cells/μL).

2.7.4.1.3.3. Phase 2b/3 Studies – Demography

The treatment-experienced study population was predominantly male (85-90%) and white (~80%), which is consistent with other recently conducted clinical trials in this population.[ii, iii] Very few patients fell outside the age range of 16 to 64 years, with a similar racial mix for all treatment groups (Table 8).

Table 8. Demographics for the Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

Characteristic	Maraviroc QD		Maraviroc BID		Placebo	
	R5	Non-R5	R5	Non-R5	R5	Non-R5
N	**414**	**63**	**426**	**61**	**209**	**62**
Sex						
Male	363 (87.7)	53 (84.1)	382 (89.7)	55 (90.2)	185 (88.5)	53 (85.5)
Female	51 (12.3)	10 (15.9)	44 (10.3)	6 (9.8)	24 (11.5)	9 (14.5)
Age (years)						
<16 or <18	0	2 (3.2)	0	2 (3.3)	0	0
16 or 18-44	203 (49.0)	33 (52.4)	196 (46.0)	35 57.4)	99 (47.4)	34 (54.8)
45-64	201 (48.6)	28 (44.4)	225 (52.8)	24 (39.3)	107 (51.2)	27 (43.5)
≥65	10 (2.4)	0	5 (1.2)	0	3 (1.4)	1 (1.6)
Mean	**45.6**	**42.7**	**46.3**	**42.5**	**45.7**	**44.6**
Range	**17-75**	**16-59**	**21-73**	**16-62**	**29-72**	**23-65**
Race						
White	336 (81.2)	46 (73.0)	363 (85.2)	44 (72.1)	178 (85.2)	40 (64.5)
Black	70 (16.9)	17 (27.0)	51 (12.0)	13 (21.3)	26 (12.4)	18 (29.0)
Asian	3 (0.7)	0	5 (1.2)	1 (1.6)	1 (0.5)	3 (4.8)
Other	4 (1.0)	0	7 (1.6)	3 (4.9)	4 (1.9)	1 (1.6)
Unspecified	1 (0.2)	0	0	0	0	0

Source: SCS Table 3.3.1.2 and A4001029 24 Week Clinical Study Report Table 13.2.1.1
Key: MVC – maraviroc
R5 = Studies A4001027 and A4001028
Non-R5 = Study A4001029
Age <16 years for CCR5-Tropic and All MVC and <18 for A4001029

The demographic characteristics were comparable between treatment groups for each population, and were similar between R5 TE patients (Studies A4001027 and A4001028) and non-R5 TE patients (Study A4001029).

For Studies A4001027 and A4001028, the duration since diagnosis and mean number of antiretroviral treatments since diagnosis indicate that the study population was highly TE (Table 9). The percentage of patients with screening multi-class resistance (GSS, PSS and OSS ≤ 2) was likewise consistent with a TE population and was similar between treatment groups.

Table 9. Characteristics for the Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

Characteristic	Maraviroc QD N (%)[a]		Maraviroc BID N (%)[a]		Placebo N (%)[a]	
	R5	Non-R5	R5	Non-R5	R5	Non-R5
N	**414**	**63**	**426**	**61**	**209**	**62**
Duration since first diagnosis (years)						
Mean	14.2	13.8	13.9	13.8	14.3	12.9
Range	1-28	6-21	2-26	5-24	3-25	2-20
ARVs taken						
Median number	11	12	11	10	11	11
Median duration (years)	9.9	9.6	9.8	9.4	10	9.0
HIV-1 Exposure Category						
Male to male sexual contact	291	40	289	35	146	40
Injection drug use	18	4	22	4	16	1
Other	5	1	16	4	15	2
Blood products	6	0	11	2	3	4
Heterosexual	88	15	83	13	34	15
Perinatal	3	3	1	2	0	0
Hepatitis B surface antigen positive at baseline	22 (5.3)	-	28 (6.6)	-	17 (8.1)	-
Hepatitis C virus RNA positive at baseline	16 (3.9)	5 (7.9)	29 (6.8)	4 (6.6)	19 (9.1)	2 (3.2)
Delta 32 status						
Deletion/WT	32 (7.7)	12 (19.0)	28 (6.6)	5 (8.2)	16 (7.7)	9 (14.5)
WT/WT	357 (86.2)	44 (69.8)	373 (87.6)	54 (88.5)	176 (84.2)	46 (74.2)
Missing	25 (6.0)	7 (11.1)	25 (5.9)	2 (3.3)	17 (8.1)	7 (11.3)
CD4 Cell count at baseline (cells/μL)						
<50	85	31	85	27	37	29
≥50	322	26	334	25	169	25
Missing	1	6	0	9	1	8
Mean	195.7	84.9	189.2	102.4	187.2	104.7
Median	171.0	40.8	166.8	59.0	171.3	50.3
HIV-1 RNA baseline (mean of 3)						
Mean	4.86	5.03	4.85	5.10	4.86	5.01
Median	4.89	5.10	4.86	5.17	4.89	5.10
(min, max)	(2.5,6.8)	(3.4-5.9)	(3.0-6.9)	(3.6-6.7)	(3.5-7.1)	(3.6-6.2)

Source: Summary of Clinical Safety Tables 3.3.3.3, 3.3.3.4, 3.4.9.8, 3.4.9.4, 3.4.9.14, 3.4.9.5, 3.4.9.13, 13.4.9.14 and Summary of Clinical Efficacy Tables 13.4.3.1.1 and 13.4.4.1.1; and A4001029 Clinical Study Report Tables 13.2.2,13.2.4, 13.10.1, 13.7.8.1.

[a] N shown where applicable

WT = wild type

R5 = Studies A4001027 and A4001028

Non-R5 = Study A4001029

The most common HIV exposure category in each treatment group was male-to-male sexual contact, followed by heterosexual exposure. Baseline viral loads and CD4 counts were similar between treatment groups and between populations. Relatively few patients were positive for

hepatitis B surface antigen or hepatitis C virus (HCV) RNA. There was a similar frequency of the CCR5Δ32 deletion genotype in the maraviroc QD, maraviroc BID and placebo groups.

2.7.4.1.3.3.1. Dose Adjustment

Patients whose OBT included a PI (except tipranavir/ritonavir) and/or delavirdine received a maraviroc unit dose of 150 mg, because these drugs are CYP3A4 inhibitors and maraviroc is a CYP3A4 substrate. Drug-drug interaction data indicated that this adjustment should ensure that a maraviroc 300 mg equivalent maximum plasma concentration would not be exceeded. Patients on all other OBT regimens received a maraviroc unit dose of 300 mg. Most patients in the TE studies had an OBT regimen that included at least 1 PI. The percentage of patients dosed with 150 mg maraviroc was similar between treatment groups within each study (Table 10).

Table 10. Dose Adjustments for Concomitant OBT Containing PI (Except Tipranavir/Ritonavir) and/or Delavirdine in Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

	Maraviroc QD n/N (%)	Maraviroc BID n/N (%)	Placebo n/N (%)
A4001027	202/232 (87%)	191/235 (81%)	99/118 (84%)
A4001028	118/182 (65%)	144/191 (75%)	72/91 (79%)
A4001029	57/63 (91%)	57/61 (93%)	61/62 (98%)

Source: A4001027, A4001028 and A4001029 Week 24 Clinical Study Reports.
QD = Once daily dosing; BID = Twice daily dosing.

2.7.4.2. Adverse Events

2.7.4.2.1. Analysis of Adverse Events

In general, the AE profile for unit doses ≤300 mg in Phase 1 resembled that observed with placebo. The dose-limiting AE identified by the Phase 1 clinical programme was postural hypotension. Few patients discontinued due to postural hypotension during the Phase 2b/3 studies. Potential safety issues identified pre-clinically or during the Phase 1 clinical programme such as postural hypotension and effects on QTc interval are discussed further in Section 2.7.4.2.1.5.

2.7.4.2.1.1. Common Adverse Events

The Investigator rated the maximum intensity of each AE reported in the Phase 2b/3 studies as MILD, MODERATE, SEVERE or VERY SEVERE. Provided in the protocol were both the standard grading of AE severity by the Sponsor and the more specific ACTG grading, which includes a general description but also, for many AEs, a clear definition of specific features required for each grade of severity:

Pfizer standard Grading

MILD	Events which are usually transient, requiring no special treatment, do not interfere with the patient's daily activities.
MODERATE	Events which introduce a low level of inconvenience or concern patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
SEVERE	Events that interrupt the patient's usual daily activity and traditionally require systemic drug therapy or other treatment.
VERY SEVERE	Events which are unacceptable and intolerable or which are irreversible or cause the patient to be in imminent danger of death.

The ACTG toxicity table was used to grade severity for the AEs; for abnormalities not explicitly defined, the following scale was used to attribute grade of severity:

ACTG toxicity table

GRADE 1 MILD	Transient or mild discomfort; no limitation in activity; no medical intervention/ therapy required.
GRADE 2 MODERATE	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3 SEVERE	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4 LIFE THREATENING	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

2.7.4.2.1.1.1. Phase 1 Studies – Adverse Events

The incidence of AEs in these studies was low for unit doses less than 600 mg.

2.7.4.2.1.1.1.1. Phase 1 Single-Dose Studies

A total of 250 all-causality AEs were reported by 135 of the 262 subjects who received maraviroc in the Phase 1 single-dose studies. The AE profile reported for the single-dose studies is similar to that of the multiple-dose studies. Most AEs reported during these studies were classified as treatment-related (177 AEs, reported by 100 of the 262 patients) (SCS Tables 1.4.1.1 and 1.4.1.2). Postural hypotension was the dose-limiting AE in these studies.

2.7.4.2.1.1.1.2. Phase 1 Multiple-Dose Studies

All-Causality Adverse Events

A total of 790 all-causality AEs were reported by 188 of the 297 individual subjects who received 1 or more doses of maraviroc alone (without interactant) in any period of the Phase 1 multiple-dose studies. Most were mild or moderate in severity.

The most frequent all-causality AEs of maraviroc-treated subjects (occurring in ≥2%) following multiple doses are presented in Table 11.

Table 11. All-Causality Adverse Events Reported in ≥2% of Subjects in the Phase 1 Multiple-Dose Studies

System Organ Class Preferred Term	Placebo	Dose of MVC (mg) [a]									All MVC Doses [b]
	N (%)	<100 N (%)	100 BID N (%)	150 BID N (%)	300 BID N (%)	600 QD N (%)	600 BID N (%)	900 QD N (%)	900 BID N (%)	1200 QD N (%)	N (%)
N	57	19	149	12	81	18	17	9	8	9	297
Eye Disorders											
Ocular hyperaemia	0	0	0	0	0	0	0	5 (55.6)	5 (62.5)	5 (55.6)	11 (3.7)
Visual blurred	1 (1.8)	0	3 (2.0)	0	0	3(16.7)	3(17.6)	3 (33.3)	3 (37.5)	0	14 (4.7)
Gastrointestinal Disorders											
Abdominal discomfort	2 (3.5)	0	2 (1.3)	4(33.3)	0	0	1 (5.9)	0	0	0	7 (2.4)
Abdominal pain	1 (1.8)	2 (10.5)	0	0	4 (4.9)	1 (5.6)	0	0	0	2 (22.2)	9 (3.0)
Diarrhoea	3 (5.3)	1 (5.3)	3 (2.0)	0	4 (4.9)	1 (5.6)	0	0	0	0	9 (3.0)
Dry Mouth	0	0	3 (2.0)	0	2 (2.5)	0	2 (11.8)	2 (22.2)	1 (12.5)	3 (33.3)	12 (4.0)
Dyspepsia	3 (5.3)	1 (5.3)	2 (1.3)	1 (8.3)	3 (3.7)	1 (5.6)	0	0	0	0	8 (2.7)
Flatulence	6 (10.5)	1 (5.3)	4 (2.7)	3(25.0)	8 (9.9)	6 (33.3)	1 (5.9)	1 (11.1)	0	0	24 (8.1)
Nausea	6 (10.5)	2 (10.5)	6 (4.0)	0	7 (8.6)	1 (5.6)	6 (35.3)	4 (44.4)	3 (37.5)	2 (22.2)	26 (8.8)
Vomiting	1 (1.8)	1 (5.3)	2 (1.3)	0	2 (2.5)	1 (5.6)	0	0	0	0	6 (2.0)
General Disorders and Administration Site Conditions											
Fatigue	4 (7.0)	0	8 (5.4)	1 (8.3)	4 (4.9)	2 (11.1)	3 (17.6)	6 (66.7)	1 (12.5)	3 (33.3)	25 (8.4)
Infections and Infestations											
Nasopharyngitis	5 (8.8)	1 (5.3)	7 (4.7)	0	2 (2.5)	1 (5.6)	1 (5.9)	0	0	0	12 (4.0)
Musculoskeletal and Connective Tissue Disorders											
Back Pain	3 (5.3)	1 (5.3)	3 (2.0)	0	1 (1.2)	2 (11.1)	1(5.9)	0	0	0	8 (2.7)
Pain in extremity	2 (3.5)	0	2 (1.3)	0	4 (4.9)	0	0	0	1 (12.5)	0	7 (2.4)
Nervous System Disorders											
Dizziness	6 (10.5)	0	7 (4.7)	1 (8.3)	5 (6.2)	5 (27.8)	6 (35.3)	3 (33.3)	7 (87.5)	3 (33.3)	32 (10.8)
Dizziness postural	1 (1.8)	2 (10.5)	0	0	0	4 (22.2)	3 (17.6)	0	2 (25.0)	0	11 (3.7)
Headache	15 (26.3)	2 (10.5)	16 (10.7)	3 (25.0)	24 (29.6)	5 (27.8)	3 (17.6)	3 (33.3)	5 (62.5)	3 (33.3)	60 (20.2)
Somnolence	2 (3.5)	0	0	0	0	2 (11.1)	4 (23.5)	0	6 (75.0)	0	8 (2.7)
Respiratory, Thoracic and Mediastinal Disorders											
Cough	2 (3.5)	0	3 (2.0)	0	2 (2.5)	0	1 (5.9)	0	1 (12.5)	0	7 (2.4)
Epistaxis	1 (1.8)	2 (10.5)	1 (0.7)	0	0	1 (5.6)	2(11.8)	0	2 (25.0)	1 (11.1)	9 (3.0)
Nasal Congestion	0	1 (5.3)	3 (2.0)	0	1 (1.2)	1 (5.6)	4(23.5)	2 (22.2)	3 (37.5)	1 (11.1)	15 (5.1)
Pharyngolaryngeal pain	3 (5.3)	1 (5.3)	5 (3.4)	0	7 (8.6)	1 (5.6)	1 (5.9)	0	0	0	14 (4.7)
Skin and Subcutaneous Tissue Disorders											
Dry skin	0	0	5 (3.4)	0	1 (1.2)	0	0	0	1 (12.5)	0	7 (2.4)
Vascular Disorders											
Orthostatic hypotension	1 (1.8)	0	2 (1.3)	0	3 (3.7)	3(16.7)	0	5 (55.6)	0	6 (66.7)	14 (4.7)

Source: SCS Table 1.4.2.1; [a] Subjects who received maraviroc without interactant for a period of the study; [b] Subjects who have received >1 dose of maraviroc in crossover studies, are counted once for each dose they received. AEs are counted for each dose; [c] subjects who have received > 1 dose of maraviroc in the crossover studies, are counted only once. AEs are counted only once

Some AEs were reported exclusively or more frequently at higher doses, suggesting a dose-response relationship (although often the total number of events was small). Orthostatic hypotension, ocular hyperaemia and blurred vision showed a clear dose-response, with a distinct threshold above which they occur more frequently than with placebo. Though this threshold differed among these AEs, in all cases it was above the proposed clinical dose of 300 mg BID. Other AEs that showed some evidence for a dose-response relationship include dry mouth, nausea, fatigue, dizziness, headache and nasal congestion. Postural hypotension in particular was noted to be temporally associated with C_{max}.

There was no apparent difference between the AE profiles for males and females in these multiple-dose studies.

Treatment-Related Adverse Events

Most AEs reported during the Phase 1 multiple-dose studies were classified as treatment-related. A total of 637 treatment-related AEs were reported by 145 of the 297 individual subjects who received maraviroc alone (SCS Table 1.4.2.2).

The most frequent (≥5%) treatment-emergent, treatment-related adverse events occurring in maraviroc-treated subjects from the Phase 1 multiple-dose studies were: headache (18.2%), dizziness (10.1%), fatigue (8.1%), nausea (7.4%), flatulence (7.4%), vision blurred (4.7%) and orthostatic hypotension (4.7%).

2.7.4.2.1.1.2. Phase 2a Studies – Adverse Events

All-Causality Adverse Events

A total of 124 all-causality AEs were reported by 46 of the 66 individual patients who received 1 or more doses of maraviroc in Phase 2a Studies A4001007 and A4001015 (SCS Table 2.4.1.1).

The AE profile in these studies was similar to that seen in the Phase 1 studies. The most frequently reported events were: headache (25.8%, 17/66), dizziness (10.6%, 7/66) fatigue (10.6%, 7/66), nausea (7.6%, 5/66) and flatulence (6.1%, 4/66). The majority of the AEs were mild or moderate. The AE profile for all treatment groups (including placebo) was similar, with no evidence of a dose relationship for any AE at the doses studied in the Phase 2a population; however, the doses studied are below the threshold at which dose relationships became apparent in the healthy volunteer Phase 1 database (i.e., unit doses of 600 mg).

Treatment-Related Adverse Events

A total of 67 treatment-related AEs were reported by 30 of the 66 individual subjects who received 1 or more doses of maraviroc in the Phase 2a studies. The most frequently reported treatment-related AEs were headache, dizziness and fatigue (SCS Table 2.4.1.2).

2.7.4.2.1.1.2.1. Adverse Events in Phase 2b/3 Studies

2.7.4.2.1.1.2.2. Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028) - Adverse Events

All-Causality Adverse Events

Altogether, 749 of the 840 TE R5 patients (89.2%) who received at least 1 dose of maraviroc in the Phase 3 studies reported at least 1 AE. The proportion of patients reporting AEs was similar between the 2 maraviroc regimens, and only slightly higher than that in the placebo group (Table 12). Of note, these rates do not take into account duration of treatment, which was considerably longer for both maraviroc treatment groups (Table 6).

The most common AEs (occurring in ≥5% of patients in the combined maraviroc treatment group) reported during the Phase 3 studies, in decreasing order of frequency, were: diarrhoea, nausea, headache, fatigue, cough, upper respiratory tract infection, pyrexia, dizziness, vomiting, rash, nasopharyngitis, injection site reaction, insomnia, bronchitis, back pain and constipation (Table 12).

Most AEs that were reported at incidences of ≥2% in either maraviroc regimen were reported at similar incidences in the placebo group. AEs that occurred at ≥2%, and at a higher incidence than placebo (differing by at least 3% or by 3-fold), were: pyrexia, cough, upper respiratory tract infection, rash, herpes simplex, myalgia, dysuria, dyspnoea, ALT increased, AST increased, blood creatine phosphokinase increased and influenza (Table 12).

Table 12. All-Causality Adverse Events Reported in ≥2% of Patients in the Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

System Organ Class MedDRA Preferred Term	Maraviroc QD N (%)	Maraviroc BID N (%)*	Placebo N (%)	Combined Maraviroc Doses N (%)
Subjects Evaluable for AEs	**414**	**426**	**209**	**840**
Subjects With AEs	**366 (88.4)**	**383 (89.9)**	**175 (83.7)**	**749 (89.2)**
Blood and Lymphatic System Disorders				
Anaemia	9 (2.2)	12 (2.8)	6 (2.9)	21 (2.5)
Gastrointestinal Disorders				
Abdominal distension	14 (3.4)	10 (2.3)	6 (2.9)	24 (2.9)
Abdominal pain	18 (4.3)	19 (4.5)	7 (3.3)	37 (4.4)
Abdominal pain upper	20 (4.8)	14 (3.3)	7 (3.3)	34 (4.0)
Constipation	19 (4.6)	23 (5.4)	6 (2.9)	42 (5.0)
Diarrhoea	94 (22.7)	89 (20.9)	45 (21.5)	183 (21.8)
Dyspepsia	10 (2.4)	11 (2.6)	5 (2.4)	21 (2.5)
Flatulence	14 (3.4)	16 (3.8)	9 (4.3)	30 (3.6)
Nausea	75 (18.1)	73 (17.1)	39 (18.7)	148 (17.6)
Vomiting	38 (9.2)	31 (7.3)	20 (9.6)	69 (8.2)
General Disorders and Administration Site Conditions				
Asthenia	16 (3.9)	11 (2.6)	5 (2.4)	27 (3.2)
Fatigue	45 (10.9)	54 (12.7)	31 (14.8)	99 (11.8)
Injection site reaction	28 (6.8)	31 (7.3)	18 (8.6)	59 (7.0)
Oedema peripheral	14 (3.4)	9 (2.1)	6 (2.9)	23 (2.7)
Pain	5 (1.2)	9 (2.1)	4 (1.9)	14 (1.7)
Pyrexia	30 (7.2)	51 (12.0)	17 (8.1)	81 (9.6)
Infections and Infestations				
Bronchitis	23 (5.6)	23 (5.4)	8 (3.8)	46 (5.5)
Condyloma acuminatum	6 (1.4)	9 (2.1)	2 (1.0)	15 (1.8)
Folliculitis	7 (1.7)	14 (3.3)	4 (1.9)	21 (2.5)
Herpes simplex	14 (3.4)	26 (6.1)	6 (2.9)	40 (4.8)
Influenza	14 (3.4)	6 (1.4)	0	20 (2.4)
Nasopharyngitis	30 (7.2)	30 (7.0)	9 (4.3)	60 (7.1)
Oesophageal candidiasis	12 (2.9)	2 (0.5)	2 (1.0)	14 (1.7)
Oral candidiasis	13 (3.1)	10 (2.3)	7 (3.3)	23 (2.7)
Pneumonia	11 (2.7)	6 (1.4)	7 (3.3)	17 (2.0)
Rhinitis	9 (2.2)	4 (0.9)	2 (1.0)	13 (1.5)
Sinusitis	15 (3.6)	25 (5.9)	7 (3.3)	40 (4.8)
Upper respiratory tract infection	38 (9.2)	44 (10.3)	11 (5.3)	82 (9.8)
Investigations				
Alanine aminotransferase increased	7 (1.7)	10 (2.3)	1 (0.5)	17 (2.0)
Aspartate aminotransferase increased	7 (1.7)	15 (3.5)	1 (0.5)	22 (2.6)
Blood creatine phosphokinase increased	5 (1.2)	9 (2.1)	1 (0.5)	14 (1.7)
Weight decreased	17 (4.1)	13 (3.1)	4 (1.9)	30 (3.6)
Metabolism and Nutrition Disorders				
Anorexia	17 (4.1)	16 (3.8)	8 (3.8)	33 (3.9)
Decreased appetite	10 (2.4)	14 (3.3)	5 (2.4)	24 (2.9)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	18 (4.3)	22 (5.2)	6 (2.9)	40 (4.8)
Back pain	22 (5.3)	21 (4.9)	6 (2.9)	43 (5.1)
Muscle spasms	13 (3.1)	9 (2.1)	9 (4.3)	22 (2.6)
Myalgia	19 (4.6)	12 (2.8)	1 (0.5)	31 (3.7)
Pain in extremity	12 (2.9)	11 (2.6)	5 (2.4)	23 (2.7)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)				

Table 12. All-Causality Adverse Events Reported in ≥2% of Patients in the Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

System Organ Class MedDRA Preferred Term	Maraviroc QD N (%)	Maraviroc BID N (%)*	Placebo N (%)	Combined Maraviroc Doses N (%)
Skin papilloma	11 (2.7)	8 (1.9)	3 (1.4)	19 (2.3)
Nervous System Disorders				
Dizziness	39 (9.4)	34 (8.0)	14 (6.7)	73 (8.7)
Dysgeusia	3 (0.7)	12 (2.8)	2 (1.0)	15 (1.8)
Headache	61 (14.7)	54 (12.7)	32 (15.3)	115 (13.7)
Hypoaesthesia	10 (2.4)	11 (2.6)	2 (1.0)	21 (2.5)
Neuropathy peripheral	9 (2.2)	9 (2.1)	4 (1.9)	18 (2.1)
Paraesthesia	11 (2.7)	11 (2.6)	5 (2.4)	22 (2.6)
Psychiatric Disorders				
Anxiety	8 (1.9)	12 (2.8)	5 (2.4)	20 (2.4)
Depression	13 (3.1)	14 (3.3)	6 (2.9)	27 (3.2)
Insomnia	23 (5.6)	29 (6.8)	9 (4.3)	52 (6.2)
Sleep disorder	9 (2.2)	6 (1.4)	3 (1.4)	15 (1.8)
Renal and Urinary Disorders				
Dysuria	6 (1.4)	11 (2.6)	1 (0.5)	17 (2.0)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	35 (8.5)	48 (11.3)	10 (4.8)	83 (9.9)
Dyspnoea	13 (3.1)	11 (2.6)	2 (1.0)	24 (2.9)
Nasal congestion	10 (2.4)	12 (2.8)	5 (2.4)	22 (2.6)
Pharyngolaryngeal pain	17 (4.1)	10 (2.3)	6 (2.9)	27 (3.2)
Skin and Subcutaneous Tissue Disorders				
Night sweats	13 (3.1)	16 (3.8)	6 (2.9)	29 (3.5)
Pruritus	11 (2.7)	13 (3.1)	3 (1.4)	24 (2.9)
Rash	27 (6.5)	34 (8.0)	8 (3.8)	61 (7.3)
Vascular Disorders				
Hypertension	8 (1.9)	13 (3.1)	3 (1.4)	21 (2.5)

Source: Tables 3.4.3.1, 3.4.3.3, 3.4.5.1 and 3.4.5.3 Summary of Clinical Safety
*Does not include AEs experienced by patients who switched to open label BID treatment.

All analyses of AEs in the SCS are based on tables at the Preferred Term level. All-causality AEs in Studies A4001027 and A4001028 by MedDRA Higher Level Terms are presented in Table 3.4.3.4 Summary of Clinical Safety.

An apparent imbalance in cardiac events related to coronary artery disease (CAD) was noted, with cardiovascular ischaemic events (including myocardial infarctions) occurring infrequently in the maraviroc groups but not at all in the placebo group. Six maraviroc treated subjects (4 QD, 2 BID) reported 8 SAEs suggestive of coronary artery disease (CAD). These are discussed in more detail in Section 2.7.4.2.1.5.1.

Hepatic and eye-related AEs and postural hypotension are discussed in more detail in Section 2.7.4.2.1.5.

Laboratory abnormalities were occasionally reported as adverse events, but Investigators did not do so consistently. Therefore, assessment of laboratory data is best accomplished with reference to the laboratory data presented in Section 2.7.4.3.

After adjusting for duration of exposure (see Table 6), the disparity between maraviroc treatment groups and the placebo group with respect to frequency of certain AEs, already relatively unremarkable, diminishes further and often disappears altogether. Although events of upper respiratory tract infection, influenza, cough, rash, herpes simplex (although when combined with herpes virus, the rate in either maraviroc group does not exceed that in the placebo group by ≥ 3%), myalgia, dysuria, dyspnoea, AST increased, ALT increased and blood creatine phosphokinase remained more frequent in at least 1 of the maraviroc groups than in the placebo group, the incidences of dizziness, insomnia, arthralgia and back pain become quite similar to placebo (<2-fold different) following adjustment for exposure (Table 13).

Table 13. Adverse Events Reported In Either Maraviroc Treatment Group At ≥2% At A Rate Exceeding That In The Placebo Treatment Group By 3% Or 3-Fold, Adjusted For Exposure Per 100 Patient Years, In The Phase 3 Studies In R5 TE Patients (Studies A4001027 And A4001028)

	Incidences per 100 Years of Patient Exposure		
	Maraviroc QD N= 414	Maraviroc BID N= 426	Placebo N= 209
Upper respiratory tract infection	15.8	17.7	11.6
Cough	14.3	19.4	10.5
Rash	11.1	13.5	8.5
Herpes simplex	5.6	10.2	6.1
AST increased	2.7	5.8	1.0
Myalgia	7.6	4.6	1.0
Dysuria	2.3	4.2	1.0
Dyspnoea	5.1	4.2	2.0
ALT increased	2.7	3.8	1.0
Blood creatine phosphokinase increased	1.9	3.4	1.0
Influenza	5.5	2.3	0.0

Source: Table 3.4.4.4 Summary of Clincal Safety.
QD = Once daily dosing; BID = Twice daily dosing.

The incidence of Grade 3 AEs was similar between the 2 maraviroc and placebo treatment groups, though more Grade 4 AEs were reported in the maraviroc BID group (Table 15).

Subgroup analysis of treatment emergent AE data was performed by gender (SCS Table 3.4.9.1), age (SCS Table 3.4.9.2), race (SCS Table 3.4.9.3), HIV-1 exposure category (SCS Table 3.4.9.4), baseline CD4 cell count (SCS Table 3.4.9.5), screening HIV-1 RNA level (SCS Table 3.4.9.6), CCR5Δ32 status (SCS Table 3.4.9.13), previous AIDS defining illness (SCS Table 3.4.9.7), hepatitis B or hepatitis C infection at baseline (SCS Table 3.4.9.8), inclusion of saquinavir/ritonavir in OBT (SCS Table 3.4.9.9), concomitant anti-hypertensive/PDE5-inhibitor/nitrate/alpha-blocker use (SCS Table 3.4.9.12) and treatment failure status (SCS Table 3.4.9.11). In general, there were few differences between subgroups in AE frequency, although in most cases (exceptions being age and concomitant antihypertensive/PDE5 inhibitor use) subgroups numbers were small and therefore often imbalanced between treatment groups, making any apparent differences difficult to interpret.

Treatment-Related Adverse Events

During the Phase 3 studies, approximately 50% of maraviroc patients reported at least 1 treatment-related AE. The incidence of treatment-related AEs was similar between the treatment groups, as summarised in Table 14.

The most common treatment-related AEs (occurring in ≥5% of patients in the combined maraviroc treatment group) reported during the Phase 3 studies were diarrhoea, nausea, headache and fatigue. Most treatment-related AEs reported at incidences of ≥2% in either of the 2 maraviroc regimens were reported at similar incidences in the placebo group.

Treatment-related AEs that occurred at ≥2% and at a higher incidence than placebo (2% or 2-fold) are rash, abdominal pain, dyspepsia, constipation, cough, muscle spasms, myalgia and dysgeusia. No correction has been applied for duration of treatment.

Table 14. Treatment-Related Adverse Events Reported in ≥2% of Patients in the Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

System Organ Class MedDRA Preferred Term	Maraviroc QD N (%)	Maraviroc BID N (%)*	Placebo N (%)	All Maraviroc Doses N (%)
Subjects Evaluable for AEs	**414**	**426**	**209**	**840**
Subjects With AEs	**205 (49.5)**	**213 (50.0)**	**93 (44.5)**	**418 (49.8)**
Gastrointestinal Disorders				
Abdominal pain	11 (2.7)	11 (2.6)	2 (1.0)	22 (2.6)
Abdominal pain upper	11 (2.7)	8 (1.9)	5 (2.4)	19 (2.3)
Constipation	10 (2.4)	13 (3.1)	3 (1.4)	23 (2.7)
Diarrhoea	54 (13.0)	37 (8.7)	25 (12.0)	91 (10.8)
Dyspepsia	2 (0.5)	10 (2.3)	2 (1.0)	12 (1.4)
Flatulence	10 (2.4)	10 (2.3)	7 (3.3)	20 (2.4)
Nausea	39 (9.4)	51 (12.0)	24 (11.5)	90 (10.7)
Vomiting	18 (4.3)	17 (4.0)	8 (3.8)	35 (4.2)
General Disorders and Administration Site Conditions				
Fatigue	24 (5.8)	31 (7.3)	16 (7.7)	55 (6.5)
Pyrexia	9 (2.2)	7 (1.6)	7 (3.3)	16 (1.9)
Metabolism and Nutrition Disorders				
Anorexia	12 (2.9)	9 (2.1)	5 (2.4)	21 (2.5)
Musculoskeletal and Connective Tissue Disorders				
Muscle spasms	9 (2.2)	6 (1.4)	2 (1.0)	15 (1.8)
Myalgia	12 (2.9)	2 (0.5)	0	14 (1.7)
Nervous System Disorders				
Dizziness	20 (4.8)	21 (4.9)	8 (3.8)	41 (4.9)
Dysgeusia	1 (0.2)	9 (2.1)	2 (1.0)	10 (1.2)
Headache	41 (9.9)	30 (7.0)	21 (10.0)	71 (8.5)
Psychiatric Disorders				
Insomnia	10 (2.4)	14 (3.3)	4 (1.9)	24 (2.9)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	9 (2.2)	8 (1.9)	1 (0.5)	17 (2.0)
Skin and Subcutaneous Tissue Disorders				
Rash	12 (2.9)	18 (4.2)	3 (1.4)	30 (3.6)

Source: SCS Tables 3.4.4.1, 3.4.4.3, 3.4.6.1 and 3.4.6.3
*Does not include AEs experienced by patients who switched to OL BID treatment.

A slightly greater number of Grade 3 treatment-related AEs were reported on maraviroc QD and BID, and Grade 4 AEs on maraviroc BID, than on placebo during these studies (Table 15).

2.7.4.2.1.1.2.3. Phase 2b Study in Non-R5 TE Patients (Study A4001029)—Adverse Events

Among maraviroc-treated patients in Study A4001029, the all-causality AE profile was similar between the 2 maraviroc treatment groups and placebo. For further details on the AE profile in this population, please refer to the individual CSR, Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.

In Study A4001029, the AE profile was comparable to that of the R5 TE population in Studies A4001027 and A4001028; for further details please refer to the CSR (Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

2.7.4.2.1.1.3. Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029) - Adverse Events

During the Phase 2b/3 studies, 1089 of 1235 patients (88.2%) reported at least 1 AE. The number of patients reporting an AE was similar between the 2 maraviroc regimens and the placebo group, as summarised in Table 15.

Table 15. Incidence of Adverse Events Reported during the Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

Number (%) of Subjects	Maraviroc QD		Maraviroc BID		Placebo	
	R5	Non-R5	R5	Non-R5	R5	Non-R5
N	414	63	426	61	209	62
All-causality	366 (88.4)	54 (85.7)	383 (89.9)	56 (91.8)	175 (83.7)	55 (88.7)
Grade 3	77 (18.6)	9 (14.3)	92 (21.6)	8 (13.1)	43 (20.6)	10 (16.1)
Grade 4	33 (8.0)	7 (11.1)	42 (9.9)	6 (9.8)	13 (6.2)	6 (9.7)
Treatment-related	205 (49.5)	28 (44.4)	213 (50.0)	30 (49.2)	93 (44.5)	38 (61.3)
Grade 3	24 (5.8)	1 (1.6)	23 (5.4)	2 (3.3)	7 (3.3)	3 (4.8)
Grade 4	5 (1.2)	0	14 (3.3)	0	4 (1.9)	1 (1.6)

Source: SCS Tables 3.4.3.1 and 3.4.4.1 and A4001029 24 Week CSR Tables 13.6.2.1 and 13.6 3.1, Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.
R5 = Studies A4001027 and A4001028
Non R5 = Study A4001029

The incidence of AEs was evenly distributed between the treatment groups. The frequency of severe AEs was slightly higher in the maraviroc-treated groups than in the placebo group for the R5 population; however, these numbers are not adjusted for duration of treatment, which was longer for the maraviroc treatment groups (Table 6). The incidence of AEs reported for the Phase 2b Study A4001029 was similar across the dosing groups.

2.7.4.2.1.1.3.1. Open Label Maraviroc BID Treatment in R5 TE Patients (Studies A4001027 and A4001028)

Patients who experienced protocol-defined treatment failure at any time during therapy but whose virus remained CCR5-tropic had the option of changing to OL treatment with maraviroc BID. One hundred and nine (109) patients have received OL BID treatment with maraviroc within Studies A4001027 and A4001028. Of these, 64 (58.7%) reported at least 1 AE (Table 16).

Table 16. Adverse Events Reported in ≥2% in the Open Label Maraviroc BID Treatment in R5 TE Patients (Studies A4001027 and A4001028)

System Organ Class MedDRA Preferred Term	All Maraviroc Doses N (%) N=109	
	All-Causality	Treatment-Related
Number of Subjects with AEs	**64**	**24**
Blood and Lymphatic System Disorders		
Anaemia	3 (2.8)	0
Gastrointestinal Disorders		
Diarrhoea	7 (6.4)	1 (0.9)
Dyspepsia	3 (2.8)	0
Nausea	6 (5.5)	3 (2.8)
Vomiting	6 (5.5)	1 (0.9)
General Disorders and Administration Site Conditions		
Chills	3 (2.8)	0
Fatigue	6 (5.5)	3 (2.8)
Pyrexia	3 (2.8)	0
Infections and Infestations		
Condyloma acuminatum	5 (4.6)	1 (0.9)
Folliculitis	4 (3.7)	2 (1.8)
Herpes simplex	3 (2.8)	2 (1.8)
Nasopharyngitis	5 (4.6)	2 (1.8)
Sinusitis	3 (2.8)	1 (0.9)
Investigations		
Blood triglycerides increased	6 (5.5)	3 (2.8)
Gamma-glutamyltransferase increased	4 (3.7)	0
Weight decreased	3 (2.8)	0
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)		
Skin papilloma	3 (2.8)	1 (0.9)
Nervous System Disorders		
Headache	6 (5.5)	2 (1.8)
Psychiatric Disorders		
Depression	4 (3.7)	1 (0.9)
Skin and Subcutaneous Tissue Disorders		
Dermatitis	3 (2.8)	1 (0.9)
Rash	4 (3.7)	2 (1.8)

Source: SCS Tables 3.4.7.1, 3.4.7.3, 3.4.8.1 and 3.4.8.3

Fewer patients reported AEs whilst on OL therapy for Studies A4001027 and A4001028 than during blinded therapy on these studies. However, the spectrum of AEs reported during OL treatment was similar to that reported on blinded therapy. Less than half of the OL AEs were considered to be treatment-related by the Investigator (Table 16).

Fewer Grade 3 AEs (all-causality and treatment-related) were reported during treatment with OL maraviroc BID than with blinded maraviroc BID, but Grade 4 AEs were reported at similar frequencies in OL and blinded therapy (Tables 3.4.7.1 and 3.4.8.3 Summary of Clinical Safety).

2.7.4.2.1.1.3.2. Discontinued QD Arm from Phase 2b/3 study in R5 treatment-naïve patients (Study A4001026)

At least 1 all-causality AE was reported by 85% of subjects in the maraviroc 300 mg QD treatment group. The most frequently reported was nausea, followed by headache, fatigue and diarrhoea. Most AEs were graded as mild or moderate (Abbreviated CSR A4001026 Tables 13.6.2.2.1, 13.6.2.3.1, Module 5.3.5.4 Other Study Reports).

2.7.4.2.1.2. Deaths in the Maraviroc Clinical Programme

Deaths are recorded in the SAE database, which includes all treatment-related deaths regardless of time post therapy, and all other deaths (not necessarily treatment-related) up to a standard capture time of 28 days after discontinuation of therapy. In addition, all other deaths reported to the Sponsor have been listed regardless of duration of time since the patient discontinued from therapy or study. Narratives for all deaths are included in the individual clinical study reports.

No deaths were reported from the Phase 1 or Phase 2a clinical programmes.

2.7.4.2.1.2.1. Deaths in the Phase 2b/3 clinical programme (Studies A4001027, A4001028, A4001029 and A4001026)

As of the database cut-off date of 15 September 20[redacted] a total of 42 deaths have been reported in the maraviroc Phase 2b/3 programme (Studies A4001027, A4001028, A4001029 and A4001026). However, this figure includes 12 deaths reported during the 5-6 week period between the screening and randomisation visits. These deaths resulted from a variety of causes associated with HIV-1 disease progression, and underscore the advanced nature of HIV-1 disease in patients recruited into these studies (discussed in Section 2.5.5.3 Module 2.5 Clinical Overview). Of the remaining 30 deaths, reported in patients who had received at least 1 dose of blinded study drug, 11 occurred in the maraviroc QD treatment group, 9 in the maraviroc BID group, 5 in the placebo group, 2 in the efavirenz treatment group of Study A4001026, 2 in patients receiving OL maraviroc BID after initial treatment failure in Study A4001027, and 1 patient was designated as ISOD. Additional narratives for the deaths described in Table 17 below are provided in the relevant study reports as appropriate and may include additional information than is provided in the source tables. The table reflects the relevant information available from all sources. Table 17 provides the details of the 30 deaths occurring after start of study treatment (post-randomisation) for Studies A4001027, A4001028 and A4001029 and A4001026.

Table 17 Deaths Occurring Post-Randomisation in the Maraviroc Phase 2b/3 Clinical Programme

PID	Unblinded Treatment	Cause of Death	Total Days on Therapy	Days Post-Therapy	Related
Study A4001026 – Treatment-Naïve Patients Infected with CCR5 Tropic HIV-1a					
1[redacted]0006	Maraviroc QD	Suicide	34	7	No
1[redacted]0003	*Maraviroc QD*	*Non-Hodgkin's lymphoma (confirmed)*	*35*	*92*	*No*
1[redacted]0006	*Maraviroc BID*	*Liver failure; pneumonia.*	*11*	*120*	*No*
1[redacted]0002	Efavirenz	Castleman's Disease.	30	15	No
1[redacted]0006	*Efavirenz*	*Hodgkin's lymphoma (confirmed).*	*11*	*180*	*No*
Study A4001027 – Treatment-Experienced Patients Infected with CCR5 Tropic HIV-1					
1[redacted]0010	Maraviroc QD	Right cerebrovascular accident	11	2	No
1[redacted]0011	Maraviroc QD	Respiratory failure.	84	19	No
1[redacted]0007	Maraviroc BID	Stroke	142	2	No
1[redacted]0022	*Maraviroc BID Open Label [Randomised to maraviroc BID]*	*HIV disease progression.*	*153 [including 50 days blinded therapy]*	*73*	*No*
1[redacted]0002	*Maraviroc BID Open Label [Randomised to placebo]*	*Large B cell lymphoma (confirmed)*	*143 [74 days on blinded placebo]*	*39*	*Yes*
1[redacted]0006	*ISOD[b] [Randomised to maraviroc BID]*	*Treatment-resistant giardiasis and end-stage AIDS.*	*82*	*>6 months*	*No*
1[redacted]0007	Placebo	Pneumonia	88	On Treatment	No
1[redacted]0001	*Placebo*	*Neck mass (Large Cell lymphoma)*	*298*	*84*	*No*
Study A4001028 – Treatment-Experienced Patients Infected with CCR5 Tropic HIV-1.					
1[redacted]0002	Maraviroc QD	Anorexia	198	26	No
1[redacted]0032	Maraviroc QD	Septic shock	79	2	No
1[redacted]0018	Maraviroc QD	Myocardial infarction/acute heart failure/coronary artery atheroma.	206	On Treatment	No
1[redacted]0011	Maraviroc QD	Bacterial pneumonia.	63	25	No
1[redacted]0001	*Maraviroc QD*	*End stage HIV-1 disease.*	*56*	*249*	*No*
1[redacted]0012	Maraviroc BID	Death (found dead)	62	1	No
1[redacted]0004	Maraviroc BID	Pneumonia/endocarditis bacterial/multiple organ failure.	190	18	No
1[redacted]0001	Maraviroc BID	HIV disease progression	18	1	No
1[redacted]0009	Maraviroc BID	Worsening chronic obstructive pulmonary disease (COPD)	35	On Treatment	No
1[redacted]0011	*Maraviroc BID*	*Central nervous system lymphoma*	*62*	*48*	*No*
Study A4001029 – Treatment-Experienced Patients Infected with Non-CCR5 Tropic HIV-1[c]					
1[redacted]0001	Maraviroc QD	Pneumonia, possible chest mass.	63	6	No
1[redacted]0003	Maraviroc QD	Advanced HIV/AIDS Infection	195	19	No
1[redacted]0005	Maraviroc BID	*Pneumocystis carinii* Pneumonia	31	23	No
1[redacted]0002	*Maraviroc BID*	*Bacterial pneumonia*	*88*	*29*	*No*
1[redacted]0001	Placebo	Worsening renal failure/ ascites/ haemothorax/ disease progression.	92	On Treatment	No
1[redacted]0004	Placebo	Multiple cerebral lesions	Unknown[d]	Unknown	No
1[redacted]0003	*Placebo*	*Multifocal leucoencephalopathy.*	*36*	*29*	*No*

Source: SCS Tables 3.8.1.3 and 3.8.4.3. CSR A4001029 Table 13.6.6, Table 13.6.5 and Table B1.2 CSR 1028.
Those deaths italicised in this table are those that occurred more than 28 days after discontinuation of treatment.
[a] Study A4001026 is an ongoing study and therefore treatments remain blinded except for deaths and patient management. The maraviroc QD treatment group was unblinded due to efficacy, as described previously.
[b] Patient in-study-off-drug, previously randomised to receive maraviroc BID.
[c] Patients were infected with dual/mixed, CXCR4-tropic or non-phenotypable HIV-1.
[d] This patient died on day 85 but dosing data is not available.

A summary of deaths that occurred during the studies in TE patients only (Studies A4001027, A4001028 and A4001029) is presented in Table 18. There were a total of 25 deaths in these 3 studies (2.0% of treated subjects [N= 1235]), including 2 patients receiving OL maraviroc BID and 1 patient designated as ISOD. Of these 25 deaths, 17 (1.4%) occurred in patients who were still on treatment or who had discontinued study drug, but died within 28 days of drug discontinuation (Table 18). The proportion of deaths, irrespective of whether patients were on or off study drug, was similar between treatment groups.

Table 18.Summary of All Deaths and Deaths on Treatment Occurring in the Phase 2b/3 Treatment Experienced Studies

Study	Maraviroc QD (N= 477)	Maraviroc BID (N= 487)	Placebo (N= 271)	Maraviroc BID Open Label	ISOD[a]
All Deaths Irrespective of Time on or Off Study Treatment					
A4001027	2	1	2	2	1
A4001028	5	5	0	0	0
A4001029	2	2	3	0	0
Total	**9 (1.9%)**	**8 (1.6%)**	**5 (1.8%)**	**2**	**1**
Deaths Occurring on Study Drug or Within 28 Days of Discontinuing Study Treatment[b]					
A4001027	2	1	1	0	0
A4001028	4	4	0	0	0
A4001029	2	1	2	0	0
Total	**8 (1.7%)**	**6 (1.2%)**	**3 (1.1%)**	**0**	**0**

[a] Patients in-study-off-drug.
[b] Standard 28-day post-treatment capture period for serious adverse events and deaths.

Details of these deaths, by patient population, are included as brief narratives in the following sections of this summary document.

2.7.4.2.1.2.1.1. Studies in R5 TE Patients (Studies A4001027 and A4001028)

Brief Narratives for Study A4001027

There were 4 deaths in A4001027, which occurred on treatment or within 28 days of discontinuing study drug (2 on maraviroc QD, 1 on maraviroc BID and 1 on placebo). An additional 4 deaths occurred after the 28 day capture period (2 in patients who received maraviroc BID OL, 1 in patients receiving placebo and 1 ISOD patient).

Maraviroc QD Treatment Group:

Patient 1[redacted]0010, a [redacted]year old [redacted]male, received maraviroc QD for a total of 11 days; he died 2 days after stopping study drug because of a cerebrovascular accident secondary to cavernous sinus thrombosis. The patient was also found to be bacteraemic with *Mycobacterium avium intracellulaire*. The cerebrovascular accident was considered by the Investigator to be due to HIV infection and not related to study drug.

Patient 1[redacted]0011, a 5[redacted]year old[redacted]female, received maraviroc QD for a total of 84 days and died 19 days after stopping study drug from respiratory failure. The respiratory failure was considered due to HIV infection and not related to study drug by the Investigator.

Maraviroc BID Treatment Group:

Patient 10[redacted]0007, a 4[redacted]year old[redacted]male, received maraviroc BID for a total of 142 days. The drug was discontinued when the patient suffered a stroke; he died 2 days later. This event was not considered related to study drug by the Investigator.

Patient 10[redacted]50022, a 4[redacted]year old[redacted]male, received maraviroc BID for a total of 50 days and then OL maraviroc for a combined total of 153 days. The patient died from advanced HIV-related disease 73 days after stopping open-label treatment. This event was not considered related to study drug by the Investigator.

Maraviroc BID Open Label Treatment Group:

Patient 10[redacted]0002, a 5[redacted]year old male, received placebo as blinded therapy, then OL maraviroc for 143 days, and died from a large B cell lymphoma approximately 6 weeks after stopping treatment. The large B cell carcinoma had been diagnosed 3 days after the end of maraviroc treatment. This event was considered related to maraviroc by the Investigator; of note is that this investigator attribution occurred after the reports of lymphoma in vicriviroc treated patients were made public.[iv]

Placebo Treatment Group:

Patient 10[redacted]50007, a 4[redacted]year old[redacted]female, received placebo for a total of 88 days and died from pneumonia while still on treatment. This event was not considered related to study drug by the Investigator.

Patient 10[redacted]0001, a 5[redacted]year old male, received placebo for a total of 298 days and died 79 days after stopping study drug from a mass on the left side of the neck. This mass had appeared on Day 121 of treatment and was diagnosed as a large cell lymphoma. This event was not considered related to study drug by the Investigator.

Patients In-Study-Off-Drug (ISOD):

One death in Study A4001027 occurred whilst the patient was in study but had been off drug for ≥28 days and was therefore assigned to the ISOD treatment group. This patient (10[redacted]30006) stopped maraviroc BID in May 20[redacted] was lost to follow-up, but was reported to have died in 20[redacted](date unknown).

Brief Narratives for Study A4001028

There were 8 deaths in Study A4001028, which occurred on treatment or within 28 days of discontinuation of study drug (4 on maraviroc QD and 4 on maraviroc BID). An additional 2 deaths occurred after the 28 day capture period (1 patient who received maraviroc QD and 1 patient who received maraviroc BID).

Maraviroc QD Treatment Group:

Patient 10[redacted]0002, a 7[redacted]year old[redacted]male, received maraviroc QD for approximately 7 months and died approximately 3 weeks after stopping study drug from AIDS after his weight decreased and he developed anorexia and coronary artery occlusion. He had discontinued study drug because he was no longer willing to participate in the study. None of the events was considered related to study drug by the Investigator.

Patient 10[redacted]0032, a 5[redacted]year old[redacted]male, received maraviroc QD for a total of 79 days. Study drug was temporarily discontinued on Day 79 because of the development of septic shock, from which he died 2 days later (Day 81). This event was not considered related to study drug by the Investigator.

Patient 10[redacted]20018, a 4[redacted]year old[redacted]male, received maraviroc QD for approximately 7 months and died on Day 206 from myocardial infarction, acute heart failure and coronary artery atheroma. These events were not considered related to study drug by the Investigator.

Patient 1[redacted]40011, a 5[redacted]year old[redacted]male, received maraviroc QD for a total of 65 days and died approximately 3 weeks after stopping study drug from end-stage AIDS after developing neutropaenia (recurrent) and sepsis secondary to bacterial pneumonia. Study drug had been discontinued as the subject did not wish to continue with aggressive treatment. These events were not considered related to study drug by the Investigator.

Subject 1[redacted]50001, a 5[redacted]year old[redacted]male, received maraviroc QD and died 249 days after the end of treatment due to end stage HIV. On Study Day 31, his haemoglobin decreased to 9.2 g/dL, and he was diagnosed with aplastic anaemia. In response to the aplastic anaemia, maraviroc treatment was permanently discontinued on Study Day 56. The aplastic anaemia was considered resolved on Post-Therapy Day 133. In the opinion of the Investigator, the aplastic anaemia was possibly related to maraviroc.

Maraviroc BID Treatment Group:

Patient 10[redacted]40012, a 5[redacted]year old[redacted]male, received maraviroc BID for a total of 62 days and died suddenly on Day 63. The Investigator suspected pulmonary embolism as the cause of death. This event was not considered related to study drug by the Investigator.

Patient 1[redacted]30004, a 6[redacted]year old[redacted]male, received maraviroc BID for a total of 190 days and died approximately 2 weeks after stopping treatment from pneumonia, aortic valve endocarditis and multiple organ failure. Study drug had been discontinued as the subject required intubation due to worsening aortic valve endocarditis. These events were not considered related to study drug by the Investigator.

Patient 1[redacted]30001, a 5[redacted]year old[redacted]male, received maraviroc BID and died on Day 19 from cholestatic jaundice, acute haemolytic anaemia and cardiac arrhythmias. On Day 11, he presented with mild rash (macular eruption on trunk) and mild jaundice. Cholestatic jaundice was considered due to opportunistic infection. Following an upper endoscopy, a cardiac arrhythmia was reported (supraventricular tachycardia). Acute haemolytic anaemia was also suspected and attempts were made to contact the patient urgently to no avail. On Day 19, the

subject was found dead at home. The events were not considered related to study drug by the Investigator.

Patient 12[redacted]0009, a 4[redacted]year old[redacted]male, received maraviroc BID and died on Day 35 from end stage chronic obstructive pulmonary disease. This event was not considered related to study drug by the Investigator.

Patient 12[redacted]0011, a 4[redacted]year old[redacted]male, received maraviroc BID for a total of 62 days and died 48 days after the end of treatment. The cause of death was listed as central nervous system lymphoma, following identification of an intracranial mass on CT and MRI, which was suggestive of an infectious process, although a tumour could not be excluded. No autopsy was performed. He reportedly experienced altered mental status from approximately Day 40 of treatment. This event was not considered related to study drug by the Investigator.

Deaths Occurring During the Pre-Randomisation Period in Studies A4001027 and A4001028:

There were 11 additional deaths that occurred during the 5-6 week period between screening and randomisation visits (4 during A4001027 and 7 during A4001028), 2 of which were screen failures. This highlights the background morbidity of the study population and is discussed in Section 2.5.5.3 Module 2.5 Clinical Overview.

2.7.4.2.1.2.1.2. Phase 2b Study in Non-R5 TE Patients (Study A4001029)

There were 5 deaths in Study A4001029, which occurred on treatment or within 28 days of discontinuing study drug (2 on maraviroc QD, 1 on maraviroc BID and 2 on placebo). An additional 2 deaths occurred after the 28 day capture period (1 patient who received maraviroc BID and 1 patient who received placebo).

Maraviroc QD Treatment Group:

Patient 10[redacted]0001, a 4[redacted]year-old[redacted]male, received maraviroc QD for 63 days and died 6 days after receiving his last dose. Maraviroc was temporarily discontinued in the setting of *Pneumocystis* pneumonia but was restarted on study day 32. It was discontinued permanently when he was re-admitted to hospital with pneumonia and possible chest mass; the patient suffered a cardiac arrest and died while awaiting mediastinoscopy. It is not known whether an autopsy was performed.

Patient 12[redacted]0003, a 4[redacted]year-old[redacted]male, received maraviroc QD for 195 days and died 19 days after receiving his last dose. The patient was admitted to hospital on study day 185 for histoplasmosis. Ten days later the patient elected to discontinue all his HIV medication, including study drug, and he went under hospice care. He required transfusions for HIV-related anaemia. The reported cause of death was HIV disease progression.

Maraviroc BID Treatment Group:

Patient 12[redacted]40005, a 4[redacted]year-old[redacted]male, received maraviroc BID for 31 days. Maraviroc was discontinued in the setting of *Pneumocystis* pneumonia and *Clostridium difficile* colitis. He died 50 days after his last maraviroc dose from *Pneumocystis* pneumonia.

Patient 10[redacted]90002, a 4[redacted]year-old[redacted]male, received maraviroc BID for 88 days at which point it was discontinued for lack of efficacy. He died 29 days later of bacterial pneumonia.

Placebo Treatment Group:

Patient 10[redacted]70001, a 3[redacted]year-old[redacted]male, died after 92 days of receiving placebo with causes of death reported as worsening renal failure, ascites, haemothorax and HIV disease progression.

Patient 11[redacted]10004, a 5[redacted]year-old[redacted]male, received placebo. The patient was admitted to hospital for multiple cerebral lesions (which was also reported as the cause of death), which may have spread from a fungal sinusitis that had extended into bone, and may have been associated with thrombosis of the internal jugular vein.

Patient 11[redacted]50003, a 3[redacted]year-old[redacted]male, received placebo for 36 days, which was permanently discontinued after a diagnosis of progressive multifocal leukoencephalopathy, from which the patient died 29 days later.

2.7.4.2.1.2.1.3. Discontinued QD Treatment Group from Phase 2b/3 study in R5 treatment-naïve patients (Study A4001026)

There were 2 deaths reported on treatment or within 28 days of discontinuation of study treatment in Study A4001026 (1 on maraviroc QD and on efavirenz). There were an additional 3 deaths reported after the 28 day capture period (1 patient who received maraviroc QD, 1 patient who received maraviroc BID and 1 patient who received efavirenz). None of these deaths was considered related to study treatment.

Maraviroc QD Treatment Group:

Patient 11[redacted]10006 received 34 days of treatment with maraviroc QD. She died 7 days post-therapy with a cause of suicide.

Patient 11[redacted]70003 discontinued treatment with maraviroc QD after 35 days of treatment. He died on post-therapy Day 127 with a cause reported as Non-Hodgkin's lymphoma.

Maraviroc BID Treatment Group:

Patient 10[redacted]30006 received 11 days of maraviroc BID and then discontinued because of nausea and vomiting. Screening Hepatitis C antibody had been reactive. She died on post-therapy Day 120 with cause of death reported as liver failure and pneumonia.

Efavirenz Treatment Group:

Patient 1[redacted]50006 received efavirenz 600 mg QD, also for 11 days, before treatment was discontinued in the setting of sepsis, acute renal failure, pancytopenia, fever and diarrhoea. He was later diagnosed with Hodgkin's lymphoma, which was reported as the cause of death (post-therapy Day 180).

Patient 1[redacted]00002 discontinued treatment with efavirenz after 30 days of treatment. He died post-therapy on Day 45 of study with a cause of death reported as Castleman's disease.

2.7.4.2.1.3. Other Serious Adverse Events

The definition of an SAE used for the maraviroc clinical programme is outlined in Section 2.7.4.1.1.3. The safety narratives for treatment-related SAEs can be found in the individual CSRs Module 5.3.

2.7.4.2.1.3.1. Phase 1/2a Studies – Serious Adverse Events

Two SAEs were reported during Phase 1 studies, both unrelated to treatment (Study A4001040, Subject 1[redacted]1019 - vasovagal syncope, A4001042, Subject 6 - severely burned hands in a house fire).

No SAEs were reported during the conduct of the Phase 2a studies. However, a case of large B-cell non-Hodgkins lymphoma was diagnosed more than 3 years after completion of 10 days of maraviroc dosing. The investigator causality was 'possibly study drug related'; this event was reported following the publication of the vicriviroc data.

2.7.4.2.1.3.2. Phase2b/3 TE Studies – Serious Adverse Events

The safety narratives for the SAEs can be found in the individual CSRs in Section 15.2 Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.

2.7.4.2.1.3.2.1. Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028) - Serious Adverse Events

A total of 162 subjects reported SAEs during the two Phase 3 trials. Fifty-six subjects reported at least 1 SAE on maraviroc QD, 70 subjects on maraviroc BID and 36 on placebo (Table 3.8.3.1 Summary of Clinical Safety)[1] (2 subjects are still recorded as 'blinded therapy';1 with increased nausea and increased vomiting, the other with pregnancy [Table 3.8.4.2 Summary of Clinical Safety]).

[1] In some of the Summary of Clinical Safety Tables, up to 3 of these 162 patients from R5 TE Studies A4001027 and A4001028 who experienced SAEs are recorded as having 'blinded therapy', but unblinded information is available in the CSRs. These patients are: Patient 1[redacted]0001 (Study A4001028), increase in vomiting and increase in nausea; Patient 1[redacted]0015 (Study A4001027, maraviroc QD), pregnancy; and Patient 1[redacted]0014 (Study A4001028, maraviroc QD), pregnancy.

For 19 of these subjects, the Investigator judged the SAEs to be at least possibly treatment-related [8 (1.9%) receiving maraviroc QD, 9 (2.1%) receiving maraviroc BID and 2 (1.0%) receiving placebo]. Table 19 provides brief details of these treatment-related SAEs.

Table 19. Treatment-Related Serious Adverse Events Reported During Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

Study Drug	Study	PID	SAE	Action (re study drug)
Maraviroc QD	A4001027	10[redacted]0003	Hypersensitivity reaction and acute renal failure	Discontinued
Maraviroc QD	A4001027	11[redacted]0002	Epigastric pain and vomiting	Discontinued
Maraviroc QD	A4001027	11[redacted]0006	Worsening anaemia	Discontinued
Maraviroc QD	A4001027	11[redacted]0008	Pancreatitis	Temporarily discontinued; the subject later withdrew[a]
Maraviroc QD	A4001027	10[redacted]0006	Abdominal pain and nausea	Continued dosing and event resolved on therapy[a]
Maraviroc QD	A4001028	10[redacted]0007	Myositis	Discontinued
Maraviroc QD	A4001028	11[redacted]0001	Aplastic anaemia	Discontinued
Maraviroc QD	A4001028	11[redacted]0001	Thrombosis (Chest pain)	Discontinued On Day 128 (chest pain Day 43) due to a number of none serious AEs. Thrombosis diagnosed approx 8 months post discontinuation†
Maraviroc BID	A4001027	10[redacted]0016	Heat exhaustion with rhabdomyolysis and elevated transaminases	Discontinued
Maraviroc BID	A4001027	11[redacted]0003	Generalised rash	Discontinued
Maraviroc BID	A4001027	10[redacted]0050	Mucormycosis myositis	Continued dosing event resolved
Maraviroc BID[b]	A4001028	10[redacted]0001	Increased nausea and vomiting	Temporary discontinuation No further episodes following recommencing therapy
Maraviroc BID	A4001028	10[redacted]0006	Transaminase elevations	Discontinued
Maraviroc BID	A4001028	11[redacted]0002	Syncope and pancytopaenia	Discontinued
Maraviroc BID	A4001028	11[redacted]0010*	Diarrhoea	Temporary discontinued. Restarted therapy with no further events
Maraviroc BID	A4001028	11[redacted]0004	Syncope and orthostatic hypotension	Discontinued
Maraviroc BID	A4001028	11[redacted]0004	Increased hepatic enzymes	Temporary discontinuation No further episodes after restarting therapy
Placebo	A4001028	10[redacted]0005	Fever, worsening of dyspnoea and acute renal failure	Temporary discontinuation
Placebo	A4001027	11[redacted]0012	Transient ischaemic attack	Continued

Source: Table 3.8.4.2 and Table 3.1.3.2 Summary of Clinical Safety.
[a] Further clarification provided in clinical study report narrative.
[b] Information regarding unblinding can be found in A4001028 Clinical Study Report Table B 3.1.
* Patient subsequently permanently discontinued due to lack of efficacy.

2.7.4.2.1.3.2.2. Phase 2b Study in Non-R5 TE Patients (Study A4001029) - Serious Adverse Events

During Study A4001029 there were 30 subjects with at least 1 SAE: 10 on maraviroc QD, 9 on maraviroc BID and 11 on placebo. Five subjects in this study had SAEs which occurred whilst they were still in study but had been off drug for ≥28 days, and their SAEs were

assigned to ISOD as treatment group. There were 2 subjects who experienced SAEs during the period between screening and maraviroc treatment.

None of these SAEs was considered related to maraviroc treatment. The SAEs for this study are presented in the A4001029 24 Week Clinical Study Report and SCS Table 3.8.2.3.

2.7.4.2.1.3.2.3. Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

One hundred ninety-two (192) patients in the Phase 2b/3 TE population were reported as having at least 1 SAE. Further details are provided in the sections above.

2.7.4.2.1.3.2.4. Discontinued QD Arm from Phase 2b/3 study in R5 treatment-naïve patients (Study A4001026)—Serious Adverse Events

During Study A4001026 there were 21 subjects with SAEs among patients in the discontinued QD arm. Four were considered treatment-related:

- Subject 1[redacted]0009 – This 3[redacted]year old male subject initiated maraviroc 300 mg QD on 25 April 2[redacted] On 30 July the subject experienced fever, aches/myalgias and arthralgias. On 07 August the subject's condition worsened and he was taken to the emergency room. He developed a diffuse erythematous rash on his abdomen and hips. On 08 August he experienced increased weakness and all study medications were withheld including maraviroc 300 mg QD, which was permanently discontinued on this day. The patient was hospitalised twice in August for fever of unknown origin with associated myalgias, arthralgias, cough, mild headache, enlarged tonsils, and morbilliform rash. Weakness was considered resolved on 10 August 2[redacted] fever was considered resolved on 06 September 2[redacted] and myalgias and arthralgias were considered resolved on 15 May 2[redacted] All the events were considered related to maraviroc and background therapy by both the Investigator and the Sponsor.

- Subject 1[redacted]50005 – Toxic hepatitis, described below in Section 2.7.4.2.1.5.3.

- Subject 1[redacted]50006 – This 3[redacted]year old female had been receiving concurrent therapy with TM8* for *Pneumocystis jiroveci* pneumonia prophylaxis, which was changed to dapsone from 14 November 2[redacted] On 16 December, the subject developed Stevens-Johnson syndrome with a skin biopsy diagnosis of erythema multiforme exudativum. Dapsone and all study medications were permanently discontinued. The Investigator causality was maraviroc; however, the Sponsor considers dapsone the most probable causative agent.

- Subject 1[redacted]50003 – This 4[redacted]year old male subject initiated maraviroc 300 mg QD on 9 August 2[redacted] On 5 December (Day 119), results of laboratory tests revealed anaemia and leucopaenia, with a haematocrit of 0.26, haemoglobin of 8.6 g/dL and white blood cell count of 3.07/μL. The subject was admitted to the hospital on 9 December with general asthenia, malaise, dyspnoea during normal activity and retrosternal pain. Maraviroc 300 mg QD was temporarily interrupted that day. The Investigator considered the anaemia and leucopaenia to be related to maraviroc and

*:新薬承認情報提供時に置換えた。
TM8*はsulfamethoxazole/trimethoprimを示す。

lopinavir/ritonavir*. On 16 December 2[redacted] the following haematology results were obtained: haemoglobin 10.5 g/dL, neutrophil count 2.84 /μL and WBC count 5.85 /μL. Treatment with zidovudine/lamivudine was substituted with tenofovir 300 mg once daily and lamivudine 300 mg once daily which was restarted together with maraviroc 300 mg QD on 19 December 2[redacted] On 5 January 2[redacted] (following rechallenge), the following haematology results were obtained: haemoglobin 13.2 g/dL, neutrophil count 1.67 /μL and WBC count 3.87 /μL.

Six SAEs resulted in discontinuation, including 3 of the treatment-related events summarised above (see A4001026 24 Week CSR, Module 5.3).

Ten patients in the ongoing OL BID extension arm experienced SAEs as of 15 September 2[redacted] (see A4001026 24 Week CSR, Module 5.3).

2.7.4.2.1.4. Other Significant Adverse Events

2.7.4.2.1.4.1. Adverse Events Associated with Discontinuations

2.7.4.2.1.4.1.1. Phase 1/2a Studies – Adverse Events Associated with Discontinuations

The treatment-related AEs associated with discontinuation from the Phase 1 studies are summarised in Table 20. There were 14 discontinuations due to treatment-related AEs, 1 from a single-dose study and 13 from multiple-dose studies. Of these discontinuations, 5 subjects were receiving maraviroc treatment alone, 7 subjects were receiving maraviroc in combination with interactants and 2 subjects were receiving placebo alone.

Table 20. Discontinuations Due to Treatment-Related Adverse Events – Phase 1 Single- and Multiple-Dose Studies

Study Number	Dose of Maraviroc	N	Adverse Event Leading to Discontinuation
Phase 1 Single Dose-Studies			
A4001040	300 mg	1	Dizziness
Phase 1 Multiple-Dose Studies			
A4001002	<100 mg BID	1	Transaminases increased
	600 mg QD	2	Orthostatic hypotension
	Placebo	1	Orthostatic hypotension
A4001018	Maraviroc + Interactant	1	Vomiting
A4001019	Placebo	1	Rash Pruritic
A4001020	Maraviroc + Interactant	1	Arthralgia Headache Influenza like illness Myalgia Nausea
A4001021	300 mg BID	1	Alanine aminotransferase increased
	Maraviroc + Interactant	5	Blood triglycerides increased (1) Malaise (1) Nausea (1) Blood bilirubin increased (2)

* ：新薬承認情報提供時に置換えた。

In addition, in Study A4001021, treatment with maraviroc 100 mg BID with saquinavir 1000 mg BID, TM2* BID and efavirenz 600 mg QD was not tolerated because of gastrointestinal AEs; this arm of the study (12 subjects) was therefore discontinued by the Sponsor.

There were no discontinuations due to treatment-related AEs in the Phase 2a clinical programme. One patient, in the 100 mg QD fasted dosing arm of A4001015, withdrew due to headache of moderate severity, but the events were judged by the Investigator to be unrelated to study drug.

2.7.4.2.1.4.1.2. Phase 2b/3 Studies – Adverse Events Leading to Discontinuations

2.7.4.2.1.4.1.2.1. Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028) - Adverse Events Leading to Discontinuations

Permanent Discontinuations

There were 414 discontinuations during Studies A4001027 and A4001028 (Table 21). Most were due to lack of efficacy and, as such, were over-represented in the placebo arm. Full details are reported in the individual CSRs Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.

Table 21. Discontinuation from Study in the Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

System Organ Class MedDRA Preferred Term	Maraviroc QD N (%)	Maraviroc BID N (%)	Placebo N (%)
N	414	426	209
Subject Died on Therapy	3 (0.7)	5 (1.2)	1 (0.5)
Related to study drug			
Due to adverse events	12 (2.9)	10 (2.3)*	5 (2.4)
Due to lack of efficacy	81 (19.6)	91 (21.4)	106 (50.7)
Unrelated to study drug			
Due to adverse events	4 (1.0)	6 (1.4)	3 (1.4)
Due to other	12 (2.9)	4 (0.9)	5 (2.4)
Subject defaulted	31 (7.5)	22 (5.2)	13 (6.2)
Total	143 (34.5)	138 (32.4)	133 (63.6)

Source: SCS Table 3.1.4.1
Subject defaulted = patient no longer willing to participate or lost to follow-up.
One subject's disposition was given as discontinued due to treatment related AE but the adverse event was not attributed to study drug. This subject was initially temporarily discontinued before permant discontinuation, see CSR A4001028, in text table 68 and Section 9.2.3

During these studies, 40 patients permanently discontinued due to AEs: 16 (3.9%) from the maraviroc QD treatment group, 16 (3.8%) from the maraviroc BID group and 8 (3.8%) from the placebo group. For discontinuations due to AEs that were not related to study drug, please refer to the individual CSRs, Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.

*:新薬承認情報提供時に置換えた。
TM2*はlopinavir/ritonavirを示す。

For 26 of these patients, the AEs that led to discontinuation were considered to be treatment-related (12 maraviroc QD [2.9%], 9 maraviroc BID [2.1%] and 5 placebo [2.4%]). These are presented in Table 22.

Table 22. Permanent Discontinuations Due to Treatment-Related Adverse Events for the Phase 3 Studies in R5 TE (Studies A4001027 and A4001028)

Dose	Study	Subject Number	Adverse Event(s) Leading to Permanent Discontinuation (severity)
Maraviroc QD	A4001027	1[redacted]0001	Abdominal distension (Grade 2)
Maraviroc QD	A4001027	1[redacted]0002	Abdominal pain upper (Grade 3) [a]
Maraviroc QD	A4001027	1[redacted]0006	Anaemia (Grade 2) [a]
Maraviroc QD	A4001028	1[redacted]0001	Anaemia (Grade 3)
Maraviroc QD	A4001027	1[redacted]0003	Renal failure (Grade 3) [a] Rash (Grade 3) [a]
Maraviroc QD	A4001028	1[redacted]0035	ALT increased (Grade 2) AST increased (Grade 2)
Maraviroc QD	A4001027	1[redacted]0008	AST increased (Grade 3)
Maraviroc QD	A4001028	1[redacted]0003	Diarrhoea (Grade 2)
Maraviroc QD	A4001028	1[redacted]0011	Myalgia (Grade 3)
Maraviroc QD	A4001028	1[redacted]0001	Myalgia (Grade 1)
Maraviroc QD	A4001028	1[redacted]0007	Muscular weakness (Grade 3)
Maraviroc QD	A4001028	1[redacted]0001	Oedema peripheral (Grade 1)
Maraviroc BID	A4001027	1[redacted]0016	Transaminases increased (Grade 4) [a] *Heat exhaustion (Grade 3)* [a] *Rhabdomyolysis (Grade 3)* [a]
Maraviroc BID	A4001027	1[redacted]0021	Abdominal pain upper (Grade 2) LFT abnormal (Grade 4)
Maraviroc BID	A4001028	1[redacted]0006	ALT increased (Grade 4) [a] AST increased (Grade 4) [a]
Maraviroc BID	A4001027	1[redacted]0003	Convulsion (Grade 4) [a]
Maraviroc BID	A4001028	1[redacted]0004	Orthostatic hypotension (Grade 3) [a]
Maraviroc BID	A4001027	1[redacted]0009	Pyrexia (Grade 2) [a]
Maraviroc BID	A4001027	1[redacted]0003	Rash generalised (Grade 3) [a]
Maraviroc BID	A4001028	1[redacted]0002	Syncope (Grade 4) [a]
Maraviroc BID	A4001028	1[redacted]0003	Viral load increased (grade 1)
Placebo	A4001027	1[redacted]0004	Pyrexia (Grade 1)
Placebo	A4001027	1[redacted]0001	LFT abnormal (Grade 4) *White blood cell count decreased (Grade 1)*
Placebo	A4001027	1[redacted]0019	Gingivitis (Grade 2)
Placebo	A4001028	1[redacted]0003	Hepatic cytolysis (Grade 2)
Placebo	A4001028	1[redacted]0034	Dizziness (Grade 2)

Source: Individual Clinical Study Report Table 13.6.1.1 and Appendix B6.1
[a] Serious adverse event
Terms in italics were recorded in the SAE case but were not considered treatment-related

AEs that led to discontinuations in 2 or more patients are: LFTs increased/abnormal (2 on maraviroc QD, 3 on maraviroc BID and 1 placebo), myalgia/muscle weakness (3 on maraviroc QD), abdominal pain upper (1 on maraviroc QD and 1 on maraviroc BID), rash (1 on maraviroc QD and 1 on maraviroc BID), and pyrexia (1 on maraviroc BID and 1 on placebo).

AEs potentially related to postural hypotension[2] (2 on maraviroc BID and 1 placebo). Narratives for these events are located in Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.

Overall, the frequency of permanent discontinuations for treatment-related AEs was lower in the maraviroc arms. There were no differences between the numbers of males or females who discontinued treatment during these studies. The numbers and types of AEs leading to discontinuation are summarised in SCS Table 3.1.3.2 and Table 3.1.5.1; these were also comparable between males and females. Similarly, there was no apparent relationship between age or race and discontinuations (SCS Table 3.1.7.1, Table 3.1.7.2 and Table 3.1.7.3).

Dose Reductions or Temporary Discontinuations

Sixty-one patients underwent a reduction in dose or temporarily discontinued from study drug due to AEs (20 [4.8%] receiving maraviroc QD, 28 [6.6%] receiving maraviroc BID and 13 [6.2%] receiving placebo). In addition, 6 patients (2 maraviroc QD, 3 maraviroc BID, 1 placebo) temporarily discontinued and later permanently discontinued. The AEs leading to temporary discontinuation were considered treatment-related by the Investigator for 25 of these patients (7 [1.7%] receiving maraviroc QD, 16 [3.8%] receiving maraviroc BID and 2 [1.0%] receiving placebo). Details of the AEs leading to temporary discontinuation are provided in the individual CSRs (Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

Further details are provided below for subjects who were rechallenged following temporary discontinuation due to study drug-related rash, dizziness or an AE related to laboratory test abnormalities (Table 23). In the majority of cases the event resolved or stabilised and the subject either continued treatment until cut-off date or discontinued for another reason.

Table 23. Re-challenge Following Temporary Discontinuations Due to Adverse Events in Phase 3 Studies in R5 TE (Studies A4001027 and A4001028)

Dose	Study	Patient	Adverse Event(s) Leading to Temporary Discontinuation	Comment
Maraviroc QD	A4001027	1[redacted]0004	Rash	This AE started on Day 1 of treatment and resolved on Day 29. Study drug was restarted and no further AEs of rash were reported. The subject had taken study drug up to Day 349 at the date of cut-off.
Maraviroc QD	A4001027	1[redacted]0005	Rash	This AE started on Day 8 of treatment and resolved on Day 16. Study drug was restarted and no further AEs of rash were reported. The subject had taken study drug up to Day 339 at the date of cut-off.

[2] Includes syncope, orthostatic hypotension and dizziness.

Table 23. Re-challenge Following Temporary Discontinuations Due to Adverse Events in Phase 3 Studies in R5 TE (Studies A4001027 and A4001028)

Dose	Study	Patient	Adverse Event(s) Leading to Temporary Discontinuation	Comment
Maraviroc QD	A4001027	1[redacted]0006	Dizziness	This AE started on Day 125 of treatment and resolved on Day 128. Study drug was restarted and no further AEs of dizziness were reported. The subject had taken study drug up to Day 183 at the date of cut-off.
Maraviroc QD	A4001027	1[redacted]0008	Pancreatitis	This AE started on Day 89 of treatment. The subject was told to restart study drug but he was no longer willing to participate in the study so study drug was permanently discontinued. The pancreatitis resolved. This event was reported as an SAE.
Maraviroc QD	A4001028	1[redacted]0011	Neutropaenia	The neutropaenia started on Day 19. Maraviroc was discontinued for 15 days. Thirteen days after restarting therapy, the patient developed pneumonia, sepsis and neutropaenia. Two days later, maraviroc was stopped for 9 days again, and then restarted. Nine days later the subject withdrew from the study and ultimately died of end stage AIDS 23 days later.
Maraviroc QD	A4001028	1[redacted]0002	Increased ALT and AST	Elevated ALT and AST were present at baseline and ALT had increased from Day 59 to 65. The abnormalities resulting in temporary discontinuation started on Day 85 and resolved on Day 93. Study drug was restarted, ALT and AST had decreased on Day 93 but remained above normal limits for the remainder of the study. The subject had taken study drug up to Day 164 and was then lost to follow up.
Maraviroc BID	A4001027	1[redacted]0003	Increased AST	Increased AST started on Day 15 of treatment and resolved on Day 27. Study drug was restarted and no further increases in AST were reported. The subject had taken study drug up to Day 334 at the date of cut-off.
Maraviroc BID	A4001027	1[redacted]0009	Increased ALT, AST and GGT	These elevations were first reported on Day 147 and did not resolve. Study drug was restarted. The subject had taken study drug up to Day 173 at the date of cut-off.
Maraviroc BID	A4001028	1[redacted]0003	Increased ALT, AST and GGT	This AE started on Day 283 and did not resolve. The subject had taken study drug up to Day 323 at the date of cut-off.

Table 23. Re-challenge Following Temporary Discontinuations Due to Adverse Events in Phase 3 Studies in R5 TE (Studies A4001027 and A4001028)

Dose	Study	Patient	Adverse Event(s) Leading to Temporary Discontinuation	Comment
Maraviroc BID	A4001028	1[redacted]0004	Increased hepatic enzymes	This patient experienced increased hepatic enzymes from Day 150 of treatment. This was considered related to study drug by the Investigator. Study drug and OBT were temporarily discontinued. ALT and AST normalised and remained within normal levels after study drug was restarted. The patient took study drug up to Day 191 when it was permanently discontinued and the patient later died due to aortic valve endocarditis with *Streptococcus* pneumonia. These events were not considered related to study drug by the Investigator.
Maraviroc BID	A4001028	1[redacted]0004	Increased AST and blood creatine phosphokinase	Study drug was temporarily stopped due to increased AST from Day 15 to 22 and increased creatine phosphokinase from Day 15 to 22 and Day 29 to 37. These resolved and the subject had taken study drug up to Day 182 at the time of cut-off. The subject had increased creatine phosphokinase on a number of other occasions during treatment; these all resolved with study drug continued unchanged
Maraviroc BID	A4001027	1[redacted]0025	Skin eruptions	The AE started on Day 158 of treatment and resolved on Day 179. Study drug was restarted and no further AEs of skin eruptions or rash were reported. The subject had taken study drug up to Day 273 at the date of cut-off.
Maraviroc BID	A4001028	1[redacted]0005	Rash	The rash started on Day 13 of treatment and resolved on Day 20. Study drug was restarted and no further AEs of rash were reported. The subject had taken study drug up to Day 338 at the date of cut-off.
Maraviroc BID	A4001027	1[redacted]0022	Pancreatitis	This AE started on Day 57 and did not resolve. The patient was asymptomatic and study drug was restarted. The subject had taken study drug up to Day 337 at the date of cut-off.
Maraviroc BID	A4001027	1[redacted]0014	Blood creatine phosphokinase and increased hepatic enzymes	These laboratory abnormalities started on Day 335 and did not resolve when study drug was stopped. Study drug was restarted. The subject had taken study drug up to Day 347 at the date of cut-off.
Maraviroc BID	A4001027	1[redacted]0061	Decreased haemoglobin	Decreased haemoglobin started on Day 19 of treatment and resolved on Day 56. Study drug was restarted before the decreased haemoglobin resolved. The subject had taken study drug up to Day 214 at the time of discontinuation due to insufficient clinical response.

Table 23. Re-challenge Following Temporary Discontinuations Due to Adverse Events in Phase 3 Studies in R5 TE (Studies A4001027 and A4001028)

Dose	Study	Patient	Adverse Event(s) Leading to Temporary Discontinuation	Comment

Five patients temporarily discontinued due to treatment-related rash (or skin eruptions). Four (2 maraviroc QD and 2 maraviroc BID) were re-challenged with maraviroc, without further episodes of rash being reported.

Seven patients were re-challenged after temporary discontinuation for treatment-related raised LFTs (1 on maraviroc QD and 6 on maraviroc BID). Five were re-challenged with maraviroc and remained on drug. The other patient (Patient 1[redacted]30004 from Study A4001028) was re-challenged with maraviroc BID and later permanently discontinued because of pneumonia and aortic valve endocarditis, and later died from pneumonia, aortic valve endocarditis and multiple organ failure.

2.7.4.2.1.4.1.2.2. Phase 2b Study in Non-R5 TE Patients (Study A4001029) - Adverse Events Leading to Discontinuations

There were 6 discontinuations related to AEs in Study A4001029 (out of a total study population of 186). The discontinuations for this study are presented in the A4001029 Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication. In this study, lack of efficacy was the most common reason for discontinuation, accounting for 35, 24 and 24 subjects in the maraviroc QD, maraviroc BID and placebo groups, respectively. Otherwise, the number and types of AEs leading to discontinuation in this study were similar to those observed in the 2 Phase 3 studies.

2.7.4.2.1.4.1.2.3. Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029) - Adverse Events Leading to Discontinuations

Forty-six patients discontinued because of AEs in the 3 TE studies. Further detail is provided in the sections immediately above.

2.7.4.2.1.4.1.2.4. Open Label Maraviroc BID Treatment in R5 TE Patients (Studies A4001027 and A4001028) – Adverse Events leading to Discontinuation

Of the 109 patients who were receiving OL maraviroc BID just 1 had discontinued due to an AE at the time of data cut-off (Table 3.4.7.1 Summary of Clinical Safety).

2.7.4.2.1.4.1.2.5. Discontinued QD Treatment Group of the Phase 2b/3 Study in Treatment-Naïve Patients (A4001026)

Thirteen of 174 patients (7.5%) discontinued due to AEs from the maraviroc 300 mg QD treatment group in Study A4001026. For 8 of these subjects, the AEs that led to discontinuation were considered to be treatment-related. Just 1 patient discontinued during the

OL maraviroc BID follow on, due to a treatment-related AE. Full details are reported in the individual CSR in Module 5.3.5.4 Other Study Reports.

2.7.4.2.1.5. Analysis of Adverse Events by Organ System or Syndrome

This section highlights the clinical experience with safety issues that were raised as potential concerns the development programme, including cardiovascular safety (QTc prolongation, postural hypotension, myocardial ischaemic events), eye-related events, hepatic safety, infections and development of malignancies are discussed.

2.7.4.2.1.5.1. Cardiovascular Safety

In pre-clinical studies, in vitro, maraviroc was shown to inhibit binding of dofetilide to the hERG channel at a concentration of 1541 ng/mL (15% inhibition) and 5316.8 ng/mL (43% inhibition). These concentrations represent approximately 10-fold and 35-fold the free C_{max} concentrations observed with the target 300 mg BID dose regimen. In toxicology studies in dogs and monkeys, QTc prolongation was observed at concentrations equivalent to 6- and 12-fold the free C_{max} concentrations of maraviroc with the target dose regimen of 300 mg BID. No arrhythmias were observed in these studies at up to 43-fold concentrations in studies in monkeys (see Section 2.4.5.3 Module 2.4 Non-clinical Overview).

In pre-clinical studies in vitro, maraviroc was shown to bind to alpha 2a adrenergic receptors, and was associated with 24% inhibition of yohimbine binding at 5316.8 ng/mL. Exploratory evaluation of human saphenous vein contraction mediated by MIP-1β, a CCR5 ligand, demonstrated that maraviroc at clinically relevant concentrations inhibited contraction. A reduction in blood pressure together with a reduction in heart rate was observed in macaques at concentrations approximately 10-fold the human C_{max} concentration seen at 300 mg BID (Module 2.4 Non-clinical Overview).

Prior to commencing the Phase 2b/3 programme with maraviroc an extensive programme of investigations was undertaken. Most importantly, Study A4001016 was conducted to evaluate QTc prolongation, Study A4001033 was conducted to evaluate the impact of maraviroc on systemic vascular resistance and cardiac index, and all Phase 2b/3 studies incorporated monitoring of postural blood pressure.

2.7.4.2.1.5.1.1. QTc Interval Analyses

Study A4001001 evaluated single doses of maraviroc, escalating to a maximum of 1200 mg. This dose was associated with spontaneously observed postural hypotension in 4 of 9 subjects with associated changes in heart rate. ECG data collected in this study 2 hours after the 1200 mg dose showed a mean increase in QTcP (corrected for the specific population due to heart rate variability at this dose) of 7.8 msec; the corresponding QTcF value was 10.7 msec. The QTc observations from this study prompted the design of Study A4001016, a thorough QTc study.

2.7.4.2.1.5.1.1.1. QTc Study A4001016

This was a single-dose, 5-way crossover study using 3 doses of maraviroc (100, 300 and 900 mg) and both a placebo and an active (moxifloxacin) control. Thirty male and 31 female subjects were enrolled. ECGs were recorded at 75 and 45 minutes pre-dose and immediately before dosing; a mean of these 3 readings was considered the "baseline" QT value. Post-dose ECGs were recorded and blood was drawn for maraviroc concentration measurement at 1, 2, 3, 4, 8 and 12 hours post-dose. All ECGs were sent for independent central analysis. Based on resting and post-exercise data collected during a "run-in" day, a non-linear mixed effect model was used to estimate an individual correction factor (b) for each patient; the resulting individually corrected QT ($QTcI=QT\times RR^{-b}$) values were used as the primary analysis. Fridericia's and Bazett's corrections ($QTcF=QT\times RR^{-1/3}$, $QTcB=QT\times RR^{-1/2}$) were also calculated (Clinical Study Report A41001016 Section 13 Table 19.1).

As suggested by regulatory guidance[v], the study analysis paid particular attention to (1) central tendency (mean change for each dosing group in QTc) in relation to C_{max}, (2) categorical increase in QTc, and (3) categorical magnitude of QTc change. A single dose study was regarded as adequate because of limited, if any, accumulation observed with multiple dosing at 300 mg BID in healthy volunteers and in HIV-1 infected patients in Phase 2a Study A4001007 (see Module 2.7.2 Summary of Clinical Pharmacology).

The mean individual correction factor b for all 60 patients was 0.3304 (± SD 0.05006), quite close to Fridericia's factor (0.33), with a range of 0.233 to 0.466 (Clinical Study Report Section 11, Item 11, Table 3.3).

The individual (total) C_{max} ranged from 17.7 ng/mL to 2360 ng/mL across the 60 subjects (for comparison, in Study A4001007 the mean total C_{max} observed after maraviroc 300 mg BID was 618 ng/mL). Table 24 summarises the changes in QTcI data from this study.

Table 24. Pharmacokinetic Parameters and Pre- and Post-Dose QTc in Study A4001016

Endpoint	Comparison	N	Adjusted Means (milliseconds)		Mean Difference[a] (90% CI)
			Active	Placebo	
QTcI at median Tmax	Maraviroc 100 mg vs Placebo	59	399.67	400.39	-0.72 (-3.03, 1.59)
	Maraviroc 300 mg vs Placebo	58	400.84	400.59	0.24 (-1.85, 2.34)
	Maraviroc 900 mg vs Placebo	58	402.76	399.15	3.61 (1.01, 6.21)
	Moxifloxacin 400 mg vs Placebo	58	412.67	398.71	13.96 (11.49, 16.44)
Maximum Increase in QTcI from 1-4 hours after dosing	Maraviroc 100 mg vs Placebo	59	5.00	7.33	-2.33 (-4.44/-0.22)
	Maraviroc 300 mg vs Placebo	58	6.87	7.46	-0.59 (-2.55/1.37)
	Maraviroc 900 mg vs Placebo	58	8.68	7.70	0.98 (-0.85/2.80)
	Moxifloxacin 400 mg vs Placebo	58	21.11	8.18	12.93 (10.88/14.97)
Average QTcI from 1-4 hours post-dose	Maraviroc 100 mg vs Placebo	59	399.44	401.12	-1.68 (-3.29, -0.06)
	Maraviroc 300 mg vs Placebo	58	401.46	401.38	0.08 (-1.35, 1.50)
	Maraviroc 900 mg vs Placebo	58	401.95	400.76	1.19 (-0.30, 2.68)
	Moxifloxacin 400 mg vs Placebo	58	412.44	400.32	12.11 (10.68, 13.55)

Source: A4001016 Clinical Study Report Table 5.4.
[a] Difference between active and placebo
[b] Median Tmax for Maraviroc 100 mg = 3 hours, for Maraviroc 300 mg = 3 hours, for Maraviroc 900 mg = 2 hours, for Moxifloxacin 400 mg = 2 hours.

No clinically meaningful differences were seen compared to placebo for any of the 3 maraviroc doses. The upper limit of the 90% confidence interval for change in QTcI of the difference from placebo at the 900 mg dose was less than 7 msec excluding a clinically meaningful effect at a supratherapeutic dose and concentration (×2) of maraviroc.

An exposure-response analysis of the study data (Exposure-Response Modelling Report for UK-427,857 Exposure on QT interval corrected for heart rate. Phase 1 Data (Protocol A4001016) Module 5.3.4.1. Healthy Subject PD and PK/PK Study Reports) concluded that there was a small mean increase in QTcI (less than 3 msec) at 1 and 2 hour post-dose in subjects who received 900 mg maraviroc, but not in those who received 100 mg and 300 mg. The estimate of the slope describing the QT-concentration relationship within the concentration range studied (up to 2360 ng/mL) was 0.00097; thus, an increase of 1000 ng/mL in maraviroc concentration (unbound) might be expected to be associated with an increase in QTc interval duration of 0.97 msec.

No maraviroc-treated subjects experienced increases in QTcI into the ≥450 msec (male) or ≥470 msec (female) (Table 25). The number of maraviroc patients whose QTcI increased into the 430-450 (male) /450-470 (female) msec range was comparable to that in the placebo group.

Table 25. Categorical Summary of Numbers of Patients with Abnormal QTcI

	Males				Females			
Treatment	N	< 430 msec	≥430 to <450 msec	≥450 msec	N	<450 msec	≥450 to <470 msec	≥470 msec
100 mg	30	27	3	0	30	29	1	0
300 mg	30	29	1	0	29	28	1	0
900 mg	30	28	2	0	28	27	1	0

Moxifloxacin	30	25	4	1	28	25	2	1
Placebo	30	28	2	0	29	28	1	0

Source: CSR A4001016 Tables 5.5.1 and 5.5.2.

Similarly, few maraviroc-treated subjects experienced post-dose QTc increases from baseline of 30-60 msec, and none >60 msec (Table 26).

Table 26. Number of Patients with Categorical Increase in QTcI

Treatment	N	<0 msec	0 to <10 msec	10 to <30 msec	30 to <60 msec	≥60 msec
100 mg	60	12	29	19	0	0
300 mg	59	9	28	21	1	0
900 mg	58	7	25	24	2	0
Moxifloxacin 400 mg	58	0	3	41	14	0
Placebo	59	7	28	23	1	0

Source: CSR A4001016 Table 5.5.3.

2.7.4.2.1.5.1.1.2. Study A4001019

In Phase 1 dose escalation study (A4001019), 3 cohorts of patients were enrolled and received an initial dose (or placebo) for 7 days, with a further dose 7-day period escalation for non-placebo patients commencing on Day 8. The highest doses studied were 600 mg BID, 900 mg BID and 1200 mg QD. Apart from Study A4001001, no other study in the clinical programme used doses as high as 1200 mg. This is of particular relevance because of an increase in mean QTcF and QTcI duration demonstrated in Study A4001001. Twice-daily ECGs were recorded (prior to dosing and 4 hours post-dose) throughout each of the two 7-day dosing periods.

Mean QTcF, categorical QTcF values and categorical increases in QTcF are summarised in CSR A4001019 Tables 9.1 and Table 10.4.1, Table 10.5.2 and Table 10.4.3. With 1 exception, described below, no subject had a QTcF of >430 msec (male) or >450 msec (female), or a QTcF increase from baseline of >30 msec.

- Subject 1[redacted]1039, a [redacted]year-old male, had a QTcF >450 msec while receiving 600 mg BID and an increase ≥ 60 msec over baseline while receiving 900 mg BID. This subject had QTcF values of 445 and 450 msec at screening and 397, 400, and 383 msec at baseline. On Day 2 of 600 mg BID, a QTcF of 455 msec was observed; on Day 3, 450 msec. The greatest increase in QTcF from baseline was a 69 msec increase to 462 msec (study Day 13, which was Day 6 on 900 mg BID), which actually represents a change from his average screening value of <15 msec (CSR A4001019 Table 10.4.1; CSR A4001019 Section 13 Table 19.1).

2.7.4.2.1.5.1.1.3. Phase 2b/3 QTc Data

In the Phase 2b/3 treatment-experienced population (Studies A4001027, A4001028 and A4001029), ECGs were to be recorded at baseline, at Weeks 24 and 48, and at early

termination. ECGs were transmitted to a central laboratory (eResearch Technology, US) for semi-automated reading of QTc.

Mean change in QTc interval duration from baseline was similar between maraviroc groups and the placebo group at all timepoints (Table 27).

Table 27. Mean Baseline QTcF Intervals and Changes from Baseline (± SD) (msec) in Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

	Maraviroc QD		Maraviroc BID		Placebo	
Baseline	360	404.6 ± 19.8	386	404.5 ± 21.1	186	403.6 ± 21.0
Week 24	156	1.7 ± 18.4	159	1.3 ± 18.6	63	2.2 ± 17.6
Week 48	117	-0.5 ±19.7	136	0.6 ± 16.3	31	5.2 ± 20.5
Early Term	67	-1.9 ±19.9	73	-3.6 ± 20.1	82	0.9 ± 19.0
Unplanned	20	-2.0 ±14.4	18	2.8 ± 14.6	10	1.7 ± 14.2

Source: Table 3.7.7.1. Includes data from Studies A4001027, A4001028 and A4001029.

Among males, the numbers of patients with categorical change in maximum QTc was similar across all treatment groups (Table 28).

Table 28. Numbers of Patients by QTcF Category, Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

	Males				Females			
Treatment Group	**N**	**<430 msec**	**<450 msec**	**≥450 msec**	**N**	**<450 msec**	**<470 msec**	**≥470 msec**
maraviroc QD	329	294	30	5	47	45	0	2
maraviroc BID	361	318	35	8	38	35	3	0
Placebo	169	148	14	7	24	22	2	0

Source: Tables 3.7.7.2 and 3.7.7.3. Includes data from Studies A4001027, A4001028 and A4001029.

For males, the numbers of patients with ≥450 msec were evenly distributed and when corrected for randomisation there are fewer in the maraviroc arms. Among females, whose numbers were lower, there were 2 patients (both in Study A4001027) with maximum QTc values ≥470 msec:

- Patient 1[redacted]0006, a [redacted]year old [redacted]female in the maraviroc QD treatment group, with a past medical history of diabetes mellitus, hypertension, renal insufficiency and anaemia, was receiving atazanavir, delavirdine, emtricitabine/tenofovir and ritonavir as OBT and was also treated with azithromycin, sulphamethoxazole/trimethoprim, diltiazem, erythropoietin, fosinopril, gabapentin, glibenclamide, glibomet, loratadine, ondansetron, tamsulosin, valganciclovir. Her QTcF intervals were 483 msec and 484 msec on study Days 170 and 344 (at Weeks 24 and 48) respectively. The changes from baseline QTcF at these visits were 46 and 47 msec respectively. No cardiac SAEs were reported at the time of the elevated QTcF interval.

- Patient 1[redacted]0011, a 4[redacted]year old female in the maraviroc QD treatment group with minimal past medical history other than that related to HIV infection, was receiving atazanavir, ritonavir, and [redacted](zidovudine/lamivudine/abacavir) and was also treated with atovaquone, calcium carbonate, cyproheptadine, loratadine, oxandrolone and zolpidem. Her QTcF interval was 474 msec on study Day 339 (at the Week 48 visit), representing a change from baseline QTcF of 11 msec. No cardiac SAEs were reported at the time of the elevated QTcF interval.

Categorical changes to >30 msec were similar between all 3 treatment groups. Three of the 399 patients (0.8%) in the maraviroc BID treatment group had values ≥60 msec.

Table 29. Numbers of Patients by Categorical Change in QTcF from Baseline, Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

Treatment Group	N	<30 msec	≥30 msec to <60 msec	≥60 msec	Missing
Maraviroc QD	376	332	28 (7.4%)	0	16
Maraviroc BID	399	363	20 (5.0%)	3 (0.8%)[a]	13
Placebo	193	171	13 (6.7%)	0	7

Source: Table 3.7.7.4. Includes data from Studies A4001027, A4001028 and A4001029.
[a] This value includes subject 1[redacted]0008 (Study A4001028), who was erroneously reported to have a maximum increase from baseline in QTcF ≥ 60 msec (data error). See CSR A4001028 Section 9.5.2. Another patient, Patient 1[redacted]0004 (A4001028), was not included in the database but is described in text below.
Missing values are subjects missing baseline or 24 week or end of treatment ECG

There were 3 patients with an increase in QTcF from baseline of ≥60 msec, although 1 was later found to have been identified as such in error:

- Patient 1[redacted]0021 (A4001027), a 4[redacted]year old [redacted]male in the maraviroc BID treatment group, with a past medical history of coronary artery disease, hypertension, and a previous myocardial infarction, received emtricitabine/tenofovir, enfuvirtide, and [redacted](lopinavir/ritonavir) as OBT and also received aspirin, sulphamethoxazole/trimethoprim, gemfibrozil, and metoprolol. His QTcF interval was 457 msec on study Day 171 (at the Week 24 visit), representing a change from baseline QTcF of 79 msec. No cardiac SAEs were reported at the time of the elevated QTcF interval.

- Patient 1[redacted]0038 (A4001027), a [redacted]year old [redacted]male in the maraviroc BID treatment group, with a past medical history of hypothyroidism and tobacco use, received atazanavir, enfuvirtide, lamivudine, ritonavir and tenofovir as OBT and also received bupropion, gabapentin, ibuprofen, levothyroxine, loperamide, minocycline, pentamidine, tocopherol, tretinoin and valciclovir. A change from baseline QTcF of 68 msec on Study Day 83 (at the early termination visit) was noted. The QTcF interval at the baseline visit was 358 msec and on Day 83 the QTcF interval was 426 msec. Study drug was stopped on Day 83 due to insufficient clinical response. No cardiac SAEs were reported at the time of the elevated QTcF interval.

- Patient 1[redacted]0008 from the maraviroc BID treatment group (Study A4001028) was erroneously reported to have a ≥60 msec increase from baseline in QTcF. The error was identified after database lock.

Another patient, who was reported as having an AE of 'Electrocardiogram QT prolonged' but was not identified as having QT prolongation on the centrally read ECGs, is discussed below.

Sparse sampling was conducted during the Phase 3 programme to derive population pharmacokinetic parameters. Inspection of the these maraviroc plasma concentration data (from the first 500 patients recruited into Studies A4001027 and A4001028, and from all patients recruited into Study A4001029 collected from the maraviroc BID dosing arm) revealed only 1 concentration that was outside of the range seen in Phase 1/2a studies utilising the 300 mg dose. This suggests that the selected clinical doses and dose adjustments for maraviroc are appropriate and that the thorough QT study has evaluated an appropriate range of concentrations (See Module 2.7.2 Summary of Clinical Pharmacology).

2.7.4.2.1.5.1.1.4. Adverse Events

No AEs of torsade de pointes (TdP) were reported in the programme. A search of the Phase 3 database was conducted for AE terms that may reflect either an increased risk for the arrhythmia (e.g., QT interval prolonged) or its unrecognised occurrence (e.g., sudden death). A Standard MedDRA Query (SMQ) was used for this purpose, which is summarised in Table 30.

Table 30. Events Possibly Associated with TdP (per SMQ[a]) Occurring in Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

	Maraviroc QD N= 477	Maraviroc BID N= 487	Placebo N= 271
Electrocardiogram QT prolonged	0	1 (0.2)	0
Loss of consciousness	0	1 (0.2)	0
Syncope	2 (0.5)	5 (1.0)	2 (0.7)
Death	-	-	-

Source: SCS Tables 3.1.4.2, 3.4.2.5, 3.4.3.3, 3.8.3.1 and 3.8.4.3.
[a] Standard MedDRA Query for Torsade de pointes : Loss of consciousness, Sudden cardiac death, Sudden death, Syncope, Syncope vasovagal, Ventricular arrhythmia, Ventricular fibrillation, Ventricular flutter, Electrocardiogram QT corrected interval prolonged, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Long QT syndrome, Long QT syndrome congenital, Torsade de pointes, Ventricular tachyarrhythmia, Ventricular tachycardia, Cardiac arrest, Cardiac death, Cardiac fibrillation, Cardio-respiratory arrest, Electrocardiogram repolarisation abnormality, Electrocardiogram U-wave abnormality, Electrocardiogram U-wave biphasic.

The patient reported with an AE of 'Electrocardiogram QT prolonged' (uncorrected QT 537 msec, local laboratory result) was Patient 1[redacted]0004 from Study A4001028, who had a past medical history of chronic renal failure and HIV-associated neuropathy, and received delavirdine, ritonavir and [redacted](zidovudine/lamivudine/abacavir) as OBT as well as azithromycin and sulphamethoxazole/trimethoprim. The QT prolongation was reported as occurring on Day 99 and was considered treatment-related by the Investigator. From Day 90

he had experienced syncope, fatigue and orthostatic hypotension and study drug was permanently discontinued. He took his last dose on Day 98. However, this subject had a prolonged QTcF at baseline (466 msec), and the QTcF remained prolonged after discontinuation of study drug (474 and 463 msec on Day 128 and 479 msec on Day 163) (CSR A4001028, Appendix B6.1; Narrative for Patient 1[redacted]0004).

The loss of consciousness and 4 of the cases of syncope (1 maraviroc QD, 2 maraviroc BID and 1 placebo) were considered SAEs (Section 8 App B 6.1 in CSRs A4001027 and A4001028).

Events potentially related to TdP were infrequent, and occurred with similar frequency across the 2 maraviroc and the placebo groups. No AEs with potential association to TdP have been reported from the 109 TE R5 patients who began OL maraviroc after initial failure on blinded therapy in Studies A4001027 and A4001027 (SCS Table 3.4.7.3).

2.7.4.2.1.5.1.1.5. Conclusions regarding QTc prolongation

Although pre-clinical studies suggest a potential for maraviroc to prolong QT at high concentration, at clinically relevant concentrations no clinically significant effect on QTc has been seen in the clinical studies. Few outliers are observed in the Phase 3 clinical programme. Furthermore, on inspection of AE terms there is no evidence of an excess of AEs suggestive of a potential of maraviroc to cause ventricular arrrhythmias.

2.7.4.2.1.5.1.2. Postural Hypotension and Dizziness

The dose-limiting AE in the initial first-in-human single-dose Study A4001001 was postural hypotension, which occurred at 1200 mg in 4 of 9 subjects. In the next study conducted, multiple-dose Study A4001002, dosing was halted in 1 cohort when clinically significant postural hypotension occurred in 2 of 9 subjects receiving maraviroc 600 mg QD and 1 of 3 subjects receiving placebo. When, however, another subject cohort was dosed at 600 mg QD, only 1 subject experienced transient postural hypotension, described as mild by the Investigator. These events prompted further non-clinical investigation into the physiologic mechanism of this finding (Module 2.4 Non-clinical Overview) and inclusion of specific measurements of postural vital signs in subsequent protocols. A Phase 1 Study A4001033 was conducted specifically to investigate the effects of a single maraviroc 900 mg dose on haemodynamic parameters, especially cardiac index.

2.7.4.2.1.5.1.2.1. AEs relating to Postural Hypotension: Phase 1/2a Studies

Most of the postural events reported as AEs in the Phase 1/2a studies occurred during protocol-defined postural blood pressure measurements. Events were coded as the Preferred Term 'postural hypotension' if the subject complained of symptoms of dizziness or light-headedness on standing and had a recorded postural drop in blood pressure of greater than 20 mmHg systolic or 10 mmHg diastolic. If the subject was symptomatic without a recordable drop in blood pressure, this was recorded as 'dizziness on standing', which was coded as the Preferred Term 'dizziness'. If the subject was dizzy and could not stand for a BP reading, but the Investigator felt that postural hypotension was the most likely cause, the AE was recorded

as 'symptomatic postural hypotension', which was coded as the Preferred Term 'postural hypotension'.

These postural events were managed with supportive care, which in some instances included placing the subject in the Trendelenberg position. These AEs were usually temporally associated with C_{max} and lasted from a few minutes to a few hours. The all-causality AEs of postural hypotension and dizziness for the Phase 1 multiple-dose studies are presented in Table 31. A similar pattern was seen in the Phase 1 single-dose studies (SCS Table 1.5.1.1).

Table 31. Adverse Events of Postural Hypotension and Dizziness – Phase 1 Multiple-Dose Studies (All Causality)

	Placebo	MVC Dose (mg)									MVC only
		<100	100 BID	150 BID	300 BID	600 QD	600 BID	900 QD	900 BID	1200 QD	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total N	**57**	**19**	**149**	**12**	**81**	**18**	**17**	**9**	**8**	**9**	**297**
Postural Hypotension	1 (1.8)	0	2 (1.3)	0	3 (3.7)	3 (16.7)	0	5 (55.6)	0	6 (66.7)	14 (4.7)
Dizziness	7 (12.3)	2 (10.5)	7 (4.7)	1 (8.3)	5 (6.2)	7 (38.9)	7 (41.2)	3 (33.3)	7 (87.5)	3 (33.3)	36 (12.1)

Source: SCS Table 1.5.2.1.
'Postural hypotension' includes preferred terms of 'hypotension' and 'orthostatic hypotension'.
'Dizziness' includes preferred terms of 'dizziness' and 'dizziness postural'.
Includes Studies A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042

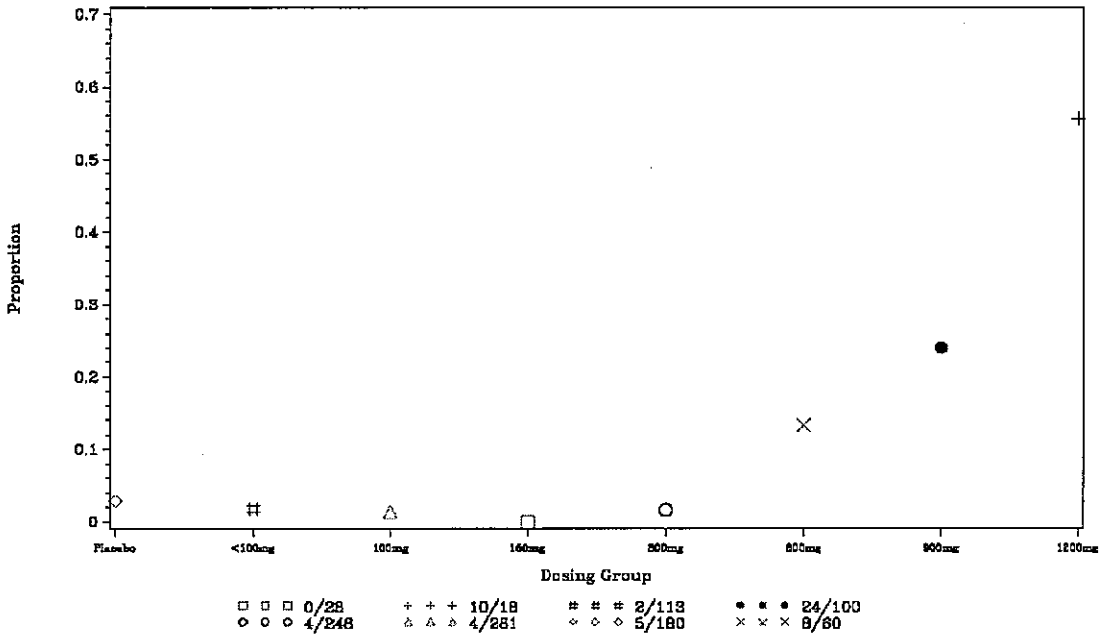
All of the AEs of postural hypotension were considered treatment-related by the Investigator. Most events of dizziness were also considered treatment-related in both the single-dose (18 of 20) and the multiple-dose studies (34 of 36) (SCS Table 1.5.1.2 and Table 1.5.2.2).

Eight AEs of postural hypotension were reported as severe in subjects receiving maraviroc alone; 1 at 300 mg and 2 at 1200 mg in single-dose studies, and 2 at 600 mg QD, 1 at 900 mg QD, 1 at 1200 mg QD and 1 on placebo in multiple-dose studies. Three of these 8 severe events resulted in discontinuation (2 subjects receiving 600 mg QD and the subject on placebo at Day 7 in Study A4001002).

In Phase 2a Studies A4001007 and A4001015, 'orthostatic hypotension' was reported in 1 of 16 (6.3%) placebo subjects and 'dizziness' in 7 of 66 (10.6%) maraviroc subjects (including 3 who were receiving a dose of 25 mg) (SCS Table 2.4.1.1).

The relationship between unit dose and AEs of postural hypotension is schematised in Figure 2. These events were rare at the therapeutic dose, with a similar rate to placebo; however, a dose response was demonstrated with the frequency increasing at unit doses ≥600 mg.

Figure 2. Observed Occurrence of Postural Hypotension by Unit Dose of Maraviroc in Phase 1/2a Studies



Source: SCS Figure 1.1.
Subjects are counted at every exposure level that they had evaluable data. As such, a subject may appear more than once.

Phase 1 Single-Dose Haemodynamic Study A4001033

Phase 1 Study A4001033 was designed to study the haemodynamic effects of oral maraviroc in healthy male subjects. The study consisted of a single dose comparison of the haemodynamic effects of a single 0.4 mg dose of glyceryl trinitrate (GTN) with GTN placebo, followed (at least 5 days later) by a similar comparison of a single dose of maraviroc 900 mg with maraviroc placebo. Impedence cardiography (ICG) was conducted to non-invasively measure stroke index, cardiac index and systemic vascular resistance in supine positions, and 12-lead ECGs and postural vital signs were measured at specified intervals. Cardiac monitoring via telemetry was also conducted.

Maraviroc at 900 mg did not cause a clinically significant change in supine systolic or diastolic blood pressure but did (to a lesser extent than GTN) decrease systemic vascular resistance (largest mean decrease –3.9%) and stroke index (largest mean decrease –5.6%) and increase cardiac index (largest mean increase 6.8%) and heart rate. These effects were mostly sustained over the 4 hours post-dose measurement period.

These effects are consistent with a mild vasodilator with a compensated haemodynamic response maintaining supine blood pressure. However, 3 of 16 subjects experienced postural hypotension, suggesting that there was not always complete compensation for orthostatic changes. No relationship was detected between maraviroc plasma concentration and change

from baseline in ECG parameters or change from baseline in supine blood pressure and pulse rate.

One Subject (7) had 3 hours 4 minutes of moderate and approximately 22 minutes of mild orthostatic hypotension from 2.68 and 8.35 hours post-dose, respectively. He also had outlying pharmacokinetic parameters and a high outlying cardiac index value 2.5 hours after maraviroc 900 mg (4.9 L/min/m^2, compared with a range of 2.0 to 3.3 L/min/m^2 for the other subjects).

Conclusions from the Phase 1/2a Programme

At maraviroc concentrations approximating to C_{max} at 300 mg, the risk of postural hypotension was similar to that of placebo. The 300 mg dose was therefore selected as the nominal dose for the Phase 2b/3 programme, with dosing adjustments for interacting medications aimed at maintaining a C_{max} equivalent to 300 mg.

2.7.4.2.1.5.1.2.2. Postural Blood Pressure Measurements Phase 2b/3 Studies

In the Phase 2b/3 studies, supine and standing blood pressure and pulse rate measurements were recorded at screening, Day 1, Weeks 2, 24 and 48 and (if applicable) at early termination. As in the Phase 1/2a studies, supine measurements were recorded after 5 minutes in the supine posture; subjects sat for 2 minutes and then stood for 2 minutes before standing measurements were recorded.

Results for the Phase 2b/3 studies are summarised in Table 32. Postural hypotension at these timepoints was slightly more frequent in the 2 maraviroc treatment groups than in the placebo group.

Table 32. Number (%) of Patients with Postural Hypotension[a] in Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

	Maraviroc QD (N= 477)	Maraviroc BID (N= 487)	Placebo (N= 271)
Baseline	15/399 (3.8)	14/423 (3.3)	6/235 (2.6)
Week 2	27/446 (6.1)	33/462 (7.1)	11/251 (4.4)
Week 24	16/311 (5.1)	19/323 (5.9)	5/117 (4.3)
Unplanned	0/11	1/17 (5.9)	1/11 (9.1)
Early Term	4/79 (5.1)	8/95 (8.4)	6/89 (6.7)

Source: Table 3.7.2.1 Summary of Clinical Safety.
[a] Includes patients who experienced any of these criteria: decrease in supine to standing blood pressure of ≥ 10 mmHg (diastolic) or ≥ 20 mmHg (systolic), or a standing systolic blood pressure of < 90 mmHg.

When the analysis was restricted to patients who were taking concomitant antihypertensives, nitrates, alpha blockers, and PDE5 inhibitors that are expected to lower blood pressure, the incidence of postural hypotension was likewise similar across treatment groups. At Week 2, for example, among patients who were receiving at least 1 of these concomitant agents,

10/147 (6.8%) patients receiving maraviroc QD, 9/172 (5.2%) receiving maraviroc BID and 4/75 (5.3%) receiving placebo met criteria for postural hypotension (Table 3.7.3).

2.7.4.2.1.5.1.2.3. Adverse Events Possibly Associated with Postural Hypotension: Phase 2b/3 Studies

AEs reported in Studies A4001027 and A4001028 with potential relationship to blood pressure are summarised in Table 33. Except perhaps for 'dizziness', where there was a slight trend towards a greater incidence in maraviroc treated patients, these AEs occurred with similar frequencies across all 3 treatment groups. Interestingly, AEs relating to blood pressure elevation were reported more commonly than those relating to low blood pressure. This analysis includes Studies A4001027 and A4001028 and is not adjusted for differential duration of follow up.

Table 33. Number (%) of Patients with All-Causality AEs with Potential Relationship to Orthostatic Hypotension in Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

	Maraviroc QD N=414	Maraviroc BID N=426	Placebo N=209
Hypotension	5 (1.2)	1 (0.2)	1 (0.5)
Orthostatic hypotension	2 (0.5)	2 (0.5)	1 (0.5)
Hypertension	8 (1.9)	13 (3.1)	3 (1.4)
Blood pressure diastolic increased	0	0	1 (0.5)
Blood pressure increased	3 (0.7)	1 (0.2)	0
Dizziness	39 (9.4)	34 (8.0)	14 (6.7)
Dizziness postural	5 (1.2)	1 (0.2)	2 (1.0)
Circulatory collapse	1 (0.2)	0	0
Loss of consciousness	0	1 (0.2)	0
Syncope	2 (0.5)	3 (0.7)	2 (1.0)

Source: SCS Table 3.4.3.3. Includes data from Studies A4001027 and A4001028

Few of these AEs were of Grade 3/4 severity (Table 3.4.3.3). In the placebo group, none of these AEs with a potential relationship to postural hypotension was reported as an SAE. From the maraviroc treatment groups, 1 episode of hypotension (BID group), the circulatory collapse, the loss of consciousness, and 3 of the episodes of syncope (1 maraviroc QD, 2 maraviroc BID) were reported as SAEs (SCS Table 3.8.3.1).

Saquinavir/ritonavir was noted in the Phase 1 drug-drug interaction programme to have the greatest impact on maraviroc C_{max} (SCP Module 2.5.2). Therefore an analysis (Table 3.4.9.9) was conducted to identify hypotension-related AEs reported in patients with saquinavir in their OBT. Dizziness was observed among maraviroc-treated patients receiving saquinavir, but not among placebo-treated patients who received saquinavir (Table 34). These findings are of questionable significance, as (given the small numbers of this subpopulation) the incidence of dizziness reported among these maraviroc-treated patients who were also receiving saquinavir is consistent with that in maraviroc-treated population as a whole.

Table 34. Number (%) of Patients with AEs possibly related to Postural Hypotension in Phase 3 Studies in TE Patients (Studies A4001027 and A4001028), by Presence or Absence of Saquinavir in OBT

	Maraviroc QD N=56	Maraviroc BID N=47	Placebo N=25
Hypotension	1 (1.8)	1 (2.1)	1 (4)
Orthostatic hypotension	0	2 (4.3)	0
Hypertension	0	1 (2.1)	0
Blood pressure diastolic increased	0	0	0
Blood pressure increased	0	0	0
Dizziness	7 (12.5)	3 (6.4)	0
Dizziness postural	0	1 (2.1)	0
Circulatory collapse	1 (1.8)	0	0
Loss of consciousness	0	1 (2.1)	0
Syncope	0	1 (2.1)	0

Source: SCS Table 3.4.9.9

In Study A4001029, which was conducted in non-R5 TE patients and in which duration of exposure to study drug was similar between the maraviroc treatment groups and the placebo group, AEs related to postural hypotension occurred at a similar frequency as in the Phase 3 R5 TE studies (CSR A4001029 Table 13.6.2.3).

One AE of hypotension (Grade 3 severity) has been reported from the 109 R5 TE patients who began OL maraviroc after initial failure on blinded therapy in Studies A4001027 and A4001028 (SCS Table 3.4.7.3).

Postural hypotension was thus reported infrequently in the Phase 2b/3 programme, consistent with the observation from the Phase 1 studies that this event tended to occur at unit doses of >300 mg. Therefore, during the conduct of the Phase 3 studies and while recruitment was still underway, the DSMB recommended that the protocols be amended to allow enrolment of patients with severe cardiovascular and cerebrovascular co-morbidities, who had initially been excluded.

In Study A4001026 12.1% of patients reported dizziness during the double-blind maraviroc QD phase, and just 0.6% reported dizziness on OL maraviroc BID. One patient reported syncope on maraviroc QD and 1 patient had hypotension reported on maraviroc BID. (See A4001026 CSR Module 5.3.4 Other Study Reports)

2.7.4.2.1.5.1.2.4. Postural Hypotension: Conclusions

Maraviroc QD and BID dose regimens of 300 mg (adjusted where appropriate to 150 mg) are associated with a slightly greater incidence of measured postural hypotension and related adverse events than placebo. However few patients discontinued, and the difference in event rate from placebo is not enhanced by the background use of drugs known to reduce blood pressure.

2.7.4.1.1.1.2.3 Cardiac Adverse Events associated with Ischaemia

Table 35 details the AEs possibly linked to cardiac and cerebrovascular ischaemia. More such events were reported for patients on maraviroc than on placebo. Six subjects reported 8 SAEs that may be linked to coronary artery disease (4 maraviroc QD and 2 maraviroc BID). None of these events led to permanent or temporary discontinuation of study drug.

Table 35. Cardiovascular Adverse Events (All-Causality) Reported for the Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

	Maraviroc QD N=414		Maraviroc BID N=426		Placebo N=209	
	N (%)	Exposure adjusted[a]	N (%)	Exposure adjusted[a]	N (%)	Exposure adjusted[a]
Angina pectoris	2 (0.5)	0.8	1 (0.2)	0.4	0	0
Angina unstable	1 (0.2)	0.4	1 (0.2)	0.4	0	0
Coronary artery disease	2 (0.5)	0.8	0	0	0	0
Coronary artery occlusion	2 (0.5)	0.8	0	0	0	0
Myocardial infarction[b,c]	2 (0.5)	0.8	0	0	0	0
Myocardial ischaemia	0	0	2 (0.5)	0.8	0	0
Prinzmetal angina	0	0	1 (0.2)	0.4	0	0
CVA	1 (0.2)	0.4	1 (0.2)	0.4	0	0
TIA	0	0	0	0	3 (1.4)	3.0
Stroke	0	0	0	0	0	0
Cerebrovascular haemorrhage	1 (0.2)	0.4	0	0	0	0

Source: SCS Tables 3.4.3.3 and 3.4.4.4
CHD – coronary heart disease; CAD – coronary artery disease; CAO coronary artery occulsion
[a] Events per 100 patients years
[b] Includes terms acute MI and MI
[c] 2 AEs are reported but 3 SAEs for the same category. PID 1[redacted]20018 - a case of acute heart failure that was also reported an SAE/death of MI

One of the myocardial infarctions, reported as an SAE only, was reported for a subject found dead (Subject 1[redacted]20018, A4001028). The post-mortem examination concluded that the most likely cause of death was acute heart failure due to atherosclerosis. Coronary arteries had severe atheroma with near 100% occlusion but no acute thrombus.

None of the remaining subjects experienced cardiac AEs that led to permanent or temporary discontinuation of study drug.

One myocardial infarction was reported in the screening period, prior to dosing with study drug.

All patients reported for cardiovascular events had significant risk factors for cardiac disease. The past medical histories of these subjects included diabetes mellitus, hypertension, previous myocardial infarction, known coronary artery disease, hyperlipidaemia and smoking. Dyslipidaemia, insulin resistance and altered fat distribution are common in HIV infected adults who are receiving highly active antiretroviral therapy [HAART]), which appears to increase their risk of cardiovascular disease.

Of note, there was an imbalance between the maraviroc-treated groups and the placebo group in Studies A4001027 and A4001028 with respect to past history of myocardial ischaemia. Fourteen patients in the maraviroc QD group and 15 in the maraviroc BID group reported a previous myocardial infarction, compared to just 1 in the placebo group. Other risk factors are typical for this advanced HIV population and balanced across treatment groups.

These data are broadly similar to those from published cohort studies which include all HIV-1 patients, which report adjusted rates of myocardial infarction in the range of 3.5/1000 patient-years (PY)[vi] to 3.6/1000 PY[vii]. The observed rate of myocardial infarction in the combined maraviroc QD and BID treated patients (Table 35) was 3.80 per 1000 patient-years (PY) (2 events); with inclusion of the Patient 1[redacted]20018 (Study A4001028), whose death at home was attributed after autopsy to acute heart failure, coronary atheroma, and myocardial infarction, the observed rate was 5.70/1000 PY (3 events).

The only cardiovascular or cerebrovascular ischaemic event reported in Study A4001029 was a myocardial infarction in Patient 1[redacted]30003 in the maraviroc BID treatment group. Study drug was continued and the event was described as unrelated to treatment.

No AEs relating to myocardial ischaemia have been reported from the 109 R5 TE patients who began OL maraviroc after initial failure on blinded therapy in Studies A4001027 and A4001028. One cerebral infarction and 1 cerebrovascular accident have been reported from that population (SCS Table 3.4.7.3). No notable cardiac events were reported in Study A4001026 (see A4001026 CSR, Module 5.3.4 Other Study Reports).

Overall, ischaemia-related events were rare in these studies, but have been reported more frequently in the maraviroc treatment groups. This is possibly due to imbalance in medical history between groups, and may also be related to the longer follow-up on maraviroc compared to placebo with concomitant longer exposure to other OBT, including drugs (PIs and NNRTIs) that have been associated with cardiovascular risk.

Cardiovascular safety overall conclusions

Both maraviroc treatment groups appear well-tolerated from a cardiovascular perspective. Systematic evaluation of QTc and postural blood pressure changes have shown no clinically relevant differences from placebo. Reported cardiac AEs are infrequent and rarely led to discontinuation. There is an imbalance between ischaemic events reported in patients receiving maraviroc, but no dose response is noted and rates for rare events such as myocardial infarction are consistent with published cohorts. See further discussion in the Risk Management Plan.

2.7.4.2.1.5.2. Eye-Related Adverse Events

During review of the data from the Phase 1 multiple-dose Study A4001019, it was noted that at higher doses episodes of events coded to 'conjunctivitis' (which could include the Investigator terms red eye, bloodshot eye and conjunctival infection) and 'abnormal vision' (which could include the Investigator terms blurred vision, blurred peripheral vision, difficulty focusing and abnormality of accommodation) occurred. These findings appeared to have a

dose relationship. It seems likely that these events were related to the mechanism (still unknown) of vasodilation and postural hypotension.

Phase 1/2a Studies

In the high-dose multiple dose Study A4001019, episodes of 'conjunctivitis' were noted at unit doses of ≥900 mg, and 'abnormal vision' at unit doses of ≥600 mg. Most events coded to 'conjunctivitis' were bloodshot eyes and did not appear to be infectious in origin. Most of these findings were considered treatment-related. Abnormal vision was not reported after 4 days of dosing at any dose.

Phase 2b/3 Studies

Eye-related events reported during the TE studies (A4001027, A4001028, A4001029 and OL treatment in A4001027 and A4001028) were sporadic and the numbers were small. The events occurred at similar rates in all treatment groups, including placebo, and there have been no discontinuations due to eye-related AEs during these studies. The exposure adjusted incidences for "conjunctivitis" was 1.9/100PY, 3.0/100PY and 3.0/100PY and for blurred vision were 2.3/100PY, 1.5/100PY and 4.1/100PY for maraviroc QD, maraviroc BID and placebo, respectively (SCS Tables 3.4.4.4).

2.7.4.2.1.5.3. Hepatic Safety

Hepatic safety was monitored with regular LFT evaluations throughout the Phase 1/2a and the Phase 2b/3 maraviroc clinical programme.

2.7.4.2.1.5.3.1.1.1. Phase 1/2a

Hepatic Adverse Events

The Phase 1 and Phase 2a AE data have been scrutinised for hepatic-related AEs falling within the "hepatobiliary disorders" and "investigations" SOCs of the MedDRA dictionary.

No such hepatic AEs were reported during the Phase 1 single-dose studies. No symptomatic AEs were reported during Phase 1 multiple dose studies. One subject (Subject 1[redacted]1009) who received maraviroc and atazanavir in interaction Study A4001025 was reported with jaundice, which is known to be associated with atazanavir.[viii]

In Phase 2a Study A4001007, 1 subject (1[redacted]1424) who had an elevated ALT level at baseline (86U/L) had a maximum ALT of 180U/L, which was recorded as an AE on Day 5 of taking maraviroc 300 mg BID. His final value while receiving study drug was also abnormally high (153U/L). The event did not lead to discontinuation and he continued on study drug until the end of the dosing period. His ALT and AST concentrations started to reduce while still on study drug, reaching baseline levels by Day 45. On Day 12 he was IgM negative, but antigen positive and IgG positive, for Epstein Barr virus, which may have played a role in the event.

No SAEs relating to hepatotoxicity were reported. There were no episodes of transaminase abnormalities associated with hyperbilirubinaemia. Two subjects discontinued due to liver

function test abnormalities: a subject with abnormal LFTs in the placebo run-in period (A4001008), and a subject in Study A4001021 who had an ALT 3.7 x ULN at discontinuation on Day 10 of maraviroc 300 mg BID.

Liver Function Tests

LFT abnormalities were observed during 4 of the Phase 1 studies, but these were sporadic in nature and these transaminase elevations were not associated with hyperbilirubinaemia. The incidences of increased LFTs relative for the Phase 1 multiple-dose studies are summarised in Table 36.

Table 36. Incidences of Increase in Liver Function Tests Relative to ULN (Normal Baseline) for the Phase 1 Multiple-Dose Studies (subjects only receiving maraviroc or placebo)

	Maximum value on Treatment					
	≤ULN	>ULN to ≤2 ULN	>2 ULN to ≤3 ULN	>3 ULN to ≤5 ULN	>5 ULN	Total
ALT (IU/L)						
Placebo	39	3	0	0	0	42
Maraviroc	240	23	6	2	1	272
AST (IU/L)						
Placebo	41	1	0	0	0	42
Maraviroc	266	11	2	1	1	281
Alkaline phosphatase (IU/L)						
Placebo	41	0	0	0	0	41
Maraviroc	274	4	0	1	0	279
Gamma GT (IU/L)						
Placebo	41	1	0	0	0	42
Maraviroc	270	4	0	2	1	277
	≤ULN	>ULN to ≤1.25 ULN	>1.25 ULN to ≤2 ULN	>2 ULN	Total	
Total bilirubin (mg/dL)						
Placebo	41	0	0	0	41	
Maraviroc	263	6	3	0	272	

Source: SCS Tables 1.6.2.1.1, 1.6.2.2.1, 1.6.2.3.1, 1.6.2.4.1 and 1.6.2.5.1
There were very few subjects with an abnormal baseline, therefore this data is not summarised here
Key: AST – aspartate aminotransferase GOT; ALT – alanine aminotransferase GPT; Gamma GT – gamma glutamyltransferase

In Study A4001002, a multiple dose study of maraviroc in healthy subjects, 8 of 55 (15%) subjects receiving maraviroc had 1 or more abnormal liver enzyme values. All 8 had elevations in ALT without an associated elevation in bilirubin. There was no dose relationship. Sporadic elevations in bilirubin were also noted, with no associated increase in transaminases.

During study A4001042, a drug interaction study with tipranavir/ritonavir, there were no clinically relevant changes in hepatic enzymes during treatment with maraviroc (150 mg BID) and placebo. However, 5 subjects, all receiving maraviroc and tipranavir/ritonavir in combination, had elevation in hepatic transaminases, which were not associated with changes in bilirubin. All resolved spontaneously following the end of dosing. Tipranavir/ritonavir is known to cause elevations in LFTs.[ix]

No elevations in liver enzymes or bilirubin were noted during the healthy volunteer 28-day safety study (A4001008) at doses up to 300 mg BID. Likewise, no unexplained abnormalities in liver enzymes, or dose effect up to doses of 1200 mg maraviroc, were seen in the high dose study (A4001019).

In Phase 2a Studies A4001007 and A4001015, no hepatic abnormalities were observed except for the single patient in Study A4001007, described above, who experienced elevated ALT concentrations.

In summary, the Phase 1 and 2a studies (including a safety study of 28 days duration in healthy volunteers) provided no evidence of an association between maraviroc and clinically significant LFT abnormalities in healthy volunteers or HIV-infected subjects.

2.7.4.2.1.5.3.1.2. Phase 2b/3 Studies

The Phase 2b/3 programme was designed to allow patients with limited treatment options and a degree of hepatic compromise access to maraviroc, which also allowed for the generation of safety data in a population that realistically represented the target population. Given the high background rates of elevated liver enzymes in this population and in view of the unmet medical need, exclusion criteria of >5× ULN for transaminases and >2.5× ULN for bilirubin were used. However, for the treatment-naïve study, patients with transaminase values >3× ULN and bilirubin >1.5× ULN were excluded.

2.7.4.2.1.5.3.1.2.1. Hepatic Adverse Events

The Phase 2b/3 AE data were scrutinised for AEs relating to hepatic safety using a standard MedDRA query (SMQ) for hepatic disorders. This search included possible hepatic disorders likely to be drug-related, but excluded "liver neoplasms benign" and "chronic active hepatitis", which were included in searches for malignancies and infections.

The incidence of Grade 3/4 AEs that might be linked to the hepatobiliary system from the Phase 3 R5 TE studies is summarised in Table 37. In the maraviroc QD, maraviroc BID and placebo arms of the studies 26, 37 and 13 all causality Grade 3 or 4 hepatic AEs were reported respectivily. These slight differences may be explained by the difference in exposure (exposure adjusted 1.2, 3.5 and 5.3 events per 100 PY for maraviroc QD, BID and placebo, respectively). Of these AEs 9, 19, 5 (maraviroc QD, maraviroc BID and placebo, respectively) were considered treatment-related by the Investigator. The incidence of exposure-unadjusted AEs is slightly higher for the maraviroc BID arm than the maraviroc QD and placebo arms.

The imbalance is mainly the result of laboratory results being on occasion reported as AEs. The actual laboratory values are discussed later in this section.

Table 37. Grade 3 and 4 Hepatic Adverse Events in Phase 3 Studies in TE Patients (Studies A4001027 and A4001028)

Event	Maraviroc QD		Maraviroc BID		Placebo	
	All causality	Treatment-related	All causality	Treatment-related	All causality	Treatment-related
Number of subjects	414		426		209	
Alanine aminotransferase increased	6 (1.4%)	3 (0.7%)	6 (1.4%)	4 (0.9%)	0	0
Aspartate aminotransferase increased	6 (1.4%)	4 (1.0%)	11 (2.6%)	7 (1.6%)	1 (0.5%)	0
Blood alkaline phosphatase increased	1 (0.2%)	1 (0.2%)	0	0	0	0
Blood bilirubin increased	3 (0.7%)	0	2 (0.5%)	0	1 (0.5%)	0
Cholecystitis	0	0	1 (0.2%)	0	0	0
Cholecystitis acute	0	0	1 (0.2%)	0	0	0
Cholelithiasis	0	0	0	0	1 (0.5%)	0
Cytolytic hepatitis	0	0	0	0	1 (0.5%)	1 (0.5%)
Gamma-glutamyltransferase increased	5 (1.2%)	2 (0.4%)	4 (0.9%)	4 (0.9%)	3 (1.4%)	0
Hepatic cirrhosis	0	0	2 (0.5%)	1 (0.2%)	0	0
Hepatic enzyme increased	0	0	1 (0.2%)	1 (0.2%)	0	0
Hepatic failure	1 (0.2%)	0	0	0	0	0
Hepatomegaly	0	0	0	0	1 (0.5%)	0
Hyperbilirubinaemia	2 (0.5%)	0	4 (0.9%)	0	1 (0.5%)	0
Jaundice cholestatic	0	0	1 (0.2%)	0	0	0
Liver function test abnormal	1 (0.2%)	1 (0.2%)	2 (0.5%)	1 (0.2%)	2 (1.0%)	1 (0.5%)
Portal vein thrombosis	0	0	1 (0.2%)	0	0	0
Hepatitis toxic	0	0	0	0	1 (0.5%)	0
Transaminases increased	1 (0.2%)	0	1 (0.2%)	1 (0.2%)	0	0
Total number of Events	**26**	**11**	**37**	**19**	**13**	**2**

Source: Tables 3.4.3.3 and 3.4.4.3 Summary of Clinical Safety.

Five cases of ocular icterus were reported (3 Grade 1 and 2 Grade 2); 2 in the maraviroc QD group and 3 in the maraviroc BID group. Three of these cases were attributed to atazanavir, 1 to study drug and 1 to disease under study. Nine events of jaundice were reported by 8 patients (5 in maraviroc QD, 3 in maraviroc BID and 1 in placebo). All the patients on maraviroc QD received concomitant atazanavir, as was the placebo patient and 1 of the 3 patients receiving maraviroc BID. The only case of treatment-related jaundice occurred in Patient 1[redacted]20011 (maraviroc BID), who reported jaundice on Day 2; no abnormal bilirubin was recorded and the patient withdrew consent on Day 15. The third maraviroc BID patient (Patient 1[redacted]30001) had an AE of cholestatic jaundice on Day 19, which was attributed to an opportunistic infection.

One AE each of 'liver tenderness', 'hepatitis C' and 'hepatic enzyme increased' and 4 AEs of 'GGT increased' have been reported from the 109 R5 TE patients who began OL maraviroc

after initial failure on blinded therapy in Studies A4001027 and A4001028 (SCS Table 3.4.7.3).

SAEs and Discontinuations in Phase 2b/3 studies related to Hepatic Events

Serious Adverse events

A total of 15 SAEs (13 cases) that might be linked to the hepatobiliary system were reported by 13 TE patients (Table 38). Three (including 1 case reported 20 days post-dose), 8 and 2 of these cases were reported in the maraviroc QD, maraviroc BID, and placebo groups, respectively. Three of these cases, all on BID maraviroc, were described as possibly treatment-related.

Table 38. Hepatobiliary SAEs Related to Maraviroc During the Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

Drug Dose or Placebo	Study	PID Sex/ Age(yrs)/Race	Event	Start date Stop date	Outcome Action *Investigator Causality*
Maraviroc QD	A4001028	10[redacted]50024 M/3[redacted]	Blood bilirubin increased	82 >112	**Still present** No action *Concomitant treatment-atazanavir treatment*
Maraviroc QD	A4001029	10[redacted]70004 M/3[redacted]	Hepatitis (also pancreatitis)	20 days post therapy-	**Recovered** Not related *Disease under study*
Maraviroc QD	A4001027	10[redacted]30008 M/4[redacted]	Hepatic failure	35/42	**Resolved** Permanently discontinued *Other event – possibly related to recreational drug use or interaction with antiretrovirals, also Campylobacter septicaemia. Discussed below*
Maraviroc BID	A4001028	10[redacted]30006 M/4[redacted]	ALT	127 135	**Resolved** Permanently discontinued *Study Drug*
			AST	127 134	**Resolved** Permanently discontinued *Study Drug*
Maraviroc BID	A4001027	10[redacted]30053 M/4[redacted]	ALT increased	55 77	**Resolved** No action taken *related to Hepatitis B*
			AST increased	55 77	**Resolved** No action taken *related to Hepatitis B*
Maraviroc BID	A4001028	1[redacted]30004 M/6[redacted]	Hepatic enzyme increased	150 >150	**Still present** Study drug stopped temporarily *Study drug*

Table 38. Hepatobiliary SAEs Related to Maraviroc During the Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

Drug Dose or Placebo	Study	PID Sex/ Age(yrs)/Race	Event	Start date Stop date	Outcome Action *Investigator Causality*
Maraviroc BID	A4001027	1[redacted]0007 M/4[redacted]	Hyperbilirubinaemia	42 >42	**Still present** Permanently discontinued *Other event – other illness – HCV/alcohol*
Maraviroc BID	A4001027	1[redacted]40016 M/6[redacted]	Transaminase increased	187 193	**Resolved** Permanently discontinued *Study drug*
Maraviroc BID	A4001028	1[redacted]30001 M/5[redacted]	Jaundice Cholestatic	11 19	**Resolved** No action taken *Other event – opportunistic infection.*
Maraviroc BID	A4001027	1[redacted]30002 M/4[redacted]	Hepatic cirrhosis	18 >18	**Still present** No action taken *Other event – portal vein thrombosis*
Maraviroc BID	A4001027	1[redacted]00004 M/5[redacted]	Cholecyctitis	134 206	**Resolved** No action taken *Other event – other illness*
PBO	A4001027	1[redacted]70012 F/3[redacted]	Hepatomegaly	96 101	**Resolved** No action taken *Other event – rule out malignancy*
PBO	A4001027	1[redacted]10012 F/5[redacted]	Gamma-Glutamyltransferase	1 14	**Resolved** No action taken *Other event - hepatitis*

Source: A4001027 and A4001028 Clinical Study Report Table 3.8.4.2.

The 3 treatment-related SAEs occurred at Day 127, 150 and 187 of therapy. Two of these subjects permanently discontinued study drug and the other temporarily discontinued study drug:

- Subject 1[redacted]30006, a 4[redacted]year old male, experienced Grade 4 transaminase elevations on Day 127 of treatment with maraviroc BID. This subject was also receiving OBT, which included enfuvirtide, lamivudine, abacavir, tipranavir, ritonavir. He was clinically stable and well. Study drug and OBT were discontinued as the consulting hepatologist indicated that the abnormalities were compatible with drug hepatotoxicity. These events were considered related to study drug, tipranavir and ritonavir by the investigator. The transaminases subsequently normalised, but the subject permanently discontinued from the study because of treatment (virologic) failure.

- Subject 1[redacted]40016, a 6[redacted]year old male, received maraviroc BID for a total of 177 days. He had elevated transaminases on 2 separate occasions. On Day 3 he had a Grade 3 elevation in transaminase which occurred at the time of a nevirapine hypersensitivity reaction. On Day 184 he experienced heat exhaustion with rhabdomyolysis, which

was still ongoing when on Day 187 he had another SAE of elevated transaminases, at which point he was discontinued from the study. Although the transaminase elevation was reported separately and ascribed to study drug by Investigator, it seems likely that it was related to the previously reported event. He was diagnosed with hepatic cirrhosis on Day 190.

- Subject 1[redacted]0004, a [redacted] year old [redacted] male, experienced increased hepatic enzymes from Day 150 of treatment with maraviroc BID. This was considered related to study drug by the Investigator. Study drug and OBT were temporarily discontinued. ALT and AST subsequently normalised and remained within normal levels after study drug was restarted. The subject later developed aortic valve endocarditis with *Streptococcus pneumoniae* and died (see CSR Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

The case of hepatic failure was unrelated to study drug and is described below.

- Subject 1[redacted]0008 (maraviroc QD) experienced hepatic failure on Day 35 of treatment. This event was Grade 4 and it was considered related to another factor (possible interaction between a recreational drug and antiretrovirals) by the Investigator. The subject was also septic from *Campylobacter jejuni* with disseminated intravascular coagulation and subsequently admitted to crystal methamphetamine use. Study drug was permanently discontinued and the event resolved. This event was not managed by the study Investigator and the laboratory tests with abnormal results were performed at a different hospital to the admitting institution, and so are not captured in the study database. The results of these tests are documented in the narrative.

Detailed narratives of these related cases are located in the individual CSRs Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.

No SAE of potential relationship to liver toxicity was reported in the non-R5 TE patients infected (CSR A4001029).

No SAEs of a hepatobiliary nature (including laboratories) have been reported from the 109 TE R5 patients who began OL maraviroc after initial failure on blinded therapy in Studies A4001027 and A4001028 (SCS Table 3.8.3.1).

Discontinuations for Hepatobiliary Events in the Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

There were 2 discontinuations due to liver-related SAEs in the TE studies, as described above.

Overall, 9 patients receiving maraviroc treatment (including the 2 subjects described above) discontinued due to liver-related AEs in Phase 3 Studies A4001027 and A4001028. The discontinuation rate is evenly balanced across the treatment arms (Table 39). There were no liver-related discontinuations in Study A4001029.

Table 39. Summary of Discontinuations due to Hepatic-Related AEs Reported in the Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

	Maraviroc QD N (%)	Maraviroc BID N (%)	Placebo N (%)
N	414	426	209
Hepatic Failure	1	0	0
ALT increased	2	1	0
AST increased	2	2	0
LFT abnormalities (LFT increased)	0	1	1
Transaminase increased	0	1	0
Hepatic cytolysis	0	0	1
Hyperbilirubinaemia	0	1	0
Total number of subjects	**4 (1.0%)**	**5 (1.2%)**	**2 (1.0%)**

Source: SCS Table 3.1.4.2
Hepatic including liver abnormalities

Temporary discontinuations for Hepatobiliary Events in the Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

There were 11 temporary discontinuations due to hepatic events (maraviroc QD 4, maraviroc BID 5 and placebo 2) (Table 3.1.3.3). Six of these subjects were rechallenged and are described below. The LFT abnormalities resolved for 3 subjects; for a further 3, LFT abnormalities persisted but patients were able to continue study drug to time of data cut or discontinuation due to other causes.

- Subject 1[redacted]0003/A4001027 (maraviroc BID) temporarily discontinued study drug due to increased AST. Increased AST started on Day 15 of treatment and resolved on Day 27. Study drug was restarted and no further increases in AST were reported. The subject had taken study drug up to Day 334 at the date of cut-off.

- Subject 1[redacted]0004/A4001028 (maraviroc BID), a [redacted]year old[redacted]male, experienced increased hepatic enzymes from Day 150, which was considered related to study drug by the investigator. Study drug and OBT were temporarily discontinued. ALT and AST normalised and remained within normal levels after study drug was restarted. The subject subsequently developed aortic valve endocarditis with *Streptococcus pneumoniae* and died.

- Subject 1[redacted]0004/A4001028 (maraviroc BID) temporarily discontinued study drug due to increased AST and blood creatine phosphokinase. Study drug was temporarily stopped due to increased AST from Day 15 to 22 and increased creatine phosphokinase from Day 15 to 22 and Day 29 to 37. These resolved and the subject had taken study drug up to Day 182 at the time of cut-off.

- Subject 1[redacted]0002/A4001028 (maraviroc QD) temporarily discontinued study drug due to increased ALT and AST. This subject had elevated ALT and AST at baseline and had increased ALT from Day 59 to 65. The abnormalities resulting in temporary discontinuation started on Day 85 and were lower on Day 93. Study drug was restarted.

Although ALT and AST had decreased on Day 93 these parameters remained above ULN for the remainder of the study. The subject had taken study drug up to Day 164 at time of loss to follow up.

- Subject 1[redacted]0009/A4001027 (maraviroc BID) temporarily discontinued study drug due to increased ALT, AST and GGT. These elevations were first reported on Day 147 and did not resolve. Study drug was restarted. The subject had taken study drug up to Day 173 at the date of cut-off.

- Subject 1[redacted]0003/A4001028 (maraviroc BID) temporarily discontinued study drug due to increased ALT, AST and GGT. This adverse event started on Day 283 and did not resolve. The subject had taken study drug up to Day 323 at the date of cut-off.

The negative rechallenge in these patients illustrates the difficulty in definitively assessing the causality of hepatic enzyme abnormalities in a population that consists of patients being treated with multiple medications for complex and often serious conditions, many of which might cause hepatic abnormalities.

There were no temporary discontinuations resulting from liver-related AEs in non-R5 TE Study A4001029 (CSR A4001029 Table 13.6.1.2).

Discontinuation for Hepatobiliary Event in the Discontinued QD Arm from Phase 2b/3 study in R5 treatment-naïve patients (Study A4001026)

The most severe event of hepatotoxicity in the clinical programme occurred in this study and is described below. This was a complicated case for which a contributory role of maraviroc could not be excluded. However, following detailed review it is most likely to be due to isoniazid and/or trimethoprim-sulphamethoxazole toxicity, compounded by ongoing therapy with other known hepatotoxic drugs.

- Patient 1[redacted]0005, a 2[redacted]year old [redacted]female who had increased LFTs at baseline (normal at screening) after having initiated trimethoprim-sulphamethoxazole and isoniazid therapy 7 weeks prior to commencing maraviroc in Study A4001026. She presented with pyrexia, rash and elevated liver function test on day 5 of dosing with maraviroc (had erroneously been receiving 150 mg QD). Although maraviroc dosing was discontinued, she continued to receive drugs that have been implicated in hepatotoxicity for several more days (including intravenous paracetamol, lopinavir/ritonavir, zidovudine/lamivudine and trimethoprim-sulphamethoxazole). Her condition deteriorated and she received a liver transplant on Day 16. The abnormal liver function tests at baseline (increased from normal values at screening) indicate that trimethoprim-sulphamethoxazole and isoniazid (which were initiated at the screening visit) are most likely to have been the cause of her hepatic dysfunction. Rash and fever are typical of trimethoprim-sulphamethoxazole toxicity[x], although the hepatic abnormalities are less common. Of note is that the patient was rechallenged with trimethoprim-sulphamethoxazole post-transplant without ensuing derangements in transaminases or bilirubin, although the outcome of this rechallenge may be confounded by the presence of immunosuppressive agents. This patient was found to

possess the NAT2 alleles that are associated with slow acetylation phenotype and an increased risk of isoniazid induced hepatitis, and CYP21E genotype that is also associated with increased susceptibility to hepatoxicity in slow acetylators. Although it is not possible to exclude a causative role for maraviroc in this case of hepatotoxicity, isoniazid and trimethoprim-sulphamethoxazole are thought the more likely causal factors. The DSMB subsequently recommended that isoniazid use be excluded from the Phase 2b/3 programme.

In the terminated 300 mg QD arm there were 3 subjects (including the subject with toxic hepatitis described above) who permanently discontinued the study in the maraviroc 300 mg QD treatment group. Another subject discontinued from the OL maraviroc 300 mg BID group due to Grade 3 abnormalities in hepatic enzymes (ALT or AST).

Two cases of severe LFT abnormalities were reported in this study; 1[redacted]0005 on maraviroc QD (described above) and 1[redacted]0013 on efavirenz treatment (unblinded for patient management purposes):

- Patient 1[redacted]0013, a 3[redacted]year-old male patient experienced a Grade 2 generalised macular rash and Grade 3 elevations of ALT/AST 30 days after randomisation to efavirenz 600 mg QD. Bilirubin was within the normal range, ALT and GGT increased to Grade 4 three days later. The case was diagnosed as efavirenz hypersensitivity. One month after discontinuation of therapy, the rash resolved and LFTs returned to normal. A causal relationship between the occurrence of the reported events in this patient and the administration of efavirenz cannot be excluded.

One subject discontinued from OL maraviroc 300 mg BID in Study A4001026 due to a Grade 3 increase in ALT, which was considered related to study drug

Summary of Hepatic AEs, SAEs and Discontinuations

There have been no deaths related to hepatic AEs in the clinical programme. Although there is a higher number of liver-related SAEs in the maraviroc BID group, only 3 of these cases were thought by the Investigator to be possibly related to study drug. Two of these 3 cases had alternative explanations for the observed liver enzyme abnormalities (tipranavir usage and rhabdomyolysis), and the third had a negative rechallenge. The single case of severe hepatotoxicity in Study A4001026, which was considered possibly related to maraviroc, is more likely to be due to isoniazid and/or trimethoprim-sulphamethoxazole toxicity. Grade 3 and 4 hepatobiliary AEs are infrequent but occur more commonly in the maraviroc BID treatment group. There was no corresponding imbalance in the frequency of permanent and temporary discontinuation related to hepatic events that might indicate that this imbalance in liver-related SAEs is of clinical significance. For hepatic safety, the laboratory data provides additional objective data for safety assessment.

2.7.4.2.1.5.3.1.2.1.1. Clinically significant (Grade 3/4) LFT abnormalities

LFTs were performed at screening, baseline and at the 2-week and 1-month visits, and then monthly until 24 weeks. Thereafter they were assessed every 8 weeks.

Table 40. Frequency of Grade 3 and 4 laboratory LFT values in Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

	Maraviroc QD (N= 408)			Maraviroc BID (N= 421)			Placebo (N= 207)		
	Gr 3	Gr 4	Gr 3+4	Gr 3	Gr 4	Gr 3+4	Gr 3	Gr 4	Gr 3+4
AST	11	2	**13 (3.2%)**	13	6	**19 (4.5%)**	6	0	**6 (2.9%)**
ALT	14	1	**15 (3.7%)**	6	4	**10 (2.4%)**	6	1	**7 (3.4%)**
Bilirubin	28	4	**32 (7.8.%)**	21	3	**24/420 (5.7%)**	8	3	**11/206 (5.3%)**

Source: Tables 3.6.8.1, 3.6.8.2, 3.6.8.3 Summary of Clinical Safety.
Patient 1[redacted]0008 with hepatic failure (maraviroc QD – Grade 4 ALT and AST and Grade 3 bilirubin) does not appear in this table.

The numbers of subjects with grade 3 or 4 LFT abnormalities are very low and fairly evenly distributed across the treatment groups (Table 40). Although there are slightly higher numbers of Grade 3 and 4 AST abnormalities in the maraviroc BID treatment group, for ALT the numbers of subjects with such abnormalities are higher in the placebo and maraviroc QD groups. Most bilirubin abnormalities were associated with concomitant atazanavir use (Table 3.6.11.3 Summary of Clinical Safety).

Shifts in ALT levels, generally considered the most sensitive biomarker for hepatotoxicity (since AST is also present in muscle), are presented in Table 41. Three patients with normal or Grade 1 abnormal baseline ALT experienced an increase to a Grade 4 level, 1 in each treatment group.

Table 41. Shift Table for Liver Function Test Maximum ALT Value on Treatment versus Baseline, Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

	Maximum Alanine Aminotransferase ALT (IU/L)														
	Ungraded N			Grade 1 N			Grade 2 N			Grade 3 N			Grade 4 N		
Baseline	**QD**	**BID**	**Pbo**	**QD**	**BID**	**Pbo**	**QD**	**BID**	**Pbo**	**QD**	**BID**	**Pbo**	**QD**	**BID**	**Pbo**
Ungraded	232	241	110	71	57	35	8	21	8	6	1	2	0	1	1
Grade 1	25	23	14	37	39	21	9	14	5	2	0	1	1	0	0
Grade 2	2	2	0	5	7	5	4	4	2	4	4	2	0	2	0
Grade 3	0	0	0	0	0	0	0	3	0	2	1	1	0	1	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	259	266	124	113	103	61	21	42	15	14	6	6	1	4	1

Source – SCS Table 3.6.8.2
Pbo – placebo
Ungraded - <1.25 ULN; Grade 1 - ≥1.25 ULN to ≤2.5 ULN; Grade 2 - >2.5 ULN to ≤5.0 ULN; Grade 3 - >5.0 to ≤10.0 ULN; Grade 4 - >10.0 ULN.
Shading represents no change in grade from baseline to last on treatment value.
ULN – upper limit of normal
Only subjects with both a valid baseline and an on-treatment value for the parameter were included in the table.
PID 1[redacted]0008 with hepatic failure (maraviroc QD – Gr 4 ALT and AST and Gr 3 bilirubin) does not appear in this table

In each maraviroc treatment group, 101 subjects increased their ALT by a Grade or more compared with 54 subjects on placebo. For normal baseline ALT the frequency of subjects with a Grade 3 or 4 ALT abnormality is equivalent to placebo for QD dosing but slightly lower than placebo for BID dosing. For an abnormal baseline ALT the frequency of subjects

with a Grade 3 or 4 ALT abnormality is equivalent to placebo for BID maraviroc but slightly higher for QD maraviroc. In summary, there is no evidence of a greater shift from baseline in subjects receiving maraviroc and there does not appear to be a clinically significant difference between the BID and the QD doses.

In Study A4001029 in non-R5 tropic patients, the incidence of LFT abnormalities was low, and similar between treatment groups (CSR A4001029).

No Grade 3 or 4 LFT abnormalities have been identified from among 99 TE R5 patients evaluable for laboratory data who began OL maraviroc after initial failure on blinded therapy in Studies A4001027 and A4001027 (SCS Table 3.6.4.1).

Eight patients were recorded to have Grade 3 or 4 ALT abnormalities during the double-blind treatment phase of maraviroc QD in Study A4001026; just 2 patients were observed to have Grade 3 or 4 elevations during the maraviroc BID open label phase (see Study A4001026).

Subjects with combined, clinically significant transaminase and bilirubin elevations

Analysis of those cases that showed an increase in either ALT or AST >3x ULN combined with an increase in total bilirubin >3 mg/dL is presented in Table 42. Such elevations, without evidence of biliary obstruction and in the absence of any other evident possible explanation ("Hy's Law," first proposed in 1978 by Hyman Zimmerman [xi]), are an ominous marker for drug-induced liver injury.

Table 42. Cases with Episode of >3x ULN Transaminases and >3 mg/dL Total Bilirubin in Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

PID (study)	Dose	Time of event (Week)	Alternative pathology	Hy's Law
10[redacted]20014 (1027)	MVC BID	48	Atazanavir	No
10[redacted]70001 (1027)	MVC QD	16	Atazanavir	No
11[redacted]10018 (1027)	MVC QD	2	Atazanavir	No
11[redacted]00007 (1027)	MVC BID	8	Alcohol , active HCV	Possible
10[redacted]30008 (1027)	MVC QD	5	Campylobacteraemia, methamphetamine use	No
10[redacted]10014 (1028)	Placebo	4	Atazanavir	No
11[redacted]30001 (1028)	MVC BID	2	Cholestatic jaundice	No
12[redacted]50010 (1028)	MVC BID	8	Atazanavir	No

Source CSR Table B3.1, B3.8, B6.1 and Appendix B Listing 2 Patient profiles
Key: MVC – maraviroc

Patients potentially meeting the criteria for Hy's Law whilst on study drug in the Phase 3 studies were few and evenly distributed between treatment groups: 3 (0.7%) maraviroc QD, 4 (1.0%) maraviroc BID, 1 (0.5%) placebo. However, all the cases noted in these studies with an increase of ≥3 ×ULN in ALT or AST and a simultaneous increase of ≥3 mg/dL in total bilirubin had an identifiable cause for these abnormalities apart from study drug. Therefore no subjects met the criteria for Hy's Law.

Summary

These data do not provide evidence that maraviroc has an adverse effect on hepatic function in this heavily TE population.

2.7.4.2.1.5.3.1.2.2. HCV and HBV co-infection

The numbers of subjects enrolled in the Phase 3 trials co-infected with HCV (HCV RNA positive at baseline) and HBV (HBsAg positive at screening) were low. Co-infection rates with HCV were 4%, 7% and 9% and for HBV were 5%, 7% and 3% for maraviroc QD, maraviroc BID and placebo groups, respectively, making it difficult to interpret AE data in these subgroups.

Table 43. Percentage of co-infected subjects with a Grade 3 or 4 abnormality regardless of baseline in the Phase 2b/3 Studies in TE Patients (Studies A4001027, A4001028 and A4001029)

		Co-infection positive			Co-infection negative		
HCV or HBV co-infection	lab	MVC QD	MVC BID	Placebo	MVC QD	MVC BID	Placebo
HCV RNA detectable	ALT	3/20	2/30	1/20	13/448	8/449	8/243
HBV Surface Ag positive	ALT	0/26	1/31	2/22	15/438	9/447	7/240

Patients may appear be co-infected with both HCV and HBV
Source SCS: Table 3.6.9.5, Table 3.6.9.2

Although the numbers are small, it appears that within both the HCV and HBV co-infected populations, Grade 3 and 4 hepatic abnormalities are evenly distributed among the treatment groups. Generally, the frequency of Grade 3 and 4 hepatic events is higher in hepatitis co-infected patients, as might be expected.

No hepatobiliary AEs were reported for patients in the Phase 3 maraviroc QD and placebo groups who were co-infected with HCV. However, there were 4 (14%) events reported in patients who received maraviroc BID (cholecystitis, cholelithiasis, hepatosplenomegaly and hyperbilirubinaemia) (SCS Table 3.4.9.8). In the HBV co-infected subjects (Phase 3), there was only 1 adverse event, a case of cytolytic hepatitis on placebo (SCS Table 3.4.9.14).

In patients co-infected with HCV at baseline, HCV RNA was measured again at Week 12 and Week 24. By Week 24 the mean HCV RNA in subjects in both maraviroc arms was reduced relative to baseline, but in placebo patients it had increased. However the subject numbers are very small and data are highly variable (SCS Table 3.6.20).

Hepatic Safety Conclusion

There were no deaths related to hepatic AEs in the clinical programme. Although there is a higher number of hepatic-related SAEs in the maraviroc BID group only 3 of these cases were

judged possibly related to study drug. Of these 3 cases, 2 were in patients who had alternative pathology that could readily explain the hepatic abnormalities seen (i.e., tipranavir usage, rhabdomyolysis), and the third had a negative rechallenge. The single case of severe hepatotoxicity, which was judged by the Investigator to be possibly related to maraviroc and resulted in transplantation, appears more likely to be due to isoniazid and trimethoprim-sulphamethoxazole toxicity. Grade 3 and 4 hepatobiliary AEs were infrequent but tended to occur more commonly with maraviroc BID dosing, but there was no imbalance in the frequency of permanent and temporary discontinuation to indicate that this imbalance is of clinical significance. Of the patients rechallenged following elevations in liver enzymes all but 1 (who discontinued for another reason) continued dosing.

The numbers of subjects with a Grade 3 or 4 liver function test abnormalities are low and fairly evenly distributed across the treatment arms. Although there are slightly higher numbers of Grade 3 or 4 AST in the maraviroc BID treatment group, for ALT, the numbers of subjects with Grade 3 or 4 is higher on placebo than on maraviroc BID. Most of the bilirubin abnormalities are due to concomitant atazanavir usage.

There is also no evidence that there is a greater shift in LFT values from baseline on maraviroc versus placebo; in fact, there is a trend to a greater shift downwards in ALT and AST (Table 51 below).

The subjects with a combination of elevated bilirubin and transaminases were equally distributed across the treatment arms and all of these subjects had an alternative explanation for the abnormal values, often atazanavir usage.

The clinical and laboratory data generated during this development program do not indicate that maraviroc has an adverse effect on hepatic function.

2.7.4.2.1.5.4. Immune Function

There was no clinical or laboratory evidence suggesting an increased susceptibility to infection or malignancy in either healthy or HIV-infected subjects. These subjects are discussed in more detail in the Safety Review of Immunotoxic Potential of Maraviroc, Module 5.3.5.3), but are reviewed briefly here.

Phase 1/2a Studies

The Phase 1/2a studies included a detailed collection and review of clinical data for any evidence of an effect of the drug on the immune system, which was expected to provide the most valuable indication of any effect of maraviroc on immunity. Certain studies provided for detailed monitoring of laboratory effectors of immune function, and all Phase 1 studies included routine full blood counts for all subjects. Table 44 provides details of the immune function markers that were collected.

Results for the multiple-dose healthy volunteer studies were assessed for immunologic parameter changes. The single-dose study data are not considered in detail here, as any effect should be more noticeable in the multiple dose studies.

Table 44 Monitoring of Effectors of Immune Function by Study for the Phase 1/2a Studies

	A4001001 FIH	A4001002 Dose-escalation multiple dose	A4001008 28 day safety study	A1001005 OC-interaction study	A4001007, A4001015 2a studies
Timing of assessment	Pre-dose; 24 hours; Follow-up.	Day 1 (pre-dose); Day 7; Day 13; Follow up.	Pre-dose on days 15, 27 and 42 and at follow-up	Pre-dose on days 15, 27 and 42 and at follow-up	Day 1 (pre-dose), Day 11 and follow up (day 40).
Immunophenotyping (T and B cell subsets , macrophage/monocyte and NK cell subsets)	X	X	X	X	X
Dendritic cells			X	X	
CD21 /CD86			X	X	
Immunoglobulins (IgA, IgD, IgE, IgG [including subclasses] and IgM).	X	X	X		
CD4 count					At screening

FIH = First-in-human study.

Immune effector and haematology monitoring - Phase 1/2a studies

Immunophenotypic data collected in several Phase 1 studies, particularly in Study A4001008, but data were variable and no effect of maraviroc could be discerned (see Safety Review of the Immunotoxic Potential of Maraviroc Module 5.3.5.3).

In the Phase 2a studies, neither the haematological parameters nor the immunophenotyping data showed dose-related changes in response to treatment with maraviroc.

Immune function related safety data - Phase 1/2a Clinical Studies

A thorough review of clinical data from the multiple-dose studies of Phase 1 and 2a was carried out for any indication of a deleterious effect of maraviroc on immunity. There was no clinical or laboratory evidence suggesting an increased susceptibility to infection in non-HIV-1 infected and HIV-1 infected subjects who were administered various multiple doses (up 1200 mg QD of maraviroc) during Phase 1 and 2a studies. There was no dose- or duration-event relationship for events possibly related to immune function except for rhinitis (26.9% of subjects receiving ≥600 mg/day in comparison to 3.6% of subjects receiving placebo). However, vasodilatation secondary to higher doses of maraviroc may produce similar symptomatology to rhinitis (see Phase 1 AE analysis in Section 2.7.4.2.1.1.1.2).

Three subjects[3] were identified as having an Epstein Barr virus infection whilst being investigated for asymptomatic elevated liver enzymes. Another subject in Study A4001002, randomised to 25 mg of maraviroc, was initially recorded as having herpes zoster but actually had varicella infection (Day 5 of the study, Day 3 of the multiple dosing phase). This event was moderate and considered not related to study drug by the Investigator, and as the incubation period of varicella zoster virus infection is 21 days, a causal relationship with maraviroc is extremely unlikely.

There was no evidence of unusual or unexpected infections in the Phase 1/2a studies.

2.7.4.2.1.5.4.1. Phase 2b/3 Studies A4001027, A4001028, A4001029 and A4001026: Examination of Clinical Data Related to Infection

The assessment of these data include a brief overview of the infection/infestation AEs, discontinuations and laboratory abnormalities, followed by a more detailed presentation of the infection/infestation SAEs, deaths, and category C illnesses. The incidence of category C illnesses is stratified by CD4 cell count.

The CDC HIV classification system was used throughout the Phase 2b/3 clinical programme; a list of category C AIDS-defining events may be found in each relevant protocol. Where possible, the incidence of category C events has been stratified by CD4 cell count.

Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

The mean CD4 count in each of the 3 treatment groups in the 2 R5 TE Studies A4001027 and A4001028 was approximately 200 cells/μL. Approximately 20% of patients in each treatment group had baseline CD4 counts less than 50 cells/μL. These patients were heavily TE with few or no treatment options.

As noted previously (Section 2.7.4.1.2.3), there was a shorter duration of exposure for patients in the placebo group, resulting primarily from discontinuations for lack of efficacy.

2.7.4.2.1.5.4.2. Infections

In the Phase 3 TE population, AEs relating to the SOC 'infections and infestations' were reported for 198 (48%), 214 (50%) and 80 (38%) patients in the maraviroc QD and BID and placebo groups, respectively. The infections with higher frequencies among maraviroc patients tended to be either those common in the general healthy population (such as respiratory tract infections) or opportunistic infections common in the TE population (such as *Candida*, herpes and staphylococcal infections). Indeed, when the frequency of all infections was adjusted for exposure, no clear difference was observed between treatment groups: 121/100 PY for maraviroc QD, 126/100 PY for maraviroc BID and 118/100 PY for placebo. The difference between treatment groups in the non-adjusted analysis may therefore be

[3] Patient #10 in study A4001006 receiving 100 mg of maraviroc BID, Patient #1[redacted]1425 in study A4001007 receiving 300 mg of maraviroc BID and Patient #1[redacted]1027 in study A4001019 receiving 300 mg of maraviroc BID)

explained by the longer treatment duration in the maraviroc treatment arms. No unusual infections occurred and there was no clear difference in the severity of the infections between treatment groups, with most being mild to moderate in severity (SCS Table 3.5.1.4). For father details please see Section 4.1.3.1 of the Safety Review of Immunotoxic Potential of Maraviroc, Module 5.3.5.3.

Three patients were permanently discontinued due to AEs related to infections: 2 on placebo (pneumonia and infection with mycobacterium, both SAEs), and 1 on maraviroc BID (gastrointestinal infection). Thirteen patients were discontinued temporarily due to AEs related to infection, 3 in the placebo group and 5 each in the maraviroc QD and maraviroc BID groups.

The overall incidence of AEs related to infection or infestation was not affected by the baseline value of CD4 count in the maraviroc treatment groups (Table 45).

Table 45. Incidence of Adverse events of infections and infestations by baseline CD4 cell count in Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

	Maraviroc QD	Maraviroc BID	Placebo
System organ class by CD4 ≥50 cells/μL	**N = 325 (%)**	**N= 340 (%)**	**N = 171 (%)**
Infections/Infestations	153 (47.1)	171 (50.3)	68 (39.8)
System organ class by CD4 <50 cells/μL	**N= 88 (%)**	**N=86 (%)**	**N=37 (%)**
Infections/Infestations	44 (50)	43 (50)	11 (29.7)

Source: SCS Table 3.4.9.5

Serious adverse events and deaths resulting from Infections/Infestations

The total numbers of SAEs recorded within the infections and infestations SOC were 24 (5.8%), 29 (6.8%) and 23 (11.0%) in the maraviroc QD, maraviroc BID and placebo arms of the studies. Two cases were reported to be related to study drug (pneumonia and severe diarrhoea), both of which were on maraviroc BID. Brief narratives are included in Section 2.7.4.2.1.3.2.1. Detailed narratives are provided in Safety Review of Immunotoxic Potential of Maraviroc (Module 5.3.5.3).

Four deaths due to infection were reported (Table 46). One death occurred in the placebo arm, compared to 2 in the maraviroc QD and 1 in the maraviroc BID treatment arms. Brief narratives are provided in Section 2.7.4.2.1.2 and detailed narratives in the individual CSRs Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.

Table 46. Death Resulting from Infections in Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

	CD4 count Units/μl		Length of treatment (days)	Treatment	Time to death (days)
	At Baseline	At Time of death (or closest timepoint)			
Patient; Infection					
10[redacted]0007 [A4001027]; Pneumonia	231	256 (57)	88	Placebo	88
10[redacted]0032 [A4001028]; Septic shock	63	92 (55)	79	MVC QD	81
11[redacted]0011 [A4001028]; Pneumonia Bacterial	0	3 (30)	63	MVC QD	88
11[redacted]0004 [A4001028]; Pneumonia, Endocarditis bacterial	111	101 (169)	190	MVC BID	208

CSR A4001027, Appendix B, Table B4.3; A4001028, Appendix B, Table B4.3

It is worth noting that 11 subjects died in the 5 to 6 weeks between screening and randomisation, including 5 deaths due to infections, which reflect the advanced stage of disease of this study population.

2.7.4.2.1.5.4.3. Safety Data Specific to Category C Infections

There were 47 subjects reporting Category C infections, with a similar incidence in the 3 treatment groups: 23 (5.6%), 16 (3.8%) and 9 (4.3%) in maraviroc QD, BID and placebo, respectively. Herpes simplex and oesophageal candidiasis were those most commonly reported, with slightly higher rates of herpes virus/herpes simplex infections in the maraviroc QD treatment group, 10 (2.4%) than in the maraviroc BID group, 6 (1.4%), or in the placebo group and 2 (1.0%).

Table 47. Incidence of Category C AIDS-defining Infections in Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

	Maraviroc QD N (%)	Maraviroc BID N (%)	Placebo N (%)
N	**414**	**426**	**209**
Candidiasis	2 (0.5)	1 (0.2)	0
Cytomegalovirus choriortinitis	2 (0.5)	0	0
Cytomegalovirus gastrointestinal infection	0	1 (0.2)	0
Cytomegalovirus infection	0	1 (0.2)	0
Gastroenteritis cryptosporidial	0	0	1 (0.5)
Herpes simplex	7 (1.7)	6 (1.4)	1 (0.5)
Herpes virus infection	3 (0.7)	0	1 (0.5)
Lobar pneumonia	0	0	1 (0.5)
Mycobacterial infection	0	1 (0.2)	0
Mycobacterial avium complex infection	0	1 (0.2)	3 (1.4)
Oesophageal candidiasis	11 (2.7)	2 (0.5)	2 (1.0)
Pneumocystis jiroveci pneumonia	0	2 (0.5)	0
Pneumonia	1 (0.2)	0	1 (0.5)
Pneumonia bacterial	0	0	1 (0.5)
Progressive multifocal leukoencephalopathy		1 (0.2)	
Total subjects	23 (5.6)	16 (3.8)	9 (4.3)
Total events	**26**	**16**	**11**

Source: SCS Table 3.5.3.2 Table 3.5.3.1

One patient experienced exacerbation of CMV retinitis, which occurred 21 days post-therapy and pre-open label maraviroc and therefore does not appear in the above table. A brief narrative for this patient is included below.

- Patient 1[redacted]30011 (in Study A4001027) is a 3[redacted]-year-old [redacted] male with a screening viral load of 4.91 $\log_{10}$ copies/mL and a screening CD4 cell count of 3 cells/μL, with a past history of CMV retinitis, HIV-associated wasting and herpes simplex virus infection. The patient received 28 days of blinded study drug (maraviroc 150 mg BID) until early termination due to lack of efficacy. On Day 21 post therapy, he was diagnosed with bilateral progression of CMV retinitis. The patient had been on valganciclovir which was continued. He was started on open label maraviroc BID 10 days after the diagnosis of CMV exacerbation was made. The event was considered moderate in severity, not related to study drug and resolved on Day 41 of open-label therapy.

A total of 24 subjects (12 [2.8%] subjects receiving maraviroc QD, 8 [1.8%] subjects receiving maraviroc BID and 4 [1.9 %] subjects receiving placebo) experienced a Category C infection during the first 4 weeks of treatment in comparison to 3 (0.7%), 2 (0.5%) and 4 (1.9%) respectively at ≥ 6 months on treatment. The reduced rate of events on maraviroc after 6 months of treatment suggests it is unlikely that maraviroc has a negative effect on immune function.

Two recurrent Category C AIDS defining infections were reported by 3 patients: Patient 12[redacted]40014 (maraviroc QD; A4001028) and Patient 10[redacted]0001 (maraviroc BID; A4001028) each had 2 episodes of oesophageal candidiasis, and Patient 10[redacted]0013 (maraviroc QD; A4001027) had 2 episodes of herpes simplex virus. Patients who experienced Category C AIDS-defining infections had a lower median baseline CD4 cell count than those who did not experience such events.

In summary, the rate of infection is similar between both maraviroc treatment arms and placebo. There were no unusual or unexpected infections reported. The incidence of category C infections in patients receiving maraviroc was similar to that seen in the placebo group. A slightly higher frequency of cases of herpes simplex was observed in the maraviroc groups, but this may be explained by their longer duration of exposure.

Phase 2b Study in non-R5 TE Patients (Study A4001029)

In Study A4001029, maraviroc had little effect on viral load and exposure was similar to placebo. Therefore safety data from this study are not confounded by the superiority to placebo seen in the studies conducted in patients with R5 virus leading to much greater duration of exposure to maraviroc.

The most common AEs associated with infection in the non-R5 TE population from Study A4001029 were similar to those in combined R5 TE population (CSR A4001029 Table 50). Nasopharyngitis and bronchitis were slightly more common in the maraviroc treatment groups than the placebo group. One patient permanently discontinued due to an infection (a non treatment-related SAE of asthenia, fatigue, candidiasis, pneumonia, dehydration and pleural effusion). Only 2 patients experienced Grade 4 infections while receiving maraviroc BID (diarrhoea and lymphadenitis).

There were 5 deaths due to infection: 1 in the maraviroc QD group (1 with pneumonia and possible chest mass), 2 in the maraviroc BID group (1 with bacterial pneumonia and 1 with pneumocystis pneumonia) and 2 in the placebo group (1 with progressive multifocal leukoencephalopathy and 1 with multiple cerebral lesions) (see individual CSR, Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication, for narratives).

There was a slight imbalance of category C infections in the maraviroc QD group (7) when compared with maraviroc BID (3) and placebo (3) groups. One subject in the maraviroc QD group accounted for 2 infections (disseminated MAI and histoplasmosis, CSR A4001029 Table 53). There were 4 cases of *Pneumocyctis jiroveci* pneumonia, which occurred in patients receiving maraviroc (3 QD and 1 BID); none occurred in the placebo group. These patients had a mean CD4 count of 11 cells/μL. Conversely, 1 case of recurrent pneumonia was recorded in the placebo group but none in the maraviroc treatment arms. The small numbers of patients, however, precludes the drawing of any definitive conclusions. The subjects in Study A4001029 were in a very advanced disease state, evident from the low mean (approximately 90 cells/μL) and median (approximately 40 cells/μL) baseline CD4 counts, and so were at high risk for developing category C infections. There were no subjects with baseline CD4 counts >50 cells/μL who had a category C infection.

In summary, there is no evidence of any untoward effect of maraviroc on immune function from the data that have been generated from the Phase 2b safety study in patients with dual/mixed tropic HIV-1 infection.

Open Label TE R5 Patients (Studies A4001027 and A4001028)

AEs of infections or infestations have been reported for 27 of the 109 TE R5 patients who began OL maraviroc after initial failure on blinded therapy in Studies A4001027 and A4001028, of which the most commonly reported were condyloma acuminatum and nasopharyngitis, each with 5 events (SCS Table 3.4.7.3).

Discontinued QD Arm from Phase 2b/3 study in R5 treatment-naïve patients (Study A4001026)

There were 74 (42.5%) AEs of the system organ class infection/infestation reported in the maraviroc QD arm of the study and 41 (31.8%) in the maraviroc BID OL arm of the study. There were 2 permanent discontinuations, both in the maraviroc QD arm (Patient 1[redacted]0022 with disseminated tuberculosis; Patient 1[redacted]0005 with 2 episodes of pulmonary tuberculosis, 1 on active therapy and 1 post therapy.) There were no deaths related to infection.

Six treatment-emergent category C AIDS-defining illnesses were reported in the maraviroc 300 mg QD treatment group (2 cases of tuberculosis, 3 cases of *Pneumocystis* pneumonia and 1 case of Kaposi's sarcoma), 3 of which were categorised as SAEs. There were no category C infection events in the OL maraviroc 300 mg BID group. However there was 1 event of herpes zoster that was incorrectly reported as a category C event in the OL maraviroc 300 mg BID group.

In summary, the incidence of category C infections was low in this population. Additional narratives for category C infections are included in Appendix C of this summary document.

2.7.4.2.1.5.4.4. Malignancies

Infection with HIV increases the risk of Kaposi's sarcoma, non-Hodgkin's lymphoma and a number of malignancies, including cervical cancer, lip cancer, lung cancer, connective tissue cancer, anal and penile cancer, testicular seminoma, multiple myeloma and leukaemia (see Safety Review of Immunotoxic Potential of Maraviroc (Module 5.3.5.3)).

The role of CCR5, and indeed of chemokine receptors in general, with respect to both immunosurveillance and neoplastic cell behaviour (malignant transformation, cell proliferation and survival, invasion and metastasis, etc.) remains as yet largely undefined. Accordingly, the safety data have been carefully and systematically monitored and analysed for evidence of any effect of maraviroc, positive or negative, on the incidence of malignancies.

Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

Thirty-one patients reported all-causality AEs of neoplasm (neoplasms benign, malignant and unspecified). There was no difference in the incidence between treatment arms (12 (2.9%) on maraviroc QD, 10 (2.3%) maraviroc BID and 9 (4.3%) on placebo). Two patients in the BID

maraviroc treatment arm permanently discontinued due to a malignancy (Patient 10[redacted]50010, anal carcinoma; Patient 1[redacted]50002, squamous cell carcinoma of the tongue). Both events were considered to be an SAE and neither was attributed to study drug.

Serious Adverse Events and Deaths Resulting from Malignancies

There were 15 SAEs of neoplasm (including neoplasms benign, malignant and unspecified): 7 (1.7%) on maraviroc QD; 6 (1.4%) on maraviroc BID and 2 (1.0%) on placebo. None was considered to be treatment-related. There was no difference in the incidence of neoplasm-specific SAEs between treatment groups.

None of the deaths that occurred within 28 days of study therapy during Studies A4001027 and A4001028 resulted from malignancy. However, in both studies deaths resulting from malignancy did occur later than 28 days post-treatment. Full narratives can be found in the individual CSRs, Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.

Safety Data Specific to Malignancies

The incidence of malignancy was fairly evenly distributed across the study arms (Table 48).

Table 48. Incidence of Malignancies by Baseline CD4 Cell Count, Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

	Maraviroc QD	Maraviroc BID	Placebo
Malignancies at CD4 ≥50 cells/μL	**N= 325 (%)**	**N= 340 (%)**	**N= 171 (%)**
Anal cancer	1 (0.3)	3 (0.9)	2 (1.2)
Basal cell carcinoma	1 (0.3)	1 (0.3)	0
Bowens disease	0	1 (0.3)	0
Diffuse large B cell lymphoma	0	0	1 (0.6)
Kaposi's sarcoma	0	0	1 (0.6)
Lymphoma	1 (0.3)	0	1 (0.6)
Metastases to liver	1 (0.3)	0	0
Oesophageal carcinoma	1 (0.3)	0	0
Squamous cell carcinoma	1 (0.3)		1 (0.6)
Squamous cell carcinoma of the skin	1 (0.3)	0	0
Sweat gland tumour	0	1 (0.3)	0
Tongue neoplasm	0	1 (0.3)	0
Malignancies at CD4 <50 cells/μL	**N= 88 (%)**	**N=86 (%)**	**N=37 (%)**
Anal cancer	2 (2.3)	0	1 (2.7)
Kaposi's sarcoma	1 (1.1)[a]	2 (2.3)	2 (5.4)
Lymphoma	1 (1.1)	1 (1.2)	0

Source: Table 3.4.9.5 Summary of Clinical Safety and Individual Clinical Study Reports Appendix B 6.1.
Benign tumors not included.
Abdominal neoplasms actually abdominal lump/nodule (Patients A4001028/1[redacted]0011 and A4001027/1[redacted]0019) not included.
Anal carcinoma and anal carcinoma Grade 0 are combined.
[a] Patient A4001028/12[redacted]0002. Testicular neoplasm was actually a Kaposi's sarcoma so has been included here
Patient A4001028/12[redacted]0011 (maraviroc BID) – presumptive CNS lymphoma – not included as not on the clinical database.
One event of anal cancer occurring in the maraviroc BID treatment group (Subject A4001028/1[redacted]0035) was noted to be due to a relapse. One subject (A4001028/12[redacted]0009) in the maraviroc QD treatment group had a past medical history of adenocarcinoma of the colon and was reported to have developed liver metastases during the study.
Treatment-emergent benign neoplasms not included are: 1 benign neoplasm of the orbit (maraviroc QD), 2 events of seborrheic keratosis (maraviroc BID), 2 hemangiomas (maraviroc QD), 22 events of skin papilloma (11 maraviroc QD, 8 maraviroc BID and 3 placebo) and 1 sweat gland tumour (maraviroc QD).

As expected, the rates of malignancies were higher in all treatment groups in patients with CD4 counts <50 cells/μL.

Category C malignancies in R5 TE patients are summarised in Table 49. The incidence of documented lymphoma was 2 (0.5%) for maraviroc QD, 1 (0.2%) for maraviroc BID and 2 (1.0%) for placebo. To provide the most conservative assessment however, an analysis was conducted, which also includes Patient 12[redacted]0011 (in Study A4001028) receiving maraviroc BID, with the presumptive central nervous system lymphoma. Therefore, the lymphoma (documented or presumed) rates during the randomised period of the trials in the treatment-experienced patient population infected with CCR5 tropic HIV-1 at the date of database cut-off were 2/259 (0.8 per 100 patient-years) on maraviroc QD, 2/269 (0.8 per 100 patient-years) on maraviroc BID respectively and 2/99 (2.0 per 100 patient-years) on placebo. When Patient 1[redacted]0002 (in Study A4001027) who, following treatment failure on placebo, developed a

large B cell lymphoma after >4 months of open label maraviroc BID is included, this provides an overall lymphoma rate. The overall numbers of lymphoma cases reported in treatment-experienced patients, regardless of time post therapy, are 2 cases on maraviroc QD, 3 on maraviroc BID (including Patient 1[redacted]0002 on open label) and 2 on placebo. When the randomisation schedule of approximately 2:2:1 is considered this also demonstrates no difference in frequency between maraviroc and placebo, despite the extended treatment duration on maraviroc. A similar picture was seen for Kaposi's sarcoma and anal carcinoma.

Table 49. Incidence of Category C Malignancies in Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

	Maraviroc QD	Maraviroc BID	Placebo
Diffuse large B-cell lymphoma	0	0	1 (0.5)
Kaposi's sarcoma	1 (0.2)	2 (0.5)	3 (1.4)
Lymphoma	2 (0.5)	1 (0.2)	1 (0.5)
Total events (subjects)	3 (3)	3 (3)	5 (5)

Source: SCS Table 3.5.3.2 Table 3.5.3.1

In summary, the incidence and severity of malignancies between treatment groups were similar between the maraviroc treatment arms and slightly higher in the placebo arm. There were no unusual or unexpected malignancies. No evidence for an increased risk of malignancy has emerged from the data generated in the Phase 3 R5 TE programme. The overall rates of malignancy are similar between treatment arms.

Phase 2b Study in non-R5 TE Patients (Study A4001029)

There were no deaths or SAEs due to malignancy and no Category C malignancies in this study.

Malignancy was diagnosed during treatment in 3 patients. Patient 1[redacted]0001 had basal cell carcinoma diagnosed after 148 days of placebo. Patient 1[redacted]0001 had Grade 3 bowenoid papulosis diagnosed after 80 days of maraviroc BID. Patient 12[redacted]0003 had moderate intestinal mass (anal carcinoma) diagnosed after 218 days of maraviroc QD. (See CSR, Table 15.4 Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

In summary, although the numbers are small, these data provides further confidence that the inadvertent use of a CCR5 antagonist in this population would not increase the risk for development of malignancies.

Open Label TE R5 Patients (Studies A4001027 and A4001028)

Seven of 109 TE R5 patients who began OL maraviroc after initial failure on blinded therapy in Studies A4001027 and A4001028 were reported with AEs of 'neoplasms benign, malignant and unspecified', including 3 events of skin papilloma and 1 event each of anal cancer, B-cell lymphoma, conjunctival neoplasm, skin neoplasm, skin cancer, and squamous cell carcinoma. The lymphoma in a patient on OL maraviroc BID therapy (Patient 1[redacted]0002 in Study

A4001027, initially randomised to placebo) was reported and considered treatment-related (SCS Table 3.4.7.3).

Discontinued QD Arm from Phase 2b/3 study in R5 treatment-naïve patients (Study A4001026)

There were 11 AEs in the categories of neoplasm benign, malignant and unspecified (5 [2.9%] on maraviroc QD and 3 [2.3%] on maraviroc BID OL). All of the neoplasms were recorded as mild in severity with one exception (a uterine leiomyoma in the BID OL arm of the study, not considered related to study drug, for which no action was taken, which was reported to have resolved 3 days after diagnosis).

Three deaths have been reported in Study A4001026 that relate to malignancy.

- A [redacted]-year old male [redacted] patient (Patient 1[redacted]0003; Case No. 2005115924) from Switzerland permanently discontinued blinded therapy (maraviroc QD) and zidovudine/lamivudine ([redacted]®) on Day 35 of dosing, with a reason of refusal to participate further in the study. On Day 36 of study the Investigator reported the following SAEs for this patient: pericardial effusion, ascites and pleural effusion. All AEs were Grade 3 in severity and attributed as possibly related to study drug by the Investigator. This patient died on 07 November 2[redacted] (Day 127 of study) with a reported cause of death of non-Hodgkin's lymphoma. The Investigator causality assessment was 'disease under study'.

- A [redacted]-year old male [redacted] subject (Patient 1[redacted]0002; Case No. 2005075016) from the USA permanently discontinued blinded therapy (efavirenz) on Day 30 of dosing. This patient died on 26 May 2[redacted] (Day 45 of study), with a reported cause of death as Castleman's disease. The Investigator causality assessment was 'other illness'.

- A [redacted]-year old male [redacted] (PID 1[redacted]0006 Case No 2006039441) received blinded therapy (efavirenz) for 11 days. The patient discontinued with sepsis. Hodgkin's disease was diagnosed 43 days later. He died 180 days post therapy.

2.7.4.2.1.5.4.4.1. Lymphoma

Lymphomas were reported in 4 patients of 90 subjects who received vicriviroc in ACTG Study 5211. Up to 15 September 2[redacted] 12 confirmed lymphomas and 2 suspected lymphomas have been reported in the maraviroc ARISg or Oracle Clinical databases. Of the 12 confirmed lymphomas, 5 were reported in the R5 TE studies A4001027 and A4001028, 2 in the maraviroc QD arm, 1 in the maraviroc BID arm and 2 on placebo. One further case of lymphoma occurred in a patient randomised to placebo and then switched to OL maraviroc BID. One case of presumptive CNS lymphoma was reported on maraviroc BID. A recent study of TNF alpha-associated tumours[xii] used a cut-off period of 6 weeks after initiation of therapy for sensitivity analysis. Of these 7 cases reported in the maraviroc R5 TE patient population, 3 presented with symptoms and signs that led to diagnosis of lymphoma within 6 weeks of starting therapy, 1 maraviroc QD and 2 maraviroc BID. No lymphomas have been reported in the non-R5 TE Study A4001029.

In the treatment-naïve study A4001026, 4 confirmed and 1 suspected case of lymphoma have been reported. Of the confirmed cases, 1 has been reported on maraviroc QD, 1 on efavirenz and 2 cases remain blinded. One suspected lymphoma was reported from the efavirenz arm. In all but 1 case (double-blind therapy), symptoms and signs leading to the diagnosis of lymphoma were present before 6 weeks of therapy had been given.

Table 50. Cases of Lymphoma in the Maraviroc Phase 2b/3 Clinical Program

Study No.	Patient ID	Treatment	Event Name: Preferred Term	Active/Post-treatment	Start Date of Event[a]	Scr[b] CD_4 (cells/μL)	Scr[b] HIV-1 RNA(log_{10})	Patient Disposition	Biopsy	Definite	Related	Death[c]
1007	10[redacted]41301	Maraviroc BID (100 mg 10 days monotherapy)	Large cell B-cell non-Hodgkin lymphoma	Post	>2 years	698	3.99	Post-study	Yes	Yes	Yes	No
1026	1[redacted]70003	Maraviroc QD	Non-Hodgkin's Lymphoma	Active	36	434	5.13	Discontinued on day 35	Yes	Yes	No	Yes
	1[redacted]60006	Still blinded	Non-Hodgkin's Lymphoma	Active	108	232	5.42	Ongoing	Yes	Yes	No	No
	10[redacted]70003	Still blinded	Hodgkin's lymphoma	Active	11	96	5.69	Discontinued on day 15	Yes	Yes	No	No
	1[redacted]60006	Efavirenz	Hodgkin's lymphoma	Active	11	87	5.78	Discontinued on day 11	Yes	Yes	No	Yes
	*1[redacted]00002**	*Efavirenz*	*Castleman's disease*	*Active*	*33*	*218*	*5.15*	*Discontinued on Day 30*	*Yes*	*No*	*No*	*Yes*
1027	10[redacted]70010	Maraviroc QD	B cell lymphoma	Active	25	55	4.88	Discontinued day 176	Yes	Yes	No	No
	10[redacted]10001	Placebo	Large cell lymphoma	Active	118	144	4.01	Discontinued day 298	Yes	Yes	No	Yes
	1[redacted]90008	Placebo	Large B-cell lymphoma	Active	209	178	4.83	Ongoing	Yes	Yes	No	No
	10[redacted]10002	Placebo to day 85 MVC BID OL from day 1-143	Large B-cell lymphoma	Post Blinded Active (OL)	146 (OL phase)	191	5.4	Discontinued OL MVC on day 143	N/K	Yes	Yes	Yes
1028	10[redacted]40009	Maraviroc BID	B cell lymphoma	Active	7	26	5.82	Ongoing	Yes	Yes	No	No
	10[redacted]90013	Pre-randomisation	Hodgkin's lymphoma	N/A	N/A	150	3.8	Pre-randomisation	N/K	Yes	No	No
	10[redacted]10032	Maraviroc QD	Non-Hodgkin's Lymphoma	Active	75	107	5.16	Discontinued day 79	Yes	Yes	No	Yes

Table 50. Cases of Lymphoma in the Maraviroc Phase 2b/3 Clinical Program

Study No.	Patient ID	Treatment	Event Name: Preferred Term	Active/Post-treatment	Start Date of Event[a]	Scr[b] CD_4 (cells/μL)	Scr[b] HIV-1 RNA(log_{10})	Patient Disposition	Biopsy	Definite	Related	Death[c]
	*12[redacted]0011***	*Maraviroc BID*	*CNS lymphoma*	*Active*	*40*	*4*	*5.53*	*Discontinued day 62*	*No*	*No*	*No*	*Yes*

[a] Relative days post **initiation** of blinded study drug
[b] If screening value was not available, baseline value is given
[c] last information known to sponsor
Cases in italics are possible lymphoma
* *Histology possible plasmablastic, large cell lymphoma*
** *Presumptive CNS lymphoma not biopsy confirmed.*
N/K = not known
Source: Safety Review of Immunotoxic Potential of Maraviroc, Module 5.3.5.3.

Conclusion

The rates of infection reported during these studies are similar between both maraviroc treatment arms and placebo. There were no unusual or unexpected infections, and the incidence rate of category C infections in patients receiving maraviroc were similar to that seen in the placebo group.

The incidence and severity of malignancies between treatment groups was similar between the maraviroc treatment arms and slightly higher in the placebo arm. There were no unusual or unexpected malignancies, and no evidence of any increased risk of malignancy has emerged from the data generated in the Phase 2b/3 TE programme.

In the 2 pivotal studies the overall rates of malignancy are similar between treatment arms. The rates of lymphoma are slightly lower in the maraviroc arms, as are the rates of Kaposi's sarcoma and anal cell carcinoma, but including open label reports of lymphoma are in keeping with what would be expected from this population.

Although the numbers are small of non-R5 patients with malignancies were low, the similarity in frequency across treatment groups provide further confidence that the inadvertent use of maraviroc in this population would not adversely affect immune function.

When adjusted for exposure per 100 patient years, the incidence of lymphoma in the Phase 3 R5 population (including B cell lymphoma) was 0.8, 0.4 and 2.0 in the maraviroc QD, BID and placebo arms (SCS Table 3.4.4.4).

2.7.4.2.2. Narratives

Safety narratives of the treatment-related serious AEs and all deaths are reported in the individual study reports in Module 5.3.

2.7.4.3. Clinical Laboratory Evaluations

Median changes from baseline in laboratory parameter for subjects receiving maraviroc QD, maraviroc BID or placebo in Studies A4001027 and A4001028 are presented in Table 51. Similar changes were seen across the 3 treatment groups, apart from lymphocytes (absolute and percentages), cholesterol (HDL, LDL and total), triglycerides and creatine kinase, where larger mean increases were observed in the maraviroc treatment arms compared to the placebo group.

Median changes from baseline in serum ALT, AST, GGT, lactate dehydrogenase, alkaline phosphatase and bilirubin were similar across the 3 treatment arms. A detailed discussion of changes in LFTs is given in Section 2.7.4.2.1.5.3.

Table 51. Laboratory test data: Median changes from baseline to last observation, Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

Parameter	Units	Maraviroc QD			Maraviroc BID			Placebo		
		N	Baseline Median	Median Change from Baseline	N	Baseline Median	Median Change from Baseline	N	Baseline Median	Median Change from Baseline
Haemoglobin	G/DL	406	14.9	0	419	14.9	0.1	207	14.9	0
Haematocrit	%	406	44.6	0	419	44.4	0.8	207	44.4	0
Red blood cells	10**6/MM**3	406	4.67	0	418	4.67	0	207	4.6	0
Mean corpuscular volume	10**-15L	406	95	1	419	95	0	207	95	1
Mean corpuscular haemoglobin	PG	406	31	0	419	31	0	207	31	0
MCH concentration	G/DL	406	33	0	419	33	0	207	33	0
Platelets	10**3/MM**3	401	194	17	411	191	23	202	194	13
White blood cells	10**3/MM**3	406	4.5	1	419	4.3	1.2	207	4.3	0.6
Lymphocytes (Abs)	10**3/MM**3	406	1.49	0.33	419	1.48	0.32	207	1.43	0.08
Lymphocytes (%)	%	406	34.9	2.9	419	35.6	1.7	207	35.3	-1.3
Neutrophils (Abs)	10**3/MM**3	376	2.29	0.47	388	2.11	0.56	193	2.12	0.42
Neutrophils (%)	%	406	54.8	-1.2	419	53.7	0.1	207	54.4	1.9
Basophils (Abs)	10**3/MM**3	406	0.02	0.01	419	0.03	0.01	207	0.02	0
Basophils (%)	%	406	0.6	0	419	0.6	0.1	207	0.5	0
Eosinophils (Abs)	10**3/MM**3	406	0.08	0.01	419	0.08	0.01	207	0.07	0.01
Eosinophils (%)	%	406	2	0	419	2	0	207	1.8	0
Monocytes (Abs)	10**3/MM**3	406	0.28	0.03	419	0.28	0.03	207	0.27	0.02
Monocytes (%)	%	406	6.5	-0.7	419	6.6	-0.8	207	6.7	-0.2
Total bilirubin	MG/DL	397	0.5	0.1	409	0.5	0.1	200	0.4	0.1
Direct bilirubin	MG/DL	20	0.2	0	24	0.2	0	15	0.2	0
Indirect bilirubin	MG/DL	20	0.6	0.1	24	0.7	0.2	15	0.7	0
AST	IU/L	408	43	-6	421	45	-5	207	44	-2
ALT	IU/L	408	46	-7	421	48	-5	206	46	-4
GGT	IU/L	68	107	-4	62	152	-17	31	202	-8
Lactate dehydrogenase	IU/L	408	183	-9	420	177	-13	206	178	-8
Alkaline phosphatase	IU/L	408	90	4	421	91	3	207	91	4
Total Protein	G/DL	408	7.9	-0.2	421	7.8	-0.2	207	7.9	-0.1
Albumin	G/DL	408	4.3	0	421	4.3	0.1	207	4.3	0
Blood Urea nitrogen	MG/DL	408	33.6	0	421	33.4	0	207	32.4	1.3

Table 51. Laboratory test data: Median changes from baseline to last observation, Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

Parameter	Units	Maraviroc QD			Maraviroc BID			Placebo		
		N	Baseline Median	Median Change from Baseline	N	Baseline Median	Median Change from Baseline	N	Baseline Median	Median Change from Baseline
Creatinine	MG/DL	408	1.2	0	421	1.2	0	207	1.2	0
Uric acid	MG/DL	407	4.9	-0.2	421	4.8	-0.2	207	4.9	-0.2
Fasting total cholesterol	MG/DL	346	130	14	375	132	10	168	138	3
Fasting HDL cholesterol	MG/DL	329	34	3	359	33	2	164	35	0
Fasting LDL cholesterol[a]	MG/DL	257	68	7	274	69	5	133	74	-1
Fasting triglycerides*	MG/DL	346	148	11	375	156	15	168	159	6
Sodium	MEQ/L	408	140	0	421	140	0	207	140	0
Potassium	MEQ/L	408	4.1	0	421	4	0	207	4.1	-0.1
Chloride	MEQ/L	408	103	0	421	103	0	207	103	0
Corrected calcium	MG/DL	408	9.4	0.2	419	9.4	0.2	207	9.3	0.1
Bicarbonate	MEQ/L	408	27.1	-0.1	421	27.2	0	207	27.2	-0.2
Free T4 (thyroxine)	NG/DL	346	0.8	0	373	0.8	0	166	0.8	0
Fasting glucose	MG/DL	408	90	4	421	90	5	207	90	5
Creatine kinase	U/L	408	215	20	420	202	20	207	179	6
Amylase	U/L	408	75	-5	419	73	-5	207	77	0
Lipase	U/L	122	47	1	102	51	-2	63	44	0

Source: SCS Table 3.6.2.5
Normalized data has been used in the computations
Key: MCH – mean corpuscular haemoglobin, AST – aspartate aminotransferase, ALT- alanine aminotransferase, GGT – gamma glutamyltransferase
[a]Friedewald estimation by PEG

The ACTG Severity of Adult Adverse Events Grading Scale for Laboratory Parameters was used to categorise the severity of abnormal laboratory results. Those portions of the scale pertaining to laboratory tests discussed in detail in this section are provided in Table 52.

Table 52. ACTG Laboratory Parameter Grades

Laboratory Test	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin	8.0 to 9.4 gm/dL	7.0 to 7.9 gm/dL	6.5 to 6.9 gm/dL	<6.5 gm/dL
Absolute Neutrophil Count (ANC)	1000 to 1500/mm3	750 to 999/mm3	500 to 749/mm3	<500/mm3
Platelet count	75,000 to 99,000/mm3	50,000 to 74,999/mm3	20,000 to 49,999	<20,000/mm3
Hyponatraemia	130-135 meq/L	123 to 129 meq/L	116 to 122 meq/L	<116 meq/L
Hypernatremia	146 to 150 meq/L	151 to 157 meq/L	158 to 165 meq/L	>165 meq/L
Hypokalaemia	3.0 to 3.4 meq/L	2.5 to 2.9 meq/L	2.0 to 2.4 meq/L	<2.0 meq/L
Hyperkalaemia	5.6 to 6.0 meq/L	6.1 to 6.5 meq/L	6.6 to 7.0 meq/L	>7.0 meq/L
Hypocalcaemia	7.8 to 8.4 mg/dL	7.0 to 7.7 mg/dL	6.1 to 6.9 mg/d/L	<6.1 mg/dL
Hypercalcaemia	10.6 to 11.5 mg/dL	11.6 to 12.5 mg/dL	12.6 to 13.5 mg/dL	>13.5mg/dL
Amylase	>1.0-1.5 ULN	>1.5-2.0 ULN	>2.0-5.0 ULN	>5 ULN
Lipase	>1.0-1.5 ULN	>1.5-2.0 ULN	>2.0-5.0 ULN	>5 ULN
AST	>1.25-2.5 ULN	>2.5-5.0 ULN	>5.0-10.0 ULN	>10 ULN
ALT	>1.25-2.5 ULN	>2.5-5.0 ULN	>5.0-10.0 ULN	>10 ULN
GGT	>1.25-2.5 ULN	>2.5-5.0 ULN	>5.0-10.0 ULN	>10 ULN
Alkaline Phosphatase	>1.25-2.5 ULN	>2.5-5.0 ULN	>5.0-10.0 ULN	>10 ULN
Creatinine	>1.0-1.5 ULN	>1.5-3.0 ULN	>3.0-6.0 ULN	>6 ULN
Total Bilirubin	>1.0-1.5 ULN	>1.5-2.0 ULN	>2.0-5.0 ULN	>5 ULN

2.7.4.3.1. Changes in fasting lipid concentrations

Apparent dose-related increases in total cholesterol and LDL-cholesterol were noted in Phase 1 multiple-dose escalation Study A4001002, but similar changes were not consistently seen in other Phase 1 studies, including Study A4001008, the 28-day safety study in healthy volunteers evaluating 300 mg BID.

In Studies A4001027 and A4001028, a slightly higher proportion of subjects in the maraviroc QD and maraviroc BID groups than in the placebo treatment group experienced maximum increases in cholesterol, LDL cholesterol, and triglycerides of ≥20% (Table 53). However, none of these changes was statistically significant (SCS Tables 3.6.18.1, 3.6.18.3, 3.6.18.5, 3.6.19.1, 3.6.19.3 and 3.6.19.5). Since the vast majority of patients received PIs (which are associated with lipid abnormalities[xiii]) as part of their OBT in these studies (90.1%, 90.4% and 92.3% for maraviroc QD, maraviroc BID and placebo, respectively), the most likely explanation for the different rates of increases in these lipid concentrations in the maraviroc treatment arms is the longer duration of exposure for the maraviroc treatment arms (258.7 and 266.8 patient years for maraviroc QD and BID, respectively) compared to placebo (99.3 patient years) (Table 6).

A slightly higher proportion of subjects in the maraviroc QD and maraviroc BID groups (33.2% and 34.9%, respectively) than in the placebo treatment group (28.0%) had

maximum increases in HDL cholesterol of ≥20% (Table 53), though these differences were not statistically significant (SCS Table and 3.6.19.3). Similarly, a slightly higher proportion of subjects in the maraviroc groups than in the placebo group had an increase in HDL/LDL ratio of more ≥20%.

Table 53. Maximum Increases from Baseline in Lipid Concentration in Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

Parameter	Range	Maraviroc QD N (%)	Maraviroc BID N (%)	Placebo N (%)
Cholesterol	**n**	**408**	**421**	**207**
	20 to <30%	36 (8.8)	40 (9.5)	17 (8.2)
	≥30%	97 (23.8)	95 (22.6)	21 (10.1)
LDL cholesterol	**n**	**408**	**421**	**207**
	20 to <30%	31 (7.6)	23 (5.5)	11 (5.3)
	≥30%	83 (20.3)	76 (18.1)	30 (14.5)
HDL cholesterol	**n**	**408**	**421**	**207**
	20 to <30%	42 (10.3)	35 (8.3)	19 (9.2)
	≥30%	79 (19.4)	104 (24.7)	33 (15.9)
HDL/LDL ratio	**n**	**257**	**273**	**133**
	20 to <30%	11 (4.3)	11 (4.0)	4 (3.0)
	≥30%	22 (8.6%)	15 (5.5%)	3 (2.3)
Triglycerides	**n**	**408**	**421**	**207**
	20 to <30%	13 (3.2)	27 (6.4)	9 (4.3)
	≥30%	161 (39.5)	165 (39.2)	59 (28.5)

Source: SCS Tables 3.6.15.1 to 3.6.15.5
n = number of subjects evaluable for laboratory abnormalities

In contrast, in Study A4001029 in non-R5 TE patients, the incidence of increases in cholesterol, LDL cholesterol or triglyceride concentration was similar between treatment groups. There was some evidence of an increase in HDL cholesterol in the maraviroc groups compared to placebo, but again, subject numbers were small. Table 54 summarises the number of subjects with maximum increases from baseline of 20 to <30% and ≥ 30% in cholesterol, LDL cholesterol, HDL cholesterol and triglycerides.

Table 54. Maximum Increases from Baseline in Lipid Concentration in Phase 2b Study in non-R5 TE Patients (Study A4001029)

Parameter	Range	Maraviroc QD N (%)	Maraviroc BID N (%)	Placebo N (%)
Cholesterol	**n**	**50**	**49**	**45**
	20 to <30%	7 (14.0)	6 (12.2)	4 (8.9)
	≥30%	7 (14.0)	8 (16.3)	6 (13.3)
LDL cholesterol	**n**	**38**	**41**	**36**
	20 to <30%	4 (10.5)	3 (7.3)	0
	≥30%	7 (18.4)	10 (24.3)	10 (27.8)
HDL cholesterol	**n**	**45**	**48**	**44**
	20 to <30%	2 (4.4)	8 (16.7)	4 (9.1)
	≥30%	9 (20.0)	11 (22.9)	5 (11.4)
Triglycerides	**n**	**50**	**49**	**45**
	20 to <30%	3 (6)	5 (10.2)	2 (4.4)
	≥30%	16 (32)	17 (34.7)	18 (40)

Source: A4001029 Tables 13.7.6.1 to 13.7.6.4
n = number of subjects evaluable for laboratory abnormalities

2.7.4.3.2. Changes in Serum Creatinine, blood urea nitrogen and electrolytes

In a Phase 1 Study A4001019, 7 out of 9 subjects who received 1200 mg QD and 1 subject who received placebo experienced increases in creatinine concentrations; however, all these occurred in a single analytical batch analysed on the same day. The creatinine concentration for the other subject who received 1200 mg QD and the other subject who received placebo, analysed on a different day, were within the normal range. For 5 subjects (4 who received 1200 mg QD and 1 who received placebo), these creatinine concentration increases were above 1.3x ULN at steady-state. The median creatinine concentration after 1200 mg QD was above the normal range but did not exceed 1.3x ULN. Increases in serum creatinine have not been observed in any other Phase 1/2a study, including those where high exposures to maraviroc were achieved.

The incidence of Grade 3 or 4 electrolyte and creatinine abnormalities observed Studies A4001027 and A400128 was low (Table 55), and there was no evidence of a median change from baseline in creatinine or blood urea nitrogen concentration in patients receiving maraviroc (Table 51), or an increased incidence of creatinine, blood urea nitrogen or electrolyte abnormalities in patients receiving maraviroc compared to placebo (SCS Table 3.6.3.2). There was no evidence that the presence of tenofovir in OBT had any affect on creatinine levels (see individual CSRs, Module 5.3.51 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

Two patients in the R5 TE phase 3 studies were reported to have experienced acute renal failure and were discontinued:

- Patient 1[redacted]0003 in Study A4001027 was a [redacted]year-old [redacted]male who received maraviroc QD for a total of 12 days in combination with OBT, consisting of delavirdine, abacavir sulfate/lamivudine/zidovudine [redacted]®), lopinavir/ritonavir [redacted]®) and tenofovir. He experienced a hypersensitivity reaction on Day 10 and acute renal failure on Day 12 and was permanently discontinued. The Investigator ascribed causality of the events to maraviroc and delavirdine (see A4001027 CSR, Module 5.3.51 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication). Causality in this case is confounded by the fact that delavirdine is associated with rash and hypersensitivity.[xiv]

- Subject 1[redacted]0005, a [redacted]year old [redacted]male in Study A4001028, was hospitalised on 25 March 2[redacted] due to fever, dyspnoea and acute renal failure. He had received placebo and OBT which included enfuvirtide, tenofovir, emtricitabine, lopinavir/ritonavir and saquinavir since July 2[redacted] The subject was also receiving clarithromycin and ethambutol for mycobacterium avium infection. Study drug, OBT and concomitant medications were stopped. The renal failure resolved: creatinine improved from 6x ULN to 2 – 2.5x ULN, and remained below 2x ULN (Grade 2) after study drug and OBT were restarted approximately 2 weeks later. These events were considered related to concomitant treatment (clarithromycin and tenofovir) and study drug by the Investigator (A4001028 CSR).

Table 55. Grade 3 and 4 Serum Electrolyte and Creatinine Abnormalities, Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

Laboratory Test	Grade	Maraviroc QD			Maraviroc BID			Placebo		
		N	n	(%)	N	n	(%)	N	n	(%)
Renal Function										
Creatinine	3	408	2	(0.5)	421	1	(0.2)	207	1	(0.5)
	4		0			1	(0.2)		0	
Electrolytes										
Sodium	3	408	0		421	0		207	0	
(hypernatraemia)	4		0			0			0	
Sodium	3	408	1	(0.2)	421	1	(0.2)	207	0	
(hyponatraemia)	4		0			0			0	
Potassium	3	408	0		421	0		207	0	
(hyperkalaemia)	4		0			0			0	
Potassium	3	408	1	(0.2)	421	0		207	0	
(hypokalaemia)	4		0			0			0	
Calcium*	3	408	0		419	0		207	0	
(hypercalcaemia)	4		0			0			0	
Calciuma[a]	3	408	2	(0.5)	419	2	(0.5)	207	0	
(hypocalcaemia	4		0			1	(0.2)		1	(0.5)

Source: SCS Table 3.6.2.1

[a] - corrected for albumin

In Study A4001029, the only significant increase in creatinine concentration was in 1 subject with a Grade 3 increase (3 to 6x ULN). Subject 1[redacted]0003, in the maraviroc BID group, had an abnormal baseline creatinine of 1.3 mg/dL which 84 days after starting maraviroc increased to 5.6 mg/dL, at which time there was an associated increase in blood urea concentration (>2x ULN). This subject was also reported with SAEs of dehydration and candida oesophagitis 20 days after starting therapy, which were attributed to the disease under study. This did not lead to discontinuation. A further subject in Study A4001029 (1[redacted]0001) receiving placebo died on Day 92 from aggravated renal failure, ascites, haemothorax and disease aggravation (A4001029 CSR, Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

There were no Grade 3 or 4 creatinine abnormalities among subjects receiving maraviroc QD or maraviroc BID OL in Study A4001026.[4]

2.7.4.3.3. 2.7.4.1.3. Changes in Serum Amylase and Lipase

In Studies A4001027 and A4001028 there was no evidence of an increase from baseline in median amylase and lipase concentrations in any of the treatment groups (Table 52). The incidence of Grade 3 and 4 amylase and lipase abnormalities was low and there was no evidence of an increased incidence of Grade 3 and 4 abnormalities in subjects receiving maraviroc compared to placebo (Table 56). Four cases of pancreatitis reported as AEs, 1 on maraviroc QD, 1 on maraviroc BID and 2 on placebo (see individual CSRs, Module 5.3.51 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

Table 56. Grade 3 and 4 Amylase and Lipase Abnormalities, Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

	Grade	Maraviroc QD			Maraviroc BID			Placebo		
		N	n	(%)	N	n	(%)	N	n	(%)
Amylase	3	408	25	(6.1)	419	23	(5.5)	207	12	(5.8)
(U/L)	4		3	(0.7)		1	(0.2)		0	
Lipase	3	165	13	(7.9)	158	8	(5.1)	89	7	(7.9)
(U/L)	4		1	(0.6)		2	(1.3)		0	

Source: SCS Table 3.6.2.1

In Study A4001029 there was some evidence of a higher incidence of Grade 3/4 increases in serum amylase and lipase in the maraviroc groups compared to placebo, and there were more Grade 4 abnormalities in the maraviroc BID group than the other 2 groups. However, the number of subjects was small and there were no subjects with Grade 3 or 4 increase in amylase or lipase who were reported with pancreatitis (Table 57).

[4] See Erratum to CSR A4001026.

Table 57. Grade 3 and 4 Amylase and Lipase Abnormalities, Phase 2b Study in non-R5 TE Patients (Study A4001029)

	Grade	Maraviroc QD			Maraviroc BID			Placebo		
		N	n	(%)	N	n	(%)	N	n	(%)
Amylase	3	63	6	(9.5)	61	5	(8.2)	58	3	(5.2)
(U/L)	4	63	1	(1.6)	61	2	(3.3)	58	0	(0)
Lipase	3	32	1	(3.1)	29	1	(3.4)	24	1	(4.2)
(U/L)	4	32	1	(3.1)	29	3	(10.3)	24	0	(0)

Source: A4001029 Clincal Study Report Table 13.7.2.3

In Study A4001026 there were six Grade 3 or 4 amylase abnormalities reported in the maraviroc QD treatment arm and 3 in the maraviroc BID OL group (A4001026 CSR, Module 5.3.5.4 Other Study Reports). There were no Grade 3 or 4 lipase abnormalities reported, and no AEs of pancreatitis (A4001026 CSR Table 13.6.2.3.1).

2.7.4.1.4. Thyroid Function abnormalities

Thyroid follicular cell hypertrophy was observed at high doses in rats in the pre-clinical toxicology program (see Section 2.4.5.5 Module 2.4 Non-clinical Overview). Although these changes were thought to be related to enzyme induction at high maraviroc concentration, provision was made in Studies A4001027 and A4001028 for assessment of free T4 (thyroxine) and thyroid stimulating hormone (TSH) concentrations at baseline and at 24 weeks.

There was no evidence of an increased frequency of abnormal free T4 or TSH values, or a median change from baseline for free T4, in patients receiving maraviroc compared to those receiving placebo (Summary of Clinical Safety Table 3.6.1.4) (Table 51). Five cases of hypothyroidism were reported in these studies, 3 on maraviroc QD, 1 on maraviroc BID and 1 on placebo. These were all Grade 1 or 2 and were not considered related to study drug by the Investigator (see individual CSRs, Module 5.3.51 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

Similarly, in Study A4001029 there was no evidence of an increased frequency of abnormal levels of free T4 or TSH values in patients receiving maraviroc compared to those receiving placebo (CSR Table 13.7.2.2). A single AE of hypothyroidism was reported in the placebo group in this study (CSR Table 13.6.2.3).

2.7.4.3.4. Abnormalities in Haematology Parameters

There were greater median changes from baseline for total lymphocyte count and differential lymphocyte count for subjects receiving maraviroc compared to placebo in Studies A4001027 and A4001028 (Table 51). This is expected as subjects receiving maraviroc had significantly higher increases in CD4 and CD8 lymphocyte counts than patients who received placebo (Summary of Clinical Efficacy Table 13.4.6.11). There were no clinically relevant differences in median change from baseline for subjects receiving maraviroc compared to placebo for any other haematology parameter (Table 51).

Subjects receiving maraviroc were less likely to have lymphocytopaenia (<0.8x lower limit of normal [LLN]) compared to placebo: the incidence was 11% for both maraviroc treatment groups and 17% for subjects receiving placebo. Increases in absolute lymphocyte count (>1.2x ULN) were observed in 4% and 6% of subjects receiving maraviroc QD and maraviroc BID, respectively, compared to 2% in subjects receiving placebo. Similarly, increases in lymphocyte percentage were noted for 15 and 16% of subjects receiving maraviroc QD and BID, respectively, compared to 7% in subjects receiving placebo (Summary of Clinical Safety Table 3.6.1.4).

A low absolute neutrophil count (<0.8x LLN) was slightly more common in subjects receiving placebo (35%) than in subjects receiving maraviroc (28% and 31 % for maraviroc QD and maraviroc BID, respectively). However, the incidence of subjects with neutrophil count percentage (<0.8x LLN) was 19 and 21% in subjects receiving maraviroc QD and BID, respectively, compared to 13% in subjects receiving placebo (Summary of Clinical Safety Table 3.6.1.4).

The incidence of Grade 3 and 4 abnormalities in haemoglobin, platelet count and absolute neutrophil count was low across all 3 treatment arms, and there was no evidence for a significantly increased incidence in subjects receiving maraviroc compared to placebo (Table 58). A subject in Study A4001028 (Patient 1[redacted]0001) was diagnosed with aplastic anaemia on Day 31 of treatment with maraviroc QD (150 mg). This subject was also receiving enfuvirtide, lopinavir/ritonavir, didanosine, saquinavir, lamivudine, zidovudine as OBT, and was concomitantly treated with dapsone, amphotericin B, valganciclovir, esomeprazole, diazepam, fluconazole, and voriconazole. This event was considered related to study drug by the Investigator. Study drug was stopped and OBT continued (with zidovudine replaced by stavudine). The aplastic anaemia resolved, but the subject died approximately 8 months after discontinuation due to HIV disease progression (see Section 2.7.4.2.1.2.1.1 for narrative). Assessment of the causality of the aplastic anaemia is confounded by the fact that the subject was receiving multiple drugs that are potentially toxic to the bone marrow, including zidovudine, dapsone, amphotericin B and valganciclovir.

Table 58. Grade 3 and 4 Abnormalities in Haematology Parameters, Phase 3 Studies in R5 TE Patients (Studies A4001027 and A4001028)

	Grade	Maraviroc QD			Maraviroc BID			Placebo		
		N	n	(%)	N	n	(%)	N	n	(%)
Hb (G/DL)	3	408	1	(0.2)	420	1	(0.2)	207	0	
	4		2	(0.5)		1	(0.2)		0	
Platelets (10^3/mm^3)	3	407	2	(0.5)	418	1	(0.2)	206	2	(1.0)
	4		0			0			0	
ANC (10^3/mm^3)	3	408	6	(1.5)	420	11	(2.6)	207	4	(1.9)
	4		3	(0.7)		5	(1.2)		0	

Source: SCS Table 3.6.2.1
Hb – haemoglobin, ANC – absolute neutrophil count

In Study A4001029 very few grade 3 or 4 abnormalities in haemoglobin, platelet count or neutrophil count were recorded, and these were fairly evenly balanced across the 3 treatment groups (Table 59).

Table 59. Grade 3 and 4 Abnormalities in Haematology Parameters, Phase 2b Study in non-R5 TE Patients (Study A4001029)

	Grade	Maraviroc QD			Maraviroc BID			Placebo		
		N	n	(%)	N	n	(%)	N	n	(%)
Hb (G/DL)	3	63	0		61	0		58	0	
	4		0			1	(1.6)		0	
Platelets	3	63	1	(1.6)	60	0		57	0	
(10^3/mm^3)	4		0			0			0	
ANC	3	63	4	(6.3)	61	4	(6.6)	58	3	(5.2)
(10^3/mm^3)	4		1	(1.6)		1	(1.6)		0	

Source: A4001029 CSR Table 13.7.2.3
Hb – haemoglobin, ANC – absolute neutrophil count

In Study A4001026, 11 subjects receiving maraviroc QD and 3 subjects receiving OL maraviroc BID had grade 3 or 4 decreases in absolute neutrophil count. Grade 3 or 4 decreases in haemoglobin were recorded in 4 subjects receiving maraviroc QD and in 1 receiving maraviroc BID open label. Clinically significant haematological abnormalities were reported as SAEs in 5 subjects in the maraviroc 300 mg QD treatment group, but only the anaemia and leucopaenia in Subject 1[redacted]0003 was considered related to study drug. No haematological abnormalities resulted in permanent discontinuation from the study (CSR A4001026, Module 5.3.5.4 Other Study Reports). Assessment of causality of these events is confounded by the fact that the Sponsor remains blinded to the comparator arm of the study and the fact that zidovudine, which is associated with bone marrow suppression,[xv] was a background drug in this study.

2.7.4.3.5. Increases in Creatine Kinase

Subjects receiving maraviroc had a higher median change from baseline in creatine kinase compared to placebo (Table 51). There was also a higher incidence of creatine kinase abnormalities (>2x ULN) in subjects receiving maraviroc: 30% and 29% on maraviroc QD and BID, respectively, compared to 20% on placebo. Creatine kinase abnormalities are very common in this population, as is evidenced by the fact that 257 patients (115 on maraviroc QD, 103 on maraviroc BID and 40 on placebo) had abnormal creatine kinase values at baseline (Summary of Clinical Efficacy Table 3.6.2.3). The slight excess of creatine kinase increase in the maraviroc treatment arms may be explained by the longer duration of exposure (258.7 and 266.8 PY for maraviroc QD and BID, respectively) compared to placebo (99.3 PY) (Table 6).

Three patients in Studies A4001027 and A4001028 reported AEs of rhabdomyolysis or myositis and discontinued study drug.

- Subject 1[redacted]40016, a [redacted]year old male, received maraviroc BID for a total of 177 days in Study A4001027. He experienced heat exhaustion with rhabdomyolysis on Day 184. He had elevated creatine kinase on Day 1 (423 U/L) which increased to 3318 U/L by Day 3, but returned to normal by Day 8. All other creatine kinase values up to Day 193 (when a minor increase to 215 U/L was recorded) were within normal limits (A4001027 CSR Table B7.1). He also had elevated transaminases on 2 separate

occasions starting on Day 2 and then again on Day 177 and, at that time, he was discontinued from the study. The elevated transaminases were considered related to study drug by the Investigator (A4001027 CSR).

- Subject 1[redacted]0018 in Study A4001027 presented on Day 7 with rhabdomyolysis, candidiasis and hyponatraemia. Study drug (maraviroc BID) was temporarily discontinued. The rhabdomyolysis had resolved on Day 10 and was considered related to concomitant therapy (Patient profile A4001027). Creatine kinase was increased at baseline (345 U/L), and further increased to 501 U/L by Day 21. The Day 28 value was 466 U/L. Serum sodium was normal at all timepoints, apart from a Grade 1 abnormality on Day 28 (A4001027 CSR Table B7.1). The patient was permanently discontinued from the study on Day 56 as he was no longer willing to participate and no further follow-up is available (Patient profile A4001027).

- Subject 1[redacted]0007, a 3[redacted]year old female subject participating in Study A4001028, was hospitalised on 20 March 2[redacted]due to weakness in both legs and was diagnosed with myositis. She had stopped study drug on 17 February 2[redacted]when the weakness had started. Prior to this, she had received maraviroc QD (150 mg) for 79 days. She also received tenofovir, emtricitabine, zidovudine and lopinavir/ritonavir as OBT. Screening and baseline creatine kinase were abnormal with values of 363 and 247 U/L, respectively. By Day 62 values have increased to 829 U/L (A4001028 CSR Table B7.1). The muscle biopsy revealed marked CD8+ T cell infiltration of the muscle tissues compatible with T cell mediated (possibly autoimmune) myositis in conjunction with some evidence of zidovudine induced toxic muscle fibre damage. In the opinion of the Investigator, there was a reasonable possibility that the myositis was related to maraviroc (Table 19).

Two further subjects receiving maraviroc QD in study A4001028 discontinued due to myalgia. In 1 subject (PID 1[redacted]0011) no abnormal creatine kinase was recorded. In the second subject (PID 1[redacted]0001) the highest recorded creatine kinase values were pre-dose (1020 U/L and 281 U/L on day -6 and day 1, respectively) (A4001028 Table B7.1, Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

- Subject 1[redacted]0014 receiving maraviroc BID in Study A4001027 temporarily discontinued study drug due to blood creatine kinase and increased hepatic enzymes on Day 335. The subject was in study at Day 347 (the date of cut-off). Creatine kinase values were 6566 U/L on Day 335 and had reduced to 492 U/L on Day 340. Creatine kinase was within normal limits on Day 347 (Table 23 and Table 38) (A4001027 CSR Table B7.1, Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

- Subject 1[redacted]0004 (maraviroc BID) in study A4001028 temporarily discontinued study drug due to Grade 4 AST and blood creatine kinase abnormalities. Study drug was temporarily stopped due to increased AST from Day 15 to 22 and increased creatine phosphokinase from Day 15 to 22 and Day 29 to 37. These resolved and the subject had taken study drug up to Day 182 at the time of cut-off. The subject had increased creatine phosphokinase on a number of other occasions during treatment; these all

resolved with study drug continued unchanged (A4001028 CSR; also see Table 23 and narratives following Table 38).

In study A4001029, which lacked significant differences in duration of exposure among treatment arms, the incidence of creatine kinase abnormalities (>2x ULN) in subjects receiving maraviroc QD and BID was 16% and 26%, respectively, compared to 26% on placebo (A4001029 CSR Table 13.7.2.2, Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication). There were no temporary or permanent discontinuations due to increased creatine kinase, myalgia, myositis or rhabdomyolysis.

Lab abnormalities in the OL phase of Studies A4001027 and A4001028

Among the 99 TE R5 patients who began OL maraviroc after initial failure on blinded therapy in Studies A4001027 and A4001028 and were evaluable for laboratory data, Grade 3 or 4 laboratory abnormalities have been reported for: decreased in absolute neutrophil count (3 events), decreased platelet count (2 events), decreased haemoglobin (1 event) and increased potassium level (1 event) (SCS Table 3.6.4.1).

2.7.4.4. Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital signs

Analysis of mean changes in systolic and diastolic blood pressure at Weeks 2 and 24 did not reveal any remarkable differences between treatment groups, including placebo (SCS Tables 3.7.2.2 to 3.7.2.6 and 3.7.5.2 to 3.7.5.6).

Postural hypotension is discussed in Section 2.7.4.2.1.5.1.

ECG

Analysis of changes in ECG parameters (including heart rate and PR interval duration) did not reveal any remarkable differences between treatment groups, including placebo (SCS Table 3.7.7.1).

The QTc interval is discussed in more detail above in Section 2.7.4.2.1.5.1.

2.7.4.5. Safety in Special Groups and Situations

2.7.4.5.1. Intrinsic Factors

The AEs reported for the Phase 3 studies were analysed to determine whether the safety profile of maraviroc was affected by sex, age, race, baseline CD4 count, HIV RNA level or CCR5Δ32 genotype, or by hepatitis B or hepatitis C co-infection at baseline or the presence of a previous AIDS defining illness. The AE profiles were worse for patients with lower CD4 counts and higher HIV-1 RNA levels, as expected. However there were no differences between the maraviroc treatment groups and placebo for these parameters.

The preponderance of white males, <65 years of age, wt/wt CCR5Δ32 genotype without concomitant hepatitis, recruited into the treatment-experienced studies means that other subgroups are more difficult to assess. In general no marked differences are seen between the predominant population and the smaller subgroups (SCS Tables 3.4.9.1 to 3.4.9.12).

2.7.4.5.2. Extrinsic Factors

The AEs reported for the Phase 3 studies were analysed to determine whether the safety profile of maraviroc was affected by HIV-1 exposure category, or whether saquinavir/tipranavir were used as OBT, PDE5-inhibitors/antihypertensives/nitrates/alpha-blockers were used as concomitant medications or by treatment failure status. The AE profiles were worse for intravenous drug users, as expected. However there were no differences between the maraviroc treatment groups and placebo for these parameters (SCS Tables 3.4.9.1 to 3.4.9.12).

2.7.4.5.3. Drug Interactions

As discussed in detail in Module 2.7.2, maraviroc exposure is increased when co-administered with CYP3A4 inhibitors, which includes PIs and/or delavirdine and a considerable number of other drugs that are likely to be used by the target population. Saquinavir/ritonavir, in particular, causes pronounced increases in maraviroc exposure. Based on this, patients whose OBT included a PI (except tipranavir/ritonavir) and/or delavirdine were dosed with 150 mg maraviroc rather than 300 mg (see Section 2.7.4.1.3.3.1).

In the Phase 2b/3 programme, AEs were analysed according to the presence or absence of saquinavir in OBT. Altogether, 128 patients (12.2%) received saquinavir. No difference in the AE profile was identified in this subpopulation compared to that of the population as a whole (SCS Table 3.4.9.9).

2.7.4.5.4. Use in Pregnancy and Lactation

Pregnancy and lactation were specific exclusion criteria for the maraviroc clinical studies and subjects were to discontinue from study drug immediately in the event of pregnancy.

Nevertheless, several pregnancies were reported from the Phase 2b/3 studies, including 5 in patients who were actually receiving maraviroc. These are presented in Table 60.

Table 60. Exposure During Pregnancy

SAE	PID	STUDY	Study drug	AE
2006060395	12[redacted]0001	A4001026	Efavirenz	Spontaneous abortion
2005143494	11[redacted]0006	A4001026	Pre randomisation	Induced abortion
2006030016	11[redacted]0004	A4001026	MVC BID	Induced abortion
2006045891	12[redacted]0001	A4001026	Efavirenz	Spontaneous abortion
2006055386	10[redacted]0016	A4001026	1 dose of MVC	Induced abortion
2006088245	10[redacted]0004	A4001026	Efavirenz	Induced abortion
2006088410	10[redacted]0020	A4001026	Efavirenz	Induced abortion
2006099986	12[redacted]0006	A4001026	MVC BID	Unknown
2006029284	11[redacted]0015	A4001027	MVC QD	Healthy delivery
2006030025	10[redacted]0014	A4001028	MVC QD	Induced abortion
2006068169	10[redacted]0002	A4001029	Placebo	Spontaneous abortion
2006066991	10[redacted]0002	A4001029	Placebo	Spontaneous abortion

Source: extracted from ARISg SAE database

Five Patients became pregnant whilst exposed to maraviroc. Only Patient 11[redacted]0015 (A4001027) is known to have had a healthy delivery; the outcome of Patient 12[redacted]0006 (A4001026) is unknown and the other 3 ended with induced abortion. There is therefore very little data on the effect of exposure to maraviroc in utero in humans.

2.7.4.5.5. Overdose

No cases of overdose of maraviroc have been reported in the maraviroc clinical programme.

There have been 2 overdoses reported in A4001026, 1 of efavirenz and the other of amitriptyline (SCS Table 3.8.1.4).

2.7.4.5.6. Drug Abuse

There has been no evidence of abuse potential for maraviroc.

2.7.4.5.7. Withdrawal and Rebound

There is no evidence to suggest that withdrawal or rebound symptoms will accompany cessation of maraviroc therapy.

2.7.4.5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies on the effects on the ability to drive and use machines have been performed. However, maraviroc can cause dizziness, and it is possible that if severe this may impair a patient's ability to drive or operate machinery

2.7.4.6. Post-marketing Data

Maraviroc has not been approved for marketing in any country, and therefore no post-marketing data are available.

2.7.4.7. References

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*:新薬承認情報提供時に置換えた。
TM4*はatazanavir sulfateを示す。

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Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001009 (Belgium – Single centre) .	Design: Cohort 1: double-blind (third party open), four-way crossover study Cohort 2: open, two-way crossover study Duration Cohort 1 Four periods of single doses separated by at least 7 days Cohort 2 Two periods of single doses separated by at least 7 days	Maraviroc Route: IV fusion over 60 minutes (solution at 2.5 mg/mL) Route: 1x100 mg research tablet COHORT 1 3 mg maraviroc IV 10 mg maraviroc IV 30 mg maraviroc IV	Sex: 20 M/0 F Mean/Median Age (min/max): 33.0 (22/42) years Race: W/B/O: 20/0/0	**Analysed for safety: N=8** All causality AE: 0 Treatment Related AE: 0 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0 **Analysed for safety: N=8** All causality AE: 2 Treatment Related AE: 2 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0 **Analysed for safety: N=8** All causality AE: 2 Treatment Related AE: 2 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	A4001009 Module 5.3.1.1

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001009 continued		Placebo		**Analysed for safety: N=8** All causality AE: 2 Treatment Related AE: 2 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	
		<u>COHORT 2</u> 30 mg maraviroc IV		**Analysed for safety: N=12** All causality AE: 3 Treatment Related AE: 3 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	
		1x100 mg maraviroc tablet		**Analysed for safety: N=12** All causality AE: 4 Treatment Related AE: 3 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	

Source: A4001009 Clinical Study Report (CSR) Tables 6.1.1 and 6.1.2

Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event

[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001040 (Singapore – Single centre)	Design Single dose open, randomised, 2 way crossover study Duration. Two periods of single doses separated by at least 5 days	Maraviroc Route: Commercial Tablet; Dose Regimen: 300 mg Maraviroc Route: Research Tablet; Dose Regimen: 300 mg (2x150 mg)	Sex: 33 M/11 F Mean/Median Age (min/max): 27.1 (21/54) years Race: W/B/O: 0/0/44	**Analysed for safety: N=44** All causality AE: 17 Treatment Related AE: 7 SAE: 1 Deaths: 0 Discontinuations Due to AE: 2 **Analysed for safety: N=42** All causality AE: 20 Treatment Related AE: 9 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	A4001040 Module 5.3.1.2

Source: A4001040 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001001 (Belgium – Single centre) .	Design: Double-blind (3rd party open), placebo-controlled, dose escalating, crossover study Duration: Five periods of single doses separated by at least 7 days	Maraviroc Route: Powder for oral solution Placebo Route: Powder for oral solution COHORT A 1 mg maraviroc solution	Sex: 24 M/0 F Mean/Median Age (min/max): 28.6 (21/45) years Race: W/B/O: 23/1/0	**Analysed for safety: N=9** All causality AE: 0 Treatment Related AE: 0 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	A4001001 Module 5.3.3.1
		10 mg maraviroc solution (fasted)		**Analysed for safety: N=9** All causality AE: 0 Treatment Related AE: 0 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	
		100 mg maraviroc solution (fasted)		**Analysed for safety: N=9** All causality AE: 1 Treatment Related AE: 1 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001001 continued		900 mg maraviroc solution (fasted)		**Analysed for safety: N=9** All causality AE: 6 Treatment Related AE: 6 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	
		100 mg maraviroc solution (fed)		**Analysed for safety: N=12** All causality AE: 2 Treatment Related AE: 1 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	
		Placebo		**Analysed for safety: N=12** All causality AE: 2 Treatment Related AE: 2 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	
		COHORT B 3 mg maraviroc solution		**Analysed for safety: N=42** All causality AE: 20 Treatment Related AE: 9 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001001 continued		30 mg maraviroc solution		**Analysed for safety: N=42** All causality AE: 20 Treatment Related AE: 9 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	
		300 mg maraviroc solution		**Analysed for safety: N=9** All causality AE: 1 Treatment Related AE: 1 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	
		1200 mg maraviroc solution		**Analysed for safety: N=9** All causality AE: 9 Treatment Related AE: 8 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	
		Placebo		**Analysed for safety: N=12** All causality AE: 3 Treatment Related AE: 2 SAE: 0 Deaths: 0 Discontinuations Due to AE: 0	

Source: A4001001 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001002 (Belgium – Single centre)	Design: Double-blind (3rd party open), parallel group, placebo controlled single dose and multiple escalating oral dose study Duration: 12 days	Maraviroc Route: Powder for oral solution (3, 10, 25, 100 & 300 mg) Route: Oral tablet (600 mg) COHORT 6 3 mg BID COHORT 6 10 mg BID COHORT 4 25 mg BID	Sex: 72 M/0 F Mean/Median Age (min/max): 29.3 (18/41) years Race: W/B/O: 66/3/3	**Analysed for safety: N=5** All causality AEs: 4 Treatment related AEs: 4 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 1 **Analysed for safety: N=5** All causality AEs: 3 Treatment related AEs: 0 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for safety: N=9** All causality AEs: 6 Treatment related AEs: 2 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001002 Module 5.3.3.1

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001002 continued		COHORT 1 100 mg BID		**Analysed for safety: N=9** All causality AEs: 5 Treatment related AEs: 3 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		COHORT 2 300 mg BID		**Analysed for safety: N=9** All causality AEs: 7 Treatment related AEs: 5 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		COHORT 3 600 mg QD		**Analysed for safety: N=9** All causality AEs: 8 Treatment related AEs: 8 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 3	
		COHORT 5 600 mg QD		**Analysed for safety: N=9** All causality AEs: 7 Treatment related AEs: 4 SAEs: 0 Deaths: Discontinuations due to AEs: 0	

Source: A4001002 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001003 (Belgium – Single centre	Design: Open, randomised, five-way crossover study. Duration: Five periods of single dose separated by at least 5 days	Maraviroc Route: Oral tablet (50, 100 & 600 mg) Route: Powder for oral solution (100 mg) 1 x 50 mg maraviroc tablet (fasted) 1 x 100 mg maraviroc tablet (fasted) 100 mg maraviroc solution (fasted)	Sex: 15 M/0 F Mean/Median Age (min/max): 31.3 (20/44) years Race: W/B/O: 14/1/0	**Analysed for safety: N=15** All causality AEs: 7. Treatment related AEs: 4. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for safety: N=15** All causality AEs: 5 Treatment related AEs: 3 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for safety: N=15** All causality AEs: 6 Treatment related AEs: 3 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001003 Module 5.3.3.1

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001003 continued		600 mg (4 x 150 mg tablets) maraviroc (fasted)		**Analysed for safety: N=15** All causality AEs: 9 Treatment related AEs: 8 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		600 mg (4 x 150 mg tablets) maraviroc (fed)		**Analysed for safety: N=15** All causality AEs: 6 Treatment related AEs: 4 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Source: A4001003 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001008 (UK – 2 centres)	Design: Randomised, double-blind, placebo-controlled, multiple dose study. Duration: 42 days	Maraviroc Route: Oral tablet (100 & 300 mg BID) Placebo Route: Oral tablets 100 mg BID maraviroc 300 mg BID maraviroc Placebo	Sex: 39 M/15 F Mean/Median Age (min/max): 31.4 (18/52) years Race: W/B/O: 51/1/2	**Analysed for safety: N=16** All causality AEs: 11 Treatment related AEs: 9 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 1 **Analysed for safety: N=16** All causality AEs: 15 Treatment related AEs: 15 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for safety: N=16** All causality AEs: 14 Treatment related AEs: 9 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001008 Module 5.3.3.1

Source: A4001008 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001010 (UK – Single centre)	Design: Single centre, open study Duration: Single dose	Maraviroc ^{14}C Route: Powder for oral solution (300 mg)	Sex: 3 M/0 F Mean/Median Age (min/max): 49.0 (45/53) years Race: W/B/O: 3/0/0	**Analysed for safety: N=3** All causality AEs: 1 Treatment related AEs: 1 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001010 Module 5.3.3.1

Source: A4001010 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1

Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event

[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001019 (UK – Single centre)	Design: Randomised, double blind, 3rd party open, placebo-controlled, parallel group study with three cohorts of 12 subjects (9 active treatment, 3 placebo per cohort). Duration: 14 days	Maraviroc Route: Oral tablet (300 & 600 mg BID) Placebo Route: Oral tablet	Sex: 19 M/17 F Mean/Median Age (min/max): 28.1 (18/44) years Race: W/B/O: 36/0/0		A4001019 Module 5.3.3.1
		Maraviroc 300 mg BID (days 1-7)		**Analysed for safety: N=9** All causality AEs: 9/9. Treatment related AEs: 9/9. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 1	
		Maraviroc 600 mg BID (days 8-14)		**Analysed for safety: N=8** All causality AEs: 8 Treatment related AEs: 6 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		Maraviroc 600 mg BID (days 1-7)		**Analysed for safety: N=9** All causality AEs: 8 Treatment related AEs: 8 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 1	

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001019 continued		Maraviroc 900 mg BID (days 8-14)		**Analysed for safety: N=8** All causality AEs: 8 Treatment related AEs: 8 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		Maraviroc 900 mg QD (days 1-7)		**Analysed for safety: N=9** All causality AEs: 8 Treatment related AEs: 8 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		Maraviroc 1200 mg QD (days 8-14)		**Analysed for safety: N=9** All causality AEs: 9 Treatment related AEs: 8 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		Placebo		**Analysed for safety: N=9** All causality AEs: 9 Treatment related AEs: 9 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 1	

Source: A4001019 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001038 (Belgium, Singapore – Two centres)	Design: An open study Duration: single dose	Maraviroc single oral 300 mg tablet	Sex: 24 M/0 F Mean/Median Age (min/max): 28.3 (22/40) years Race: W/B/O: 12/0/12		A4001038 Module 5.3.3.3
		Asian		**Analysed for safety: N=12** All causality AEs: 3. Treatment related AEs: 2. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		Caucasian		**Analysed for safety: N=12** All causality AEs: 3. Treatment related AEs: 1. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Source: A4001038 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001004 (Belgium – Single centre)	Design: An open study Duration: Five periods of single doses separated by at least 5 days	Maraviroc single oral 100 mg tablet	Sex: 15 M/0 F Mean/Median Age (min/max): 34.5 (20/45) years Race: W/B/O: 15/0/0		A4001004 Module 5.3.3.4
		Fasted		**Analysed for safety: N=15** All causality AEs: 1 Treatment related AEs: 0 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		Dosing 1 hour prior to food		**Analysed for safety: N=11** All causality AEs: 4 Treatment related AEs: 2 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		Dosing with food		**Analysed for safety: N=11** All causality AEs: 1 Treatment related AEs: 0 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		Dosing 1 hour post food		**Analysed for safety: N=12** All causality AEs: 2 Treatment related AEs: 0 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001004 continued		**Dosing 2 hour post food**		**Analysed for safety: N=11** All causality AEs: 2 Treatment related AEs: 0 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		Dosing 4 hour post food		**Analysed for safety: N=11** All causality AEs: 3 Treatment related AEs: 1 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Source: A4001004 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001005 (UK – 2 centres)	Design: Randomised, double blind, placebo-controlled, two way crossover study. Duration: Two periods of 11 days separated by at least 7 days		Sex: 0 M/15 F Mean/Median Age (min/max): 38.0 (32/45) years Race: W/B/O: 15/0/0		A4001005 Module 5.3.3.4
		100 mg maraviroc Day 1		**Analysed for Safety, N=15** All causality AEs: 4. Treatment related AEs: 2. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		100 mg maraviroc + OC Day 2-11		**Analysed for Safety, N=15** All causality AEs: 13. Treatment related AEs: 12. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		Placebo Day 1		**Analysed for Safety, N=15** All causality AEs: 9. Treatment related AEs: 7. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001005 continued		Placebo + OC Day 2-11		**Analysed for Safety, N=15** All causality AEs: 15. Treatment related AEs: 14. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Source: A4001005 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001006 (Belgium – Single centre)	Design: An open, randomised, placebo controlled, 2 way crossover study. Duration: Two periods of 9 days separated by at least 7 days.	COHORT 1 100 mg maraviroc (+saquinavir 1200 mg TID) 100 mg maraviroc (+ placebo TID) COHORT 2 100 mg maraviroc (+ketoconazole 400 mg QD)	Sex: 24 M/0 F Mean/Median Age (min/max): 30.3 (18/43) years Race: W/B/O: 23/1/0	**Analysed for Safety, N=12** All causality AEs: 12. Treatment related AEs: 12. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for Safety, N=12** All causality AEs: 7. Treatment related AEs: 6. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for Safety, N=12** All causality AEs: 4. Treatment related AEs: 2. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001006 Module 5.3.3.4

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001006 continued		100 mg maraviroc (+ placebo QD)		**Analysed for Safety, N=12** All causality AEs: 6. Treatment related AEs: 3. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Source: A4001006 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001011 (Belgium – Single centre)	Design: Open, randomised, placebo-controlled, parallel group study. Duration: 28 days		Sex: 36 M/0 F Mean/Median Age (min/max): 31.1 (18/45) years Race: W/B/O: 32/2/2		A4001011 Module 5.3.3.4
		GROUP 1 100 mg maraviroc BID (Day 7)		**Analysed for Safety, N=12** All causality AEs: 3. Treatment related AEs: 2. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		100 mg maraviroc BID + Rifampicin 600 mg QD (Day 21)		**Analysed for Safety, N=12** All causality AEs: 6. Treatment related AEs: 4. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		200 mg maraviroc BID + Rifampicin 600 mg QD (Day 28)		**Analysed for Safety, N=12** All causality AEs: 5. Treatment related AEs: 4. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001011 continued		GROUP 2 100 mg maraviroc BID (Day 7)		**Analysed for Safety, N=12** All causality AEs: 0. Treatment related AEs: 0. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		100 mg maraviroc BID + Efavirenz 600 mg QD (Day 21)		**Analysed for Safety, N=12** All causality AEs: 12. Treatment related AEs: 12. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		200 mg maraviroc BID + Efavirenz 600 mg QD (Day 28)		**Analysed for Safety, N=12** All causality AEs: 9. Treatment related AEs: 9. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		GROUP 3 100 mg maraviroc BID (Day 7)		**Analysed for Safety, N=12** All causality AEs: 1. Treatment related AEs: 1. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001011 continued		100 mg maraviroc BID (Day 21) + placebo		**Analysed for Safety, N=12** All causality AEs: 4. Treatment related AEs: 2. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Source: A4001011 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001012 (Belgium – Single centre)	Design: Randomised, double blind, placebo-controlled, two-period crossover study. Duration: Two periods of 7 days, separated by at least 7 days.	300 mg (3x100 mg tablets) maraviroc BID + 7.5 mg midazolam Placebo tablets + 7.5 mg midazolam	Sex: 6 M/6 F Mean/Median Age (min/max): 31.1 (23/44) years Race: W/B/O: 12/0/0	**Analysed for Safety, N=12** All causality AEs: 9. Treatment related AEs: 9. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for Safety, N=12** All causality AEs: 5. Treatment related AEs: 5. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001012 Module 5.3.3.4

Source: A4001012 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001013 (Belgium – Single centre)	Design: Open label, randomised, placebo-controlled, four treatment, four group, parallel group study. Duration: 28 days	GROUP 1 100 mg maraviroc BID	Sex: 20 M/12 F Mean/Median Age (min/max): 30.8 (19/44) years Race: W/B/O: 28/4/0	**Analysed for Safety, N=8** All causality AEs: 5. Treatment related AEs: 4. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001013 Module 5.3.3.4
		100 mg maraviroc BID + ritonavir 100 mg BID		**Analysed for Safety, N=8** All causality AEs: 5. Treatment related AEs: 5. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		50 mg maraviroc BID + ritonavir 100 mg BID		**Analysed for Safety, N=8** All causality AEs: 2. Treatment related AEs: 1. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001013 continued		GROUP 2 100 mg maraviroc BID		**Analysed for Safety, N=8** All causality AEs: 4. Treatment related AEs: 4. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		100 mg maraviroc BID + saquinavir 1000 mg BID + ritonavir 100 mg BID		**Analysed for Safety, N=8** All causality AEs: 7. Treatment related AEs: 7. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		25 mg maraviroc BID + saquinavir 1000 mg BID + ritonavir 100 mg BID		**Analysed for Safety, N=8** All causality AEs: 7. Treatment related AEs: 6 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		GROUP 3 100 mg maraviroc BID		**Analysed for Safety, N=8** All causality AEs: 3. Treatment related AEs: 2. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001013 continued		100 mg maraviroc BID + lopinavir 400 mg BID + ritonavir 100 mg BID		**Analysed for Safety, N=8** All causality AEs: 6. Treatment related AEs: 5. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		50 mg maraviroc BID + lopinavir 400 mg BID + ritonavir 100 mg BID		**Analysed for Safety, N=8** All causality AEs: 6. Treatment related AEs: 4. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		<u>GROUP 4</u> 100 mg maraviroc BID		**Analysed for Safety, N=8** All causality AEs: 3. Treatment related AEs: 3. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		100 mg maraviroc BID + placebo		**Analysed for Safety, N=8** All causality AEs: 6. Treatment related AEs: 4. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Source: A4001013 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001017 (UK – Single centre)	Design: Open, single period, single centre study. Duration: Single dose	Maraviroc Route: Single oral tablets (300 mg) COHORT 1 300 mg maraviroc + efavirenz 600 mg QD + [redacted] (lamivudine 150 mg + zidovudine 300 mg) COHORT 2 300 mg maraviroc + efavirenz 600 mg QD + didanosine 250 mg enteric coated QD + tenofovir 300 mg QD. COHORT 3 300 mg maraviroc + Nevirapine 200 mg BID + lamivudine 150mg BID, + tenofovir 300 mg QD.	Sex: 37 M/0 F Mean/Median Age (min/max): 38.1 (28/52) years Race: W/B/O: 35/1/1	**Analysed for Safety, N=8** All causality AEs: 4. Treatment related AEs: 4. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for Safety, N=8** All causality AEs: 0. Treatment related AEs: 0. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for Safety, N=8** All causality AEs: 1. Treatment related AEs: 1. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001017 Module 5.3.3.4

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001017 continued		COHORT 4 300 mg maraviroc + [redacted]® (lopinavir + ritonavir) 400mg BID + stavudine 40 mg BID + lamivudine 150 mg BID		**Analysed for Safety, N=5** All causality AEs: 2. Treatment related AEs: 2. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Source: A4001017 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001018	Design: Open label, randomised, placebo-controlled, two-period crossover study. Duration: Two periods of 7 days separated by at least 7 days	Maraviroc Route: Oral tablets (3 x 100 mg) BID TM13* Route: Oral tablets (800mg/160mg tablets) BID Placebo Route: Oral tablets BID 300mg maraviroc + TM13* 960 mg (800/160 mg) 300 mg maraviroc + placebo	Sex: 8 M/4 F Mean/Median Age (min/max): 31.4 (21/45) years Race: W/B/O: 12/0/0	**Analysed for Safety, N=15** All causality AEs: 10. Treatment related AEs: 6. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 1 **Analysed for Safety, N=13** All causality AEs: 6. Treatment related AEs: 2. SAEs: 0 Deaths: 0 Discontinuations due to AEs: 1	A4001018 Module 5.3.3.4

Source: A4001018 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

*:新薬承認情報提供時に置換えた。
TM13*はtrimethoprim/sulfamethoxazoleを示す。

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001020 (UK – Single centre)	Design: Double-blind, third party open, randomised, placebo-controlled, two-period crossover study. Duration: Two periods of 7 days separated by at least 7 days	Maraviroc Route: Oral tablets (100 mg) TM1* Route: 300 mg tablet BID Placebo Route: 3 Oral tablets BID 300 mg maraviroc BID + [redacted](lamivudine 150 mg + zidovudine 300 mg) Placebo + [redacted] (lamivudine 150 mg + zidovudine 300 mg)	Sex: 8 M/4 F Mean/Median Age (min/max): 31.4 (21/45) years Race: W/B/O: 12/0/0	**Analysed for Safety, N=12** All causality AEs: 10 Treatment related AEs: 9 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for Safety, N=11** All causality AEs: 8 Treatment related AEs: 6 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001020 Module 5.3.3.4

Source: A4001020 Clinical Study Report (CSR) Tables 6.1.3 and 6.2.3
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

*:新薬承認情報提供時に置換えた。
TM1*はzidovudine/lamivudineを示す。

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001021 (UK – Two centres)	Design: Open, randomised, placebo-controlled, 2-way crossover study. Duration: Two periods of 21 days separated by at least 14 days	Maraviroc Route: Oral tablets (100 mg) 100 or 300 mg BID COHORT 1 300 mg maravirocBID + TM2* BID (Days 1-21) plus efavirenz 600 mg QD (Days 8-21) 300 mg maravirocBID + placebo BID (Days 1-21) plus placebo QD (Days 8-21) COHORT 2 100 mg maraviroc BID + boosted saquinavir BID (Days 1-21) plus efavirenz 600 mg QD (Days 8-21)	Sex: 33 M/3 F Mean/Median Age (min/max): 27.4 (18/44) years Race: W/B/O: 34/1/1	**Analysed for Safety, N=11** All causality AEs: 11 Treatment related AEs: 11 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 1 **Analysed for Safety, N=11** All causality AEs: 10 Treatment related AEs: 10 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 1 **Analysed for Safety, N=11** All causality AEs: 10 Treatment related AEs: 10 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 1	A4001021 Module 5.3.3.4

*:新薬承認情報提供時に置換えた。
TM2*はlopinavir/ritonavirを示す。

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001021 continued		100 mg maravirocBID + placebo BID (Days 1-21) plus placebo QD (Days 8-21) <u>COHORT 3</u> 100 mg maraviroc BID + saquinavir 1000 mg BID + TM2* BID (Days 1-21) +efavirenz 600 mg QD (Days 8-21) 100 mg maraviroc BID + placebo BID (Days 1-21) + placebo QD (Days 8-21)		**Analysed for Safety, N=11** All causality AEs: 9 Treatment related AEs: 9 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for Safety, N=6** All causality AEs: 6 Treatment related AEs: 6 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 4 **Analysed for Safety, N=6** All causality AEs: 4 Treatment related AEs: 1 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Source: A4001021 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

*:新薬承認情報提供時に置換えた。
TM2*はlopinavir/ritonavirを示す。

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001022 (Singapore – Single centre) .	Design: Open, randomised, placebo-controlled, two-way crossover study Duration: Two periods of 7 days separated by at least 14 days	Maraviroc Route: Oral tablet (50 mg) 300 mg BID Tenofovir Route: 300 mg oral tablet QD Placebo Route: Oral tablet Maraviroc 300 mg BID + tenofovir Maraviroc 300 mg BID + placebo	Sex: 10 M/2 F Mean/Median Age (min/max): 31.8 (22/44) years Race: W/B/O: 0/0/12	**Analysed for safety: N=12** All causality AEs: 8 Treatment related AEs: 5 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for safety: N=11** All causality AEs: 9 Treatment related AEs: 3 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001022 Module 5.3.3.4

Source: A4001022 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001025 (Singapore – Single centre).	Design Open, randomised, placebo-controlled, two-period crossover study. Duration: Two periods of 14 days separated by at least 14 days	Maraviroc Route: Oral tablet (50 mg) 300 mg BID Atazanavir Route: Oral tablet 400 mg QD Placebo Route: Oral tablet Maraviroc 300 mg BID + atazanavir Maraviroc 300 mg BID + placebo	Sex: 12 M/0 F Mean/Median Age (min/max): 28.7 (21/43) years Race: W/B/O: 1/0/11	**Analysed for safety: N=12** All causality AEs: 12 Treatment related AEs: 12 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for safety: N=12** All causality AEs: 11 Treatment related AEs: 7 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001025 Module 5.3.3.4

Source: A4001025 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001042 (Belgium – Single centre) .	Design: Open, randomized, 2 way crossover study. Duration: Two periods of 8 days separated by at least 14 days	Maraviroc Route: Oral tablet (50 mg) 150 mg BID Boosted tipranavir Route: Oral tablet (500 mg tipranavir /200 mg ritonavir) BID Placebo Route: Oral tablet Maraviroc 150 mg BID + boosted tipranavir BID Maraviroc 150 mg BID + placebo	Sex: 6 M/6 F Mean/Median Age (min/max): 32.7 (22/43) years Race: W/B/O: 11/0/1	**Analysed for safety: N=12** All causality AEs: 11 Treatment related AEs: 11 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for safety: N=12** All causality AEs: 9 Treatment related AEs: 8 SAEs: 1 Deaths: 0 Discontinuations due to AEs: 0	A4001042 Module 5.3.3.4

Source: A4001042 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001046 (UK - Single centre)	Design: Open, single period, single centre study. Duration: Single dose	Maraviroc Route: Single oral tablet (150 mg) Maraviroc 150 mg	Sex: 7 M/1 F Mean/Median Age (min/max): 45.9 (38/56) years Race: W/B/O: 7/1/0	**Analysed for safety: N=8** All causality AEs: 0 Treatment related AEs: 0 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001046 Module 5.3.3.4

Source: A4001046 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001043 (Singapore – Single centre)	Design: Open label, randomized, single dose 2-way crossover. Duration: Two periods of single doses separated by at least 5 days	Maraviroc Route: Commercial tablet (300 mg) Maraviroc 300 mg Fed Maraviroc 300 mg Fasted	Sex: 8 M/4 F Mean/Median Age (min/max): 28.5 (21/40) years Race: W/B/O: 0/0/12	**Analysed for safety: N=12** All causality AEs: 3 Treatment related AEs: 1 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for safety: N=12** All causality AEs: 5 Treatment related AEs: 2 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001043 Module 5.3.3.4

Source: A4001043 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1

Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event

[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001016 (Belgium – Single centre)	Design: Randomised, single dose, placebo and active controlled five way crossover Study. Duration: Five periods of single doses separated by at least 7 days	Maraviroc Route: Oral tablets (100 and 150 mg) Moxifloxacin Route: Oral tablet 400 mg Placebo Route: Oral tablets Maraviroc 100 mg Maraviroc 300 mg Maraviroc 900 mg	Sex: 30 M/31 F Mean/Median Age (min/max): 29.9 (19/44) years Race: W/B/O: 58/1/2	**Analysed for safety: N=61** All causality AEs: 16 Treatment related AEs: 10 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 2 **Analysed for safety: N=59** All causality AEs: 16 Treatment related AEs: 11 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 1 **Analysed for safety: N=58** All causality AEs: 29 Treatment related AEs: 26 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001016 Module 5.3.4.1

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001016 continued		Moxifloxacin 400 mg		**Analysed for safety: N=58** All causality AEs: 17 Treatment related AEs: 15 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		Placebo		**Analysed for safety: N=59** All causality AEs: 16 Treatment related AEs: 10 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Source: A4001016 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001033 (Belgium – Single centre)	Design: Part 1 an open, randomized, two-period (period 1 and 2) crossover assessment of a single sublingual spray of 0.4 mg GTN v no-treatment (GTN placebo). Part 2: double blind, randomized, placebo-controlled, two period (periods 3 and 4) crossover assessment of a single oral dose of maraviroc 900 mg v placebo (maraviroc placebo). Duration: Part 1: Two single doses separated by at least 24hrs. Part 2: Two single doses separated by at least 5 days. Part 1 and 2 separated by at least 5 days	Maraviroc Route: Oral tablets (150 mg) Marviroc placebo Route: Oral tablets GTN Route: 0.4 mg sublingual spray GTN placebo Sublingual spay Maraviroc 900 mg QD Maraviroc placebo QD	Sex: 16 M/0 F Mean/Median Age (min/max): 30.2 (19/45) years Race: W/B/O: 14/1/1	**Analysed for safety: N=16** All causality AEs: 8 Treatment related AEs: 6 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for safety: N=16** All causality AEs: 3 Treatment related AEs: 1 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001033 Module 5.3.4.1

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001033 continued		GTN QD		**Analysed for safety: N=16** All causality AEs: 5 Treatment related AEs: 5 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		GTN placebo QD		**Analysed for safety: N=16** All causality AEs: 3 Treatment related AEs: 1 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Source: A4001033 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1

Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event; GTN Glyceryl trinitrate

[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001007 (Germany, Netherlands, UK – 6 centres)	Design: Randomised, double blind, placebo-controlled, multicentre study. Duration: 10 days	Maraviroc Route: Oral tablets (25 mg) Placebo Route: Oral tablets Maraviroc 25 mg QD Maraviroc 50 mg BID Maraviroc 100 mg BID	Sex: 45 M/- F Mean/Median Age (min/max): 34.2 (23/48) years Race: W/B/O: 40/4/1	**Analysed for safety: N=9** All causality AEs: 7 Treatment related AEs: 4 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for safety: N=8** All causality AEs: 7 Treatment related AEs: 5 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0 **Analysed for safety: N=8** All causality AEs: 5 Treatment related AEs: 4 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001007 Module 5.3.4.2

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001007 continued		Maraviroc 300 mg BID		**Analysed for safety: N=8** All causality AEs: 6 Treatment related AEs: 6 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		Placebo		**Analysed for safety: N=12** All causality AEs: 8 Treatment related AEs: 5 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Source: A4001007 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001015 (Germany, UK, USA – 7 centres)	Design: Randomised, double-blind, placebo-controlled, multicentre, five treatment, parallel group study. Duration: 10 days	Maraviroc Route: Oral tablets (50 mg) Placebo Route: Oral tablets Maraviroc 150 mg BID (fasted)	Sex: 35 M/2 F Mean/Median Age (min/max): 38.0 (27/53) years Race: W/B/O: 35/1/1	**Analysed for safety: N=8** All causality AEs: 5 Treatment related AEs: 3 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001015 Module 5.3.4.2
		Maraviroc 150 mg BID (fed)		**Analysed for safety: N=8** All causality AEs: 5 Treatment related AEs: 2 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		Maraviroc 100 mg QD (fasted)		**Analysed for safety: N=9** All causality AEs: 6 Treatment related AEs: 3 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 1	

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001015 continued		Maraviroc 300 mg QD (fasted)		**Analysed for safety: N=8** All causality AEs: 6 Treatment related AEs: 3 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		Placebo		**Analysed for safety: N=4** All causality AEs: 1 Treatment related AEs: 1 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Source: A4001015 Clinical Study Report (CSR) Tables 6.1.1 and 6.2.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event
[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001027 (Canada, USA – 108 centres)	Design: A 48 week, multi-centre, double-blind, randomised (2:2:1), placebo-controlled, phase 2b/3 superiority study. Duration: Minimum of 48 weeks	Maraviroc Route: Oral tablets (150 mg) Placebo Route: Oral tablets	Sex: 528 M/57 F Mean/Median Age (min/max): 45.9 (19/75) years Race: W/B/O: 483/87/15		A4001027 Module 5.3.5.1
		Maraviroc QD – 300 mg dose equivalents*		**Analysed for safety: N=232** All causality AEs: 204 (87.9%) Treatment related AEs: 95 (40.9%) SAEs: 29 (12.5%) Deaths: 2 (0.9%) Discontinuations due to AEs: 11 (4.7%)	
		Maraviroc BID – 300 mg dose equivalents*		**Analysed for safety: N=235** All causality AEs: 213 (90.6%) Treatment related AEs: 114 (48.5%) SAEs: 37 (15.7%) Deaths: 2 (0.9%) Discontinuations due to AEs: 10 (4.3%)	
		Placebo		**Analysed for safety: N=118** All causality AEs: 99 (83.9%) Treatment related AEs: 48 (40.7%) SAEs: 20 (16.9%) Deaths: 1 (0.8%) Discontinuations due to AEs: 6 (5.1%)	

Source: A4001027 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1

Note: * Patients with a protease inhibitor (other than tipranavir)/delavirdine as part of their optimized background therapy received 150 mg; No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event

AEs are presented as number of subject experiencing an event, the total of number of subjects in that treatment group and this percentage. .

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001028 (Australia, Belgium, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, UK, USA – 131 centres)	Design: A 48 week, multi-centre, double-blind, randomised (2:2:1), placebo-controlled, phase 2b/3 superiority study. Duration: Minimum of 48 weeks	Maraviroc Route: Oral tablets (150 mg) Placebo Route: Oral tablets	Sex: 402 M/62 F Mean/Median Age (min/max): 46.0 (17/75) years Race: W/B/O: 394/60/10		A4001028 Module 5.3.5.1
		Maraviroc QD – 300 mg dose equivalents*		**Analysed for safety: N=182** All causality AEs: 162 (89.0%) Treatment related AEs: 110 (60.4%) SAEs: 29 (15.9%) Deaths: 4 (2.2%) Discontinuations due to AEs: 9 (4.9%)	
		Maraviroc BID – 300 mg dose equivalents*		**Analysed for safety: N=191** All causality AEs: 170 (89.0%) Treatment related AEs: 99 (51.8%) SAEs: 30 (15.7%) Deaths: 4 (2.1%) Discontinuations due to AEs: 7 (3.7%)	
		Placebo		**Analysed for safety: N=91** All causality AEs: 76 (83.5%) Treatment related AEs: 45 (49.5%) SAEs: 14 (15.4%) Deaths: 0 Discontinuations due to AEs: 2 (2.2%)	

Source: A4001028 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1

Note: * Patients with a protease inhibitor (other than tipranavir)/delavirdine as part of their optimized background therapy received 150 mg; No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event

AEs are presented as number of subject experiencing an event, the total of number of subjects in that treatment group and this percentage.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001029 (Australia, Belgium, Canada, Germany, Netherlands, Spain, Switzerland, UK, USA – 76 centres)	Design: Multi-centre, double blind, randomised (1:1:1) placebo controlled study. Duration: 48 weeks	Maraviroc Route: Oral tablets (150 mg) Placebo Route: Oral tablets Maraviroc QD – 300 mg dose equivalents* Maraviroc BID – 300 mg dose equivalents* Placebo	Sex: 161 M/25 F Mean/Median Age (min/max): 43.3 (16/62) years Race: W/B/O: 130/48/8	**Analysed for safety: N=63** All causality AEs: 54 (86%) Treatment related AEs: 28 (44%) SAEs: 10 (16%) Deaths: 2 (3.2%) Discontinuations due to AEs: 0 **Analysed for safety: N=61** All causality AEs: 56 (92%) Treatment related AEs: 30 (49%) SAEs: 9 (15%) Deaths: 2 (3.3%) Discontinuations due to AEs: 2 (3.2%) **Analysed for safety: N=62** All causality AEs: 55 (89%) Treatment related AEs: 38 (61%) SAEs: 11 (4.8%) Deaths: 3 (4.8%) Discontinuations due to AEs: 4 (6.5%)	A4001029 Module 5.3.5.1

Source: A4001029 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1

Note: * Patients with a protease inhibitor (other than tipranavir)/delavirdine as part of their optimized background therapy received 150 mg; No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event

AEs are presented as number of subject experiencing an event, the total of number of subjects in that treatment group and this percentage.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001032 (UK – Single centre)	Design: Single blind, randomised, single study day, two-part study. Part 1: Subjects tasted 4 maraviroc and 2 comparator formulations using the *rinse and spit* method Part 2: later in the day swallowed a pre-selected maraviroc formulation. Duration: 1 day	Maraviroc Route: 20 mg/ml in 4 different formulations Marviroc 20 mg/ml	Sex: 8 M/10 F Mean/Median Age (min/max): 36.3 (19/54) years Race: W/B/O: 17/1/0	**Analysed for safety: N=18** All causality AEs: 3 Treatment related AEs: 1 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	A4001032 Module 5.3.5.4

Source: A4001032 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1

Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event

[a]AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001047 (Singapore - Single centre)	Design: Open, randomized 5-way crossover study. Duration: Five periods of single doses	Maraviroc Route: 600 mg IR tablet 600 mg MR tablet	Sex: 9 M/1 F Mean/Median Age (min/max): 27.6 (21/37) years Race: W/B/O: 0/0/10		A4001047 Module 5.3.5.4
		IR		**Analysed for safety: N=10** All causality AEs: 0 Treatment related AEs: 0 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		MR 4 hour (fasted)		**Analysed for safety: N=10** All causality AEs: 3 Treatment related AEs: 1 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		MR 6 hour (fasted)		**Analysed for safety: N=10** All causality AEs: 4 Treatment related AEs: 1 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	
		MR 6 hour (fed)		**Analysed for safety: N=10** All causality AEs: 2 Treatment related AEs: 0 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001047 continued		MR 9 hour (fasted)		**Analysed for safety: N=10** All causality AEs: 4 Treatment related AEs: 0 SAEs: 0 Deaths: 0 Discontinuations due to AEs: 0	

Source: A4001047 Clinical Study Report (CSR) Tables 13.6.2.1 and 13.6.3.1

Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event; IR = Immediate release; MR = Modified release

AEs are presented as number of subject experiencing an event.

Section 2.7.4 Table A1 Safety Results

Protocol No. (Country; No. Centers[a])	Study Design/ Duration	Treatment Groups	Demographics (No. of Subjects)	Safety Results (N)[a]	Study Report Location
A4001026 (Argentine, Australia, Belgium, Brazil, Canada, Germany, Italy, Netherlands, Poland, South Africa, Spain, Sweden, Switzerland, UK, USA – 142 centres)	Design: A global, double-blind, comparative trial of maraviroc in combination with ARTs in treatment-naïve CCR5 tropic HIV-1 infected individuals. 96 Weeks. Duration: 96 weeks	Maraviroc Route: Oral tablet 300 mg QD	Sex: 130 M/44 F Mean/Median Age (min/max): 37.6 (20/70) years Race: W/B/O: 126/34/14	Note: Only 1 treatment arm reported (maraviroc QD), which was terminated by DSMB, with the other 2 blinded treatment arms still ongoing.	A4001026 Module 5.3.5.4
		300 mg QD		**Analysed for safety: N=174** All causality AEs: 147 (84.5%) Treatment related AEs: 122 (70.1%) SAEs: 21 (12.1%) Deaths: 2 (1.1%) Discontinuations due to AEs: 13 (7.5%)	
		300 mg BID open label		**Analysed for safety: N=129** All causality AEs: 82 (63.6%) Treatment related AEs: 32 (24.8%) SAEs: 9 (7.0%) Deaths: 0 Discontinuations due to AEs: 1 (0.8%)	

Source: A4001026 Clinical Study Report (CSR) Tables 13.1.1, 13.1.1.2, 13.6.2.2.1, 13.6.2.2.2, 13.6.2.4.1, 13.6.2.4.2, 13.6.5.1, 13.6.5.2 and 13.6.6.1
Note: No. = Number; BID = Twice daily; M = Male; F = Female; W/B/O = White/black/other; AE = Adverse event; SAE = Serious adverse event; AEs are presented as number of subject experiencing an event.

Table 1.1.1
Maraviroc Summary of Clinical Safety
Subject Evaluation Groups by Dose Frequency and Gender - Phase 1

		SINGLE DOSE		MULTIPLE DOSE	
Treatment Group	N	MALE	FEMALE	MALE	FEMALE
Placebo	164	78	29	34	23
<100mg	96	67	10	19	0
100mg	264	84	31	117	32
150mg	12	0	0	6	6
300mg	232	107	44	60	21
600mg	60	24	1	27	8
900mg	100	55	28	9	8
1200mg	18	9	0	5	4
maraviroc Only	782	346	114	243	79
maraviroc + Interactant	227	36	1	139	51
Interactant	130	54	38	13	25
maraviroc Only - Distinct Subjects	559	205	57	230	67
All maraviroc - Distinct Subjects	632	241	58	254	79
All Doses - Distinct Subjects	674	241	58	288	87

The 'All Doses - Distinct Subjects' row may include subjects that receive placebo or interactant only.
The Distinct Subjects rows account for subjects counted more than once across treatment groups.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001002, A4001003, A4001004, A4001005, A4001006, A4001008, A4001009, A4001010, A4001011, A4001012, A4001013, A4001016, A4001017, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025, A4001032, A4001033, A4001038, A4001040, A4001042, A4001043, A4001046 and A4001047.
Date of Table Generation: 07SEP2006 (09:23)

Maraviroc Summary of Clinical Safety
Subject Evaluation Groups by Dose Frequency and Gender - Single Dose - Phase 1

	SINGLE DOSE		
Treatment Group	N	MALE	FEMALE
Placebo	107	78	29
<100mg	77	67	10
100mg	115	84	31
300mg	151	107	44
600mg	25	24	1
900mg	83	55	28
1200mg	9	9	0
maraviroc Only	460	346	114
maraviroc + Interactant	37	36	1
Interactant	92	54	38
maraviroc Only - Distinct Subjects	262	205	57
All maraviroc - Distinct Subjects	299	241	58
All Doses - Distinct Subjects	299	241	58

The 'All Doses - Distinct Subjects' row may include subjects that receive placebo or interactant only.
The Distinct Subjects rows account for subjects counted more than once across treatment groups.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 07SEP2006 (06:25)

Maraviroc Summary of Clinical Safety
Subject Evaluation Groups by Dose Frequency and Gender - Multiple Dose - Phase 1

		MULTIPLE DOSE	
Treatment Group	N	MALE	FEMALE
Placebo	57	34	23
<100mg unit dose	19	19	0
100mg BID	149	117	32
150mg BID	12	6	6
300mg BID	81	60	21
600mg QD	18	18	0
600mg BID	17	9	8
900mg QD	9	5	4
900mg BID	8	4	4
1200mg QD	9	5	4
maraviroc Only	322	243	79
maraviroc + Interactant	190	139	51
Interactant	38	13	25
maraviroc Only - Distinct Subjects	297	230	67
All maraviroc - Distinct Subjects	333	254	79
All Doses - Distinct Subjects	375	288	87

The 'All Doses - Distinct Subjects' row may include subjects that receive placebo or interactant only.
The Distinct Subjects rows account for subjects counted more than once across treatment groups.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.
Date of Table Generation: 15AUG2006 (10:27)

Table 1.2.1
Maraviroc Summary of Clinical Safety
Duration of Treatment (Days) - Single Dose - Phase 1

Treatment Group	N	Mean	Minimum	Maximum	Median
Placebo	107	1.0	1	1	1.0
<100mg	77	1.0	1	1	1.0
100mg	115	1.0	1	1	1.0
300mg	151	1.0	1	1	1.0
600mg	25	1.0	1	1	1.0
900mg	83	1.0	1	1	1.0
1200mg	9	1.0	1	1	1.0
maraviroc Only	262	1.0	1	1	1.0
maraviroc + Interactant	37	1.0	1	1	1.0
Interactant	92	1.0	1	1	1.0

The number of subjects (N) represents the number of unique subjects within a treatment group, however the summary statistics are based on distinct treatment periods.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 07SEP2006 (06:53)

Table 1.2.2
Maraviroc Summary of Clinical Safety
Duration of Treatment (Days) - Multiple Dose - Phase 1

Treatment Group	N	Mean	Minimum	Maximum	Median
Placebo	57	13.4	1	28	12.0
<100mg unit dose	19	11.6	5	12	12.0
100mg BID	149	11.4	1	28	8.0
150mg BID	12	8.0	8	8	8.0
300mg BID	81	14.4	3	28	12.0
600mg QD	18	9.5	7	12	9.5
600mg BID	17	6.6	1	7	7.0
900mg QD	9	7.0	7	7	7.0
900mg BID	8	7.0	7	7	7.0
1200mg QD	9	7.0	7	7	7.0
maraviroc Only	297	11.3	1	28	8.0
maraviroc + Interactant	190	10.4	3	21	9.0
Interactant	38	8.2	7	10	7.0

The number of subjects (N) represents the number of unique subjects within a treatment group, however the summary statistics are based on distinct treatment periods.
Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.
Date of Table Generation: 15AUG2006 (10:25)

Table 1.3.1
Maraviroc Summary of Clinical Safety
Demographic Characteristics - Single Dose - Phase 1

	Placebo						<100mg					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
Number (%) of Subjects	78		29		107		67		10		77	
Age (years):												
18-44	75	(96.2)	29	(100.0)	104	(97.2)	62	(92.5)	8	(80.0)	70	(90.9)
45-64	3	(3.8)	0		3	(2.8)	5	(7.5)	2	(20.0)	7	(9.1)
Mean	29.7		30.4		29.9		31.9		33.1		32.1	
SD	6.9		7.3		7.0		7.4		13.3		8.3	
Range	19-45		19-44		19-45		20-54		19-53		19-54	
Race:												
WHITE	74	(94.9)	27	(93.1)	101	(94.4)	64	(95.5)	10	(100.0)	74	(96.1)
BLACK	2	(2.6)	1	(3.4)	3	(2.8)	3	(4.5)	0		3	(3.9)
ASIAN	1	(1.3)	1	(3.4)	2	(1.9)	0		0		0	
OTHER	1	(1.3)	0		1	(0.9)	0		0		0	
Weight (kg):												
Mean	74.9		60.2		70.9		77.9		67.7		76.6	
SD	8.1		7.4		10.3		8.7		6.7		9.1	
Range	57.0-93.0		50.1-77.1		50.1-93.0		60.9-98.9		57.1-77.3		57.1-98.9	
N	78	(100.0)	29	(100.0)	107	(100.0)	67	(100.0)	10	(100.0)	77	(100.0)
Height (cm):												
Mean	176.7		164.5		173.4		178.1		162.3		176.0	
SD	6.1		5.3		8.0		6.6		7.6		8.6	
Range	163.5-191.0		156.5-176.0		156.5-191.0		162.0-198.0		154.0-178.0		154.0-198.0	
N	78	(100.0)	29	(100.0)	107	(100.0)	67	(100.0)	10	(100.0)	77	(100.0)

Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 07SEP2006 (07:01)

Table 1.3.1
Maraviroc Summary of Clinical Safety
Demographic Characteristics - Single Dose - Phase 1

	100mg						300mg					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
Number (%) of Subjects	84		31		115		107		44		151	
Age (years):												
18-44	82	(97.6)	31	(100.0)	113	(98.3)	104	(97.2)	43	(97.7)	147	(97.4)
45-64	2	(2.4)	0		2	(1.7)	3	(2.8)	1	(2.3)	4	(2.6)
Mean	30.7		30.8		30.7		28.6		29.7		28.9	
SD	6.9		7.2		6.9		6.6		7.7		6.9	
Range	19-45		19-44		19-45		19-53		19-54		19-54	
Race:												
WHITE	82	(97.6)	29	(93.5)	111	(96.5)	53	(49.5)	28	(63.6)	81	(53.6)
BLACK	1	(1.2)	1	(3.2)	2	(1.7)	0		1	(2.3)	1	(0.7)
ASIAN	1	(1.2)	1	(3.2)	2	(1.7)	54	(50.5)	15	(34.1)	69	(45.7)
OTHER	0		0		0		0		0		0	
Weight (kg):												
Mean	76.3		60.8		72.1		70.9		58.4		67.2	
SD	8.9		7.9		11.1		8.3		7.5		9.9	
Range	60.4-100.1		50.1-79.5		50.1-100.1		52.0-92.2		46.0-77.1		46.0-92.2	
N	84	(100.0)	31	(100.0)	115	(100.0)	107	(100.0)	44	(100.0)	151	(100.0)
Height (cm):												
Mean	177.4		164.6		173.9		174.7		163.0		171.3	
SD	6.6		5.2		8.4		6.3		6.1		8.2	
Range	162.0-198.0		156.5-176.0		156.5-198.0		159.5-190.0		149.0-176.0		149.0-190.0	
N	84	(100.0)	31	(100.0)	115	(100.0)	107	(100.0)	44	(100.0)	151	(100.0)

Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 07SEP2006 (07:01)

	600mg						900mg					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
Number (%) of Subjects	24		1		25		55		28		83	
Age (years):												
18-44	24	(100.0)	1	(100.0)	25	(100.0)	53	(96.4)	28	(100.0)	81	(97.6)
45-64	0		0		0		2	(3.6)	0		2	(2.4)
Mean	29.7		33.0		29.8		28.7		30.6		29.3	
SD	6.7		0.0		6.6		7.1		7.4		7.2	
Range	20-44		33-33		20-44		19-45		19-44		19-45	
Race:												
WHITE	14	(58.3)	0		14	(56.0)	52	(94.5)	26	(92.9)	78	(94.0)
BLACK	1	(4.2)	0		1	(4.0)	1	(1.8)	1	(3.6)	2	(2.4)
ASIAN	9	(37.5)	1	(100.0)	10	(40.0)	1	(1.8)	1	(3.6)	2	(2.4)
OTHER	0		0		0		1	(1.8)	0		1	(1.2)
Weight (kg):												
Mean	71.5		65.0		71.2		73.3		60.1		68.9	
SD	8.9		0.0		8.8		7.5		7.5		9.7	
Range	56.0-98.9		65.0-65.0		56.0-98.9		57.0-93.0		50.1-77.1		50.1-93.0	
N	24	(100.0)	1	(100.0)	25	(100.0)	55	(100.0)	28	(100.0)	83	(100.0)
Height (cm):												
Mean	174.2		156.0		173.5		176.1		164.4		172.2	
SD	5.9		0.0		6.8		5.8		5.4		7.9	
Range	162.0-188.0		156.0-156.0		156.0-188.0		163.5-190.0		156.5-176.0		156.5-190.0	
N	24	(100.0)	1	(100.0)	25	(100.0)	55	(100.0)	28	(100.0)	83	(100.0)

Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 07SEP2006 (07:01)

	1200mg			maraviroc Only		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
Number (%) of Subjects	9	0	9	205	57	262
Age (years):						
18-44	9 (100.0)		9 (100.0)	194 (94.6)	54 (94.7)	248 (94.7)
45-64	0		0	11 (5.4)	3 (5.3)	14 (5.3)
Mean	30.0		30.0	30.2	30.6	30.3
SD	5.7		5.7	7.4	8.8	7.7
Range	22-41		22-41	19-54	19-54	19-54
Race:						
WHITE	8 (88.9)		8 (88.9)	137 (66.8)	39 (68.4)	176 (67.2)
BLACK	1 (11.1)		1 (11.1)	4 (2.0)	1 (1.8)	5 (1.9)
ASIAN	0		0	63 (30.7)	17 (29.8)	80 (30.5)
OTHER	0		0	1 (0.5)	0	1 (0.4)
Weight (kg):						
Mean	77.5		77.5	73.9	60.4	71.0
SD	7.4		7.4	9.5	8.5	10.8
Range	68.9-92.2		68.9-92.2	52.0-100.1	46.0-79.5	46.0-100.1
N	9 (100.0)		9 (100.0)	205 (100.0)	57 (100.0)	262 (100.0)
Height (cm):						
Mean	175.3		175.3	176.1	162.9	173.2
SD	6.3		6.3	6.7	6.3	8.6
Range	166.1-186.0		166.1-186.0	159.5-198.0	149.0-178.0	149.0-198.0
N	9 (100.0)		9 (100.0)	205 (100.0)	57 (100.0)	262 (100.0)

Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 07SEP2006 (07:01)

	maraviroc + Interactant						Interactant					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
Number (%) of Subjects	36		1		37		54		38		92	
Age (years):												
18-44	25	(69.4)	1	(100.0)	26	(70.3)	48	(88.9)	36	(94.7)	84	(91.3)
45-64	11	(30.6)	0		11	(29.7)	6	(11.1)	2	(5.3)	8	(8.7)
Mean	40.8		44.0		40.9		31.0		31.2		31.1	
SD	7.4		0.0		7.3		8.8		9.2		8.9	
Range	29-56		44-44		29-56		19-54		19-53		19-54	
Race:												
WHITE	34	(94.4)	0		34	(91.9)	50	(92.6)	36	(94.7)	86	(93.5)
BLACK	1	(2.8)	1	(100.0)	2	(5.4)	2	(3.7)	1	(2.6)	3	(3.3)
ASIAN	0		0		0		1	(1.9)	1	(2.6)	2	(2.2)
OTHER	1	(2.8)	0		1	(2.7)	1	(1.9)	0		1	(1.1)
Weight (kg):												
Mean	75.1		78.0		75.2		74.7		62.1		69.5	
SD	9.0		0.0		8.8		7.9		8.0		10.0	
Range	56.0-96.6		78.0-78.0		56.0-96.6		57.0-91.1		50.1-77.3		50.1-91.1	
N	36	(100.0)	1	(100.0)	37	(100.0)	54	(100.0)	38	(100.0)	92	(100.0)
Height (cm):												
Mean	178.1		164.0		177.7		175.9		163.9		171.0	
SD	7.7		0.0		7.9		5.7		6.0		8.3	
Range	163.0-206.0		164.0-164.0		163.0-206.0		163.5-190.0		154.0-178.0		154.0-190.0	
N	36	(100.0)	1	(100.0)	37	(100.0)	54	(100.0)	38	(100.0)	92	(100.0)

Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 07SEP2006 (07:01)

	Placebo			<100mg unit dose		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
Number (%) of Subjects	34	23	57	19	0	19
Age (years):						
18-44	34 (100.0)	21 (91.3)	55 (96.5)	19 (100.0)		19 (100.0)
45-64	0	2 (8.7)	2 (3.5)	0		0
Mean	29.6	35.8	32.1	28.4		28.4
SD	7.8	6.5	7.8	6.4		6.4
Range	18-44	18-45	18-45	19-40		19-40
Race:						
WHITE	32 (94.1)	23 (100.0)	55 (96.5)	17 (89.5)		17 (89.5)
BLACK	1 (2.9)	0	1 (1.8)	2 (10.5)		2 (10.5)
ASIAN	0	0	0	0		0
HISPANIC	0	0	0	0		0
OTHER	1 (2.9)	0	1 (1.8)	0		0
Weight (kg):						
Mean	76.1	64.2	71.3	75.6		75.6
SD	9.0	6.5	10.0	8.2		8.2
Range	60.3-92.7	51.7-77.6	51.7-92.7	59.2-89.0		59.2-89.0
N	34 (100.0)	23 (100.0)	57 (100.0)	19 (100.0)		19 (100.0)
Height (cm):						
Mean	177.6	164.2	172.2	177.3		177.3
SD	6.4	5.4	8.9	6.3		6.3
Range	164.0-188.0	154.0-177.0	154.0-188.0	162.5-188.0		162.5-188.0
N	34 (100.0)	23 (100.0)	57 (100.0)	19 (100.0)		19 (100.0)

Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.

	100mg BID						150mg BID					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
Number (%) of Subjects	117		32		149		6		6		12	
Age (years):												
18-44	116	(99.1)	28	(87.5)	144	(96.6)	6	(100.0)	6	(100.0)	12	(100.0)
45-64	1	(0.9)	4	(12.5)	5	(3.4)	0		0		0	
Mean	30.0		36.3		31.4		28.5		36.8		32.7	
SD	7.0		7.5		7.6		6.0		6.5		7.4	
Range	18-45		19-52		18-52		22-37		25-43		22-43	
Race:												
WHITE	107	(91.5)	31	(96.9)	138	(92.6)	5	(83.3)	6	(100.0)	11	(91.7)
BLACK	5	(4.3)	1	(3.1)	6	(4.0)	0		0		0	
ASIAN	3	(2.6)	0		3	(2.0)	0		0		0	
HISPANIC	0		0		0		0		0		0	
OTHER	2	(1.7)	0		2	(1.3)	1	(16.7)	0		1	(8.3)
Weight (kg):												
Mean	75.3		64.1		72.9		74.8		70.5		72.7	
SD	8.4		8.6		9.6		16.9		6.4		12.4	
Range	59.0-109.3		50.4-80.7		50.4-109.3		55.0-98.0		63.0-79.0		55.0-98.0	
N	117	(100.0)	32	(100.0)	149	(100.0)	6	(100.0)	6	(100.0)	12	(100.0)
Height (cm):												
Mean	177.3		164.1		174.4		175.5		166.7		171.1	
SD	6.1		4.6		8.0		10.6		6.0		9.4	
Range	166.0-198.0		154.0-173.5		154.0-198.0		163.0-193.0		160.0-176.0		160.0-193.0	
N	117	(100.0)	32	(100.0)	149	(100.0)	6	(100.0)	6	(100.0)	12	(100.0)

Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.
Date of Table Generation: 15AUG2006 (10:24)

	300mg BID						600mg QD					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
Number (%) of Subjects	60		21		81		18		0		18	
Age (years):												
18-44	60	(100.0)	21	(100.0)	81	(100.0)	18	(100.0)			18	(100.0)
45-64	0		0		0		0				0	
Mean	28.4		34.8		30.0		26.5				26.5	
SD	6.7		9.2		7.9		4.3				4.3	
Range	18-44		19-44		18-44		21-36				21-36	
Race:												
WHITE	34	(56.7)	18	(85.7)	52	(64.2)	17	(94.4)			17	(94.4)
BLACK	4	(6.7)	1	(4.8)	5	(6.2)	1	(5.6)			1	(5.6)
ASIAN	21	(35.0)	2	(9.5)	23	(28.4)	0				0	
HISPANIC	0		0		0		0				0	
OTHER	1	(1.7)	0		1	(1.2)	0				0	
Weight (kg):												
Mean	74.5		61.7		71.2		75.3				75.3	
SD	9.6		7.9		10.8		8.2				8.2	
Range	53.5-99.3		50.1-78.0		50.1-99.3		62.2-90.7				62.2-90.7	
N	60	(100.0)	21	(100.0)	81	(100.0)	18	(100.0)			18	(100.0)
Height (cm):												
Mean	175.8		160.0		171.7		179.0				179.0	
SD	6.7		4.9		9.4		6.6				6.6	
Range	161.0-191.0		151.3-171.0		151.3-191.0		165.0-188.0				165.0-188.0	
N	60	(100.0)	21	(100.0)	81	(100.0)	18	(100.0)			18	(100.0)

Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.
Date of Table Generation: 15AUG2006 (10:24)

	600mg BID						900mg QD					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
Number (%) of Subjects	9		8		17		5		4		9	
Age (years):												
18-44	9	(100.0)	8	(100.0)	17	(100.0)	5	(100.0)	4	(100.0)	9	(100.0)
45-64	0		0		0		0		0		0	
Mean	25.7		30.6		28.0		24.4		29.3		26.6	
SD	8.3		9.2		8.8		5.5		10.8		8.1	
Range	18-42		19-44		18-44		19-33		18-42		18-42	
Race:												
WHITE	9	(100.0)	8	(100.0)	17	(100.0)	5	(100.0)	4	(100.0)	9	(100.0)
BLACK	0		0		0		0		0		0	
ASIAN	0		0		0		0		0		0	
HISPANIC	0		0		0		0		0		0	
OTHER	0		0		0		0		0		0	
Weight (kg):												
Mean	77.0		60.1		69.0		71.6		70.5		71.1	
SD	10.1		5.9		11.9		7.7		11.0		8.7	
Range	61.6-88.9		50.1-66.1		50.1-88.9		61.3-79.4		62.5-86.0		61.3-86.0	
N	9	(100.0)	8	(100.0)	17	(100.0)	5	(100.0)	4	(100.0)	9	(100.0)
Height (cm):												
Mean	178.1		161.0		170.0		179.0		165.1		172.9	
SD	5.2		7.8		10.8		3.4		5.5		8.4	
Range	168.0-184.0		152.0-175.0		152.0-184.0		176.0-184.0		160.0-173.0		160.0-184.0	
N	9	(100.0)	8	(100.0)	17	(100.0)	5	(100.0)	4	(100.0)	9	(100.0)

Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.

Date of Table Generation: 15AUG2006 (10:24)

	900mg BID						1200mg QD					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
Number (%) of Subjects	4		4		8		5		4		9	
Age (years):												
18-44	4	(100.0)	4	(100.0)	8	(100.0)	5	(100.0)	4	(100.0)	9	(100.0)
45-64	0		0		0		0		0		0	
Mean	27.8		25.5		26.6		24.4		29.3		26.6	
SD	9.9		7.3		8.2		5.5		10.8		8.1	
Range	19-42		19-36		19-42		19-33		18-42		18-42	
Race:												
WHITE	4	(100.0)	4	(100.0)	8	(100.0)	5	(100.0)	4	(100.0)	9	(100.0)
BLACK	0		0		0		0		0		0	
ASIAN	0		0		0		0		0		0	
HISPANIC	0		0		0		0		0		0	
OTHER	0		0		0		0		0		0	
Weight (kg):												
Mean	82.3		62.8		72.5		71.6		70.5		71.1	
SD	8.6		3.2		12.0		7.7		11.0		8.7	
Range	70.6-88.9		58.4-66.1		58.4-88.9		61.3-79.4		62.5-86.0		61.3-86.0	
N	4	(100.0)	4	(100.0)	8	(100.0)	5	(100.0)	4	(100.0)	9	(100.0)
Height (cm):												
Mean	179.1		167.0		173.1		179.0		165.1		172.9	
SD	4.4		5.6		8.0		3.4		5.5		8.4	
Range	173.0-183.5		162.0-175.0		162.0-183.5		176.0-184.0		160.0-173.0		160.0-184.0	
N	4	(100.0)	4	(100.0)	8	(100.0)	5	(100.0)	4	(100.0)	9	(100.0)

Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.
Date of Table Generation: 15AUG2006 (10:24)

	maraviroc Only						maraviroc + Interactant					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
Number (%) of Subjects	230		67		297		139		51		190	
Age (years):												
18-44	229	(99.6)	63	(94.0)	292	(98.3)	137	(98.6)	50	(98.0)	187	(98.4)
45-64	1	(0.4)	4	(6.0)	5	(1.7)	2	(1.4)	1	(2.0)	3	(1.6)
Mean	28.9		34.8		30.3		29.3		33.7		30.5	
SD	6.8		8.5		7.6		7.0		7.6		7.4	
Range	18-45		18-52		18-52		18-45		19-45		18-45	
Race:												
WHITE	190	(82.6)	63	(94.0)	253	(85.2)	105	(75.5)	46	(90.2)	151	(79.5)
BLACK	12	(5.2)	2	(3.0)	14	(4.7)	8	(5.8)	2	(3.9)	10	(5.3)
ASIAN	24	(10.4)	2	(3.0)	26	(8.8)	24	(17.3)	2	(3.9)	26	(13.7)
HISPANIC	0		0		0		0		1	(2.0)	1	(0.5)
OTHER	4	(1.7)	0		4	(1.3)	2	(1.4)	0		2	(1.1)
Weight (kg):												
Mean	75.1		64.2		72.6		75.8		65.5		73.0	
SD	9.0		8.4		9.9		9.2		8.0		10.0	
Range	53.5-109.3		50.1-86.0		50.1-109.3		55.0-109.3		50.4-80.7		50.4-109.3	
N	230	(100.0)	67	(100.0)	297	(100.0)	139	(100.0)	51	(100.0)	190	(100.0)
Height (cm):												
Mean	177.0		163.2		173.9		176.7		164.1		173.3	
SD	6.4		5.4		8.4		6.8		5.0		8.4	
Range	161.0-198.0		151.3-176.0		151.3-198.0		163.0-198.0		151.3-176.0		151.3-198.0	
N	230	(100.0)	67	(100.0)	297	(100.0)	139	(100.0)	51	(100.0)	190	(100.0)

Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.

Date of Table Generation: 15AUG2006 (10:24)

Table 1.3.2
Maraviroc Summary of Clinical Safety
Demographic Characteristics - Multiple Dose - Phase 1

	Interactant					
	MALE		FEMALE		TOTAL	
Number (%) of Subjects	13		25		38	
Age (years):						
18-44	12	(92.3)	24	(96.0)	36	(94.7)
45-64	1	(7.7)	1	(4.0)	2	(5.3)
Mean	30.8		34.7		33.4	
SD	7.5		6.8		7.2	
Range	22-45		21-45		21-45	
Race:						
WHITE	13	(100.0)	25	(100.0)	38	(100.0)
BLACK	0		0		0	
ASIAN	0		0		0	
HISPANIC	0		0		0	
OTHER	0		0		0	
Weight (kg):						
Mean	78.6		65.1		69.7	
SD	6.5		6.2		9.0	
Range	70.0-91.3		54.7-76.0		54.7-91.3	
N	13	(100.0)	25	(100.0)	38	(100.0)
Height (cm):						
Mean	177.3		164.4		168.8	
SD	6.1		4.5		8.0	
Range	171.0-191.0		154.0-171.0		154.0-191.0	
N	13	(100.0)	25	(100.0)	38	(100.0)

Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.
Date of Table Generation: 15AUG2006 (10:24)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Number of Subjects Evaluable for AE	107	77	115	151	25	83	9	262
Number of Subjects Experiencing Events	20	13	35	53	17	38	9	135
Number of Events	29	14	43	77	34	51	31	250
EAR AND LABYRINTH DISORDERS	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Tinnitus	0	0	0	0	0	0	1 (11.1)	1 (0.4)
EYE DISORDERS	0	0	0	4 (2.6)	2 (8.0)	2 (2.4)	5 (55.6)	13 (5.0)
Conjunctival hyperaemia	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Dry eye	0	0	0	0	1 (4.0)	0	2 (22.2)	3 (1.1)
Eyelid oedema	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Eyelid pain	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Keratitis	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Photophobia	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Vision blurred	0	0	0	1 (0.7)	1 (4.0)	2 (2.4)	2 (22.2)	6 (2.3)
GASTROINTESTINAL DISORDERS	7 (6.5)	3 (3.9)	11 (9.6)	11 (7.3)	7 (28.0)	11 (13.3)	3 (33.3)	42 (16.0)
Abdominal discomfort	1 (0.9)	0	0	1 (0.7)	0	1 (1.2)	0	2 (0.8)
Abdominal pain	3 (2.8)	0	0	0	1 (4.0)	0	0	1 (0.4)
Abdominal pain upper	0	0	1 (0.9)	1 (0.7)	0	1 (1.2)	0	3 (1.1)
Aphthous stomatitis	0	0	0	0	0	0	0	0
Constipation	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Diarrhoea	0	0	1 (0.9)	0	0	0	1 (11.1)	2 (0.8)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:15)

Table 1.4.1.1
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events (All Causality) - Single Dose - Phase 1

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Number of Subjects Evaluable for AE	37	92	236	299
Number of Subjects Experiencing Events	7	21	129	142
Number of Events	7	31	236	257
EAR AND LABYRINTH DISORDERS	0	0	1 (0.4)	1 (0.3)
Tinnitus	0	0	1 (0.4)	1 (0.3)
EYE DISORDERS	0	0	13 (5.5)	13 (4.3)
Conjunctival hyperaemia	0	0	1 (0.4)	1 (0.3)
Dry eye	0	0	3 (1.3)	3 (1.0)
Eyelid oedema	0	0	1 (0.4)	1 (0.3)
Eyelid pain	0	0	1 (0.4)	1 (0.3)
Keratitis	0	0	1 (0.4)	1 (0.3)
Photophobia	0	0	1 (0.4)	1 (0.3)
Vision blurred	0	0	6 (2.5)	6 (2.0)
GASTROINTESTINAL DISORDERS	0	8 (8.7)	40 (16.9)	42 (14.0)
Abdominal discomfort	0	1 (1.1)	2 (0.8)	2 (0.7)
Abdominal pain	0	0	1 (0.4)	1 (0.3)
Abdominal pain upper	0	0	3 (1.3)	3 (1.0)
Aphthous stomatitis	0	1 (1.1)	0	0
Constipation	0	0	1 (0.4)	1 (0.3)
Diarrhoea	0	2 (2.2)	2 (0.8)	2 (0.7)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:15)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Dry mouth	0	1 (1.3)	1 (0.9)	1 (0.7)	1 (4.0)	2 (2.4)	2 (22.2)	8 (3.1)
Dyspepsia	0	0	2 (1.7)	0	2 (8.0)	0	0	4 (1.5)
Flatulence	0	0	2 (1.7)	3 (2.0)	0	1 (1.2)	0	6 (2.3)
Frequent bowel movements	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Haemorrhoids	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Nausea	3 (2.8)	2 (2.6)	3 (2.6)	3 (2.0)	1 (4.0)	4 (4.8)	0	10 (3.8)
Rectal haemorrhage	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Salivary hypersecretion	0	0	0	0	0	1 (1.2)	0	1 (0.4)
Toothache	0	0	0	0	1 (4.0)	1 (1.2)	0	2 (0.8)
Vomiting	0	0	0	1 (0.7)	0	1 (1.2)	0	2 (0.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6 (5.6)	4 (5.2)	5 (4.3)	19 (12.6)	8 (32.0)	7 (8.4)	5 (55.6)	47 (17.9)
Asthenia	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Catheter site bruise	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Fatigue	6 (5.6)	4 (5.2)	5 (4.3)	2 (1.3)	4 (16.0)	7 (8.4)	5 (55.6)	26 (9.9)
Feeling hot	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Venipuncture site pain	0	0	0	2 (1.3)	0	0	0	2 (0.8)
Vessel puncture site bruise	0	0	0	14 (9.3)	2 (8.0)	0	0	16 (6.1)
INFECTIONS AND INFESTATIONS	4 (3.7)	2 (2.6)	3 (2.6)	2 (1.3)	4 (16.0)	1 (1.2)	0	12 (4.6)
Bronchitis	0	0	0	0	0	1 (1.2)	0	1 (0.4)
Cystitis	3 (2.8)	0	0	0	0	0	0	0
Gastroenteritis	1 (0.9)	1 (1.3)	0	0	0	0	0	1 (0.4)
Herpes simplex	0	0	0	0	0	0	0	0
Nasopharyngitis	0	0	1 (0.9)	1 (0.7)	1 (4.0)	0	0	3 (1.1)
Peritonsillar abscess	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Pharyngitis	0	1 (1.3)	0	0	0	0	0	1 (0.4)
Pyelonephritis	0	0	1 (0.9)	0	0	0	0	1 (0.4)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:15)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Dry mouth	0	0	7 (3.0)	8 (2.7)
Dyspepsia	0	0	4 (1.7)	4 (1.3)
Flatulence	0	2 (2.2)	6 (2.5)	6 (2.0)
Frequent bowel movements	0	0	1 (0.4)	1 (0.3)
Haemorrhoids	0	0	1 (0.4)	1 (0.3)
Nausea	0	3 (3.3)	9 (3.8)	10 (3.3)
Rectal haemorrhage	0	0	1 (0.4)	1 (0.3)
Salivary hypersecretion	0	0	1 (0.4)	1 (0.3)
Toothache	0	0	2 (0.8)	2 (0.7)
Vomiting	0	0	2 (0.8)	2 (0.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	43 (18.2)	47 (15.7)
Asthenia	0	0	1 (0.4)	1 (0.3)
Catheter site bruise	0	0	1 (0.4)	1 (0.3)
Fatigue	0	0	22 (9.3)	26 (8.7)
Feeling hot	0	0	1 (0.4)	1 (0.3)
Venipuncture site pain	0	0	2 (0.8)	2 (0.7)
Vessel puncture site bruise	0	0	16 (6.8)	16 (5.4)
INFECTIONS AND INFESTATIONS	1 (2.7)	3 (3.3)	10 (4.2)	13 (4.3)
Bronchitis	0	0	1 (0.4)	1 (0.3)
Cystitis	0	1 (1.1)	0	0
Gastroenteritis	0	0	0	1 (0.3)
Herpes simplex	1 (2.7)	1 (1.1)	0	1 (0.3)
Nasopharyngitis	0	1 (1.1)	3 (1.3)	3 (1.0)
Peritonsillar abscess	0	0	1 (0.4)	1 (0.3)
Pharyngitis	0	0	0	1 (0.3)
Pyelonephritis	0	0	1 (0.4)	1 (0.3)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:15)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Tonsillitis	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Upper respiratory tract infection	0	0	0	1 (0.7)	2 (8.0)	0	0	3 (1.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	2 (1.7)	1 (0.7)	1 (4.0)	0	0	4 (1.5)
Alcohol poisoning	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Contusion	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Excoriation	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Joint sprain	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Sunburn	0	0	0	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.9)	0	0	3 (2.0)	1 (4.0)	0	1 (11.1)	5 (1.9)
Back pain	1 (0.9)	0	0	1 (0.7)	0	0	1 (11.1)	2 (0.8)
Chest wall pain	0	0	0	0	0	0	0	0
Myalgia	0	0	0	2 (1.3)	0	0	1 (11.1)	3 (1.1)
Pain in extremity	0	0	0	0	1 (4.0)	0	0	1 (0.4)
NERVOUS SYSTEM DISORDERS	7 (6.5)	5 (6.5)	9 (7.8)	22 (14.6)	7 (28.0)	18 (21.7)	5 (55.6)	56 (21.4)
Dizziness	3 (2.8)	0	2 (1.7)	3 (2.0)	2 (8.0)	3 (3.6)	2 (22.2)	12 (4.6)
Dizziness postural	2 (1.9)	0	1 (0.9)	0	1 (4.0)	8 (9.6)	0	9 (3.4)
Dysgeusia	1 (0.9)	0	0	0	0	0	0	0
Head discomfort	0	0	0	0	0	1 (1.2)	0	1 (0.4)
Headache	3 (2.8)	3 (3.9)	6 (5.2)	17 (11.3)	3 (12.0)	7 (8.4)	3 (33.3)	35 (13.4)
Sciatica	0	1 (1.3)	0	0	0	0	0	1 (0.4)
Somnolence	0	1 (1.3)	1 (0.9)	3 (2.0)	1 (4.0)	0	0	4 (1.5)
Syncope	0	0	0	1 (0.7)	0	0	0	1 (0.4)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:15)

Table 1.4.1.1
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events (All Causality) - Single Dose - Phase 1

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Tonsillitis	0	0	1 (0.4)	1 (0.3)
Upper respiratory tract infection	0	0	3 (1.3)	3 (1.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (1.1)	4 (1.7)	4 (1.3)
Alcohol poisoning	0	0	1 (0.4)	1 (0.3)
Contusion	0	0	1 (0.4)	1 (0.3)
Excoriation	0	0	1 (0.4)	1 (0.3)
Joint sprain	0	0	1 (0.4)	1 (0.3)
Sunburn	0	1 (1.1)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (1.1)	5 (2.1)	5 (1.7)
Back pain	0	0	2 (0.8)	2 (0.7)
Chest wall pain	0	1 (1.1)	0	0
Myalgia	0	0	3 (1.3)	3 (1.0)
Pain in extremity	0	0	1 (0.4)	1 (0.3)
NERVOUS SYSTEM DISORDERS	5 (13.5)	10 (10.9)	55 (23.3)	61 (20.4)
Dizziness	0	2 (2.2)	12 (5.1)	12 (4.0)
Dizziness postural	0	3 (3.3)	9 (3.8)	9 (3.0)
Dysgeusia	0	0	0	0
Head discomfort	0	0	1 (0.4)	1 (0.3)
Headache	5 (13.5)	7 (7.6)	33 (14.0)	40 (13.4)
Sciatica	0	0	0	1 (0.3)
Somnolence	0	0	4 (1.7)	4 (1.3)
Syncope	0	0	1 (0.4)	1 (0.3)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:15)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Abortion spontaneous	0	0	1 (0.9)	0	0	0	0	1 (0.4)
PSYCHIATRIC DISORDERS	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Mood altered	0	0	0	1 (0.7)	0	0	0	1 (0.4)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Menstruation irregular	0	0	0	1 (0.7)	0	0	0	1 (0.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	2 (1.7)	3 (2.0)	4 (16.0)	0	1 (11.1)	10 (3.8)
Cough	0	0	0	1 (0.7)	1 (4.0)	0	0	2 (0.8)
Nasal congestion	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Pharyngolaryngeal pain	0	0	2 (1.7)	2 (1.3)	3 (12.0)	0	0	7 (2.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	2 (1.7)	2 (1.3)	0	0	0	3 (1.1)
Night sweats	0	0	0	0	0	0	0	0
Rash	0	0	2 (1.7)	2 (1.3)	0	0	0	3 (1.1)
SURGICAL AND MEDICAL PROCEDURES	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Venipuncture	0	0	0	1 (0.7)	0	0	0	1 (0.4)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:15)

Table 1.4.1.1
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events (All Causality) - Single Dose - Phase 1

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	1 (0.4)	1 (0.3)
Abortion spontaneous	0	0	1 (0.4)	1 (0.3)
PSYCHIATRIC DISORDERS	0	0	1 (0.4)	1 (0.3)
Mood altered	0	0	1 (0.4)	1 (0.3)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	1 (0.4)	1 (0.3)
Menstruation irregular	0	0	1 (0.4)	1 (0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	10 (4.2)	10 (3.3)
Cough	0	0	2 (0.8)	2 (0.7)
Nasal congestion	0	0	1 (0.4)	1 (0.3)
Pharyngolaryngeal pain	0	0	7 (3.0)	7 (2.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (2.7)	0	3 (1.3)	4 (1.3)
Night sweats	1 (2.7)	0	0	1 (0.3)
Rash	0	0	3 (1.3)	3 (1.0)
SURGICAL AND MEDICAL PROCEDURES	0	0	1 (0.4)	1 (0.3)
Venipuncture	0	0	1 (0.4)	1 (0.3)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:15)

Table 1.4.1.1
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events (All Causality) - Single Dose - Phase 1

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
VASCULAR DISORDERS	2 (1.9)	0	5 (4.3)	2 (1.3)	0	9 (10.8)	7 (77.8)	23 (8.8)
Flushing	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Haematoma	0	0	2 (1.7)	1 (0.7)	0	0	0	3 (1.1)
Hot flush	2 (1.9)	0	2 (1.7)	0	0	0	2 (22.2)	4 (1.5)
Orthostatic hypotension	0	0	1 (0.9)	1 (0.7)	0	9 (10.8)	4 (44.4)	15 (5.7)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:15)

Table 1.4.1.1
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events (All Causality) - Single Dose - Phase 1

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
VASCULAR DISORDERS	0	3 (3.3)	23 (9.7)	23 (7.7)
Flushing	0	0	1 (0.4)	1 (0.3)
Haematoma	0	1 (1.1)	3 (1.3)	3 (1.0)
Hot flush	0	0	4 (1.7)	4 (1.3)
Orthostatic hypotension	0	2 (2.2)	15 (6.4)	15 (5.0)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:15)

Table 1.4.1.2
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events (Treatment Related) - Single Dose - Phase 1

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Number of Subjects Evaluable for AE	107	77	115	151	25	83	9	262
Number of Subjects Experiencing Events	16	9	21	33	12	36	8	100
Number of Events	22	10	25	48	18	47	29	177
EAR AND LABYRINTH DISORDERS	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Tinnitus	0	0	0	0	0	0	1 (11.1)	1 (0.4)
EYE DISORDERS	0	0	0	3 (2.0)	1 (4.0)	2 (2.4)	4 (44.4)	10 (3.8)
Conjunctival hyperaemia	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Dry eye	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Eyelid oedema	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Eyelid pain	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Photophobia	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Vision blurred	0	0	0	1 (0.7)	1 (4.0)	2 (2.4)	2 (22.2)	6 (2.3)
GASTROINTESTINAL DISORDERS	7 (6.5)	2 (2.6)	7 (6.1)	9 (6.0)	6 (24.0)	10 (12.0)	2 (22.2)	33 (12.6)
Abdominal discomfort	1 (0.9)	0	0	1 (0.7)	0	1 (1.2)	0	2 (0.8)
Abdominal pain	3 (2.8)	0	0	0	1 (4.0)	0	0	1 (0.4)
Abdominal pain upper	0	0	1 (0.9)	1 (0.7)	0	1 (1.2)	0	3 (1.1)
Diarrhoea	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Dry mouth	0	1 (1.3)	1 (0.9)	1 (0.7)	1 (4.0)	2 (2.4)	2 (22.2)	8 (3.1)
Dyspepsia	0	0	0	0	2 (8.0)	0	0	2 (0.8)
Flatulence	0	0	2 (1.7)	3 (2.0)	0	1 (1.2)	0	6 (2.3)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:16)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Number of Subjects Evaluable for AE	37	92	236	299
Number of Subjects Experiencing Events	7	19	95	107
Number of Events	7	24	167	184
EAR AND LABYRINTH DISORDERS	0	0	1 (0.4)	1 (0.3)
Tinnitus	0	0	1 (0.4)	1 (0.3)
EYE DISORDERS	0	0	10 (4.2)	10 (3.3)
Conjunctival hyperaemia	0	0	1 (0.4)	1 (0.3)
Dry eye	0	0	1 (0.4)	1 (0.3)
Eyelid oedema	0	0	1 (0.4)	1 (0.3)
Eyelid pain	0	0	1 (0.4)	1 (0.3)
Photophobia	0	0	1 (0.4)	1 (0.3)
Vision blurred	0	0	6 (2.5)	6 (2.0)
GASTROINTESTINAL DISORDERS	0	8 (8.7)	31 (13.1)	33 (11.0)
Abdominal discomfort	0	1 (1.1)	2 (0.8)	2 (0.7)
Abdominal pain	0	0	1 (0.4)	1 (0.3)
Abdominal pain upper	0	0	3 (1.3)	3 (1.0)
Diarrhoea	0	2 (2.2)	1 (0.4)	1 (0.3)
Dry mouth	0	0	7 (3.0)	8 (2.7)
Dyspepsia	0	0	2 (0.8)	2 (0.7)
Flatulence	0	2 (2.2)	6 (2.5)	6 (2.0)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:16)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Frequent bowel movements	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Nausea	3 (2.8)	1 (1.3)	2 (1.7)	3 (2.0)	1 (4.0)	4 (4.8)	0	9 (3.4)
Salivary hypersecretion	0	0	0	0	0	1 (1.2)	0	1 (0.4)
Vomiting	0	0	0	1 (0.7)	0	1 (1.2)	0	2 (0.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6 (5.6)	4 (5.2)	4 (3.5)	3 (2.0)	5 (20.0)	7 (8.4)	5 (55.6)	27 (10.3)
Asthenia	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Fatigue	6 (5.6)	4 (5.2)	4 (3.5)	2 (1.3)	4 (16.0)	7 (8.4)	5 (55.6)	25 (9.5)
Feeling hot	0	0	0	1 (0.7)	0	0	0	1 (0.4)
INFECTIONS AND INFESTATIONS	0	0	0	0	0	0	0	0
Herpes simplex	0	0	0	0	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Alcohol poisoning	0	0	0	0	1 (4.0)	0	0	1 (0.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	0	2 (1.3)	0	0	1 (11.1)	3 (1.1)
Back pain	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Myalgia	0	0	0	2 (1.3)	0	0	1 (11.1)	3 (1.1)
NERVOUS SYSTEM DISORDERS	6 (5.6)	4 (5.2)	7 (6.1)	20 (13.2)	5 (20.0)	16 (19.3)	5 (55.6)	48 (18.3)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:16)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Frequent bowel movements	0	0	1 (0.4)	1 (0.3)
Nausea	0	3 (3.3)	8 (3.4)	9 (3.0)
Salivary hypersecretion	0	0	1 (0.4)	1 (0.3)
Vomiting	0	0	2 (0.8)	2 (0.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	23 (9.7)	27 (9.0)
Asthenia	0	0	1 (0.4)	1 (0.3)
Fatigue	0	0	21 (8.9)	25 (8.4)
Feeling hot	0	0	1 (0.4)	1 (0.3)
INFECTIONS AND INFESTATIONS	1 (2.7)	0	0	1 (0.3)
Herpes simplex	1 (2.7)	0	0	1 (0.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	1 (0.4)	1 (0.3)
Alcohol poisoning	0	0	1 (0.4)	1 (0.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	3 (1.3)	3 (1.0)
Back pain	0	0	1 (0.4)	1 (0.3)
Myalgia	0	0	3 (1.3)	3 (1.0)
NERVOUS SYSTEM DISORDERS	5 (13.5)	10 (10.9)	47 (19.9)	53 (17.7)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:16)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Dizziness	2 (1.9)	0	1 (0.9)	3 (2.0)	2 (8.0)	3 (3.6)	2 (22.2)	11 (4.2)
Dizziness postural	1 (0.9)	0	1 (0.9)	0	0	8 (9.6)	0	8 (3.1)
Dysgeusia	1 (0.9)	0	0	0	0	0	0	0
Head discomfort	0	0	0	0	0	1 (1.2)	0	1 (0.4)
Headache	3 (2.8)	3 (3.9)	5 (4.3)	16 (10.6)	2 (8.0)	5 (6.0)	3 (33.3)	30 (11.5)
Somnolence	0	1 (1.3)	1 (0.9)	3 (2.0)	1 (4.0)	0	0	4 (1.5)
PSYCHIATRIC DISORDERS	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Mood altered	0	0	0	1 (0.7)	0	0	0	1 (0.4)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Menstruation irregular	0	0	0	1 (0.7)	0	0	0	1 (0.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	1 (0.7)	0	0	1 (11.1)	2 (0.8)
Cough	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Nasal congestion	0	0	0	0	0	0	1 (11.1)	1 (0.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	2 (1.7)	2 (1.3)	0	0	0	3 (1.1)
Night sweats	0	0	0	0	0	0	0	0
Rash	0	0	2 (1.7)	2 (1.3)	0	0	0	3 (1.1)
VASCULAR DISORDERS	2 (1.9)	0	3 (2.6)	1 (0.7)	0	9 (10.8)	7 (77.8)	20 (7.6)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:16)

Table 1.4.1.2
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events (Treatment Related) - Single Dose - Phase 1

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Dizziness	0	2 (2.2)	11 (4.7)	11 (3.7)
Dizziness postural	0	3 (3.3)	8 (3.4)	8 (2.7)
Dysgeusia	0	0	0	0
Head discomfort	0	0	1 (0.4)	1 (0.3)
Headache	5 (13.5)	7 (7.6)	28 (11.9)	35 (11.7)
Somnolence	0	0	4 (1.7)	4 (1.3)
PSYCHIATRIC DISORDERS	0	0	1 (0.4)	1 (0.3)
Mood altered	0	0	1 (0.4)	1 (0.3)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	1 (0.4)	1 (0.3)
Menstruation irregular	0	0	1 (0.4)	1 (0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	2 (0.8)	2 (0.7)
Cough	0	0	1 (0.4)	1 (0.3)
Nasal congestion	0	0	1 (0.4)	1 (0.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (2.7)	0	3 (1.3)	4 (1.3)
Night sweats	1 (2.7)	0	0	1 (0.3)
Rash	0	0	3 (1.3)	3 (1.0)
VASCULAR DISORDERS	0	2 (2.2)	20 (8.5)	20 (6.7)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:16)

Table 1.4.1.2
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events (Treatment Related) - Single Dose - Phase 1

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Flushing	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Hot flush	2 (1.9)	0	2 (1.7)	0	0	0	2 (22.2)	4 (1.5)
Orthostatic hypotension	0	0	1 (0.9)	1 (0.7)	0	9 (10.8)	4 (44.4)	15 (5.7)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:16)

Table 1.4.1.2
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events (Treatment Related) - Single Dose - Phase 1

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Flushing	0	0	1 (0.4)	1 (0.3)
Hot flush	0	0	4 (1.7)	4 (1.3)
Orthostatic hypotension	0	2 (2.2)	15 (6.4)	15 (5.0)

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (05:16)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Number of Subjects Evaluable for AE	107	77	115	151	25	83	9	262
Number of Subjects Experiencing Events at this severity	16	7	21	46	17	29	4	106
Number of Events at this severity	20	7	24	60	25	36	4	156
EAR AND LABYRINTH DISORDERS	0	0	0	0	0	0	0	0
Tinnitus	0	0	0	0	0	0	0	0
EYE DISORDERS	0	0	0	3 (2.0)	1 (4.0)	2 (2.4)	1 (11.1)	7 (2.7)
Conjunctival hyperaemia	0	0	0	0	0	0	0	0
Dry eye	0	0	0	0	1 (4.0)	0	1 (11.1)	2 (0.8)
Eyelid oedema	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Eyelid pain	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Keratitis	0	0	0	0	0	0	0	0
Photophobia	0	0	0	0	0	0	0	0
Vision blurred	0	0	0	1 (0.7)	0	2 (2.4)	0	3 (1.1)
GASTROINTESTINAL DISORDERS	5 (4.7)	2 (2.6)	7 (6.1)	9 (6.0)	4 (16.0)	9 (10.8)	1 (11.1)	29 (11.1)
Abdominal discomfort	1 (0.9)	0	0	1 (0.7)	0	1 (1.2)	0	2 (0.8)
Abdominal pain	1 (0.9)	0	0	0	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Number of Subjects Evaluable for AE	37	92	236	299
Number of Subjects Experiencing Events at this severity	5	20	102	111
Number of Events at this severity	5	29	149	161
EAR AND LABYRINTH DISORDERS	0	0	0	0
Tinnitus	0	0	0	0
EYE DISORDERS	0	0	7 (3.0)	7 (2.3)
Conjunctival hyperaemia	0	0	0	0
Dry eye	0	0	2 (0.8)	2 (0.7)
Eyelid oedema	0	0	1 (0.4)	1 (0.3)
Eyelid pain	0	0	1 (0.4)	1 (0.3)
Keratitis	0	0	0	0
Photophobia	0	0	0	0
Vision blurred	0	0	3 (1.3)	3 (1.0)
GASTROINTESTINAL DISORDERS	0	7 (7.6)	27 (11.4)	29 (9.7)
Abdominal discomfort	0	1 (1.1)	2 (0.8)	2 (0.7)
Abdominal pain	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Abdominal pain upper	0	0	1 (0.9)	1 (0.7)	0	1 (1.2)	0	3 (1.1)
Aphthous stomatitis	0	0	0	0	0	0	0	0
Constipation	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Diarrhoea	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Dry mouth	0	1 (1.3)	0	1 (0.7)	0	2 (2.4)	0	4 (1.5)
Dyspepsia	0	0	1 (0.9)	0	2 (8.0)	0	0	3 (1.1)
Flatulence	0	0	2 (1.7)	3 (2.0)	0	1 (1.2)	0	6 (2.3)
Frequent bowel movements	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Haemorrhoids	0	0	0	0	0	0	0	0
Nausea	3 (2.8)	1 (1.3)	2 (1.7)	2 (1.3)	0	4 (4.8)	0	7 (2.7)
Rectal haemorrhage	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Salivary hypersecretion	0	0	0	0	0	0	0	0
Toothache	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Vomiting	0	0	0	0	0	1 (1.2)	0	1 (0.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5 (4.7)	1 (1.3)	3 (2.6)	18 (11.9)	7 (28.0)	4 (4.8)	0	33 (12.6)
Asthenia	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Catheter site bruise	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Fatigue	5 (4.7)	1 (1.3)	3 (2.6)	1 (0.7)	3 (12.0)	4 (4.8)	0	12 (4.6)
Feeling hot	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Venipuncture site pain	0	0	0	2 (1.3)	0	0	0	2 (0.8)
Vessel puncture site bruise	0	0	0	14 (9.3)	2 (8.0)	0	0	16 (6.1)
INFECTIONS AND INFESTATIONS	1 (0.9)	1 (1.3)	0	1 (0.7)	2 (8.0)	1 (1.2)	0	5 (1.9)
Bronchitis	0	0	0	0	0	1 (1.2)	0	1 (0.4)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Abdominal pain upper	0	0	3 (1.3)	3 (1.0)
Aphthous stomatitis	0	0	0	0
Constipation	0	0	1 (0.4)	1 (0.3)
Diarrhoea	0	2 (2.2)	1 (0.4)	1 (0.3)
Dry mouth	0	0	3 (1.3)	4 (1.3)
Dyspepsia	0	0	3 (1.3)	3 (1.0)
Flatulence	0	2 (2.2)	6 (2.5)	6 (2.0)
Frequent bowel movements	0	0	1 (0.4)	1 (0.3)
Haemorrhoids	0	0	0	0
Nausea	0	3 (3.3)	6 (2.5)	7 (2.3)
Rectal haemorrhage	0	0	1 (0.4)	1 (0.3)
Salivary hypersecretion	0	0	0	0
Toothache	0	0	1 (0.4)	1 (0.3)
Vomiting	0	0	1 (0.4)	1 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	32 (13.6)	33 (11.0)
Asthenia	0	0	1 (0.4)	1 (0.3)
Catheter site bruise	0	0	1 (0.4)	1 (0.3)
Fatigue	0	0	11 (4.7)	12 (4.0)
Feeling hot	0	0	1 (0.4)	1 (0.3)
Venipuncture site pain	0	0	2 (0.8)	2 (0.7)
Vessel puncture site bruise	0	0	16 (6.8)	16 (5.4)
INFECTIONS AND INFESTATIONS	1 (2.7)	2 (2.2)	4 (1.7)	6 (2.0)
Bronchitis	0	0	1 (0.4)	1 (0.3)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Cystitis	1 (0.9)	0	0	0	0	0	0	0
Gastroenteritis	0	0	0	0	0	0	0	0
Herpes simplex	0	0	0	0	0	0	0	0
Nasopharyngitis	0	0	0	0	0	0	0	0
Peritonsillar abscess	0	0	0	0	0	0	0	0
Pharyngitis	0	1 (1.3)	0	0	0	0	0	1 (0.4)
Pyelonephritis	0	0	0	0	0	0	0	0
Tonsillitis	0	0	0	0	0	0	0	0
Upper respiratory tract infection	0	0	0	1 (0.7)	2 (8.0)	0	0	3 (1.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	2 (1.7)	1 (0.7)	1 (4.0)	0	0	4 (1.5)
Alcohol poisoning	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Contusion	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Excoriation	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Joint sprain	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Sunburn	0	0	0	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	0	2 (1.3)	1 (4.0)	0	0	3 (1.1)
Back pain	0	0	0	0	0	0	0	0
Chest wall pain	0	0	0	0	0	0	0	0
Myalgia	0	0	0	2 (1.3)	0	0	0	2 (0.8)
Pain in extremity	0	0	0	0	1 (4.0)	0	0	1 (0.4)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Cystitis	0	0	0	0
Gastroenteritis	0	0	0	0
Herpes simplex	1 (2.7)	1 (1.1)	0	1 (0.3)
Nasopharyngitis	0	1 (1.1)	0	0
Peritonsillar abscess	0	0	0	0
Pharyngitis	0	0	0	1 (0.3)
Pyelonephritis	0	0	0	0
Tonsillitis	0	0	0	0
Upper respiratory tract infection	0	0	3 (1.3)	3 (1.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (1.1)	4 (1.7)	4 (1.3)
Alcohol poisoning	0	0	1 (0.4)	1 (0.3)
Contusion	0	0	1 (0.4)	1 (0.3)
Excoriation	0	0	1 (0.4)	1 (0.3)
Joint sprain	0	0	1 (0.4)	1 (0.3)
Sunburn	0	1 (1.1)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (1.1)	3 (1.3)	3 (1.0)
Back pain	0	0	0	0
Chest wall pain	0	1 (1.1)	0	0
Myalgia	0	0	2 (0.8)	2 (0.7)
Pain in extremity	0	0	1 (0.4)	1 (0.3)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
NERVOUS SYSTEM DISORDERS	5 (4.7)	3 (3.9)	4 (3.5)	17 (11.3)	6 (24.0)	13 (15.7)	1 (11.1)	35 (13.4)
Dizziness	2 (1.9)	0	2 (1.7)	2 (1.3)	2 (8.0)	3 (3.6)	1 (11.1)	10 (3.8)
Dizziness postural	2 (1.9)	0	1 (0.9)	0	1 (4.0)	6 (7.2)	0	7 (2.7)
Dysgeusia	1 (0.9)	0	0	0	0	0	0	0
Head discomfort	0	0	0	0	0	1 (1.2)	0	1 (0.4)
Headache	2 (1.9)	2 (2.6)	2 (1.7)	13 (8.6)	2 (8.0)	4 (4.8)	0	19 (7.3)
Sciatica	0	0	0	0	0	0	0	0
Somnolence	0	1 (1.3)	0	3 (2.0)	1 (4.0)	0	0	3 (1.1)
Syncope	0	0	0	0	0	0	0	0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Abortion spontaneous	0	0	1 (0.9)	0	0	0	0	1 (0.4)
PSYCHIATRIC DISORDERS	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Mood altered	0	0	0	1 (0.7)	0	0	0	1 (0.4)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Menstruation irregular	0	0	0	1 (0.7)	0	0	0	1 (0.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	2 (1.7)	2 (1.3)	3 (12.0)	0	0	7 (2.7)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
NERVOUS SYSTEM DISORDERS	3 (8.1)	10 (10.9)	35 (14.8)	38 (12.7)
Dizziness	0	2 (2.2)	10 (4.2)	10 (3.3)
Dizziness postural	0	3 (3.3)	7 (3.0)	7 (2.3)
Dysgeusia	0	0	0	0
Head discomfort	0	0	1 (0.4)	1 (0.3)
Headache	3 (8.1)	7 (7.6)	18 (7.6)	22 (7.4)
Sciatica	0	0	0	0
Somnolence	0	0	3 (1.3)	3 (1.0)
Syncope	0	0	0	0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	1 (0.4)	1 (0.3)
Abortion spontaneous	0	0	1 (0.4)	1 (0.3)
PSYCHIATRIC DISORDERS	0	0	1 (0.4)	1 (0.3)
Mood altered	0	0	1 (0.4)	1 (0.3)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	1 (0.4)	1 (0.3)
Menstruation irregular	0	0	1 (0.4)	1 (0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	7 (3.0)	7 (2.3)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Cough	0	0	0	1 (0.7)	1 (4.0)	0	0	2 (0.8)
Nasal congestion	0	0	0	0	0	0	0	0
Pharyngolaryngeal pain	0	0	2 (1.7)	1 (0.7)	2 (8.0)	0	0	5 (1.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	1 (0.9)	1 (0.7)	0	0	0	1 (0.4)
Night sweats	0	0	0	0	0	0	0	0
Rash	0	0	1 (0.9)	1 (0.7)	0	0	0	1 (0.4)
SURGICAL AND MEDICAL PROCEDURES	0	0	0	0	0	0	0	0
Venipuncture	0	0	0	0	0	0	0	0
VASCULAR DISORDERS	2 (1.9)	0	2 (1.7)	1 (0.7)	0	4 (4.8)	1 (11.1)	8 (3.1)
Flushing	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Haematoma	0	0	1 (0.9)	1 (0.7)	0	0	0	2 (0.8)
Hot flush	2 (1.9)	0	0	0	0	0	0	0
Orthostatic hypotension	0	0	1 (0.9)	0	0	4 (4.8)	0	5 (1.9)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Cough	0	0	2 (0.8)	2 (0.7)
Nasal congestion	0	0	0	0
Pharyngolaryngeal pain	0	0	5 (2.1)	5 (1.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (2.7)	0	1 (0.4)	2 (0.7)
Night sweats	1 (2.7)	0	0	1 (0.3)
Rash	0	0	1 (0.4)	1 (0.3)
SURGICAL AND MEDICAL PROCEDURES	0	0	0	0
Venipuncture	0	0	0	0
VASCULAR DISORDERS	0	3 (3.3)	8 (3.4)	8 (2.7)
Flushing	0	0	1 (0.4)	1 (0.3)
Haematoma	0	1 (1.1)	2 (0.8)	2 (0.7)
Hot flush	0	0	0	0
Orthostatic hypotension	0	2 (2.2)	5 (2.1)	5 (1.7)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Number of Subjects Evaluable for AE	107	77	115	151	25	83	9	262
Number of Subjects Experiencing Events at this severity	7	7	15	11	6	14	7	52
Number of Events at this severity	8	7	17	13	9	15	18	79
EAR AND LABYRINTH DISORDERS	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Tinnitus	0	0	0	0	0	0	1 (11.1)	1 (0.4)
EYE DISORDERS	0	0	0	1 (0.7)	1 (4.0)	0	2 (22.2)	4 (1.5)
Conjunctival hyperaemia	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Dry eye	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Eyelid oedema	0	0	0	0	0	0	0	0
Eyelid pain	0	0	0	0	0	0	0	0
Keratitis	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Photophobia	0	0	0	0	0	0	0	0
Vision blurred	0	0	0	0	1 (4.0)	0	1 (11.1)	2 (0.8)
GASTROINTESTINAL DISORDERS	2 (1.9)	1 (1.3)	4 (3.5)	1 (0.7)	3 (12.0)	2 (2.4)	0	10 (3.8)
Abdominal discomfort	0	0	0	0	0	0	0	0
Abdominal pain	2 (1.9)	0	0	0	1 (4.0)	0	0	1 (0.4)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Number of Subjects Evaluable for AE	37	92	236	299
Number of Subjects Experiencing Events at this severity	2	2	49	54
Number of Events at this severity	2	2	72	81
EAR AND LABYRINTH DISORDERS	0	0	1 (0.4)	1 (0.3)
Tinnitus	0	0	1 (0.4)	1 (0.3)
EYE DISORDERS	0	0	4 (1.7)	4 (1.3)
Conjunctival hyperaemia	0	0	1 (0.4)	1 (0.3)
Dry eye	0	0	1 (0.4)	1 (0.3)
Eyelid oedema	0	0	0	0
Eyelid pain	0	0	0	0
Keratitis	0	0	1 (0.4)	1 (0.3)
Photophobia	0	0	0	0
Vision blurred	0	0	2 (0.8)	2 (0.7)
GASTROINTESTINAL DISORDERS	0	1 (1.1)	10 (4.2)	10 (3.3)
Abdominal discomfort	0	0	0	0
Abdominal pain	0	0	1 (0.4)	1 (0.3)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Abdominal pain upper	0	0	0	0	0	0	0	0
Aphthous stomatitis	0	0	0	0	0	0	0	0
Constipation	0	0	0	0	0	0	0	0
Diarrhoea	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Dry mouth	0	0	1 (0.9)	0	1 (4.0)	0	0	2 (0.8)
Dyspepsia	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Flatulence	0	0	0	0	0	0	0	0
Frequent bowel movements	0	0	0	0	0	0	0	0
Haemorrhoids	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Nausea	0	1 (1.3)	1 (0.9)	0	1 (4.0)	0	0	2 (0.8)
Rectal haemorrhage	0	0	0	0	0	0	0	0
Salivary hypersecretion	0	0	0	0	0	1 (1.2)	0	1 (0.4)
Toothache	0	0	0	0	0	1 (1.2)	0	1 (0.4)
Vomiting	0	0	0	1 (0.7)	0	0	0	1 (0.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.9)	3 (3.9)	2 (1.7)	0	1 (4.0)	3 (3.6)	2 (22.2)	11 (4.2)
Asthenia	0	0	0	0	0	0	0	0
Catheter site bruise	0	0	0	0	0	0	0	0
Fatigue	1 (0.9)	3 (3.9)	2 (1.7)	0	1 (4.0)	3 (3.6)	2 (22.2)	11 (4.2)
Feeling hot	0	0	0	0	0	0	0	0
Venipuncture site pain	0	0	0	0	0	0	0	0
Vessel puncture site bruise	0	0	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	2 (1.9)	1 (1.3)	2 (1.7)	1 (0.7)	2 (8.0)	0	0	6 (2.3)
Bronchitis	0	0	0	0	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Abdominal pain upper	0	0	0	0
Aphthous stomatitis	0	1 (1.1)	0	0
Constipation	0	0	0	0
Diarrhoea	0	0	1 (0.4)	1 (0.3)
Dry mouth	0	0	2 (0.8)	2 (0.7)
Dyspepsia	0	0	1 (0.4)	1 (0.3)
Flatulence	0	0	0	0
Frequent bowel movements	0	0	0	0
Haemorrhoids	0	0	1 (0.4)	1 (0.3)
Nausea	0	0	2 (0.8)	2 (0.7)
Rectal haemorrhage	0	0	0	0
Salivary hypersecretion	0	0	1 (0.4)	1 (0.3)
Toothache	0	0	1 (0.4)	1 (0.3)
Vomiting	0	0	1 (0.4)	1 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	8 (3.4)	11 (3.7)
Asthenia	0	0	0	0
Catheter site bruise	0	0	0	0
Fatigue	0	0	8 (3.4)	11 (3.7)
Feeling hot	0	0	0	0
Venipuncture site pain	0	0	0	0
Vessel puncture site bruise	0	0	0	0
INFECTIONS AND INFESTATIONS	0	1 (1.1)	5 (2.1)	6 (2.0)
Bronchitis	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Cystitis	2 (1.9)	0	0	0	0	0	0	0
Gastroenteritis	0	1 (1.3)	0	0	0	0	0	1 (0.4)
Herpes simplex	0	0	0	0	0	0	0	0
Nasopharyngitis	0	0	1 (0.9)	1 (0.7)	1 (4.0)	0	0	3 (1.1)
Peritonsillar abscess	0	0	0	0	0	0	0	0
Pharyngitis	0	0	0	0	0	0	0	0
Pyelonephritis	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Tonsillitis	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Upper respiratory tract infection	0	0	0	0	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0	0	0	0	0
Alcohol poisoning	0	0	0	0	0	0	0	0
Contusion	0	0	0	0	0	0	0	0
Excoriation	0	0	0	0	0	0	0	0
Joint sprain	0	0	0	0	0	0	0	0
Sunburn	0	0	0	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.9)	0	0	1 (0.7)	0	0	1 (11.1)	2 (0.8)
Back pain	1 (0.9)	0	0	1 (0.7)	0	0	1 (11.1)	2 (0.8)
Chest wall pain	0	0	0	0	0	0	0	0
Myalgia	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Pain in extremity	0	0	0	0	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Cystitis	0	1 (1.1)	0	0
Gastroenteritis	0	0	0	1 (0.3)
Herpes simplex	0	0	0	0
Nasopharyngitis	0	0	3 (1.3)	3 (1.0)
Peritonsillar abscess	0	0	0	0
Pharyngitis	0	0	0	0
Pyelonephritis	0	0	1 (0.4)	1 (0.3)
Tonsillitis	0	0	1 (0.4)	1 (0.3)
Upper respiratory tract infection	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0
Alcohol poisoning	0	0	0	0
Contusion	0	0	0	0
Excoriation	0	0	0	0
Joint sprain	0	0	0	0
Sunburn	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	2 (0.8)	2 (0.7)
Back pain	0	0	2 (0.8)	2 (0.7)
Chest wall pain	0	0	0	0
Myalgia	0	0	1 (0.4)	1 (0.3)
Pain in extremity	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
NERVOUS SYSTEM DISORDERS	2 (1.9)	2 (2.6)	5 (4.3)	4 (2.6)	1 (4.0)	5 (6.0)	4 (44.4)	20 (7.6)
Dizziness	1 (0.9)	0	0	1 (0.7)	0	0	1 (11.1)	2 (0.8)
Dizziness postural	0	0	0	0	0	2 (2.4)	0	2 (0.8)
Dysgeusia	0	0	0	0	0	0	0	0
Head discomfort	0	0	0	0	0	0	0	0
Headache	1 (0.9)	1 (1.3)	4 (3.5)	4 (2.6)	1 (4.0)	3 (3.6)	3 (33.3)	16 (6.1)
Sciatica	0	1 (1.3)	0	0	0	0	0	1 (0.4)
Somnolence	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Syncope	0	0	0	0	0	0	0	0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	0	0	0	0	0	0
Abortion spontaneous	0	0	0	0	0	0	0	0
PSYCHIATRIC DISORDERS	0	0	0	0	0	0	0	0
Mood altered	0	0	0	0	0	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	0	0	0	0	0
Menstruation irregular	0	0	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	1 (0.7)	1 (4.0)	0	1 (11.1)	3 (1.1)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
NERVOUS SYSTEM DISORDERS	2 (5.4)	0	19 (8.1)	22 (7.4)
Dizziness	0	0	2 (0.8)	2 (0.7)
Dizziness postural	0	0	2 (0.8)	2 (0.7)
Dysgeusia	0	0	0	0
Head discomfort	0	0	0	0
Headache	2 (5.4)	0	15 (6.4)	18 (6.0)
Sciatica	0	0	0	1 (0.3)
Somnolence	0	0	1 (0.4)	1 (0.3)
Syncope	0	0	0	0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	0	0
Abortion spontaneous	0	0	0	0
PSYCHIATRIC DISORDERS	0	0	0	0
Mood altered	0	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	0
Menstruation irregular	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	3 (1.3)	3 (1.0)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Cough	0	0	0	0	0	0	0	0
Nasal congestion	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Pharyngolaryngeal pain	0	0	0	1 (0.7)	1 (4.0)	0	0	2 (0.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Night sweats	0	0	0	0	0	0	0	0
Rash	0	0	0	1 (0.7)	0	0	0	1 (0.4)
SURGICAL AND MEDICAL PROCEDURES	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Venipuncture	0	0	0	1 (0.7)	0	0	0	1 (0.4)
VASCULAR DISORDERS	0	0	3 (2.6)	0	0	5 (6.0)	4 (44.4)	12 (4.6)
Flushing	0	0	0	0	0	0	0	0
Haematoma	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Hot flush	0	0	2 (1.7)	0	0	0	2 (22.2)	4 (1.5)
Orthostatic hypotension	0	0	0	0	0	5 (6.0)	2 (22.2)	7 (2.7)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Cough	0	0	0	0
Nasal congestion	0	0	1 (0.4)	1 (0.3)
Pharyngolaryngeal pain	0	0	2 (0.8)	2 (0.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	1 (0.4)	1 (0.3)
Night sweats	0	0	0	0
Rash	0	0	1 (0.4)	1 (0.3)
SURGICAL AND MEDICAL PROCEDURES	0	0	1 (0.4)	1 (0.3)
Venipuncture	0	0	1 (0.4)	1 (0.3)
VASCULAR DISORDERS	0	0	12 (5.1)	12 (4.0)
Flushing	0	0	0	0
Haematoma	0	0	1 (0.4)	1 (0.3)
Hot flush	0	0	4 (1.7)	4 (1.3)
Orthostatic hypotension	0	0	7 (3.0)	7 (2.3)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Number of Subjects Evaluable for AE	107	77	115	151	25	83	9	262
Number of Subjects Experiencing Events at this severity	1	0	2	4	0	0	4	9
Number of Events at this severity	1	0	2	4	0	0	9	15
EAR AND LABYRINTH DISORDERS	0	0	0	0	0	0	0	0
Tinnitus	0	0	0	0	0	0	0	0
EYE DISORDERS	0	0	0	0	0	0	2 (22.2)	2 (0.8)
Conjunctival hyperaemia	0	0	0	0	0	0	0	0
Dry eye	0	0	0	0	0	0	0	0
Eyelid oedema	0	0	0	0	0	0	0	0
Eyelid pain	0	0	0	0	0	0	0	0
Keratitis	0	0	0	0	0	0	0	0
Photophobia	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Vision blurred	0	0	0	0	0	0	1 (11.1)	1 (0.4)
GASTROINTESTINAL DISORDERS	0	0	0	1 (0.7)	0	0	2 (22.2)	3 (1.1)
Abdominal discomfort	0	0	0	0	0	0	0	0
Abdominal pain	0	0	0	0	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Number of Subjects Evaluable for AE	37	92	236	299
Number of Subjects Experiencing Events at this severity	0	0	9	9
Number of Events at this severity	0	0	15	15
EAR AND LABYRINTH DISORDERS	0	0	0	0
Tinnitus	0	0	0	0
EYE DISORDERS	0	0	2 (0.8)	2 (0.7)
Conjunctival hyperaemia	0	0	0	0
Dry eye	0	0	0	0
Eyelid oedema	0	0	0	0
Eyelid pain	0	0	0	0
Keratitis	0	0	0	0
Photophobia	0	0	1 (0.4)	1 (0.3)
Vision blurred	0	0	1 (0.4)	1 (0.3)
GASTROINTESTINAL DISORDERS	0	0	3 (1.3)	3 (1.0)
Abdominal discomfort	0	0	0	0
Abdominal pain	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Abdominal pain upper	0	0	0	0	0	0	0	0
Aphthous stomatitis	0	0	0	0	0	0	0	0
Constipation	0	0	0	0	0	0	0	0
Diarrhoea	0	0	0	0	0	0	0	0
Dry mouth	0	0	0	0	0	0	2 (22.2)	2 (0.8)
Dyspepsia	0	0	0	0	0	0	0	0
Flatulence	0	0	0	0	0	0	0	0
Frequent bowel movements	0	0	0	0	0	0	0	0
Haemorrhoids	0	0	0	0	0	0	0	0
Nausea	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Rectal haemorrhage	0	0	0	0	0	0	0	0
Salivary hypersecretion	0	0	0	0	0	0	0	0
Toothache	0	0	0	0	0	0	0	0
Vomiting	0	0	0	0	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	0	1 (0.7)	0	0	3 (33.3)	3 (1.1)
Asthenia	0	0	0	0	0	0	0	0
Catheter site bruise	0	0	0	0	0	0	0	0
Fatigue	0	0	0	1 (0.7)	0	0	3 (33.3)	3 (1.1)
Feeling hot	0	0	0	0	0	0	0	0
Venipuncture site pain	0	0	0	0	0	0	0	0
Vessel puncture site bruise	0	0	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	1 (0.9)	0	1 (0.9)	0	0	0	0	1 (0.4)
Bronchitis	0	0	0	0	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Abdominal pain upper	0	0	0	0
Aphthous stomatitis	0	0	0	0
Constipation	0	0	0	0
Diarrhoea	0	0	0	0
Dry mouth	0	0	2 (0.8)	2 (0.7)
Dyspepsia	0	0	0	0
Flatulence	0	0	0	0
Frequent bowel movements	0	0	0	0
Haemorrhoids	0	0	0	0
Nausea	0	0	1 (0.4)	1 (0.3)
Rectal haemorrhage	0	0	0	0
Salivary hypersecretion	0	0	0	0
Toothache	0	0	0	0
Vomiting	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	3 (1.3)	3 (1.0)
Asthenia	0	0	0	0
Catheter site bruise	0	0	0	0
Fatigue	0	0	3 (1.3)	3 (1.0)
Feeling hot	0	0	0	0
Venipuncture site pain	0	0	0	0
Vessel puncture site bruise	0	0	0	0
INFECTIONS AND INFESTATIONS	0	0	1 (0.4)	1 (0.3)
Bronchitis	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Cystitis	0	0	0	0	0	0	0	0
Gastroenteritis	1 (0.9)	0	0	0	0	0	0	0
Herpes simplex	0	0	0	0	0	0	0	0
Nasopharyngitis	0	0	0	0	0	0	0	0
Peritonsillar abscess	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Pharyngitis	0	0	0	0	0	0	0	0
Pyelonephritis	0	0	0	0	0	0	0	0
Tonsillitis	0	0	0	0	0	0	0	0
Upper respiratory tract infection	0	0	0	0	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0	0	0	0	0
Alcohol poisoning	0	0	0	0	0	0	0	0
Contusion	0	0	0	0	0	0	0	0
Excoriation	0	0	0	0	0	0	0	0
Joint sprain	0	0	0	0	0	0	0	0
Sunburn	0	0	0	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	0	0	0	0	0	0
Back pain	0	0	0	0	0	0	0	0
Chest wall pain	0	0	0	0	0	0	0	0
Myalgia	0	0	0	0	0	0	0	0
Pain in extremity	0	0	0	0	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.3
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (All Causality) - Single Dose - Phase 1

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Cystitis	0	0	0	0
Gastroenteritis	0	0	0	0
Herpes simplex	0	0	0	0
Nasopharyngitis	0	0	0	0
Peritonsillar abscess	0	0	1 (0.4)	1 (0.3)
Pharyngitis	0	0	0	0
Pyelonephritis	0	0	0	0
Tonsillitis	0	0	0	0
Upper respiratory tract infection	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0
Alcohol poisoning	0	0	0	0
Contusion	0	0	0	0
Excoriation	0	0	0	0
Joint sprain	0	0	0	0
Sunburn	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	0	0
Back pain	0	0	0	0
Chest wall pain	0	0	0	0
Myalgia	0	0	0	0
Pain in extremity	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
NERVOUS SYSTEM DISORDERS	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Dizziness	0	0	0	0	0	0	0	0
Dizziness postural	0	0	0	0	0	0	0	0
Dysgeusia	0	0	0	0	0	0	0	0
Head discomfort	0	0	0	0	0	0	0	0
Headache	0	0	0	0	0	0	0	0
Sciatica	0	0	0	0	0	0	0	0
Somnolence	0	0	0	0	0	0	0	0
Syncope	0	0	0	1 (0.7)	0	0	0	1 (0.4)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	0	0	0	0	0	0
Abortion spontaneous	0	0	0	0	0	0	0	0
PSYCHIATRIC DISORDERS	0	0	0	0	0	0	0	0
Mood altered	0	0	0	0	0	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	0	0	0	0	0
Menstruation irregular	0	0	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	0	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
NERVOUS SYSTEM DISORDERS	0	0	1 (0.4)	1 (0.3)
Dizziness	0	0	0	0
Dizziness postural	0	0	0	0
Dysgeusia	0	0	0	0
Head discomfort	0	0	0	0
Headache	0	0	0	0
Sciatica	0	0	0	0
Somnolence	0	0	0	0
Syncope	0	0	1 (0.4)	1 (0.3)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	0	0
Abortion spontaneous	0	0	0	0
PSYCHIATRIC DISORDERS	0	0	0	0
Mood altered	0	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	0
Menstruation irregular	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Cough	0	0	0	0	0	0	0	0
Nasal congestion	0	0	0	0	0	0	0	0
Pharyngolaryngeal pain	0	0	0	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Night sweats	0	0	0	0	0	0	0	0
Rash	0	0	1 (0.9)	0	0	0	0	1 (0.4)
SURGICAL AND MEDICAL PROCEDURES	0	0	0	0	0	0	0	0
Venipuncture	0	0	0	0	0	0	0	0
VASCULAR DISORDERS	0	0	0	1 (0.7)	0	0	2 (22.2)	3 (1.1)
Flushing	0	0	0	0	0	0	0	0
Haematoma	0	0	0	0	0	0	0	0
Hot flush	0	0	0	0	0	0	0	0
Orthostatic hypotension	0	0	0	1 (0.7)	0	0	2 (22.2)	3 (1.1)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Cough	0	0	0	0
Nasal congestion	0	0	0	0
Pharyngolaryngeal pain	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	1 (0.4)	1 (0.3)
Night sweats	0	0	0	0
Rash	0	0	1 (0.4)	1 (0.3)
SURGICAL AND MEDICAL PROCEDURES	0	0	0	0
Venipuncture	0	0	0	0
VASCULAR DISORDERS	0	0	3 (1.3)	3 (1.0)
Flushing	0	0	0	0
Haematoma	0	0	0	0
Hot flush	0	0	0	0
Orthostatic hypotension	0	0	3 (1.3)	3 (1.0)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Number of Subjects Evaluable for AE	107	77	115	151	25	83	9	262
Number of Subjects Experiencing Events at this severity	13	6	12	30	10	28	2	75
Number of Events at this severity	17	6	14	39	13	34	2	108
EAR AND LABYRINTH DISORDERS	0	0	0	0	0	0	0	0
Tinnitus	0	0	0	0	0	0	0	0
EYE DISORDERS	0	0	0	3 (2.0)	0	2 (2.4)	0	5 (1.9)
Conjunctival hyperaemia	0	0	0	0	0	0	0	0
Dry eye	0	0	0	0	0	0	0	0
Eyelid oedema	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Eyelid pain	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Photophobia	0	0	0	0	0	0	0	0
Vision blurred	0	0	0	1 (0.7)	0	2 (2.4)	0	3 (1.1)
GASTROINTESTINAL DISORDERS	5 (4.7)	2 (2.6)	4 (3.5)	8 (5.3)	3 (12.0)	9 (10.8)	0	23 (8.8)
Abdominal discomfort	1 (0.9)	0	0	1 (0.7)	0	1 (1.2)	0	2 (0.8)
Abdominal pain	1 (0.9)	0	0	0	0	0	0	0
Abdominal pain upper	0	0	1 (0.9)	1 (0.7)	0	1 (1.2)	0	3 (1.1)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Number of Subjects Evaluable for AE	37	92	236	299
Number of Subjects Experiencing Events at this severity	5	19	72	80
Number of Events at this severity	5	24	102	113
EAR AND LABYRINTH DISORDERS	0	0	0	0
Tinnitus	0	0	0	0
EYE DISORDERS	0	0	5 (2.1)	5 (1.7)
Conjunctival hyperaemia	0	0	0	0
Dry eye	0	0	0	0
Eyelid oedema	0	0	1 (0.4)	1 (0.3)
Eyelid pain	0	0	1 (0.4)	1 (0.3)
Photophobia	0	0	0	0
Vision blurred	0	0	3 (1.3)	3 (1.0)
GASTROINTESTINAL DISORDERS	0	8 (8.7)	21 (8.9)	23 (7.7)
Abdominal discomfort	0	1 (1.1)	2 (0.8)	2 (0.7)
Abdominal pain	0	0	0	0
Abdominal pain upper	0	0	3 (1.3)	3 (1.0)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Diarrhoea	0	0	0	0	0	0	0	0
Dry mouth	0	1 (1.3)	0	1 (0.7)	0	2 (2.4)	0	4 (1.5)
Dyspepsia	0	0	0	0	2 (8.0)	0	0	2 (0.8)
Flatulence	0	0	2 (1.7)	3 (2.0)	0	1 (1.2)	0	6 (2.3)
Frequent bowel movements	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Nausea	3 (2.8)	1 (1.3)	1 (0.9)	2 (1.3)	0	4 (4.8)	0	6 (2.3)
Salivary hypersecretion	0	0	0	0	0	0	0	0
Vomiting	0	0	0	0	0	1 (1.2)	0	1 (0.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5 (4.7)	1 (1.3)	3 (2.6)	2 (1.3)	4 (16.0)	4 (4.8)	0	14 (5.3)
Asthenia	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Fatigue	5 (4.7)	1 (1.3)	3 (2.6)	1 (0.7)	3 (12.0)	4 (4.8)	0	12 (4.6)
Feeling hot	0	0	0	1 (0.7)	0	0	0	1 (0.4)
INFECTIONS AND INFESTATIONS	0	0	0	0	0	0	0	0
Herpes simplex	0	0	0	0	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0	1 (4.0)	0	0	1 (0.4)
Alcohol poisoning	0	0	0	0	1 (4.0)	0	0	1 (0.4)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Diarrhoea	0	2 (2.2)	0	0
Dry mouth	0	0	3 (1.3)	4 (1.3)
Dyspepsia	0	0	2 (0.8)	2 (0.7)
Flatulence	0	2 (2.2)	6 (2.5)	6 (2.0)
Frequent bowel movements	0	0	1 (0.4)	1 (0.3)
Nausea	0	3 (3.3)	5 (2.1)	6 (2.0)
Salivary hypersecretion	0	0	0	0
Vomiting	0	0	1 (0.4)	1 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	13 (5.5)	14 (4.7)
Asthenia	0	0	1 (0.4)	1 (0.3)
Fatigue	0	0	11 (4.7)	12 (4.0)
Feeling hot	0	0	1 (0.4)	1 (0.3)
INFECTIONS AND INFESTATIONS	1 (2.7)	0	0	1 (0.3)
Herpes simplex	1 (2.7)	0	0	1 (0.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	1 (0.4)	1 (0.3)
Alcohol poisoning	0	0	1 (0.4)	1 (0.3)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	0	2 (1.3)	0	0	0	2 (0.8)
Back pain	0	0	0	0	0	0	0	0
Myalgia	0	0	0	2 (1.3)	0	0	0	2 (0.8)
NERVOUS SYSTEM DISORDERS	4 (3.7)	3 (3.9)	3 (2.6)	17 (11.3)	5 (20.0)	12 (14.5)	1 (11.1)	32 (12.2)
Dizziness	1 (0.9)	0	1 (0.9)	2 (1.3)	2 (8.0)	3 (3.6)	1 (11.1)	9 (3.4)
Dizziness postural	1 (0.9)	0	1 (0.9)	0	0	6 (7.2)	0	6 (2.3)
Dysgeusia	1 (0.9)	0	0	0	0	0	0	0
Head discomfort	0	0	0	0	0	1 (1.2)	0	1 (0.4)
Headache	2 (1.9)	2 (2.6)	2 (1.7)	13 (8.6)	2 (8.0)	3 (3.6)	0	18 (6.9)
Somnolence	0	1 (1.3)	0	3 (2.0)	1 (4.0)	0	0	3 (1.1)
PSYCHIATRIC DISORDERS	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Mood altered	0	0	0	1 (0.7)	0	0	0	1 (0.4)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Menstruation irregular	0	0	0	1 (0.7)	0	0	0	1 (0.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	1 (0.7)	0	0	0	1 (0.4)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	2 (0.8)	2 (0.7)
Back pain	0	0	0	0
Myalgia	0	0	2 (0.8)	2 (0.7)
NERVOUS SYSTEM DISORDERS	3 (8.1)	10 (10.9)	32 (13.6)	35 (11.7)
Dizziness	0	2 (2.2)	9 (3.8)	9 (3.0)
Dizziness postural	0	3 (3.3)	6 (2.5)	6 (2.0)
Dysgeusia	0	0	0	0
Head discomfort	0	0	1 (0.4)	1 (0.3)
Headache	3 (8.1)	7 (7.6)	17 (7.2)	21 (7.0)
Somnolence	0	0	3 (1.3)	3 (1.0)
PSYCHIATRIC DISORDERS	0	0	1 (0.4)	1 (0.3)
Mood altered	0	0	1 (0.4)	1 (0.3)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	1 (0.4)	1 (0.3)
Menstruation irregular	0	0	1 (0.4)	1 (0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	1 (0.4)	1 (0.3)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Cough	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Nasal congestion	0	0	0	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	1 (0.9)	1 (0.7)	0	0	0	1 (0.4)
Night sweats	0	0	0	0	0	0	0	0
Rash	0	0	1 (0.9)	1 (0.7)	0	0	0	1 (0.4)
VASCULAR DISORDERS	2 (1.9)	0	1 (0.9)	0	0	4 (4.8)	1 (11.1)	6 (2.3)
Flushing	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Hot flush	2 (1.9)	0	0	0	0	0	0	0
Orthostatic hypotension	0	0	1 (0.9)	0	0	4 (4.8)	0	5 (1.9)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Mild

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Cough	0	0	1 (0.4)	1 (0.3)
Nasal congestion	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (2.7)	0	1 (0.4)	2 (0.7)
Night sweats	1 (2.7)	0	0	1 (0.3)
Rash	0	0	1 (0.4)	1 (0.3)
VASCULAR DISORDERS	0	2 (2.2)	6 (2.5)	6 (2.0)
Flushing	0	0	1 (0.4)	1 (0.3)
Hot flush	0	0	0	0
Orthostatic hypotension	0	2 (2.2)	5 (2.1)	5 (1.7)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Number of Subjects Evaluable for AE	107	77	115	151	25	83	9	262
Number of Subjects Experiencing Events at this severity	5	4	9	5	5	13	7	41
Number of Events at this severity	5	4	10	6	5	13	18	56
EAR AND LABYRINTH DISORDERS	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Tinnitus	0	0	0	0	0	0	1 (11.1)	1 (0.4)
EYE DISORDERS	0	0	0	0	1 (4.0)	0	2 (22.2)	3 (1.1)
Conjunctival hyperaemia	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Dry eye	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Eyelid oedema	0	0	0	0	0	0	0	0
Eyelid pain	0	0	0	0	0	0	0	0
Photophobia	0	0	0	0	0	0	0	0
Vision blurred	0	0	0	0	1 (4.0)	0	1 (11.1)	2 (0.8)
GASTROINTESTINAL DISORDERS	2 (1.9)	0	3 (2.6)	0	3 (12.0)	1 (1.2)	0	7 (2.7)
Abdominal discomfort	0	0	0	0	0	0	0	0
Abdominal pain	2 (1.9)	0	0	0	1 (4.0)	0	0	1 (0.4)
Abdominal pain upper	0	0	0	0	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Number of Subjects Evaluable for AE	37	92	236	299
Number of Subjects Experiencing Events at this severity	2	0	38	43
Number of Events at this severity	2	0	52	58
EAR AND LABYRINTH DISORDERS	0	0	1 (0.4)	1 (0.3)
Tinnitus	0	0	1 (0.4)	1 (0.3)
EYE DISORDERS	0	0	3 (1.3)	3 (1.0)
Conjunctival hyperaemia	0	0	1 (0.4)	1 (0.3)
Dry eye	0	0	1 (0.4)	1 (0.3)
Eyelid oedema	0	0	0	0
Eyelid pain	0	0	0	0
Photophobia	0	0	0	0
Vision blurred	0	0	2 (0.8)	2 (0.7)
GASTROINTESTINAL DISORDERS	0	0	7 (3.0)	7 (2.3)
Abdominal discomfort	0	0	0	0
Abdominal pain	0	0	1 (0.4)	1 (0.3)
Abdominal pain upper	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Diarrhoea	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Dry mouth	0	0	1 (0.9)	0	1 (4.0)	0	0	2 (0.8)
Dyspepsia	0	0	0	0	0	0	0	0
Flatulence	0	0	0	0	0	0	0	0
Frequent bowel movements	0	0	0	0	0	0	0	0
Nausea	0	0	1 (0.9)	0	1 (4.0)	0	0	2 (0.8)
Salivary hypersecretion	0	0	0	0	0	1 (1.2)	0	1 (0.4)
Vomiting	0	0	0	1 (0.7)	0	0	0	1 (0.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.9)	3 (3.9)	1 (0.9)	0	1 (4.0)	3 (3.6)	2 (22.2)	10 (3.8)
Asthenia	0	0	0	0	0	0	0	0
Fatigue	1 (0.9)	3 (3.9)	1 (0.9)	0	1 (4.0)	3 (3.6)	2 (22.2)	10 (3.8)
Feeling hot	0	0	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	0	0	0	0	0	0	0	0
Herpes simplex	0	0	0	0	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0	0	0	0	0
Alcohol poisoning	0	0	0	0	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Diarrhoea	0	0	1 (0.4)	1 (0.3)
Dry mouth	0	0	2 (0.8)	2 (0.7)
Dyspepsia	0	0	0	0
Flatulence	0	0	0	0
Frequent bowel movements	0	0	0	0
Nausea	0	0	2 (0.8)	2 (0.7)
Salivary hypersecretion	0	0	1 (0.4)	1 (0.3)
Vomiting	0	0	1 (0.4)	1 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	7 (3.0)	10 (3.3)
Asthenia	0	0	0	0
Fatigue	0	0	7 (3.0)	10 (3.3)
Feeling hot	0	0	0	0
INFECTIONS AND INFESTATIONS	0	0	0	0
Herpes simplex	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0
Alcohol poisoning	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Back pain	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Myalgia	0	0	0	0	0	0	1 (11.1)	1 (0.4)
NERVOUS SYSTEM DISORDERS	2 (1.9)	1 (1.3)	4 (3.5)	3 (2.0)	0	4 (4.8)	4 (44.4)	16 (6.1)
Dizziness	1 (0.9)	0	0	1 (0.7)	0	0	1 (11.1)	2 (0.8)
Dizziness postural	0	0	0	0	0	2 (2.4)	0	2 (0.8)
Dysgeusia	0	0	0	0	0	0	0	0
Head discomfort	0	0	0	0	0	0	0	0
Headache	1 (0.9)	1 (1.3)	3 (2.6)	3 (2.0)	0	2 (2.4)	3 (33.3)	12 (4.6)
Somnolence	0	0	1 (0.9)	0	0	0	0	1 (0.4)
PSYCHIATRIC DISORDERS	0	0	0	0	0	0	0	0
Mood altered	0	0	0	0	0	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	0	0	0	0	0
Menstruation irregular	0	0	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	0	0	0	1 (11.1)	1 (0.4)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	1 (0.4)	1 (0.3)
Back pain	0	0	1 (0.4)	1 (0.3)
Myalgia	0	0	1 (0.4)	1 (0.3)
NERVOUS SYSTEM DISORDERS	2 (5.4)	0	15 (6.4)	18 (6.0)
Dizziness	0	0	2 (0.8)	2 (0.7)
Dizziness postural	0	0	2 (0.8)	2 (0.7)
Dysgeusia	0	0	0	0
Head discomfort	0	0	0	0
Headache	2 (5.4)	0	11 (4.7)	14 (4.7)
Somnolence	0	0	1 (0.4)	1 (0.3)
PSYCHIATRIC DISORDERS	0	0	0	0
Mood altered	0	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	0
Menstruation irregular	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	1 (0.4)	1 (0.3)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Cough	0	0	0	0	0	0	0	0
Nasal congestion	0	0	0	0	0	0	1 (11.1)	1 (0.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Night sweats	0	0	0	0	0	0	0	0
Rash	0	0	0	1 (0.7)	0	0	0	1 (0.4)
VASCULAR DISORDERS	0	0	2 (1.7)	0	0	5 (6.0)	4 (44.4)	11 (4.2)
Flushing	0	0	0	0	0	0	0	0
Hot flush	0	0	2 (1.7)	0	0	0	2 (22.2)	4 (1.5)
Orthostatic hypotension	0	0	0	0	0	5 (6.0)	2 (22.2)	7 (2.7)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Moderate

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Cough	0	0	0	0
Nasal congestion	0	0	1 (0.4)	1 (0.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	1 (0.4)	1 (0.3)
Night sweats	0	0	0	0
Rash	0	0	1 (0.4)	1 (0.3)
VASCULAR DISORDERS	0	0	11 (4.7)	11 (3.7)
Flushing	0	0	0	0
Hot flush	0	0	4 (1.7)	4 (1.3)
Orthostatic hypotension	0	0	7 (3.0)	7 (2.3)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Number of Subjects Evaluable for AE	107	77	115	151	25	83	9	262
Number of Subjects Experiencing Events at this severity	0	0	1	3	0	0	4	7
Number of Events at this severity	0	0	1	3	0	0	9	13
EAR AND LABYRINTH DISORDERS	0	0	0	0	0	0	0	0
Tinnitus	0	0	0	0	0	0	0	0
EYE DISORDERS	0	0	0	0	0	0	2 (22.2)	2 (0.8)
Conjunctival hyperaemia	0	0	0	0	0	0	0	0
Dry eye	0	0	0	0	0	0	0	0
Eyelid oedema	0	0	0	0	0	0	0	0
Eyelid pain	0	0	0	0	0	0	0	0
Photophobia	0	0	0	0	0	0	1 (11.1)	1 (0.4)
Vision blurred	0	0	0	0	0	0	1 (11.1)	1 (0.4)
GASTROINTESTINAL DISORDERS	0	0	0	1 (0.7)	0	0	2 (22.2)	3 (1.1)
Abdominal discomfort	0	0	0	0	0	0	0	0
Abdominal pain	0	0	0	0	0	0	0	0
Abdominal pain upper	0	0	0	0	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Number of Subjects Evaluable for AE	37	92	236	299
Number of Subjects Experiencing Events at this severity	0	0	7	7
Number of Events at this severity	0	0	13	13
EAR AND LABYRINTH DISORDERS	0	0	0	0
Tinnitus	0	0	0	0
EYE DISORDERS	0	0	2 (0.8)	2 (0.7)
Conjunctival hyperaemia	0	0	0	0
Dry eye	0	0	0	0
Eyelid oedema	0	0	0	0
Eyelid pain	0	0	0	0
Photophobia	0	0	1 (0.4)	1 (0.3)
Vision blurred	0	0	1 (0.4)	1 (0.3)
GASTROINTESTINAL DISORDERS	0	0	3 (1.3)	3 (1.0)
Abdominal discomfort	0	0	0	0
Abdominal pain	0	0	0	0
Abdominal pain upper	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Diarrhoea	0	0	0	0	0	0	0	0
Dry mouth	0	0	0	0	0	0	2 (22.2)	2 (0.8)
Dyspepsia	0	0	0	0	0	0	0	0
Flatulence	0	0	0	0	0	0	0	0
Frequent bowel movements	0	0	0	0	0	0	0	0
Nausea	0	0	0	1 (0.7)	0	0	0	1 (0.4)
Salivary hypersecretion	0	0	0	0	0	0	0	0
Vomiting	0	0	0	0	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	0	1 (0.7)	0	0	3 (33.3)	3 (1.1)
Asthenia	0	0	0	0	0	0	0	0
Fatigue	0	0	0	1 (0.7)	0	0	3 (33.3)	3 (1.1)
Feeling hot	0	0	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	0	0	0	0	0	0	0	0
Herpes simplex	0	0	0	0	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0	0	0	0	0
Alcohol poisoning	0	0	0	0	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Diarrhoea	0	0	0	0
Dry mouth	0	0	2 (0.8)	2 (0.7)
Dyspepsia	0	0	0	0
Flatulence	0	0	0	0
Frequent bowel movements	0	0	0	0
Nausea	0	0	1 (0.4)	1 (0.3)
Salivary hypersecretion	0	0	0	0
Vomiting	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	3 (1.3)	3 (1.0)
Asthenia	0	0	0	0
Fatigue	0	0	3 (1.3)	3 (1.0)
Feeling hot	0	0	0	0
INFECTIONS AND INFESTATIONS	0	0	0	0
Herpes simplex	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	0
Alcohol poisoning	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	0	0	0	0	0	0
Back pain	0	0	0	0	0	0	0	0
Myalgia	0	0	0	0	0	0	0	0
NERVOUS SYSTEM DISORDERS	0	0	0	0	0	0	0	0
Dizziness	0	0	0	0	0	0	0	0
Dizziness postural	0	0	0	0	0	0	0	0
Dysgeusia	0	0	0	0	0	0	0	0
Head discomfort	0	0	0	0	0	0	0	0
Headache	0	0	0	0	0	0	0	0
Somnolence	0	0	0	0	0	0	0	0
PSYCHIATRIC DISORDERS	0	0	0	0	0	0	0	0
Mood altered	0	0	0	0	0	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	0	0	0	0	0
Menstruation irregular	0	0	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	0	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	0	0
Back pain	0	0	0	0
Myalgia	0	0	0	0
NERVOUS SYSTEM DISORDERS	0	0	0	0
Dizziness	0	0	0	0
Dizziness postural	0	0	0	0
Dysgeusia	0	0	0	0
Head discomfort	0	0	0	0
Headache	0	0	0	0
Somnolence	0	0	0	0
PSYCHIATRIC DISORDERS	0	0	0	0
Mood altered	0	0	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	0
Menstruation irregular	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	0

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg	100mg	300mg	600mg	900mg	1200mg	maraviroc Only
Cough	0	0	0	0	0	0	0	0
Nasal congestion	0	0	0	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	1 (0.9)	0	0	0	0	1 (0.4)
Night sweats	0	0	0	0	0	0	0	0
Rash	0	0	1 (0.9)	0	0	0	0	1 (0.4)
VASCULAR DISORDERS	0	0	0	1 (0.7)	0	0	2 (22.2)	3 (1.1)
Flushing	0	0	0	0	0	0	0	0
Hot flush	0	0	0	0	0	0	0	0
Orthostatic hypotension	0	0	0	1 (0.7)	0	0	2 (22.2)	3 (1.1)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

Table 1.4.1.4
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events by Severity (Treatment Related) - Single Dose - Phase 1

Severity: Severe

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Cough	0	0	0	0
Nasal congestion	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	1 (0.4)	1 (0.3)
Night sweats	0	0	0	0
Rash	0	0	1 (0.4)	1 (0.3)
VASCULAR DISORDERS	0	0	3 (1.3)	3 (1.0)
Flushing	0	0	0	0
Hot flush	0	0	0	0
Orthostatic hypotension	0	0	3 (1.3)	3 (1.0)

Subjects are counted only once per treatment in each row.
If a subject in a given treatment had more than one occurrence in the same event category, only the most severe occurrence is taken.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001001, A4001003, A4001004, A4001009, A4001010, A4001016, A4001017, A4001032, A4001033, A4001038, A4001040, A4001043, A4001046 and A4001047.
Date of Table Generation: 13SEP2006 (06:23)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: Placebo	<100mg unit dose	100mg BID	150mg BID	300mg BID	600mg QD	600mg BID	900mg QD
Number of Subjects Evaluable for AE	57	19	149	12	81	18	17	9
Number of Subjects Experiencing Events	44	13	67	9	67	15	13	8
Number of Events	155	31	162	17	181	99	96	74
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (1.8)	0	0	0	2 (2.5)	0	0	0
Anaemia	0	0	0	0	1 (1.2)	0	0	0
Lymphadenopathy	1 (1.8)	0	0	0	0	0	0	0
Neutropenia	0	0	0	0	1 (1.2)	0	0	0
CARDIAC DISORDERS	0	0	0	0	4 (4.9)	0	1 (5.9)	1 (11.1)
Palpitations	0	0	0	0	3 (3.7)	0	1 (5.9)	1 (11.1)
Sinus tachycardia	0	0	0	0	0	0	1 (5.9)	0
Tachycardia	0	0	0	0	1 (1.2)	0	0	0
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	1 (5.3)	0	0	0	0	0	0
Epidermal naevus	0	1 (5.3)	0	0	0	0	0	0
EAR AND LABYRINTH DISORDERS	0	0	0	0	0	0	0	1 (11.1)
Hearing impaired	0	0	0	0	0	0	0	1 (11.1)
Tinnitus	0	0	0	0	0	0	0	0

Subjects are counted only once per treatment in each row.
All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.
Date of Table Generation: 13SEP2006 (05:27)

Table 1.4.2.1
Maraviroc Summary of Clinical Safety
Treatment-Emergent Adverse Events (All Causality) - Multiple Dose - Phase 1

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group 900mg BID	1200mg QD	maraviroc Only	maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Number of Subjects Evaluable for AE	8	9	297	190	38	278	333
Number of Subjects Experiencing Events	8	9	188	153	26	175	273
Number of Events	81	49	790	737	75	759	1527
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	2 (0.7)	0	0	2 (0.7)	2 (0.6)
Anaemia	0	0	1 (0.3)	0	0	1 (0.4)	1 (0.3)
Lymphadenopathy	0	0	0	0	0	0	0
Neutropenia	0	0	1 (0.3)	0	0	1 (0.4)	1 (0.3)
CARDIAC DISORDERS	0	0	6 (2.0)	6 (3.2)	3 (7.9)	6 (2.2)	12 (3.6)
Palpitations	0	0	5 (1.7)	3 (1.6)	0	5 (1.8)	8 (2.4)
Sinus tachycardia	0	0	1 (0.3)	0	0	1 (0.4)	1 (0.3)
Tachycardia	0	0	1 (0.3)	3 (1.6)	3 (7.9)	1 (0.4)	4 (1.2)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	0	1 (0.3)	0	0	0	1 (0.3)
Epidermal naevus	0	0	1 (0.3)	0	0	0	1 (0.3)
EAR AND LABYRINTH DISORDERS	0	0	1 (0.3)	2 (1.1)	0	1 (0.4)	3 (0.9)
Hearing impaired	0	0	1 (0.3)	0	0	1 (0.4)	1 (0.3)
Tinnitus	0	0	0	2 (1.1)	0	0	2 (0.6)

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Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.
Date of Table Generation: 13SEP2006 (05:27)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg unit dose	100mg BID	150mg BID	300mg BID	600mg QD	600mg BID	900mg QD
EYE DISORDERS	5 (8.8)	1 (5.3)	5 (3.4)	0	1 (1.2)	3 (16.7)	3 (17.6)	5 (55.6)
Accommodation disorder	1 (1.8)	0	0	0	0	0	0	0
Asthenopia	0	0	0	0	0	0	1 (5.9)	1 (11.1)
Conjunctival hyperaemia	0	0	0	0	0	0	0	0
Conjunctivitis	0	1 (5.3)	0	0	0	0	0	0
Dry eye	0	0	2 (1.3)	0	0	0	0	0
Eye irritation	0	0	0	0	0	0	0	0
Eye oedema	0	0	0	0	0	0	0	0
Eye pain	2 (3.5)	0	0	0	0	0	0	0
Eyelid oedema	0	0	0	0	0	0	0	0
Ocular hyperaemia	0	0	0	0	0	0	0	5 (55.6)
Vision blurred	1 (1.8)	0	3 (2.0)	0	0	3 (16.7)	3 (17.6)	3 (33.3)
Visual disturbance	1 (1.8)	0	0	0	1 (1.2)	0	0	0
GASTROINTESTINAL DISORDERS	17 (29.8)	6 (31.6)	25 (16.8)	6 (50.0)	28 (34.6)	9 (50.0)	8 (47.1)	4 (44.4)
Abdominal discomfort	2 (3.5)	0	2 (1.3)	4 (33.3)	0	0	1 (5.9)	0
Abdominal distension	1 (1.8)	0	1 (0.7)	0	2 (2.5)	1 (5.6)	0	0
Abdominal pain	1 (1.8)	2 (10.5)	0	0	4 (4.9)	1 (5.6)	0	0
Abdominal pain lower	1 (1.8)	0	0	0	2 (2.5)	0	1 (5.9)	0
Abdominal pain upper	1 (1.8)	0	4 (2.7)	0	0	1 (5.6)	0	0
Abdominal tenderness	0	0	0	0	0	0	0	0
Aphthous stomatitis	0	1 (5.3)	0	0	0	0	0	0
Change of bowel habit	0	0	0	0	0	0	0	0
Cheilitis	0	0	1 (0.7)	0	0	0	0	0
Constipation	1 (1.8)	0	2 (1.3)	1 (8.3)	1 (1.2)	0	0	0
Diarrhoea	3 (5.3)	1 (5.3)	3 (2.0)	0	4 (4.9)	1 (5.6)	0	0
Dry mouth	0	0	3 (2.0)	0	2 (2.5)	0	2 (11.8)	2 (22.2)
Dyspepsia	3 (5.3)	1 (5.3)	2 (1.3)	1 (8.3)	3 (3.7)	1 (5.6)	0	0
Dysphagia	0	0	0	0	0	0	0	0
Eructation	0	0	0	0	0	1 (5.6)	0	0

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Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.
Date of Table Generation: 13SEP2006 (05:27)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: 900mg BID	1200mg QD	maraviroc Only	maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
EYE DISORDERS	5 (62.5)	6 (66.7)	24 (8.1)	20 (10.5)	0	23 (8.3)	42 (12.6)
Accommodation disorder	0	0	0	0	0	0	0
Asthenopia	0	1 (11.1)	3 (1.0)	1 (0.5)	0	3 (1.1)	4 (1.2)
Conjunctival hyperaemia	0	0	0	1 (0.5)	0	0	1 (0.3)
Conjunctivitis	0	0	1 (0.3)	0	0	0	1 (0.3)
Dry eye	0	0	2 (0.7)	0	0	2 (0.7)	2 (0.6)
Eye irritation	2 (25.0)	0	2 (0.7)	0	0	2 (0.7)	2 (0.6)
Eye oedema	0	1 (11.1)	1 (0.3)	0	0	1 (0.4)	1 (0.3)
Eye pain	1 (12.5)	0	1 (0.3)	1 (0.5)	0	1 (0.4)	2 (0.6)
Eyelid oedema	0	0	0	1 (0.5)	0	0	1 (0.3)
Ocular hyperaemia	5 (62.5)	5 (55.6)	11 (3.7)	2 (1.1)	0	11 (4.0)	13 (3.9)
Vision blurred	3 (37.5)	0	14 (4.7)	13 (6.8)	0	14 (5.0)	25 (7.5)
Visual disturbance	0	0	1 (0.3)	3 (1.6)	0	1 (0.4)	4 (1.2)
GASTROINTESTINAL DISORDERS	6 (75.0)	5 (55.6)	86 (29.0)	89 (46.8)	10 (26.3)	80 (28.8)	149 (44.7)
Abdominal discomfort	0	0	7 (2.4)	13 (6.8)	0	7 (2.5)	18 (5.4)
Abdominal distension	0	0	4 (1.3)	0	0	4 (1.4)	4 (1.2)
Abdominal pain	0	2 (22.2)	9 (3.0)	9 (4.7)	0	7 (2.5)	18 (5.4)
Abdominal pain lower	0	0	3 (1.0)	0	0	3 (1.1)	3 (0.9)
Abdominal pain upper	1 (12.5)	0	6 (2.0)	8 (4.2)	0	6 (2.2)	13 (3.9)
Abdominal tenderness	0	0	0	1 (0.5)	0	0	1 (0.3)
Aphthous stomatitis	0	0	1 (0.3)	3 (1.6)	0	0	4 (1.2)
Change of bowel habit	0	0	0	1 (0.5)	0	0	1 (0.3)
Cheilitis	0	0	1 (0.3)	0	0	1 (0.4)	1 (0.3)
Constipation	0	0	4 (1.3)	12 (6.3)	0	4 (1.4)	15 (4.5)
Diarrhoea	0	0	9 (3.0)	20 (10.5)	3 (7.9)	8 (2.9)	28 (8.4)
Dry mouth	1 (12.5)	3 (33.3)	12 (4.0)	13 (6.8)	1 (2.6)	12 (4.3)	24 (7.2)
Dyspepsia	0	0	8 (2.7)	19 (10.0)	0	7 (2.5)	26 (7.8)
Dysphagia	0	0	0	1 (0.5)	0	0	1 (0.3)
Eructation	0	0	1 (0.3)	0	0	1 (0.4)	1 (0.3)

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All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.
Date of Table Generation: 13SEP2006 (05:27)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg unit dose	100mg BID	150mg BID	300mg BID	600mg QD	600mg BID	900mg QD
Flatulence	6 (10.5)	1 (5.3)	4 (2.7)	3 (25.0)	8 (9.9)	6 (33.3)	1 (5.9)	1 (11.1)
Gastritis	0	0	0	0	0	0	0	0
Gastrooesophageal reflux disease	0	0	0	0	0	0	0	0
Haematochezia	0	0	1 (0.7)	0	0	0	0	0
Hypoaesthesia oral	0	0	0	0	0	0	0	0
Lip dry	0	0	0	0	1 (1.2)	0	0	0
Lip ulceration	1 (1.8)	0	0	0	0	0	0	0
Mouth ulceration	0	0	1 (0.7)	0	1 (1.2)	0	0	0
Nausea	6 (10.5)	2 (10.5)	6 (4.0)	0	7 (8.6)	1 (5.6)	6 (35.3)	4 (44.4)
Odynophagia	0	0	1 (0.7)	0	0	0	0	0
Oral pain	0	0	0	0	0	0	0	0
Salivary hypersecretion	1 (1.8)	0	0	0	0	0	0	0
Stomach discomfort	1 (1.8)	0	0	0	0	0	1 (5.9)	0
Toothache	2 (3.5)	1 (5.3)	1 (0.7)	0	0	0	0	0
Vomiting	1 (1.8)	1 (5.3)	2 (1.3)	0	2 (2.5)	1 (5.6)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8 (14.0)	0	11 (7.4)	2 (16.7)	12 (14.8)	3 (16.7)	6 (35.3)	6 (66.7)
Asthenia	1 (1.8)	0	1 (0.7)	0	2 (2.5)	1 (5.6)	1 (5.9)	0
Axillary pain	0	0	0	0	1 (1.2)	0	0	0
Catheter site haemorrhage	0	0	0	0	0	0	0	0
Catheter site oedema	1 (1.8)	0	0	0	0	0	0	0
Catheter site pain	1 (1.8)	0	0	0	0	0	0	0
Catheter site related reaction	1 (1.8)	0	0	0	0	0	0	0
Chest discomfort	0	0	0	0	1 (1.2)	0	0	1 (11.1)
Chest pain	0	0	0	0	1 (1.2)	0	1 (5.9)	0
Fatigue	4 (7.0)	0	8 (5.4)	1 (8.3)	4 (4.9)	2 (11.1)	3 (17.6)	6 (66.7)
Feeling abnormal	0	0	0	0	0	0	0	0
Feeling cold	0	0	0	0	0	0	1 (5.9)	0
Feeling drunk	0	0	0	0	0	0	0	0
Feeling hot	0	0	0	0	3 (3.7)	0	1 (5.9)	0

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All maraviroc Doses includes subjects who received maraviroc + Interactant.
Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.
Date of Table Generation: 13SEP2006 (05:27)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group: 900mg BID	1200mg QD	maraviroc Only	maraviroc + Interactant	Interactant	maraviroc Only >=100mg	All maraviroc Doses
Flatulence	0	0	24 (8.1)	13 (6.8)	0	23 (8.3)	35 (10.5)
Gastritis	0	0	0	1 (0.5)	0	0	1 (0.3)
Gastrooesophageal reflux disease	0	0	0	0	1 (2.6)	0	0
Haematochezia	0	0	1 (0.3)	0	0	1 (0.4)	1 (0.3)
Hypoaesthesia oral	0	0	0	6 (3.2)	0	0	6 (1.8)
Lip dry	0	0	1 (0.3)	0	0	1 (0.4)	1 (0.3)
Lip ulceration	0	0	0	0	0	0	0
Mouth ulceration	1 (12.5)	0	3 (1.0)	0	0	3 (1.1)	3 (0.9)
Nausea	3 (37.5)	2 (22.2)	26 (8.8)	31 (16.3)	7 (18.4)	24 (8.6)	54 (16.2)
Odynophagia	0	0	1 (0.3)	0	0	1 (0.4)	1 (0.3)
Oral pain	0	0	0	0	1 (2.6)	0	0
Salivary hypersecretion	0	0	0	0	0	0	0
Stomach discomfort	0	0	1 (0.3)	4 (2.1)	0	1 (0.4)	5 (1.5)
Toothache	0	0	2 (0.7)	1 (0.5)	0	1 (0.4)	3 (0.9)
Vomiting	0	0	6 (2.0)	8 (4.2)	1 (2.6)	5 (1.8)	13 (3.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (50.0)	3 (33.3)	42 (14.1)	59 (31.1)	8 (21.1)	42 (15.1)	92 (27.6)
Asthenia	0	0	5 (1.7)	3 (1.6)	0	5 (1.8)	7 (2.1)
Axillary pain	0	0	1 (0.3)	0	0	1 (0.4)	1 (0.3)
Catheter site haemorrhage	0	0	0	0	1 (2.6)	0	0
Catheter site oedema	0	0	0	0	0	0	0
Catheter site pain	0	1 (11.1)	1 (0.3)	1 (0.5)	0	1 (0.4)	2 (0.6)
Catheter site related reaction	0	0	0	5 (2.6)	1 (2.6)	0	5 (1.5)
Chest discomfort	0	0	2 (0.7)	0	0	2 (0.7)	2 (0.6)
Chest pain	2 (25.0)	0	4 (1.3)	1 (0.5)	0	4 (1.4)	5 (1.5)
Fatigue	1 (12.5)	3 (33.3)	25 (8.4)	39 (20.5)	5 (13.2)	25 (9.0)	61 (18.3)
Feeling abnormal	1 (12.5)	0	1 (0.3)	2 (1.1)	0	1 (0.4)	3 (0.9)
Feeling cold	0	0	1 (0.3)	0	0	1 (0.4)	1 (0.3)
Feeling drunk	0	0	0	3 (1.6)	0	0	3 (0.9)
Feeling hot	0	0	4 (1.3)	3 (1.6)	0	4 (1.4)	5 (1.5)

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Includes Protocols: A4001002, A4001005, A4001006, A4001008, A4001011, A4001012, A4001013, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025 and A4001042.
Date of Table Generation: 13SEP2006 (05:27)

MEDDRA v(8.1) SYSTEM ORGAN CLASS Higher Level Term	Treatment Group							
	Placebo	<100mg unit dose	100mg BID	150mg BID	300mg BID	600mg QD	600mg BID	900mg QD
Feeling hot and cold	1 (1.8)	0	0	0	0	0	0	0
Hypothermia	0	0	0	0	1 (1.2)	0	0	0
Inflammation	0	0	0	0	0	0	1 (5.9)	0
Influenza like illness	0	0	0	0	0	0	0	0
Irritability	0	0	0	1 (8.3)	0	0	0	0
Malaise	1 (1.8)	0	0	0	0	0	0	1 (11.1)
Mucosal dryness	0	0	0	0	0	0	0	0
Oedema peripheral	0	0	0	0	0	0	0	0
Pain	0	0	1 (0.7)	0	0	0	0	0
Pyrexia	0	0	0	0	1 (1.2)	0	0	0
Thirst	0	0	1 (0.7)	0	0	0	0	0
Venipuncture site pain	1 (1.8)	0	0	1 (8.3)	0	0	0	0
Vessel puncture site bruise	1 (1.8)	0	0	0	2 (2.5)	0	0	0
Vessel puncture site reaction	0	0	0	0	0	0	0	0
HEPATOBILIARY DISORDERS	0	0	0	0	0	0	0	0
Hyperbilirubinaemia	0	0	0	0	0	0	0	0
Jaundice	0	0	0	0	0	0	0	0
IMMUNE SYSTEM DISORDERS	0	0	0	0	0	0	0	0
Seasonal allergy	0	0	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS	9 (15.8)	3 (15.8)	15 (10.1)	0	9 (11.1)	2 (11.1)	1 (5.9)	1 (11.1)
Abscess	0	0	0	0	1 (1.2)	0	0	0
Acarodermatitis	1 (1.8)	0	0	0	0	0	0	0
Bronchitis	1 (1.8)	0	0	0	0	0	0	0
Erysipelas	0	0	1 (0.7)	0	0	0	0	0

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