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

PROTOCOL NO.: A4001075

PROTOCOL TITLE: An Open-Label, Parallel Group, Single and Multiple Dose Study to Evaluate the Pharmacokinetics, Safety and Toleration of Maraviroc Administered to Subjects With Various Degrees of Renal Impaired and Normal Renal Function

Study Centers: A total of 2 centers in Germany took part in this study and randomized subjects.

Study Initiation and Final Completion Dates: 15 July 2008 to 21 November 2008

Phase of Development: Phase 4

Study Objectives:

Primary Objectives:

- To characterize the pharmacokinetics (PK) of maraviroc (MVC) (150 mg) in the presence of saquinavir 1000 mg + ritonavir 100 mg (SQV/r) (a potent cytochrome P450 3A4 [CYP3A4] inhibitor) in both healthy subjects and subjects with mild and moderate renal impairment;

- To characterize the PK of MVC (300 mg) in healthy subjects, subjects with severe renal impairment and those receiving chronic hemodialysis;

- To calculate the hemodialysis clearance of MVC in subjects with end stage renal disease (ESRD) undergoing hemodialysis.

Secondary Objective:

- To assess the safety and tolerability of MVC in the absence and presence of a potent CYP3A4 inhibitor in subjects with various degrees of renal impairment or undergoing hemodialysis.

METHODS

Study Design: This was a non-randomized, open-label, parallel group study that was conducted in 2 parts: Part 1, which included subjects with normal renal function, and mild to

severe renal impairment, and Part 2, which included subjects with ESRD on hemodialysis (Table 1). In Part 1a, 3 groups of subjects with varying degrees of renal impairment ranging from normal renal function to those with moderate renal impairment were evaluated, and in Part 1b a group of subjects with severe renal impairment was evaluated. Subjects were enrolled into 1 of the groups listed in Table 1 based on the creatinine clearance (CL_{cr}) at Screening as determined by the Cockcroft-Gault equation based on the serum creatinine. In Part 2 (Group 5), subjects with ESRD treated with hemodialysis were evaluated. The study design is presented in Table 1.

Table 1. Study Design

Part	Group	Renal Impairment	Sample Size	MVC and SQV/r Doses	Creatinine Clearance
1a	1	None (normal)[a]	6	Single dose MVC 300 mg, followed 4 days later by MVC 150 mg BID and SQV/r BID coadministered for 7 days	>80 mL/minute
1a	2	Mild	6	MVC 150 mg QD and SQV/r BID coadministered for 7 days	>50 and ≤80 mL/minute
1a	3	Moderate	6	MVC 150 mg once every 48 hours and SQV/r BID coadministered for 7 days	≥30 and ≤50 mL/minute
1b	4	Severe	3-6	Single dose MVC 300 mg	<30 mL/min
2	5	ESRD on hemodialysis	6	Single dose MVC 300 mg	Requiring regular hemodialysis 3×/week for ≥6 weeks

BID = twice daily; ESRD = end stage renal disease; MVC = maraviroc; QD = once daily; SQV/r = saquinavir 1000 mg + ritonavir 100 mg.

a. Group 1 was comprised of subjects with normal renal function who were age-, weight-, and gender-matched to subjects in Groups 2 and 3.

There was no CL_{cr} criterion for subjects undergoing hemodialysis. In Part 1 of the study, subjects with mild, moderate, or severe renal impairment were enrolled. Once these subjects in the mild and moderate group had completed the study, a cohort of age-, weight- and gender-matched healthy controls were enrolled. For the severe renal impairment group, an attempt was made across study centers to enroll at least 3 subjects up to a maximum of 6 subjects with estimated CL_{cr} values <15 mL/minute, but not requiring dialysis.

Part 1:

In Part 1a, the subjects with normal renal function received a single MVC 300 mg dose followed 4 days later by MVC 150 mg BID along with boosted SQV/r (1000/100 mg) twice daily (BID) for 6 days and a single dose of both agents on Day 7. The subjects with mild renal impairment received MVC 150 mg once daily (QD) along with boosted SQV/r (1000/100 mg) BID for 6 days and a single dose of both agents on Day 7. The subjects with moderate renal impairment received MVC 150 mg once every 48 hours (QOD) along with boosted SQV/r (1000/100 mg) BID for 6 days and a single dose of both agents on Day 7. In Part 1b, the group with severe renal impairment received a single MVC 300 mg dose.

Once tolerability data were available from 2 subjects with mild renal impairment, and had been evaluated by the Sponsor, dosing of the subjects with moderate renal impairment began.

Dosing of subjects with severe renal impairment was not dependent on this evaluation, as these subjects were not administered the potent CYP3A4 inhibitor.

The schedule of activities for Part 1 is summarized in Table 2, Table 3, and Table 4.

Table 2. Schedule of Activities: Part 1a Screening through Day 0 - Subjects with Normal Renal Function (Group 1)

	Screen	Day -4	Day -3									Day -2	Day -1	Day 0
Hours Relative to Day -3 Dosing			**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**48**	**72**
Informed consent	X													
Admission to CRU		X												
Medical history, prescription and non prescription medications, alcohol/tobacco history	X	X[a]												
FSH[b] (females only)	X													
Full physical examination	X													
Brief physical examination		X												
Weight	X	X												
Single supine blood pressure and pulse rate	X		X		X	X						X	X	
Single 12-lead ECG	X		X			X		X					X	
Safety laboratory tests	X	X										X		
Urine drug screen	X													
Serum creatinine	X		X											
MVC dosing			X											
PK samples			X[c]	X	X	X	X	X	X	X	X	X	X	X
Protein binding sample						X								
Urine collection			X[d]----------								-X	X	X	X
Adverse event monitoring						X		X		X		X	X	X
Discharge from CRU														X
Out-patient clinic visit														

CRU = clinical research unit; ECG = electrocardiogram; FSH = follicle stimulating hormone; MVC = maraviroc; PK = pharmacokinetic.

a. Review of concomitant medications.
b. FSH tests were performed at Screening only for females who were 45-60 years and amenorrheic for >2 years.
c. A blood sample was collected prior to MVC dosing.
d. A urine blank was collected prior to start of urine collection.

Table 3. Schedule of Activities: Part 1a Day 1 through Follow-Up - Subjects with Normal Renal Function (Group 1), Mild Renal Impairment (Group 2), or Moderate Renal Impairment (Group 3)

	Day 1-5	Day 6	Day 7									Day 8	Day 9	Day 10	Follow-Up
Hours Relative to Day 7 Dosing			**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	
Informed consent															
Admission to CRU		X													
Medical history, prescription and non prescription medications, alcohol/tobacco history		X[a]										X[a]			X[a]
Full physical examination															X
Brief physical examination		X												X	
Weight		X[a]													
Single supine blood pressure and pulse rate			X		X	X						X	X	X	X
Single 12-lead ECG			X			X		X				X	X		X
Safety laboratory tests		X[a]										X			X
Urine drug screen															
Serum creatinine			X												
MVC and SQV/r dosing[b]	X	X	X												
PK samples			X[c]	X	X	X	X	X	X	X	X	X	X	X	
Protein binding sample						X									
Urine collection			X[d]	----------	----------	----------	----------	----------	----------	----------	X	X	X	X	
Adverse event monitoring						X		X		X		X	X	X	X
Discharge from CRU														X	
Out-patient clinic visit	X														X

Screening for subjects in Groups 2 and 3 involved the same activities as described in Table 2.

CRU = clinical research unit; ECG = electrocardiogram; MVC = maraviroc; PK = pharmacokinetic; SQV/r = saquinavir 1000 mg + ritonavir 100 mg.

a. Review of concomitant medications.

b. Subjects attended the CRU daily on the mornings of Days 1-5 to be dosed with MVC and SQV/r concomitantly and to take their evening doses home, with the exception of the moderately impaired subjects who received MVC only on Days 1, 3, and 5 before the full evaluation on Day 7.

c. A blood sample was collected prior to MVC dosing.

d. A urine blank was collected prior to start of urine collection.

Table 4. Schedule of Activities: Part 1b - Subjects with Severe Renal Impairment (Group 4)

	Screen	Day 0	Day 1									Day 2	Day 3	Day 4	Follow-Up
Hours Relative to Day 1 Dosing			**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	
Informed consent	X														
Admission to CRU		X													
Medical history, prescription and non prescription medications, alcohol/tobacco history	X	X[a]										X			X[a]
FSH[b] (females only)	X														
Full physical examination	X														X
Brief physical examination		X												X	
Weight	X	X													
Single supine blood pressure and pulse rate	X		X		X	X						X	X[c]	X[c]	X
Single 12-lead ECG	X		X			X		X					X[c]	X[c]	X
Safety laboratory tests	X	X										X			X
Urine drug screen	X														
Serum creatinine	X		X												
MVC dosing			X												
PK samples			X[d]	X	X	X	X	X	X	X	X	X	X	X	
Protein binding sample						X									
Urine collection			X[e]----------X									X	X	X	
Adverse event monitoring						X		X		X		X	X	X	X
Discharge from CRU														X	
Out-patient clinic visit															X

CRU = clinical research unit; ECG = electrocardiogram; FSH = follicle stimulating hormone; MVC = maraviroc; PK = pharmacokinetic.

a. Review of concomitant medications.
b. FSH tests were performed at screening only for females who were 45-60 years and amenorrheic for >2 years.
c. Prior to discharge.
d. A blood sample was collected prior to MVC dosing.
e. A urine blank was collected prior to the start of urine collection.

Part 2: Part 2 was divided into 2 periods.

In Part 2, Period 1, subjects with ESRD on hemodialysis received a single dose of MVC approximately 1 hour following completion of a morning hemodialysis session and approximately 48 hours before their next hemodialysis session. PK samples were then collected for the next 48 hours following dosing, up until the start of the next hemodialysis session.

Part 2, Period 2 occurred at least 1 week following their first dose of MVC. The same ESRD subjects received another single dose of MVC 3 hours before the start of their hemodialysis session to quantify the amount of MVC removed by dialysis. Blood samples for MVC concentrations were collected for 48 hours. In addition, dialysate was collected every hour during hemodialysis and at the end of hemodialysis. The extent of plasma protein binding for MVC was determined for each subject in each group to calculate unbound oral clearance.

Subjects who withdrew were not to be replaced unless the number of completed subjects in a specific group fell below 4 subjects.

The schedules of activities for Part 2 are summarized in Table 5 and Table 6.

Table 5. Schedule of Activities: Part 2, Period 1 - Subjects on Hemodialysis (Group 5)

	Screen	Day 0	Day 1											Day 2	Day 3	Day 4
Hours Relative to Day 1 Dosing			**-5**	**-1**	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**48**	**72**
Informed consent	X															
Admission to CRU		X														
Medical history, prescription and non prescription medications, alcohol/tobacco history	X	X[a]												X[a]		X[a]
Serum FSH[b] (post menopausal women)	X															
Full physical examination	X															
Brief physical examination		X														X
Weight	X	X														
Single supine blood pressure and pulse rate	X		X	X			X	X								X
Single 12-lead ECG	X		X				X	X							X	X
Safety laboratory tests[c]	X	X												X		
Saliva drug screen	X															
Serum creatinine	X				X											
Record hemodialysis regimen		X														
Hemodialysis			start	end												
Record volume of dialysate			X													
Collect dialysate samples during hemodialysis																
MVC dosing[d]					X											
PK samples					X[e]	X	X	X		X		X	X	X	X	X
Protein binding sample								X								
Adverse event monitoring		X		X				X		X		X		X	X	X
Discharge from CRU															X	
Out-patient clinic visit																X

CRU = clinical research unit; ECG = electrocardiogram; FSH = follicle stimulating hormone; MVC = maraviroc; PK = pharmacokinetic.

a. Review of concomitant medications.
b. FSH tests were performed at screening only for females who were 45-60 years and amenorrheic for >2 years.
c. Urinalysis was not performed for hemodialysis subjects who did not produce urine.
d. Dosing occurred no sooner than 1 hour after the completion of hemodialysis.
e. A blood sample was collected prior to MVC dosing.

Table 6. Schedule of Activities: Part 2, Period 2 - Subjects on Hemodialysis (Group 5)

	Day 0	Day 1											Day 2	Day 3	Day 4	Follow-Up
Hours Relative to Day 1 Dosing		**0**	**0.5**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**24**	**48**	**72**	
Admission to CRU	X															
Full physical examination																X
Brief physical examination	X														X	
Weight	X															
Single supine blood pressure and pulse rate		X		X	X										X	X
Single 12-lead ECG		X		X	X										X	X
Safety laboratory tests[a]	X												X			X
Record hemodialysis regimen[b]	X															
Hemodialysis						start				end						
Record volume of dialysate						X	X	X	X	X						
Collect dialysate during hemodialysis[c]						X	X	X	X	X						
MVC dosing		X														
PK samples[d]		X	X	X	X		X	X	X	X[e]	X	X	X	X	X	
Adverse event monitoring	X				X		X				X	X	X	X	X	X
Review of concomitant medication	X														X	X
Discharge from CRU														X		
Out-patient clinic visit															X	X

CRU = clinical research unit; ECG = electrocardiogram; MVC = maraviroc; PK = pharmacokinetic.

a. Urinalysis was not performed for hemodialysis subjects who did not produce urine.
b. The total volume of dialysate fluid for each interval was recorded and a 20 mL aliquot was retained for analysis (depending on duration of dialysis).
c. Dialysate samples were collected hourly during the dialysis and at the completion of dialysis.
d. PK samples during hemodialysis sessions were paired with arteriovenous samples.
e. PK samples were collected at 1 and 2 hours after completion of dialysis.

Number of Subjects (Planned and Analyzed): It was planned to enroll 6 subjects in each of the 5 renal function groups, based on their degree of renal impairment (normal renal function, mild renal impairment, moderate renal impairment, severe renal impairment, and subjects with ESRD receiving hemodialysis). A total of 30 subjects were assigned to study treatment (6 in each of the 5 renal function groups) in Germany.

Diagnosis and Main Criteria for Inclusion: Male or female subjects between the ages of 18 and 85 years, having a body mass index (BMI) of approximately 18 to 40 kg/m^2 inclusive and total body weight >50 kg (110 lbs) were included in the study. All subjects were required to have stable renal function defined as ≤20% (25% for normal renal function) difference between measurements of serum creatinine obtained on 2 occasions separated by at least 2 weeks.

Exclusion Criteria: Subjects with acute renal disease and/or history of renal transplant, supine blood pressure (BP) at Screening ≥160 mmHg systolic or ≥95 mmHg diastolic or supine BP at Screening ≤80 mmHg systolic or ≤40 mmHg diastolic were excluded.

Study Treatment: The study drugs were supplied by the Sponsor as MVC 150 mg tablets, saquinavir 500 mg tablets, and ritonavir 100 mg capsules. In this open-label study, subjects were assigned to 1 of 5 treatment groups based upon degrees of renal impairment.

- Healthy subjects: single dose MVC 300 mg followed 4 days later by MVC 150 mg BID and SQV/r (1000 mg + 100 mg) BID.
- Mild renal impairment: MVC 150 mg QD and SQV/r (1000 mg + 100 mg) BID.
- Moderate renal impairment: MVC 150 mg QOD and SQV/r (1000 mg + 100 mg) BID.
- Severe renal impairment: single dose MVC 300 mg.
- ESRD on hemodialysis: single dose MVC 300 mg.

Except for an appropriate volume of water (dependent on renal impairment status) taken with the dose, fluid was restricted from 1 hour before dosing until 1 hour postdose. The MVC tablet(s) were taken orally by the subject while sitting or standing with 240 mL water (water volume was adjusted depending on individual subject restrictions on fluid intake) and where the SQV/r doses were required these were administered orally together with MVC.

In Part 1a, subjects with normal renal function received a single MVC 300 mg dose on Day 3 under the supervision of Investigator staff. All morning doses on Days 1-5 and all doses on Days 6 and 7 were also administered under supervision. Evening doses on Days 1-5 were taken at home. For Part 1b and Part 2, all doses were taken whilst under the supervision of Investigator staff.

Pharmacokinetic Endpoints:

Primary Endpoints: The area under the curve from time 0 to last observation (AUC_{last})/ area under the plasma concentration-time curve over the dosing interval tau (AUC_{tau}) and maximum plasma concentration within the dosing interval (C_{max}) for all subjects.

Secondary Endpoints: Plasma protein binding, area under the curve from time 0 to infinity (AUC_{inf}), time to C_{max} (T_{max}), and half-life ($t_{½}$).

In addition, renal clearance (CL_r) was determined for subjects with normal, mild, moderate, and severe renal function and hemodialysis clearance was determined for subjects with ESRD on hemodialysis.

No efficacy evaluations were performed for this study.

Safety Evaluations: Safety was evaluated by assessment of adverse events (AEs), laboratory tests, vital signs, electrocardiogram (ECG) data, and physical examinations.

Statistical Methods:

The PK concentration population consisted of all treated subjects with at least 1 concentration measurement. The PK parameter analysis population consisted of all treated subjects with at least 1 recorded PK parameter of interest. All subjects who received study medication were included in the safety analyses.

Analyses for Part 1a and Part 1b: The PK parameters were summarized descriptively by renal function group and dose. An ANOVA model with group as a fixed effect was used to compare the natural log transformed AUC_{inf}, AUC_{last}, and C_{max} parameters for mild and moderate renal impairment groups (test) to the normal renal function group under the treatment of MVC 150 mg + SQV/r (reference). Estimates of the adjusted mean differences (test - reference) and corresponding 90% CI were obtained from the model. The adjusted mean differences and corresponding 90% CI were exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and corresponding 90% CI for the ratios. The similar ANOVA analyses were performed for severe renal impairment group (test) to the normal renal function group under the treatment of MVC 300 mg single dose (reference).

Analysis for Part 2: PK parameters including AUC_{inf}, C_{max}, AUC_{last}, T_{max}, $t_{½}$, CLu/F and hemodialysis clearance (CL_D) were summarized descriptively by period (CL_D summarized in Period 2 only).

RESULTS

Subject Disposition and Demography: A total of 30 subjects were enrolled and received treatment. Subjects were enrolled into the treatment groups based on their CL_{cr} at Screening (with the exception of the subject group with ESRD undergoing hemodialysis).

Eighteen subjects were included in Part 1a of this study. Of these subjects, 6 had normal renal function (CL_{cr} >80 mL/minute), 6 had mild renal impairment (50 mL/min <CL_{cr} ≤80 mL/minute), and 6 had moderate renal impairment (30 mL/minute ≤CL_{cr} ≤50 mL/minute). The 6 subjects with normal renal function were treated with a single dose of MVC 300 mg followed 4 days later by treatment with MVC 150 mg BID and SQV/r (1000 mg/100 mg) BID for 7 days. The 6 subjects with mild renal impairment were treated with MVC 150 mg QD and SQV/r (1000 mg/100 mg) BID for 7 days. The 6 subjects with moderate renal impairment were treated with MVC 150 mg QOD and with SQV/r (1000 mg/100 mg) BID for 7 days.

Six subjects were included in Part 1b of this study, all of whom had severe renal impairment (CL_{cr} <30 mL/minute). These 6 subjects were treated with a single dose of MVC 300 mg.

Six subjects were included in Part 2 of this study, all of whom had ESRD and required regular hemodialysis 3 times per week for at least 6 weeks. These subjects were treated with a single dose of MVC 300 mg before and after hemodialysis.

All but 1 subject completed the study. The 1 subject that did not complete the study had moderate renal impairment and was discontinued due to a severe AE of renal function test abnormal (increase in serum creatinine) which was considered to be related to the study drug. A summary of subject disposition is presented in Table 7.

Table 7. Subject Disposition and Subjects Analyzed

Number of Subjects	Normal MVC 300 mg	Severe MVC 300 mg	ESRD MVC 300 mg Dosing After Dialysis	ESRD MVC 300 mg Dosing Before Dialysis	Normal MVC 150 mg BID + SQV/r 1000 mg/100 mg BID	Mild MVC 150 mg QD + SQV/r 1000 mg/100 mg BID	Moderate MVC 150 mg QOD + SQV/r 1000 mg/100 mg BID
Assigned to study treatment: 30							
Treated	6	6	6	6	6	6	6
Completed	6	6	6	6	6	6	5
Discontinued	0	0	0	0	0	0	1
Related to study drug	0	0	0	0	0	0	1
Adverse event	0	0	0	0	0	0	1
Analyzed for pharmacokinetics							
PK concentration	6	6	6	6	6	6	6
PK parameter	6	6	6	6	6	6	6
Analyzed for safety							
Adverse events	6	6	6	6	6	6	6
Laboratory data	6	6	6	6	6	6	6

Discontinuations occurring outside the lag period have been attributed to the last study treatment received.
BID = twice daily; ESRD = end stage renal disease; MVC = maraviroc; PK = pharmacokinetic; QD = once daily; QOD = once every 48 hours; SQV/r = boosted saquinavir (saquinavir 1000 mg + ritonavir 100 mg).

Demographic characteristics and baseline CL_{cr} are summarized in Table 8. The normal renal function group, mild, moderate, and severe renal impairment groups, and the ESRD on hemodialysis group were similar with respect to age and BMI. All subjects in all groups were white. Baseline CL_{cr} was consistent with the renal classification groups with the least CL_{cr} observed in the severe renal impairment group (arithmetic mean = 23.7 mL/minute) and the greatest CL_{cr} observed in the normal renal function group (arithmetic mean = 103.1 mL/minute).

Table 8. Demographic Characteristics and Baseline Creatinine Clearance

	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment	ESRD on Hemodialysis
Sex					
N	6	6	6	6	6
Male	4	4	4	4	6
Female	2	2	2	2	0
Age (years)					
N	6	6	6	6	6
Mean (SD)	60.2 (5.2)	62.8 (9.0)	65.0 (15.4)	58.7 (12.0)	51.3 (9.1)
Range	54-68	47-74	34-74	42-69	40-68
Race					
White	6	6	6	6	6
BMI (kg/m^2)[a]					
N	6	6	6	6	6
Mean (SD)	26.9 (2.4)	23.8 (4.4)	25.1 (2.1)	24.5 (3.5)	26.8 (3.3)
Range	22.5-29.3	18.0-27.7	22.6-27.7	19.1-29.0	22.5-31.0
CL_{cr} (mL/minute)[b] at Baseline					
N	6	6	6	6	6
Arithmetic mean (SD)	103.1 (12.2)	69.1 (7.3)	42.5 (4.4)	23.7 (7.6)	27.4 (16.0)
Range	92.6-122.4	58.0-76.7	37.8-49.0	18.0-38.0	14.4-58.4

BMI = body mass index; CL_{cr} = creatinine clearance; ESRD = end stage renal disease, N = number of subjects; SD = standard deviation.

a. BMI was calculated as weight/(height*.01)**2.

b. The values reported are mean values when >1 creatinine measurement was taken on the same study day.

Pharmacokinetic Results:

Pharmacokinetics of Multiple Dose MVC and SQV/r in Subjects With Normal Renal Function and With Mild and Moderate Renal Impairment: No clinically significant changes in MVC exposure were observed between subjects with normal renal function and those with mild or moderate renal impairment. The PK parameters are summarized in Table 9 and the results of the statistical analysis of MVC exposure are presented in Table 10.

The rate of MVC absorption was similar between the groups with median T_{max} occurring between 1.00 and 2.00 hours postdose administration (Table 9). Following attainment of C_{max}, the median MVC plasma concentration-time profiles declined in parallel with mean apparent elimination half-lives, ranging from 14.22 to 16.99 hours. Renal clearance contributed approximately 23%, 25%, and 15% to total oral MVC clearance in subjects with normal renal function, mild renal impairment, and moderate renal impairment, respectively.

Despite the moderate contribution of renal clearance to overall apparent clearance (CL/F), CL_{cr} was not shown to be a significant predictor of total unbound apparent clearance (p=0.302).

The protein unbound MVC fraction at 2 hours postdose in subjects with normal renal function, mild renal impairment, and moderate renal impairment was (range) 19.7% to 26.6%, 15.3% to 29.1%, and 18.1% to 31.6%, respectively.

There was moderate between-subject variability in estimates for AUC_{tau} (coefficient of variation [CV]=27% to 35%), C_{max} (CV=23% to 38%), and minimum observed concentration within the dosing interval (C_{min}) (CV=22% to 46%).

The ratios of the adjusted geometric means of the primary endpoints, AUC_{last}, AUC_{tau}, and C_{max}, for the comparison between subjects with mild renal impairment and subjects with normal renal function were 129.17%, 151.99%, and 121.01%, respectively.

The ratios of the adjusted geometric means of the primary endpoints, AUC_{last}, AUC_{tau}, and C_{max}, for the comparison between subjects with moderate renal impairment and subjects with normal renal function were 88.31%, 115.95% and 70.90%, respectively.

It should be noted that there was a difference in MVC dosing interval (BID in subjects with normal renal function compared to QD in subjects with mild renal impairment and QOD in subjects with moderate renal impairment).

Table 9. Geometric Mean (CV%) Plasma and Urine Maraviroc Pharmacokinetic Parameter Values Following Multiple Dose Administration With Saquinavir/Ritonavir

Pharmacokinetic Parameters (Units)	Normal MVC 150 mg BID + SQV/r BID (N=6)	Mild MVC 150 mg QD + SQV/r BID (N=6)	Moderate MVC 150 mg QOD + SQV/r BID (N=6)
Plasma Maraviroc Pharmacokinetic Parameters			
AUC_{last} (ng•h/mL)	7356 (30)	9502 (36)	6496 (27)
AUC_{tau} (ng•h/mL)	5341 (27)	8119 (35)	6193 (27)
C_{max} (ng/mL)	950.9 (23)	1151 (32)	674.2 (38)
C_{min} (ng/mL)	126.4 (46)	72.64 (36)	18.33 (22)
T_{max} [a] (h)	1.000 (0.50-2.00)	1.500 (0.50-4.00)	2.000 (0.50-4.02)
$t_{½}$ [b] (h)	14.22 (8)	16.84 (33)	16.99 (18)
CL_u/F (mL/min)	2078 (19)	1554 (31)	1832 (45)
Urine Maraviroc Pharmacokinetic Parameters			
CLR_u (mL/min)	469.6 (45)	389.8 (23)	283.7 (22)
CL_r (mL/min)	105.7 (44)	77.2 (44)	62.5 (20)
A_e (mg)	33.9 (54)	37.6 (29)	23.2 (36)

A_e = amount of drug excreted unchanged in the urine; AUC_{last} = area under the curve from time 0 to the last observation; AUC_{tau} = area under the plasma concentration-time curve over the dosing interval tau; BID = twice daily; CL_r = renal clearance; CL_u/F = apparent clearance of unbound drug in serum; CLR_u = renal clearance of unbound maraviroc; C_{max} = maximum observed concentration within the dosing interval; C_{min} = minimum observed concentration within the dosing interval; CV = coefficient of variation; h = hour; Min = minute; MVC = maraviroc; N = number of subjects; QD = once daily; QOD = every 48 hours; SQV/r = saquinavir 1000 mg + ritonavir 100 mg; T_{max} = time to maximum concentration; $t_{½}$ = terminal elimination half-life.

a. Median (range).

b. Arithmetic mean.

Table 10. Summary of Statistical Analysis of Plasma Maraviroc Exposure for Treatment Groups of 150 mg Maraviroc and Saquinavir/Ritonavir

Parameter (Units)	Test	Reference[a]	Ratio (%)[b]	90% Confidence Interval Lower	Upper
Mild Versus Normal					
AUC_{last} (ng•h/mL)	9502.07	7356.26	129.17	92.16	181.04
AUC_{tau} (ng•h/mL)	8118.70	5341.45	151.99	109.53	210.92
C_{max} (ng/mL)	1150.74	950.91	121.01	83.15	176.13
Moderate Versus Normal					
AUC_{last} (ng•h/mL)	6496.02	7356.26	88.31	61.97	125.83
AUC_{tau} (ng•h/mL)	6193.30	5341.45	115.95	82.23	163.50
C_{max} (ng/mL)	674.20	950.91	70.90	47.83	105.10

Test = mild or moderate; Reference = normal.
AUC_{last} = area under the curve from time 0 to last observation; AUC_{tau} = area under the plasma concentration-time curve over the dosing interval tau; C_{max} = maximum observed concentration within the dosing interval; h = hour.
a. Adjusted geometric mean values.
b. Ratio of adjusted geometric means.

Pharmacokinetics of Single Dose MVC in Subjects with Normal Renal Function, Severe Renal Impairment, and End Stage Renal Disease: Exposure to MVC was higher by approximately 3-fold in subjects with severe renal impairment compared to subjects with normal renal function receiving the same single dose of MVC. MVC exposures, when dosed pre and post dialysis, fell between exposures observed in subjects with normal renal function and those observed in subjects with severe renal impairment. A summary of plasma MVC PK parameters is presented in Table 11 and the results of the statistical analysis of MVC exposure are presented in Table 12.

The rate of MVC absorption was similar between the groups with median T_{max} occurring between 2.00 and 3.00 hours postdose administration. Following attainment of C_{max}, the median MVC plasma concentration-time profiles declined in parallel with mean apparent elimination half-lives ranging from 12.0 to 21.5 hours. Apparent oral clearance estimates were much lower in subjects with severe renal impairment as compared to subjects with normal renal function, despite relatively small renal clearance contributions (approximately 2% to 3%).

The protein unbound MVC fraction at 2 hours postdose in subjects with normal renal function, severe renal impairment, and ESRD were (range) 14.6% to 28.2%, 19.2% to 28.1%, and 18.2% to 27.8%, respectively.

There was moderate between-subject variability estimates for AUC_{inf} (CV=40% to 61%) and C_{max} (CV=38% to 87%).

The ratios of the adjusted geometric means of the primary endpoints, AUC_{inf}, AUC_{last} and C_{max}, for the comparison between subjects with severe renal impairment and subjects with normal renal function were 323.91%, 322.23%, and 238.73%, respectively.

Dialysis did not appear to meaningfully alter the PK profile of MVC and mean dialysate clearance was estimated to be approximately 36 mL/minute.

Table 11. Geometric Mean (CV%) Plasma and Urine Maraviroc Pharmacokinetic Parameter Values in Subjects with Normal Renal Function, Severe Renal Impairment, and End Stage Renal Disease

Pharmacokinetic Parameters (units)	Normal MVC 300 mg (N=6)	Severe MVC 300 mg (N=6)	ESRD MVC 300 mg Dosing Before Dialysis (N=6)	ESRD MVC 300 mg Dosing After Dialysis (N=6)
Plasma Maraviroc Pharmacokinetic Parameters				
AUC_{last} (ng•h/mL)	1321 (62)	4256 (51)	2637 (40)	2770 (45)
AUC_{inf} (ng•h/mL)	1348 (61)	4368 (52)	2806 (45)	2677 (40)
C_{max} (ng/mL)	335.6 (87)	801.2 (56)	478.5 (38)	576.7 (51)
T_{max} [a] (h)	2.500 (0.50-4.02)	2.500 (0.50-4.00)	2.000 (0.50-4.17)	3.000 (1.00-4.00)
$t_{½}$ [b] (h)	14.36 (28)	17.29 (24)	13.86 (8)	15.03 (22)
CLu/F (mL/min)	17760 (53)	5223 (44)	8587 (54)	8998 (45)
Urine Maraviroc Pharmacokinetic Parameters				
CLR_u (mL/min)	526.6 (51)	121.3 (61)	NA	NA
CL_D (mL/min)	NA	NA	36.42 (33)	NA
CL_r (mL/min)	110.0 (33)	26.6 (61)	NA	NA
A_e (mg)	8.9 (69)	7.0 (76)	NA	NA

A_e = amount of drug excreted unchanged in the urine; AUC_{last} = area under the curve from time 0 to the last observation; AUC_{inf} = area under the plasma concentration-time curve from time 0 to infinity; CL_r = renal clearance; CL_u/F = apparent clearance of unbound drug in serum; CLR_u = renal clearance of unbound maraviroc; CL_D = dialysate clearance; C_{max} = maximum observed concentration; CV = coefficient of variation; ESRD = end stage renal disease; h = hour; Min = minute; MVC = maraviroc; N = number of subjects; NA = not applicable; T_{max} = time to maximum concentration; $t_{½}$ = terminal elimination half-life.
a. Median (range).
b. Arithmetic mean.

Table 12. Summary of Statistical Analysis of Plasma Maraviroc Exposure for Treatment Groups Receiving Maraviroc 300 mg

Parameter (Units)	Test	Reference[a]	Ratio (%)[b]	90% Confidence Interval Lower	Upper
Severe Versus Normal					
AUC_{inf} (ng•h/mL)	4367.68	1348.41	323.91	174.32	601.88
AUC_{last} (ng•h/mL)	4255.53	1320.66	322.23	171.97	603.78
C_{max} (ng/mL)	801.16	335.60	238.73	106.83	533.48

Test = severe; Reference = normal.
AUC_{inf} = area under the plasma concentration-time curve from time 0 to infinity; AUC_{last} = area under the curve from time 0 to last observation; C_{max} = maximum observed concentration; h = hour.
a. Adjusted geometric mean values.
b. Ratio of adjusted geometric means.

No efficacy evaluations were performed in this study.

Safety Results:

Treatment-emergent (non-serious) AEs (all causalities) are presented in Table 13 and a summary of treatment-emergent AEs (treatment-related) is presented in Table 14.

Table 13. Treatment-Emergent (Non-Serious) Adverse Events (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v12.0) Preferred Term	Normal MVC 300 mg	Severe MVC 300 mg	ESRD MVC 300mg Dosing After Dialysis	ESRD MVC 300 mg Dosing Before Dialysis	Normal MVC 150 mg BID + SQV/r 1000 mg/100 mg BID	Mild MVC 150 mg QD + SQV/r 1000 mg/100 mg BID	Moderate MVC 150 mg QOD + SQV/r 1000 mg/100 mg BID
Subjects evaluable for adverse events	6	6	6	6	6	6	6
Subjects with adverse events	1 (16.7)	3 (50.0)	2 (33.3)	1 (16.7)	2 (33.3)	6 (100.0)	6 (100.0)
Eye disorders	0	0	0	0	0	2 (33.3)	0
Conjunctival hyperaemia	0	0	0	0	0	1 (16.7)	0
Visual impairment	0	0	0	0	0	1 (16.7)	0
Gastrointestinal disorders	1 (16.7)	2 (33.3)	0	1 (16.7)	2 (33.3)	2 (33.3)	2 (33.3)
Abdominal distension	0	0	0	0	0	1 (16.7)	0
Abdominal pain upper	0	0	0	0	1 (16.7)	0	1 (16.7)
Constipation	0	0	0	0	0	1 (16.7)	0
Diarrhoea	0	0	0	0	1 (16.7)	1 (16.7)	1 (16.7)
Dry mouth	0	1 (16.7)	0	0	1 (16.7)	0	0
Dyspepsia	0	0	0	0	1 (16.7)	0	0
Flatulence	1 (16.7)	0	0	0	2 (33.3)	0	0
Nausea	0	1 (16.7)	0	1 (16.7)	1 (16.7)	0	1 (16.7)
Vomiting	0	0	0	1 (16.7)	0	0	0
General disorders and administration site conditions	0	0	0	0	1 (16.7)	2 (33.3)	2 (33.3)
Fatigue	0	0	0	0	0	2 (33.3)	1 (16.7)
Pain	0	0	0	0	0	0	1 (16.7)
Sensation of foreign body	0	0	0	0	1 (16.7)	0	0
Infections and infestations	0	0	0	0	1 (16.7)	0	1 (16.7)
Rhinitis	0	0	0	0	1 (16.7)	0	1 (16.7)
Injury, poisoning and procedural complications	0	0	1 (16.7)	0	0	0	0
Wound	0	0	1 (16.7)	0	0	0	0
Investigations	0	0	0	0	0	4 (66.7)	5 (83.3)
Blood bilirubin increased	0	0	0	0	0	1 (16.7)	0
Blood creatinine increased	0	0	0	0	0	4 (66.7)	4 (66.7)
Blood urea increased	0	0	0	0	0	3 (50.0)	0
Renal function test abnormal	0	0	0	0	0	0	1 (16.7)
Metabolism and nutrition disorders	0	0	0	0	0	2 (33.3)	1 (16.7)

Table 13. Treatment-Emergent (Non-Serious) Adverse Events (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v12.0) Preferred Term	Normal MVC 300 mg	Severe MVC 300 mg	ESRD MVC 300mg Dosing After Dialysis	ESRD MVC 300 mg Dosing Before Dialysis	Normal MVC 150 mg BID + SQV/r 1000 mg/100 mg BID	Mild MVC 150 mg QD + SQV/r 1000 mg/100 mg BID	Moderate MVC 150 mg QOD + SQV/r 1000 mg/100 mg BID
Dehydration	0	0	0	0	0	1 (16.7)	0
Hyperuricaemia	0	0	0	0	0	0	1 (16.7)
Hypokalaemia	0	0	0	0	0	1 (16.7)	0
Musculoskeletal and connective tissue disorders	0	0	0	0	0	1 (16.7)	0
Muscle spasms	0	0	0	0	0	1 (16.7)	0
Nervous system disorders	0	0	0	0	2 (33.3)	4 (66.7)	1 (16.7)
Dizziness	0	0	0	0	1 (16.7)	1 (16.7)	0
Headache	0	0	0	0	2 (33.3)	3 (50.0)	1 (16.7)
Paraesthesia	0	0	0	0	0	1 (16.7)	0
Renal and urinary disorders	0	0	0	1 (16.7)	0	3 (50.0)	3 (50.0)
Nocturia	0	0	0	0	0	3 (50.0)	3 (50.0)
Renal pain	0	0	0	1 (16.7)	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	2 (33.3)	0	0
Cough	0	0	0	0	1 (16.7)	0	0
Throat irritation	0	0	0	0	1 (16.7)	0	0
Skin and subcutaneous tissue disorders	0	0	1 (16.7)	0	0	1 (16.7)	0
Hyperhidrosis	0	0	0	0	0	1 (16.7)	0
Pruritus	0	0	1 (16.7)	0	0	0	0
Vascular disorders	0	1 (16.7)	0	0	0	0	0
Orthostatic hypotension	0	1 (16.7)	0	0	0	0	0

Subjects were only counted once per treatment for each row. Includes data up to 7 days after last dose of study drug.
MedDRA (v12.0) coding dictionary applied.
BID = twice daily; ESRD = end stage renal disease; MedDRA = Medical Dictionary of Regulatory Activities; MVC = maraviroc; QD = once daily; QOD = once every 48 hours; SQV/r = boosted saquinavir (saquinavir 1000 mg + ritonavir 100 mg); v = version.

Table 14. Summary of Treatment-Emergent Adverse Events (Treatment Related)

System Organ Class and MedDRA (v12.0) Preferred Term	Normal MVC 300 mg	Severe MVC 300 mg	ESRD MVC 300mg Dosing After Dialysis	ESRD MVC 300 mg Dosing Before Dialysis	Normal MVC 150 mg BID + SQV/r 1000 mg/100 mg BID	Mild MVC 150 mg QD + SQV/r 1000 mg/100 mg BID	Moderate MVC 150 mg QOD + SQV/r 1000 mg/100 mg BID
Subjects evaluable for adverse events	6	6	6	6	6	6	6
Eye disorders	0	0	0	0	0	2	0
Conjunctival hyperaemia	0	0	0	0	0	1	0
Visual impairment	0	0	0	0	0	1	0
Gastrointestinal disorders	1	2	0	1	2	1	2
Abdominal pain upper	0	0	0	0	1	0	1
Diarrhoea	0	0	0	0	1	1	1
Dry mouth	0	1	0	0	1	0	0
Dyspepsia	0	0	0	0	1	0	0
Flatulence	1	0	0	0	2	0	0
Nausea	0	1	0	1	1	0	1
Vomiting	0	0	0	1	0	0	0
General disorders and administration site conditions	0	0	0	0	1	2	1
Fatigue	0	0	0	0	0	2	0
Pain	0	0	0	0	0	0	1
Sensation of foreign body	0	0	0	0	1	0	0
Infections and infestations	0	0	0	0	1	0	0
Rhinitis	0	0	0	0	1	0	0
Investigations	0	0	0	0	0	3	5
Blood bilirubin increased	0	0	0	0	0	1	0
Blood creatinine increased	0	0	0	0	0	3	4
Blood urea increased	0	0	0	0	0	3	0
Renal function test abnormal	0	0	0	0	0	0	1
Metabolism and nutrition disorders	0	0	0	0	0	1	1
Hyperuricaemia	0	0	0	0	0	0	1
Hypokalaemia	0	0	0	0	0	1	0
Musculoskeletal and connective tissue disorders	0	0	0	0	0	1	0
Muscle spasms	0	0	0	0	0	1	0

Table 14. Summary of Treatment-Emergent Adverse Events (Treatment Related)

System Organ Class and MedDRA (v12.0) Preferred Term	Normal MVC 300 mg	Severe MVC 300 mg	ESRD MVC 300mg Dosing After Dialysis	ESRD MVC 300 mg Dosing Before Dialysis	Normal MVC 150 mg BID + SQV/r 1000 mg/100 mg BID	Mild MVC 150 mg QD + SQV/r 1000 mg/100 mg BID	Moderate MVC 150 mg QOD + SQV/r 1000 mg/100 mg BID
Nervous system disorders	0	0	0	0	2	4	0
Dizziness	0	0	0	0	1	1	0
Headache	0	0	0	0	2	3	0
Paraesthesia	0	0	0	0	0	1	0
Renal and urinary disorders	0	0	0	1	0	3	2
Nocturia	0	0	0	0	0	3	2
Renal pain	0	0	0	1	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	2	0	0
Cough	0	0	0	0	1	0	0
Throat irritation	0	0	0	0	1	0	0
Skin and subcutaneous tissue disorders	0	0	1	0	0	1	0
Hyperhidrosis	0	0	0	0	0	1	0
Pruritus	0	0	1	0	0	0	0
Vascular disorders	0	1	0	0	0	0	0
Orthostatic hypotension	0	1	0	0	0	0	0
Total preferred term events	1	3	1	3	14	23	12

Subjects were only counted once per treatment for each row. Includes data up to 7 days after last dose of study drug.
MedDRA (v12.0) coding dictionary applied.
BID = twice daily; ESRD = end stage renal disease; MedDRA = Medical Dictionary of Regulatory Activities; MVC = maraviroc; QD = once daily; QOD = once every 48 hours; SQV/r = boosted saquinavir (saquinavir 1000 mg + ritonavir 100 mg); v = version.

There were no deaths and no other serious AEs (SAEs) reported during this study.

There was 1 subject withdrawal due to a severe AE of renal function test abnormal (increase in serum creatinine) which was considered related to the study drug. This subject was in the moderate renal impairment group and was treated with MVC 150 mg QOD and with SQV/r BID.

There were no dose reductions or temporary discontinuations due to AEs reported in this study.

In general, transient decreases in mean CL_{cr} were observed in subjects with normal renal function, and with mild, or moderate renal impairment. There was no relationship between the decreases in mean CL_{cr}, and the mean baseline serum creatinine. Mean CL_{cr} returned towards baseline values in all 3 groups. Apart from a slight increase in mean blood urea nitrogen levels, the transient change in CL_{cr} was not associated with clinically relevant changes in the mean values of other renal function parameters or urinalysis. However, the value of these data is limited by the small sample size and wide interpersonal variations.

In addition to the subject who discontinued the study due to a severe AE of renal function test abnormal (increase in serum creatinine), other AEs related to clinical laboratory tests included blood bilirubin increased (1 subject treated with 150 mg MVC QD and SVQ/r BID had mild renal impairment), blood creatinine increased (4 subjects treated with 150 mg MVC QD and SQV/r BID had mild renal impairment and 4 subjects treated with MVC 150 mg QOD and SQV/r BID had moderate renal impairment), and blood urea increased (3 subjects treated with 150 mg MVC QD and SQV/r BID had mild renal impairment). All of these AEs were considered treatment related except for 1 AE of blood creatinine increased (reported by a subject treated with 150 mg MVC QD and SQV/r BID who had mild renal impairment).

No subjects had absolute vital sign values meeting the categorical summarization criteria defined as supine systolic BP <90 mmHg, supine diastolic BP <50 mmHg, or a supine pulse rate <40 or >120 bpm. One subject with moderate renal impairment treated with MVC 150 mg QOD and SQV/r BID had a maximum increase from Baseline value in supine diastolic BP that met the categorical summarization criteria for an increase in diastolic systolic BP defined as an increase of ≥20 mmHg on Day 9. One subject with ESRD treated with MVC 300 mg dosed after dialysis had a maximum decrease from Baseline in supine systolic BP that met the categorical summarization criteria defined as a decrease of ≥30 mmHg on Day 1, 1 hour postdose.

One subject with severe renal impairment treated with MVC 300 mg reported an AE of orthostatic hypotension on Day 1 of the study. This was the only vital sign related AEs reported in this study.

ECG values meeting categorical summarization criteria, by subject, are presented in Table 15. No ECGs related AEs were reported.

Table 15. Electrocardiogram Values Meeting Categorical Summarization Criteria (msec)

Subject (Renal Function)	Treatment	Parameter	Criteria	Study Day	Value of Concern
1 (ESRD)	ESRD treated with MVC 300 mg before dialysis	QTc interval	≤30 change <60	8	429
		QTcB interval	≤30 change <60	8	420
2 (ESRD)	ESRD treated with MVC 300 mg after dialysis (pre treatment)	QTc Interval	450-<480	1	450
3 (Normal renal function)	MVC 150 mg BID + SQV/r BID	QTc interval	450-<480	11	465
		QTcB interval	450-<480	11	465
		QTcF	450-<480	11	455
	MVC 300 mg	QTc interval	450-<480	1	456 and 452
	MVC 300 mg	QTcB interval	450-<480	1 and 3	457 and 453 on Day 1, 450 on Day 3
4 (Severe renal impairment)	MVC 300 mg	QTc interval	450-<480	1	450
5 (Severe renal impairment)	MVC 300 mg	QTc interval	450-<480	1, 3, and 9	459,468 and 467
		QTcB interval	450-<480	1, 3, and 9	459, 469 and 468
		QTcF	450-<480	3	455
6 (ESRD)	MVC 300 mg after dialysis	QTcB interval	≤30 change <60	4	429

BID = twice daily; ESRD = end stage renal disease; MVC = maraviroc; QD = once daily; QOD = every 48 hours; QTc = QT interval corrected for heart rate; QTcB = QTc interval with Bazett's correction; QTcF = QTc interval with Fridericia's correction; SQV/r = saquinavir 1000 mg + ritonavir 100 mg.

CONCLUSIONS:

Multiple dose (MVC with SQV/r):

- There were no clinically significant higher MVC exposures (AUC_{tau}) in subjects with mild or moderate renal impairment compared to subjects with normal renal function.
- CL_{cr} was not shown to be a significant predictor of total unbound apparent MVC clearance (p=0.302) in subjects with mild or moderate renal impairment and in subjects with normal renal function.
- Renal clearance contributed approximately 23%, 25%, and 15% to total oral MVC clearance in subjects with normal renal function, mild renal impairment, and moderate renal impairment, respectively.

Single dose (MVC alone):

- Following a single dose of MVC, there was a significantly higher MVC exposure in subjects with severe renal impairment relative to those with normal renal function.

- MVC exposures, when dosed pre and post dialysis, fell between exposures observed in subjects with normal renal function and those observed in subjects with severe renal impairment.

- Dialysis did not appear to meaningfully alter the PK profile of MVC and mean dialysate clearance was estimated to be approximately 36 mL/minute.

- Renal clearance contributed to approximately 2% to 3% of the CL/F in subjects with severe renal impairment and normal renal function.

Safety:

- No deaths or SAEs were reported in this study. One subject withdrew from the study due to an AE of severe renal function test abnormal (increase in serum creatinine) which was considered related to the study drug. This subject had moderate renal impairment and was treated with MVC 150 mg QOD and with SQV/r BID. No temporary discontinuations or dose reductions due to AEs were reported.

- In general transient decreases in mean CL_{cr} were observed in subjects with normal renal function, and with mild, or moderate renal impairment. There was no relationship between the decreases in mean $CL_{cr,}$ and the mean baseline serum creatinine. Mean CL_{cr} returned towards Baseline values in all 3 groups.