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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Selzentry® / Celsentri® / Maraviroc

PROTOCOL NO.: A4001056

PROTOCOL TITLE: A Phase II, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety and Efficacy of Maraviroc (UK-427,857) in the Treatment of Rheumatoid Arthritis in Subjects Receiving Methotrexate

Study Centers: A total of 41 centers took part in the study and randomized subjects: 16 in the United States (US), 4 each in Spain and Australia, 3 each in Germany, India, Italy, Portugal and Ukraine, and 2 in Mexico.

Study Initiation Date and Final Completion Date: 11 February 2007 to 07 October 2008
The study was terminated prematurely.

Phase of Development: 2a

Study Objectives:

Primary Objectives:

- To evaluate the safety and tolerability of maraviroc at 150 and 300 mg twice daily (BID) administered for 4 weeks to subjects in combination with methotrexate (MTX)
- To characterize the pharmacokinetics (PK) and to investigate potential drug-drug interactions (DDIs) between maraviroc and MTX in a cohort of subjects (n=16)
- To assess the efficacy of maraviroc 300 mg versus placebo, both administered BID for 12 weeks in subjects with rheumatoid arthritis (RA) receiving MTX

Secondary Objective:

- To evaluate the effect of maraviroc treatment on patient reported outcomes and disease activity status

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled Phase 2a study of maraviroc in subjects with RA receiving MTX. The study was conducted in 2 components:

Safety/Pharmacokinetic Component: This component was a 4-week, open-label study investigating 2 dose levels of maraviroc (300 and 150 mg BID) in subjects without any disease activity requirements on stable doses of background MTX. It was conducted before the proof-of-concept (POC) Component in order to confirm the safety and lack of clinically significant DDI potential of maraviroc when administered with MTX as this combination had not previously been tested in humans. Subjects enrolled in this component of the study were not eligible for inclusion in the POC Component. If subjects discontinued from the study for reasons other than safety, they could be replaced. This component of the study was conducted only in the US.

Blood samples were obtained at Screening Visits and assessed each subject's steady-state MTX PK parameters. Additional blood samples were collected at Week 1 (steady-state) in order to assess steady-state MTX PK parameters in the presence of maraviroc. PK analyses for potential DDIs coupled with weekly monitoring of safety were utilized by an internal Risk Management Committee to select a dose for the POC Component of the study. If the safety and PK profiles of the 150 and 300-mg doses were similar, and there was no evidence of a DDI with MTX, the 300-mg dose was to be selected for the 12-week POC Component.

Proof-of-Concept Component: In this component, subjects were randomized 2:1 to maraviroc or placebo, both in combination with stable doses of MTX, in a double-blinded manner. The POC Component assessed the safety and efficacy of maraviroc dosed BID with stable weekly doses of MTX during a 12-week treatment period.

Table 1 and Table 2 summarize the schedule of study activities for the Safety/PK and POC Components, respectively.

Table 1. Schedule of Activities for Safety/PK Component

Protocol Activity	Pre-Treatment								Treatment									Post-Treatment
	Screening					Baseline												
Week	-2					0			1							2	3	4/EW	8
Day	-14					1			8±2							15±2	22±2	29±3	57±3
Hour	0	1	2	3	4	0	Dose	2-3	0	Dose	0.5	1	2	3	4				
Informed consent	X																		
Medical history	X																		
Physical examination[a]	X																	X	
Orthostatic blood pressure and HR	X					X			X							X	X	X	X[b]
Purified protein derivative skin test	X																		
Reading of purified protein derivative[c]	+48-72 hours																		
12-lead ECG			X[d] →			X[e]		X[f]					X[f] →			X[f]		X[f]	
Prior and concomitant medications	X					X			X							X	X	X	X
Methotrexate dosing (in clinic)[g]	X						X			X						X	X	X	
Maraviroc dosing (in clinic)[g]							X			X						X	X	X	
Laboratory assessment																			
Hematology	X					X			X							X	X	X	X
Chemistry	X					X			X							X	X	X	X
Urinalysis	X					X												X	
Pregnancy test	X[h]					X[i]										X[i]		X[h]	
C-Reactive protein						X[j]												X[j]	
GFR-calculated estimate	X																		
Serology																			
Human immunodeficiency virus	X																		
Hepatitis B and C	X																		
Hepatitis B surface antigen	X																		
Hepatitis C antibody	X																		

Table 1. Schedule of Activities for Safety/PK Component

Protocol Activity	**Pre-Treatment**								**Treatment**									**Post-Treatment**
	Screening					**Baseline**												
Week	**-2**					**0**			**1**							**2**	**3**	**4/EW**	**8**
Day	**-14**					**1**			**8±2**							**15±2**	**22±2**	**29±3**	**57±3**
Hour	**0**	**1**	**2**	**3**	**4**	**0**	**Dose**	**2-3**	**0**	**Dose**	**0.5**	**1**	**2**	**3**	**4**				
Pharmacokinetic assessments																			
Methotrexate samples		X	X	X	X				X		X	X	X	X	X			X[k]	
Maraviroc samples									X		X	X	X	X	X			X[k]	
Disease assessments																			
Tender/painful joint count						X												X	
Swollen joint count						X												X	
Physician's global assessment						X												X	
Patient's global assessment						X												X	
Patient's pain assessment (VAS)						X												X	
HAQ-DI						X												X	
SF-36						X												X	
Study treatment																			
Maraviroc outpatient dosing									X							X	X	X[l]	
Study med accounting									X							X	X	X	
Nonserious adverse events						X ◄	·····	·····	·····	·····	·····	·····	·····	·····	·····	·····	·····	·····	····· ► X
Serious adverse events	X ◄	·····	·····	·····	·····	·····	·····	·····	·····	·····	·····	·····	·····	·····	·····	·····	·····	·····	····· ► X

Table 1. Schedule of Activities for Safety/PK Component

AE = adverse event; BP = blood pressure; CRP = C-reactive protein; CRU = clinical research unit; ECG = electrocardiogram; EW = early withdrawal; GFR = glomerular filtration rate; HAQ-DI = Health Assessment Questionnaire-Disability Index; HR = heart rate; MTX = methotrexate; PK = pharmacokinetic; QTc = corrected QT interval; SF = short form; VAS = Visual Analog Scale.

a. Physical examination included a general external ocular examination.
b. If subject experienced on-treatment postural hypotension, orthostatic BP and HR required at Post-Treatment Visit.
c. Induration of ≥5 mm disqualified a subject from the study unless 1) a chest X-ray was normal and a history of treatment for tuberculosis was verified or 2) vaccination with Bacilli Calmette-Guerin.
d. Triplicate ECGs at the 2 to 3 hours post-MTX dose time point. A mean QTc >450 msec disqualified the subject from entering the PK/safety study.
e. Single confirmatory ECG prior to dosing at 0 hour to confirm QTc ≤450 msec.
f. Triplicate ECGs at the 2 to 3 hours post-MTX and maraviroc dose. A mean QTc >500 msec warranted discontinuation of study treatment and prolongation of QTc reported as an AE.
g. For each clinic visit the subjects had to be in a fasting state and held their MTX and/or maraviroc until their scheduled clinic visit. MTX/maraviroc dose were administered in the clinic on the scheduled visit.
h. Serum pregnancy test.
i. Urine pregnancy test.
j. CRP results were blinded to the Investigator.
k. Last dose was administered in the CRU during the subject's last visit.
l. Samples only obtained on subjects that withdrew early due to targeted treatment-related AEs.

Table 2. Schedule of Activities for POC Component

Protocol Activity	Pre-Treatment		Treatment					Post-Treatment
	Screening	Baseline						
Week	**-2**		**1**	**2**	**4**	**8**	**12/EW**	**16**
Day	**- up to 28±7**	**1**	**8±2**	**15±2**	**29±3**	**57±3**	**85±3**	**115±3**
Hour	**0**	**0**						
Informed consent	X							
Medical history	X							
Physical examination[a]	X						X	
Orthostatic blood pressure and HR	X	X	X	X	X	X	X	X[b]
Purified protein derivative skin test	X							
Reading of purified protein derivative[c]	+48-72 hrs							
12-lead ECG	X[d]	X[e]	X[f]	X[f]	X[f]	X[f]	X[f]	X[g]
Prior and concomitant medications	X	X						
Methotrexate dosing	X----------							----------X
Maraviroc dosing (in clinic)		X						
Laboratory assessment								
Hematology	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Absolute CD4 and CD8 count		X					X	
CD4 and CD8%		X					X	
CD4:CD8 ratio		X					X	
Chemistry	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Urinalysis	X	X					X	
Pregnancy test	X[i]	X[j]		X[j]	X[j]	X[j]	X[i]	
C-Reactive protein[k]	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate[l]	X							
GFR-calculated estimate	X							
Pharmacogenomics								
Genotyping for CCR5Δ32[m]	X							
Serology								
Human immunodeficiency virus	X							
Hepatitis B and C	X							
Hepatitis B surface antigen	X							
Hepatitis C antibody	X							

Table 2. Schedule of Activities for POC Component

Protocol Activity	Pre-Treatment		Treatment					Post-Treatment
	Screening	Baseline						
Week	**-2**		**1**	**2**	**4**	**8**	**12/EW**	**16**
Day	**- up to 28±7**	**1**	**8±2**	**15±2**	**29±3**	**57±3**	**85±3**	**115±3**
Hour	**0**	**0**						
Disease assessments								
Tender/painful joint count	X[n]	X	X	X	X	X	X	X
Swollen joint count	X[n]	X	X	X	X	X	X	X
Physician's global assessment		X	X	X	X	X	X	X
Patient's global assessment		X	X	X	X	X	X	X
Patient's pain assessment (VAS)		X	X	X	X	X	X	X
HAQ-DI		X	X	X	X	X	X	X
SF-36		X			X		X	
Exploratory biomarkers (voluntary)								
Deoxyribonucleic acid sample[o]		X						
Ribonucleic acid sample[o]		X		X	X	X	X	X
Exploratory proteomic sample[o]		X					X	
Pharmacokinetic assessments								
Methotrexate sample							X[p]	
Maraviroc sample							X[p]	
Study treatment								
Maraviroc dosing		X	X	X	X	X	X[q]	
Study drug accounting			X	X	X	X	X	
Nonserious adverse events		X ◄	·····	·····	·····	·····	····· ►	X
Serious adverse events	X ◄	·····	·····	·····	·····	·····	····· ►	X

AE = adverse event; BP = blood pressure; CD4 = cluster of differentiation 4; CD8 = cluster of differentiation 8; CCR5 = Chemokine receptor 5; CRP = C-reactive protein; ECR = erythrocyte sedimentation rate; ECG = electrocardiogram; EW = early withdrawal; GFR = glomerular filtration rate; HAQ-DI = Health Assessment Questionnaire-Disability Index; HR =heart rate; MTX = methotrexate; POC = proof-of-concept; QTc = corrected QT; SF = short form; VAS = Visual Analogue Scale.

a. Physical examination included a general external ocular examination.

b. If subject experienced on-treatment postural hypotension, orthostatic BP and HR required at Post-Treatment Visit.

c. Induration of ≥5 mm disqualified a subject from the study unless 1) a chest x-ray was normal and a history of treatment for tuberculosis was verified or 2) vaccination with Bacilli Calmette-Guerin.

Table 2. Schedule of Activities for POC Component

d. Regardless of MTX dosing time, triplicate ECGs were performed. A mean QTc interval >450 msec disqualified subject from study.
e. Confirmed QTc ≤450 msec via single ECG prior to administering maraviroc. If MTX was scheduled to be administered on visit day, the ECG was to be done prior to maraviroc and /MTX administration.
f. Regardless of dosing time, a single ECG was performed and assessed for safety. A QTc of >500 msec required confirmation with triplicate ECGs. A mean QTc interval of >500 msec warranted discontinuation of study drug and QTc prolongation as the AE.
g. Follow-up ECG required if abnormal ECG at the last visit.
h. Subjects were to be fasting prior to clinic visit.
i. Serum pregnancy test.
j. Urine pregnancy test.
k. C-Reactive protein results for determination of study entry criteria were blinded after the screening visit to the Investigator.
l. Erythrocyte sedimentation rate could be collected at the Screening Visit and analyzed locally to determine eligibility.
m. Subjects who were CCR5Δ32 positive were excluded from the study. If genotyping had been previously obtained, documented results could be used instead.
n. Active disease was defined as ≥6 tender/point joints (28 joint count) on motion, ≥6 swollen joints (28 joint count) and CRP ≥0.7 mg/dL or an ESR of at least 28 mm/hour.
o. Samples for exploratory biomarkers were voluntary.
p. Samples only obtained on subjects that withdraw early due to targeted drug-related AEs.
q. Last dose was the morning of the clinic visit.

Number of Subjects (Planned and Analyzed): Approximately 16 subjects were planned and enrolled in the safety/PK Component; 8 subjects received maraviroc 300 mg BID and 8 subjects received maraviroc 150 mg BID. In the POC Component, 114 subjects were planned, 112 subjects were assigned to treatment, and 110 subjects were treated and analyzed (77 subjects received maraviroc 300 mg BID and 33 subjects received placebo). A total of 128 subjects were randomized (2 in Italy, 4 each in Australia and Portugal, 5 in Germany, 11 in India, 19 in Spain, 22 in Mexico, 23 in Ukraine, and 38 in the US).

Diagnosis and Main Criteria for Inclusion: Subjects were at least 18 years old, diagnosed with active RA (required for the POC Component) based upon the American College of Rheumatology (ACR) 1987 revised criteria, had met ACR 1991 revised criteria for Global Functional Status in RA (Class I, II, or II), and had received ≥10 mg/week and ≤25 mg/week MTX for at least 12 weeks prior to study entry. The dose had to be stable for ≥4 weeks prior to study entry and had to remain unchanged throughout the 4-or 12-week treatment period.

Study Treatment: All doses of maraviroc were self-administered and taken at approximately 12-hour intervals on an empty stomach, specifically 1 hour before a meal or 4 hours following the last meal. For the safety/PK Component, subjects were randomized to receive either maraviroc 300 or 150 mg BID. During the POC Component, subjects were randomized to either oral maraviroc 300 mg BID or placebo BID. Both maraviroc and placebo treatments were added to the ongoing MTX treatment. Maraviroc (150-mg tablets) and matching placebo were packaged in high density polyethylene bottles. Subjects continued to use their own supply of MTX.

Efficacy, Pharmacokinetic, Safety and Outcomes Research Endpoints:

Primary Endpoint:

- ACR 20% response rate at Week 12

Secondary Endpoints:

Efficacy:

- ACR 20 response at Weeks 1, 2, 4, 8, and 16

The following were analyzed at Weeks 1, 2, 4, 8, 12, and 16:

- ACR 50/70 response
- Tender/painful joint count
- Swollen joint count
- Patient's Assessment of Arthritis Pain (100 mm Visual Analog Scale [VAS])
- Patient's Global Assessment of Arthritis

- Physician's Global Assessment of Arthritis
- Health Assessment Questionnaire-Disability Index (HAQ-DI)
- C-reactive protein (CRP)
- Disease Activity Score (DAS) using CRP (DAS28-4 [CRP])

Additional Assessments:

- Short form – 36 (SF-36) Health Questionnaire – Version 2, acute (SF-36) at Baseline, Week 4, and Week 12
- The overall incidence and time to withdrawal due to lack of efficacy were also analyzed

Pharmacokinetic Endpoints (4-Week Safety/PK Component only):

- Plasma concentrations of MTX and maraviroc was obtained using a validated assay

Efficacy analyses were conducted on the population of subjects in the POC Component of the study and an integrated safety analysis was conducted in all subjects from both components.

Safety Endpoints:

Safety endpoints were evaluated by comparing the 150-and 300-mg doses of maraviroc (safety/PK Component) or maraviroc to placebo (POC Component) in combination with MTX.

- Incidence and severity of adverse events (AEs)
- Incidence and severity of clinical findings on physical examination
- Incidence and severity of clinical laboratory abnormalities
- Mean change from Baseline in orthostatic blood pressure and heart rate
- Categorical summary of absolute vital signs and vital sign changes compared to Baseline
- Mean change from Baseline in 12-lead electrocardiogram (ECG) parameters
- Categorical summary of absolute ECG parameters and ECG changes compared to Baseline by subject

Safety Evaluations: Safety evaluations included AEs, laboratory evaluations, vital signs (blood pressure and pulse rate) and ECGs.

Statistical Methods:

Full Analysis Set (FAS): FAS was an intent-to-treat analysis set that included all subjects randomized to treatment who took at least 1 dose of study medication. All efficacy analyses were performed on the FAS cohort from the POC Component of the study. Safety analyses were performed on the FAS cohort from both the PK and POC Components of the study.

The sample size of 16 subjects in the open-label safety/PK Component was determined to detect a 50% decrease in MTX clearance in the presence of maraviroc at steady-state with at least 80% power using a population PK modeling approach. A formal power evaluation was not performed for the effect of MTX on maraviroc PK; however, this evaluation was prespecified in the PK analysis plan.

In the POC Component, it was anticipated that 30% of subjects assigned to receive placebo + MTX treatment and 55% of subjects assigned to receive maraviroc 300 mg BID + MTX treatment would achieve an ACR 20 response at Week 12. A sample size of 38 subjects for the placebo + MTX treatment group and 76 subjects for the maraviroc treatment BID + MTX treatment group was sufficient to detect an absolute difference of 25% in ACR 20 response with 81% power and a Type I error at 0.05 in a 1-sided test taking the planned futility interim analysis into account. The interim analysis was performed during the course of the POC Component of the study. The planned formal interim analysis indicated that it was unlikely that maraviroc was efficacious in treating RA for subjects who were also receiving MTX, therefore the study was terminated.

There was no efficacy analysis performed in the safety/PK Component due to the study being terminated. Only safety and PK were analyzed.

A subject was considered an ACR 20 responder if:

- The counts for both tender and swollen joints had reduced by 20% or more from Baseline assessment, and
- Three out of the following 5 assessments showed a reduction of 20% or more from Baseline assessment:
    - Patient's Assessment of Arthritis Pain (VAS)
    - Patient's Global Assessment of Arthritis (VAS)
    - Physician's Global Assessment of Arthritis
    - HAQ-DI
    - CRP

Categorical variables (ACR 20/50/70) were analyzed by the Chi-squared test, unless the normal approximation to the binomial distribution was not appropriate. If this was the case, the Barnard exact test was used. Analysis of covariance models including Baseline or

covariate interaction terms were only analyzed for the tender/painful joint count, swollen joint count and DAS28 endpoints.

RESULTS:

Subject Disposition and Demography:

Subject evaluation group results for safety/PK Component and POC Component are shown in Table 3 and Table 4, respectively.

Table 3. Subject Evaluation Groups – Safety/PK Component

	Maraviroc 150 mg BID	Maraviroc 300 mg BID	Total
Number of Subjects			
Screened			20
Assigned to study treatment			16
Treated	8	8	16
Completed	7	8	15
Discontinued	1	0	1
Not related to study drug	1	0	1
Adverse event	1	0	1
Analyzed for safety			
Adverse events	8	8	16
Laboratory data	8	8	16

Discontinuations occurring outside the lag period were attributed to the last study treatment received.
BID = twice daily; PK = pharmacokinetic.

Table 4. Subject Evaluation Groups – POC Component

	Maraviroc 300 mg BID	Placebo	Total
Number (%) of Subjects			
Screened			198
Assigned to study treatment			112
Treated	77	33	110
Completed	55 (71.4)	19 (57.6)	74 (66.1)
Discontinued	22 (28.6)	14 (42.4)	36 (32.1)
Related to study drug	19 (24.7)	8 (24.2)	-
Adverse event	4 (5.2)	1 (3.0)	-
Lack of efficacy	5 (6.5)	2 (6.1)	-
Other	10 (13.0)	5 (15.2)	-
Not related to study drug	3 (3.9)	6 (18.2)	-
Adverse event	1 (1.3)	3 (9.1)	-
Other	1 (1.3)	0	-
Subject no longer willing to participate in study	1 (1.3)	3 (9.1)	-
Analyzed for efficacy			
Full analysis	77 (100.0)	33 (100.0)	110 (98.2)
Interim analysis	38 (49.4)	21 (63.6)	59 (52.7)
Analyzed for safety			
Adverse events	77 (100.0)	33 (100.0)	110 (98.2)
Laboratory data	77 (100.0)	33 (100.0)	110 (98.2)

Discontinuations occurring outside the lag period had been attributed to the last study treatment received.
BID = twice daily; POC = proof-of-concept.

Demographic and Baseline characteristics are summarized in Table 5 for the safety/PK and Table 6 for the POC Component. The age range of subjects included in the safety/PK Component was 44-67 years and 20-81 years for the POC Component.

Table 5. Demographic Characteristics – Safety/PK Component

	Maraviroc 150 mg BID			Maraviroc 300 mg BID		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Number of Subjects	4	4	8	3	5	8
Age (years)						
Mean (SD)	57.0 (10.5)	60.0 (5.1)	58.5 (7.8)	60.7 (2.1)	54.2 (6.3)	56.6 (5.9)
Range	44-66	55-67	44-67	59-63	46-61	46-63
Race						
White	4	4	8	3	5	8

BID = twice daily; PK = pharmacokinetic; SD = standard deviation.

Table 6. Demographic Characteristics – POC Component

	Maraviroc 300 mg BID			Placebo		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Number of subjects	6	71	77	11	22	33
Age (years)						
Mean (SD)	68.2 (10.1)	52.4 (11.5)	53.6 (12.1)	55.1 (9.7)	52.6 (11.9)	53.4 (11.1)
Range	51-81	20-79	20-81	40-72	34-76	34-76
Race (%)						
White	5 (83.3)	46 (64.8)	51 (66.2)	9 (81.8)	12 (54.5)	21 (63.6)
Black	0	3 (4.2)	3 (3.9)	0	0	0
Asian	0	7 (9.9)	7 (9.1)	2 (18.2)	3 (13.6)	5 (15.2)
Other	1 (16.7)	15 (21.1)	16 (20.8)	0	7 (31.8)	7 (21.2)

BID = twice daily; POC = proof-of-concept; SD = standard deviation.

Efficacy, Pharmacokinetic and Outcomes Research Results:

The planned formal interim analysis indicated that it was unlikely that maraviroc was efficacious in treating RA for subjects who were also receiving MTX, therefore the study was terminated for futility.

Efficacy results are only available for the POC Component of the study.

Primary Endpoint Results:

American College of Rheumatology 20 Responder Scores: There was no significant difference between maraviroc 300 mg BID and placebo ACR 20 responder rate at Week 12 utilizing the FAS (9.09 confidence interval [CI]: -6.16, 21.83; p-value=0.155) (Table 7). Observed case analysis also showed no significant difference between maraviroc 300 mg BID and placebo ACR 20 responder rate at Week 12 (5.91 CI: -14.64, 22.85; p-value = 0.310).

Table 7. ACR 20 Response at Week 12 (Full Analysis Set - POC)

	Maraviroc 300 mg BID	**Placebo**
Number of Subjects	**77**	**33**
n (%)	21 (27.27)	6 (18.18)
Difference from placebo (90% CI)	9.09 (-6.16, 21.83)	NA
p-Value	0.155	NA

ACR = American College of Rheumatology; BID = twice daily; CI = confidence interval; n = number of subjects analyzed; NA = not applicable; POC = proof-of-concept.

Secondary Endpoint Results: The results for ACR 20 at Weeks 1, 2, 4, 8, and follow-up are summarized in Table 8. The results for ACR 50 and ACR 70 at Weeks 1, 2, 4, 8, and 12 are summarized in Table 9 Table 10, respectively.

Table 8. ACR 20 Response at Weeks 1, 2, 4, 8 and Follow-Up (Observed Case Analysis - POC)

	Maraviroc 300 mg BID	Placebo
Week 1		
Number of subjects	77	31
n (%)	8 (10.39)	4 (12.90)
Difference from placebo (90% CI)	-2.51 (-16.33, 8.12)	NA
p-Value	0.802	NA
Week 2		
Number of subjects	73	30
n (%)	12 (16.44)	5 (16.67)
Difference from placebo (90% CI)	-0.23 (-15.36, 11.76)	NA
p-Value	0.511	NA
Week 4		
Number of subjects	69	29
n (%)	20 (28.99)	8 (27.59)
Difference from placebo (90% CI)	1.40 (-15.87, 16.53)	NA
p-Value	0.444	NA
Week 8		
Number of subjects	64	25
n (%)	20 (31.25)	6 (24.00)
Difference from placebo (90% CI)	7.25 (-11.12, 22.66)	NA
p-Value	0.250	NA
Follow-Up		
Number of subjects	70	30
n (%)	14 (20.00)	9 (30.00)
Difference from placebo (90% CI)	-10.00 (-26.59, 4.75)	NA
p-Value	0.862	NA

Missing values were not imputed in observed case analysis.
p-Value (1-sided) was based on Barnard exact test if >20% of expected cell counts are <5 otherwise Pearson Chi-square test.
90% confidence interval was calculated for the difference between the treatment groups based on Chi-square/Barnard test.
ACR = American College of Rheumatology; BID = twice daily; CI = confidence interval; n = number of subjects analyzed; NA = not applicable; POC = proof-of-concept.

Table 9. ACR 50 Response at Weeks 1, 2, 4, 8 and 12 (Full Analysis Set - POC)

	Maraviroc 300 mg BID	Placebo
Number of Subjects	**77**	**33**
Week 1		
n (%)	1 (1.30)	0
Difference from placebo (90% CI)	1.30 (-6.34, 6.01)	NA
p-Value	0.420	NA
Week 2		
n (%)	2 (2.60)	0
Difference from placebo (90% CI)	2.60 (-5.08, 7.95)	NA
p-Value	0.258	NA
Week 4		
n (%)	2 (2.60)	2 (6.06)
Difference from placebo (90% CI)	-3.46 (-14.39, 3.42)	NA
p-Value	1.000	NA
Week 8		
n (%)	6 (7.79)	3 (9.09)
Difference from placebo (90% CI)	-1.30 (-13.56, 7.92)	NA
p-Value	0.899	NA
Week 12		
n (%)	8 (10.39)	3 (9.09)
Difference from placebo (90% CI)	1.30 (-11.24, 10.96)	NA
p-Value	0.489	NA

Missing values were imputed by the method of last observation carried forward.
p-Value (1-sided) was based on Barnard exact test if >20% of expected cell counts are <5 otherwise Pearson Chi-square test.
90% Confidence interval was calculated for the difference between the treatment groups based on Chi-square/Barnard test.
ACR = American College of Rheumatology; BID = twice daily; CI = confidence interval; n = number of subjects analyzed; NA = not applicable; POC = proof-of-concept.

Table 10. ACR 70 Response at Weeks 1, 2, 4, 8 and 12 (Full Analysis Set - POC)

	Maraviroc 300 mg BID	Placebo
Number of Subjects	**77**	**33**
Week 1		
n (%)	0 (0)	0 (0)
Difference from placebo (90% CI)	-	-
p-Value	-	-
Week 2		
n (%)	0 (0)	0 (0)
Difference from placebo (90% CI)	-	-
p-Value	-	-
Week 4		
n (%)	0 (0)	1 (3.03)
Difference from placebo (90% CI)	-3.03 (-13.59, 1.28)	-
p-Value	1.000	-
Week 8		
n (%)	2 (2.60)	0 (0)
Difference from placebo (90% CI)	2.60 (-5.08, 7.95)	NA
p-Value	0.258	NA
Week 12		
n (%)	0 (0)	1 (3.03)
Difference from placebo (90% CI)	-3.03 (13.59, 1.28)	NA
p-Value	1.000	NA

Missing values were imputed by the method of last observation carried forward.
p-Value (1-sided) was based on Barnard exact test if >20% of expected cell counts are <5 otherwise Pearson Chi-square test.
90% Confidence interval was calculated for the difference between the treatment groups based on Chi-square/Barnard test.
ACR = American College of Rheumatology; BID = twice daily; CI = confidence interval; n = number of subjects analyzed; NA = not applicable; POC = proof-of-concept.

Results showed a general decrease in tender/painful and swollen joint counts for both, subjects who had received maraviroc 300 mg BID or placebo, compared to Baseline when assessed at Week 12. The difference between maraviroc 300 mg BID from placebo was more pronounced at Week 8. The results for tender/painful and swollen joints counts were presented in Table 11 and Table 12 respectively.

Table 11. Analysis of Covariance of Tender/Painful Joint Count at Weeks 1, 2, 4, 8 and 12 (Full Analysis Set - POC)

	Maraviroc 300 mg BID	Placebo
Number of Subjects	**77**	**33**
Week 1		
LSM	-0.81	-1.91
Difference from placebo (90% CI)	1.10 (-0.79, 2.99)	NA
p-Value	0.335	-
Week 2		
LSM	-2.08	-2.38
Difference from placebo (90% CI)	0.30 (-1.82, 2.41)	NA
p-Value	0.816	NA
Week 4		
LSM	-4.00	-4.01
Difference from placebo (90% CI)	0.01 (-2.35, 2.36)	NA
p-Value	0.996	NA
Week 8		
LSM	-4.85	-3.24
Difference from placebo (90% CI)	-1.61 (-3.98, 0.76)	NA
p-Value	0.263	NA
Week 12		
LSM	-4.89	-3.41
Difference from placebo (90% CI)	-1.48 (-3.82, 0.85)	NA
p-Value	0.294	NA

Missing values were imputed by the method of last observation carried forward.
Estimates and p-values based on analysis of covariance with baseline tender/painful joint count as the covariate, treatment, region as fixed.
BID = twice daily; CI = confidence interval; LSM = least square mean; n = number of subjects analyzed; NA = not applicable; POC = proof-of-concept.

Table 12. Analysis of Covariance of Swollen Joint Count at Weeks 1, 2, 4, 8 and 12 (Full Analysis Set - POC)

	Maraviroc 300 mg BID	Placebo
Number of Subjects	**77**	**33**
Week 1		
LSM	-1.39	-1.07
Difference from placebo (90% CI)	-0.32 (-1.70, 1.06)	NA
p-Value	0.700	NA
Week 2		
LSM	-2.25	-2.51
Difference from placebo (90% CI)	0.26 (-1.45 , 1.97)	NA
p-Value	0.799	NA
Week 4		
LSM	-3.93	-4.08
Difference from placebo (90% CI)	0.15 (-1.35, 1.66)	NA
p-Value	0.867	NA
Week 8		
LSM	-4.48	-3.03
Difference from placebo (90% CI)	-1.45 (-3.17, 0.28)	NA
p-Value	0.167	NA
Week 12		
LSM	-3.48	-3.43
Difference from placebo (90% CI)	-0.05 (-1.91, 1.81)	NA
p-Value	0.966	NA

Missing values were imputed by the method of last observation carried forward.
Estimates and p-values based on analysis of covariance with baseline swollen joint count as the covariate, treatment, region as fixed effects.
BID = twice daily; CI = confidence interval; LSM = least square mean; n = number of subjects analyzed; NA = not applicable; POC = proof-of-concept.

Table 13, Table 14 and Table 15 summarized the analysis of covariance of Patient's Assessment of Pain, Patient's Global Assessment of Arthritis and Physician's Global Assessment of Arthritis, respectively. There was no significant difference between treatment groups for these endpoints over time.

Table 13. Analysis of Covariance of Patient's Assessment of Arthritis Pain at Weeks 1, 2, 4, 8 and 12 (Full Analysis Set - POC)

	Maraviroc 300 mg BID	Placebo
Week 1		
Number of subjects	77	33
LSM	-3.96	-3.62
Difference from placebo (90% CI)	-0.34 (-6.41, 5.72)	NA
p-Value	0.925	NA
Week 2		
Number of subjects	77	33
LSM	-8.46	-3.20
Difference from placebo (90% CI)	-5.26 (-12.62, 2.11)	NA
p-Value	0.239	NA
Week 4		
Number of subjects	77	33
LSM	-8.35	-9.08
Difference from placebo (90% CI)	0.73 (-6.79, 8.25)	NA
p-Value	0.872	NA
Week 8		
Number of subjects	77	33
LSM	-10.30	-8.67
Difference from placebo (90% CI)	-1.63 (-9.91, 6.65)	NA
p-Value	0.745	NA
Week 12		
Number of subjects	77	33
LSM	-8.30	-6.09
Difference from placebo (90% CI)	-2.22 (-10.14, 5.71)	NA
p-Value	0.644	NA

Missing values were imputed by the method of last observation carried forward.
Estimates and p-values based on analysis of covariance with baseline Patient's Assessment of Arthritis Pain as the covariate, treatment, region as fixed effects.
BID = twice daily; CI = confidence interval; LSM = least square mean; n = number of subjects analyzed; NA = not applicable; POC = proof-of-concept.

Table 14. Analysis of Covariance of Patient's Global Assessment of Arthritis at Weeks 1, 2, 4, 8 and 12 (Full Analysis Set - POC)

	Maraviroc 300 mg BID	Placebo
Week 1		
Number of subjects	77	33
LSM	-4.70	-2.34
Difference from placebo (90% CI)	-2.36 (-8.49, 3.77)	NA
p-Value	0.524	NA
Week 2		
Number of subjects	77	33
LSM	-8.85	-4.88
Difference from placebo (90% CI)	-3.96 (-10.80, 2.87)	NA
p-Value	0.338	NA
Week 4		
Number of subjects	77	33
LSM	-10.00	-9.02
Difference from placebo (90% CI)	-0.98 (-8.55, 6.58)	NA
p-Value	0.830	NA
Week 8		
Number of subjects	77	33
LSM	-11.12	-3.44
Difference from placebo (90% CI)	-7.68 (-15.76, 0.40)	NA
p-Value	0.118	NA
Week 12		
Number of subjects	77	33
LSM	-8.55	-6.78
Difference from placebo (90% CI)	-1.78 (-9.73, 6.18)	NA
p-Value	0.712	NA

Missing values were imputed by the method of last observation carried forward.
Estimates and p-values based on analysis of covariance with baseline Patient's Global Assessment of Arthritis as the covariate, treatment, region as fixed effects.
BID = twice daily; CI = confidence interval; LSM = least square mean; n = number of subjects analyzed; NA = not applicable; POC = proof-of-concept.

Table 15. Analysis of Covariance of Physician's Global Assessment of Arthritis at Weeks 1, 2, 4, 8 and 12 (Full Analysis Set - POC)

	Maraviroc 300 mg BID	Placebo
Number of Subjects	**75**	**32**
Week 1		
LSM	-0.30	-0.22
Difference from placebo (90% CI)	-0.08 (-0.28, 0.13)	NA
p-Value	0.540	NA
Week 2		
LSM	-0.44	-0.39
Difference from placebo (90% CI)	-0.04 (-0.28, 0.19)	NA
p-Value	0.757	NA
Week 4		
LSM	-0.49	-0.44
Difference from placebo (90% CI)	-0.05 (-0.31, 0.21)	NA
p-Value	0.767	NA
Week 8		
LSM	-0.63	-0.37
Difference from placebo (90% CI)	-0.26 (-0.52, 0.01)	NA
p-Value	0.112	NA
Week 12		
LSM	-0.49	-0.36
Difference from placebo (90% CI)	-0.13 (-0.42, 0.17)	NA
p-Value	0.490	NA

Missing values were imputed by the method of last observation carried forward.
Estimates and p-values based on analysis of covariance with baseline Physician's Global Assessment of Arthritis as the covariate, treatment, region as fixed effects.
BID = twice daily; CI = confidence interval; LSM = least square mean; n = number of subjects analyzed; NA = not applicable; POC = proof-of-concept.

Table 16 summarizes descriptive statistics of HAQ-DI. Mean change from Baseline was more pronounced in the maraviroc group compared to the placebo group at Week 12, however standard deviation values were large. There was a significant difference of maraviroc 300 mg BID from placebo at Weeks 2 and 8, but not in the other weeks.

Table 16. Analysis of Covariance of HAQ-DI at Weeks 1, 2, 4, 8 and 12 (Full Analysis Set - POC)

	Maraviroc 300 mg BID	Placebo
Week 1		
Number of subjects	77	31
LSM	-0.08	-0.03
Difference from placebo (90% CI)	-0.06 (-0.19, 0.07)	NA
p-Value	0.464	NA
Week 2		
Number of subjects	77	30
LSM	-0.22	-0.04
Difference from placebo (90% CI)	-0.18 (-0.35, -0.02)	NA
p-Value	0.068	NA
Week 4		
Number of subjects	77	30
LSM	-0.24	-0.18
Difference from placebo (90% CI)	-0.06 (-0.23, 0.11)	NA
p-Value	0.532	NA
Week 8		
Number of subjects	63	25
LSM	-0.25	-0.03
Difference from placebo (90% CI)	-0.22 (-0.41, -0.03)	NA
p-Value	0.063	NA
Week 12		
Number of subjects	55	20
LSM	-0.18	-0.06
Difference from placebo (90% CI)	-0.12 (-0.36, 0.12)	NA
p-Value	0.396	NA

Missing values were imputed by the method of last observation carried forward.
Estimates and p-values based on analysis of covariance with HAQ-DI as the covariate, treatment, region as fixed effects.
BID = twice daily; CI = confidence interval; HAQ-DI = Health Assessment Questionnaire-Disability Index; LSM = least square mean; n = number of subjects analyzed; NA = not applicable; POC = proof-of-concept.

Table 17 summarizes the difference from placebo of CRP at Weeks 1, 2, 4, 8 and 12 for the POC Component.

Table 17. Analysis of Covariance of C-Reactive Protein at Weeks 1, 2, 4, 8 and 12 (Full Analysis Set - POC)

	Maraviroc 300 mg BID N=73	Placebo N=31
Week 1		
LSM	1.20	3.40
Difference from placebo (90% CI)	-2.20 (-7.36, 2.96)	NA
p-Value	0.481	NA
Week 2		
LSM	3.14	1.81
Difference from placebo (90% CI)	1.33 (-4.34, 6.99)	NA
p-Value	0.698	NA
Week 4		
LSM	3.36	-1.30
Difference from placebo (90% CI)	4.65 (-1.79, 11.10)	NA
p-Value	0.233	NA
Week 8		
LSM	2.33	-1.14
Difference from placebo (90% CI)	3.48 (-2.29, 9.25)	NA
p-Value	9.25	NA
Week 12		
LSM	2.35	1.93
Difference from placebo (90% CI)	0.41 (-5.81, 6.64)	NA
p-Value	0.912	NA

Missing values were imputed by the method of last observation carried forward.
Estimates and p-values based on analysis of covariance with C-reactive protein as the covariate, treatment, region as fixed effects.
BID = twice daily; CI = confidence interval; LSM = least square mean; N = total number of subjects; n = number of subjects analyzed; NA = not applicable; POC = proof-of-concept.

In general, DAS28-4 (CRP) decreased in both treatment groups throughout the study. Analysis of covariance of DAS28-4 (CRP) is summarized in Table 18 at Weeks 1, 2, 4, 8 and 12. Mean change from Baseline was slightly more pronounced in the maraviroc group compared to the placebo group at Weeks 8 and 12, however the difference was not statistically significant.

Table 18. Analysis of Covariance of DAS28-4 (CRP) - Difference From Placebo (Full Analysis Set – POC Component)

	Maraviroc 300 mg BID N=72	Placebo N=31
Week 1		
LSM	-0.23	-0.17
Difference versus placebo (90% CI)	-0.07 (-0.31, 0.18)	NA
p-Value	0.653	NA
Week 2		
LSM	-0.41	-0.33
Difference versus placebo (90% CI)	-0.08 (-0.41, 0.26)	NA
p-Value	0.703	NA
Week 4		
LSM	-0.64	-0.65
Difference versus placebo (90% CI)	0.01 (-0.37, 0.39)	NA
p-Value	0.968	NA
Week 8		
LSM	-0.82	-0.51
Difference versus placebo (90% CI)	-0.31 (-0.72, 0.10)	NA
p-Value	0.210	NA
Week 12		
LSM	-0.73	-0.63
Difference versus placebo (90% CI)	-0.10 (-0.53, 0.33)	NA
p-Value	0.696	NA

Estimates and p-values based on analysis of covariance with baseline DAS28-4 (CRP) as the covariate, treatment, region as fixed effects.
Missing values were imputed by the method of last observation carried forward.
BID = twice daily; CI = confidence interval; CRP = C-reactive protein; DAS = Disease Activity Score; LSM = least square mean; N = number of subjects; NA = not applicable; POC = proof-of-concept.

Table 19 summarizes the incidence of withdrawal from study due to lack of efficacy and Table 20 summarizes the time to withdrawal from study due to lack of efficacy. There was no significant difference between the treatment groups.

Table 19. Incidence of Withdrawal From Study due to Lack of Efficacy - POC

Number(%) of Subjects	Maraviroc 300 mg BID N=77	Placebo N=33
Withdrawal	22 (28.6)	14 (42.4)
Lack of efficacy	5 (6.5)	2 (6.1)
p-Value	0.649	

Withdrawal was the total number of withdrawals from the study.
p-Value for testing effect of study treatment on withdrawal due to lack of efficacy was based on a 1-sided Fisher's exact test.
BID = twice daily; N = number of subjects; POC = proof-of-concept.

Table 20. Time to Withdrawal From Study due to Lack of Efficacy - POC

Visit	Maraviroc 300 mg BID	Placebo
Week 1		
Number at risk	77	33
Rate (90% CI)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Week 2		
Number at risk	77	32
Rate (90% CI)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Week 4		
Number at risk	76	32
Rate (90% CI)	1.00 (1.00, 1.00)	NA
Week 8		
Number at risk	69	31
Rate (90% CI)	0.99 (0.96, 1.00)	1.00 (1.00, 1.00)
Week 12		
Number at risk	58	21
Rate (90% CI)	0.93 (0.86, 0.99)	0.92 (0.81, 1.00)
p-Value	0.9826	

p-Value is based on log-rank test.
BID = twice daily; CI = confidence interval; NA = not applicable; POC = proof-of-concept.

Table 21 summarizes the analysis of covariance of SF-36 Physical Component summary at Weeks 4 and 12 (POC) and Table 22 summarizes the analysis of covariance of SF-36 Mental Component summary at Weeks 4 and 12 (POC).

Table 21. Analysis of Covariance of SF-36 Physical Component Summary at Weeks 4 and 12 (Full Analysis Set - POC)

	Maraviroc 300 mg BID	Placebo
Week 4		
Number of subjects	69	30
LSM	4.33	3.76
Difference from placebo (90% CI)	0.57 (-1.87, 3.01)	NA
p-Value	0.698	NA
Week 12		
Number of subjects	53	19
LSM	3.14	4.81
Difference from placebo (90% CI)	-1.68 (-4.62, 1.26)	NA
p-Value	0.344	NA

Estimates and p-values based on analysis of covariance with baseline tender/painful joint count as the covariate, treatment, region as fixed effects.
BID = twice daily; CI = confidence interval; LSM = least square mean; NA = not applicable; POC = proof-of-concept; SF = short form.

Table 22. Analysis of Covariance of SF-36 Mental Component Summary at Weeks 4 and 12 (Full Analysis Set - POC)

	Maraviroc 300 mg BID	Placebo
Week 4		
Number of subjects	69	30
LSM	1.42	0.72
Difference from placebo (90% CI)	0.70 (-2.71, 4.11)	NA
p-Value	0.734	NA
Week 12		
Number of subjects	53	19
LSM	1.17	0.61
Difference from placebo (90% CI)	0.56 (-3.50, 4.62)	NA
p-Value	0.818	NA

Estimates and p-values based on analysis of covariance with baseline tender/painful joint count as the covariate, treatment, region as fixed.
BID = twice daily; CI = confidence interval; LSM = least square mean; NA = not applicable;
POC = proof-of-concept; SF = short form.

Following oral maraviroc, absorption of maraviroc was rapid with median time for maximum plasma concentration (T_{max}) ranging from 2.00-2.50 hours in both doses studied (Table 23). In general, increases in both area under plasma concentration (AUC) and maximum plasma concentration (C_{max}) were approximately proportional to increases in dose. Between-subject variability for both AUC and C_{max} was 48-74% for both treatments.

Table 23. Summary of Plasma Maraviroc Pharmacokinetic Parameter Values Following BID Dosing – Safety/PK Component

	Parameter Summary Statistics[a] by Maraviroc Treatment	
Parameter, Units	**Maraviroc 150 mg BID**	**Maraviroc 300 mg BID**
N	8	8
AUC_{0-4}, ng∗h/mL	451.6 (48)	1107 (74)
C_{max}, ng/mL	199.59 (50)	461.0 (67)
T_{max}, h	2.00 (0.50–3.00)	2.50 (1.00–4.00)

AUC_{0-4} = area under the plasma concentration-time profile from time 0 to 4 hours postdose; BID = twice daily; C_{max} = maximum observed concentration during the dosing interval; N = number of subjects;
PK = pharmacokinetic; T_{max} = time for C_{max}.
a. Geometric mean (% coefficient of variance) for all except median (range) for T_{max}.

Mean plasma MTX concentration time profiles at screening and 1 week after co-administration of maraviroc were comparable for both treatment groups (maraviroc 150 mg and 300 mg BID).

Concomitant administration of MTX and maraviroc (150 mg BID and 300 mg BID) did not result in altered MTX exposure in RA subjects. Absorption of MTX was rapid with median T_{max} ranging from 1.00-2.00 hours across all doses studied (Table 24).

Table 24. Summary of Plasma Pharmacokinetic Methotrexate Parameter Values Following BID Dosing of Maraviroc – Safety/PK Component

	Parameter Summary Statistics[a] by Maraviroc Treatment			
Parameter, Units	**Maraviroc 150 mg BID**		**Maraviroc 300 mg BID**	
Study Day	**Screening**	**Week 1**	**Screening**	**Week 1**
N	8	8	8	8
AUC_{0-4}, ng∗h/mL	909.4 (43)	1046 (30)	888.9 (27)	844.8 (31)
C_{max}, ng/mL	338.7 (40)	403.8 (24)	352.1 (31)	322.8 (31)
T_{max}, h	2.000 (1.00-3.00)	1.000 (0.50-2.00)	1.000 (1.00-3.00)	1.500 (0.50-2.00)

AUC_{0-4} = area under the plasma concentration-time profile from time 0 to 4 hours postdose; BID = twice daily; C_{max} = maximum observed concentration during the dosing interval; N = number of subjects; PK = pharmacokinetic; T_{max} = time for C_{max}.

a. Geometric mean (% coefficient of variance) for all except median (range) for T_{max}.

Safety Results:

Safety/Pharmacokinetic Component**:** All AEs were mild to moderate with musculoskeletal and connective tissue disorders being reported in 3 out of 8 subjects dosed with maraviroc 150 mg BID (1 incidence was considered treatment-related); infections and infestations was reported in 2 out of 8 subjects dosed with maraviroc 300 mg BID (none were considered treatment-related). Treatment emergent (all causality) and treatment-related AEs by preferred term (MedDRA version 11.1) and System Organ Class are summarized in Table 25.

Table 25. Summary of Treatment Emergent and Treatment-Related Adverse Events by Preferred Term – Safety/PK Component

	Maraviroc 150 mg BID		Maraviroc 300 mg BID	
System Organ Class/Preferred Term	**Treatment Emergent**	**Treatment-Related**	**Treatment Emergent**	**Treatment-Related**
Number of subjects	8	8	8	8
Gastrointestinal disorders[a]	1	1	1	1
Abnormal feces	0	0	1	1
Dry mouth	0	0	1	1
Nausea	1	1	0	0
General disorders and administration site conditions[a]	1	1	1	0
Fatigue	1	1	0	0
Influenza like illness	0	0	1	0
Immune system disorders[a]	0	0	1	0
Seasonal allergy	0	0	1	0
Infections and infestations[a]	0	0	2	0
Sinusitis	0	0	1	0
Upper respiratory tract infection	0	0	1	0
Injury, poisoning and procedural complications[a]	1	0	0	0
Back injury	1	0	0	0
Musculoskeletal and connective tissue disorders[a]	3	1	1	0
Arthralgia	2	1	0	0
Arthritis	1	0	0	0
Back pain	1	1	0	0
Flank pain	0	0	1	0
Muscle spasms	1	1	1	0
Musculoskeletal pain	1	0	0	0
Pain in extremity	1	0	0	0
Respiratory, thoracic and mediastinal disorders[a]	0	0	1	0
Nasal congestion	0	0	1	0
Oropharyngeal pain	0	0	1	0

Adverse events/serious adverse events are not separated out.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; PK = pharmacokinetic.
a. Total number of subjects experiencing an adverse event by System Organ Class.

Proof- of-Concept Component: The most commonly reported all causality AEs (Table 26) observed in the maraviroc-treated group were constipation (7.8%), and nausea (5.2%) compared to placebo. More subjects in the placebo group had a worsening of their RA even though they were receiving background MTX compared to maraviroc-treated subjects (24.2% versus [vs] 3.9%). Eye-related AEs had been reported in healthy volunteers' studies with maraviroc and ocular examinations were required of all subjects. The rate of all causality eye-related AEs was at a similar rate across both treatment groups (6.5% maraviroc-treated vs 6.1% placebo-treated). Treatment-related AEs are summarized in Table 27.

After the database was locked, 2 additional treatment emergent AEs were discovered during the close-out visit. One subject who had received maraviroc 300 mg BID, experienced a

mild migraine and mild anxiety. None of these events were considered serious or treatment-related by the Investigator.

Table 26. Treatment Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥5 Percent

	Maraviroc 300 mg BID	Placebo
	n (%)	n (%)
Number (%) of subjects:		
Evaluable for adverse events	77	33
With adverse events	14 (18.2)	14 (42.4)
Number (%) of subjects with adverse events by:		
System Organ Class		
MedDRA (v11.1) preferred term		
Gastrointestinal disorders	11 (14.3)	2 (6.1)
Constipation	6 (7.8)	0
Diarrhoea	1 (1.3)	2 (6.1)
Nausea	4 (5.2)	0
General disorders and administration site conditions	0	2 (6.1)
Oedema peripheral	0	2 (6.1)
Infections and infestations	0	2 (6.1)
Influenza	0	2 (6.1)
Musculoskeletal and connective tissue disorders	3 (3.9)	8 (24.2)
Rheumatoid arthritis	3 (3.9)	8 (24.2)

Includes data up to 7 days after last dose of study drug.
Subjects are only counted once per treatment for each row.
MedDRA (v11.1) coding dictionary applied.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; v = version.

Table 27. Summary of Treatment-Related Adverse Events by Preferred Term in ≥2 Subjects – POC Component

	Maraviroc 300 mg BID	Placebo
Number (%) of subjects with adverse events by:		
System Organ Class		
MedDRA (v11.1) preferred term		
Gastrointestinal disorders[a]	12 (15.6)	1 (3.0)
Constipation	4 (5.2)	0
Nausea	3 (3.9)	0
General disorders and administrative site conditions[a]	4 (5.2)	2 (6.1)
Chills	2 (2.6)	0
Oedema peripheral	0	2 (6.1)
Musculoskeletal and connective tissue disorders[a]	0	2 (6.1)
Rheumatoid arthritis	0	1 (3.0)
Nervous system disorders[a]	2 (2.6)	1 (3.0)
Dizziness	1 (1.3)	1 (3.0)
Vascular disorder[a]	2 (2.6)	0
Orthostatic hypotension	1 (1.3)	0

Adverse event/serious adverse events are not separated out.
MedDRA version 11.1.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; POC = proof-of-concept.
a. Total number of subjects experiencing an adverse event by System Organ Class.

There were no SAEs in the safety/PK Component and 1 SAE in the POC Component. One subject with a history of pulmonary fibrosis experienced worsening of dyspnea during the screening period. This event occurred prior to randomization and before the subject received study treatment. The subject was hospitalized for the worsening dyspnea.

There were no deaths among subjects who participated in this study.

Permanent Discontinuations due to AEs: One subject discontinued from the study due to worsening RA (moderate) in the safety/PK Component. A total of 5 out of 77 subjects discontinued from the maraviroc group due to treatment emergent AEs (4 were considered treatment-related); a total of 4 out of 33 subjects discontinued from the placebo group due to treatment-emergent AEs (1 was considered treatment-related) in POC Component.

There were no clinically significant findings in the clinical laboratory, vital signs and ECG measurements. Hematological results showed elevated levels of CD4 counts (>1.1 x upper limit of normal [ULN]) were similar in the maraviroc and the placebo group, whereas CD8 counts (>1.1 x ULN) were elevated for 3 out of 72 (4%) subjects who had received maraviroc 300 mg BID compared to 0 out of 31 (0%) subjects who had received placebo.

No subjects in the safety/PK Component experienced a significant change from baseline at final visit in physical examinations. A significant change from baseline at final visit in physical examinations was experienced by 13 subjects (16.9%) in the 300 mg BID group and by 4 subjects (12.1%) in the placebo group.

CONCLUSIONS:

- Administration of maraviroc was generally safe and well tolerated when dosed in the range of 150 to 300 mg BID administered for 4 weeks to subjects in combination with MTX

- Concomitant administration of MTX and maraviroc (150 mg BID and 300 mg BID) did not result in altered MTX exposure in RA subjects

- Treatment with maraviroc appeared to have an improved effect on subject reported outcomes and disease activity status; though no difference in ACR 20 response rate was seen between maraviroc 300 mg and placebo-treated subjects

- Administration of maraviroc 300 mg BID was safe and well tolerated when administered in conjunction with MTX for 12 weeks to subjects with active RA