

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-128

MEDICAL REVIEW

Office Director Memo

Applicant: Pfizer

NDA #: 22-128

Drug: maraviroc 150 mg and 300 mg tablets

Trade Name: SELZENTRY

Proposed Indication

SELZENTRY, in combination with other antiretroviral agents, is indicated for treatment experienced adult patients infected with CCR5-tropic HIV-1 who have HIV-1 strains resistant to multiple antiretroviral agents.

This indication is based on analyses of plasma HIV-1 RNA levels in two controlled studies of SELZENTRY of 24 weeks duration. Both studies were conducted in clinically advanced, 3-class antiretroviral (NRTI, NNRTI, PI) treatment-experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

The following points should be considered when initiating therapy with SELZENTRY:

- Tropism testing and treatment history should guide the use of SELZENTRY.
- The safety and efficacy of SELZENTRY have not been established in treatment naïve adult patients or pediatric patients.

There are no study results demonstrating the effect of SELZENTRY on clinical progression of HIV-1.

This indication is based on safety and efficacy data from two double-blind, placebo controlled trials of 24 weeks duration in treatment-experienced subjects.

A study in antiretroviral-naïve subjects is ongoing; the benefit-risk assessment for this population is therefore not yet known.

Date of Initial Submission: December 20, 2007

PDUFA Goal Date, First Cycle: June 20, 2007

Regulatory Action, First Cycle: Approvable

- Before the application can be approved it will be necessary for the Applicant to submit final printed labeling identical to the draft labeling affixed to the approvable letter and to submit a draft medication guide

Date of Resubmission: July 30, 2007

Action Date, Second Cycle: August 6, 2007

Regulatory Action, Second Cycle: Approval, under 21CFR §314.500, Subpart H

SELZENTRY (maraviroc) is a CCR5 co-receptor antagonist, a new class of antiretroviral agent. At the end of the first cycle the remaining deficiency was the product labeling. The labeling accompanying the approvable letter included a boxed warning describing the risk of hepatotoxicity. The Applicant's resubmission included proposed labeling with a boxed warning and a medication guide. During the interval between the first cycle and the resubmission, reviews of the hepatotoxicity of maraviroc by special government employee hepatologists and Pfizer's consultants were performed. While there was variability in the consultant's assessment of the risk of hepatotoxicity, based upon the available data, labeling should inform of the risk of hepatotoxicity. In addition, a medication guide will provide an additional means to inform patients about the risk of adverse effects specifically including hepatic toxicity and to seek medical evaluation should symptoms consistent with hepatotoxicity develop. The approval under Subpart H includes the requirement to provide confirmatory evidence for the accelerated approval based on 24-week data and also postmarketing commitments to perform additional studies including a study to further characterize the safety profile of maraviroc.

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/s/

David Roeder

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David Roeder is signing this review on behalf of
Edward Cox, Office Director, OAP, due to problems
with computer connectivity

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

DATE: 25 June 2007

FROM: John R. Senior, M.D., Associate Director for Science, Office of Surveillance and Epidemiology (OSE)

TO: Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
Scott Proestel, M.D., Medical Reviewer, DAVP

VIA: Mark Avigan, M.D., Director, Division of Drug Risk Evaluation (DDRE), OSE
Gerald DalPan, M.D., Director, OSE

SUBJECT: Cases of possible liver injury in patients treated with maraviroc (UK-427857) under NDA 22-128 and IND 65,229; OSE consultation #2007-1430

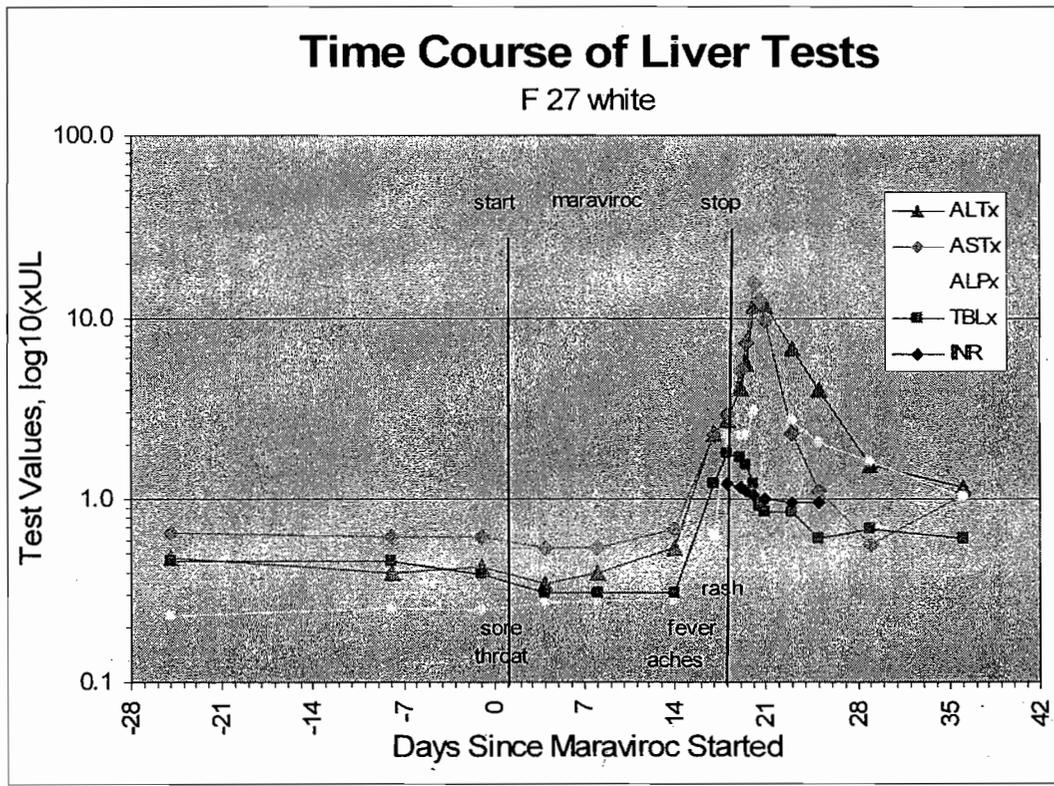
Documents reviewed:

- 1) Narrative summary and laboratory data for Subject 34 in Study A4001066
 - 2) Medical review by Dr. Scott Proestel, dated 18 June
 - 3) Documents sent by sponsor (Pfizer) on 20 June, forwarded to me 21 June
 - 4) Selected documents from Document File System on IND 65,229 and IND 21-128
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This request for consultation was prompted by the report of a second case of potentially serious liver injury that arrived just before the due date of 20 June for approvability of maraviroc for treatment of patients previously treated with other regimens. The case involved a healthy female subject aged 27 years ([REDACTED]) who developed serum transaminase elevations first on 7 June, after [REDACTED] on maraviroc 600 mg/day. The protocol provided for a screening visit up to 4 weeks before a run-in period of 1 week on placebo before 4 weeks on study drug (either placebo or maraviroc 600 mg once daily) to observe the effects of feeding or fasting.

The participant was screened on [REDACTED], and started open placebo on [REDACTED] Day 1), then started maraviroc [REDACTED]. Her baseline laboratory data were all within normal limits except for borderline anemia (red cell count $3.85 \times 10^6/\mu\text{L}$, hemoglobin 12.0 g/dL, hematocrit 34% and white cell count $4.4 \times 10^6/\mu\text{L}$ with neutrophils $2.35 \times 10^6/\mu\text{L}$). She went on a trip to Turkey from 29 April until 6 May, but remained well and asymptomatic, with normal laboratory test results normal on [REDACTED], when she was admitted to begin the placebo run-in period the next day. She complained of a sore throat on 20 May, the 6th day of the placebo run-in period, and was noted the next day to have a slightly elevated white blood cell count of 11,400/ μL and neutrophils of 9,420 (82.3%), up from 5,200/ μL and 2,550 (49.1%) on the 14th. Symptomatic treatment with microcidal mouthwash led to improvement over the next few days, and she began treatment with maraviroc as scheduled on [REDACTED]. Her elevated white cell count normalized on 25 May, to 6500/ μL with 3,710/ μL (57.0%) neutrophils, and [REDACTED] to 6,400/ μL with 2,890 neutrophils/ μL (45.2%).

On the morning of June 4th of maraviroc treatment, she reported headache, and neck pain, but had no fever [oral temperature 36.9°C (98.4°F)] and she was found to have palpable cervical and submandibular lymph nodes and trapezius muscle tenderness, which were treated with acetaminophen 500 mg. That evening she reported hot flushes, characterized as "flu-like symptoms, with dizziness on standing, and she took more acetaminophen 500 mg for headache. These symptoms continued, with weakness, shivering, and pruritus on the 5th. She called the unit on the evening of the 6th and was told to take her temperature at home, which showed fever of 39.9°C (103.8°F). She took 1 g of acetaminophen twice. On 7 June she reported feeling better but still weak, and her white blood cell count was 4,500/ μ L with neutrophils of 2,000/ μ L (44.4%) but there was slight elevation of her eosinophils to 8.4%, previously in the low-normal range at 1.2-1.7% when she had the sore throat. On examination she had no postural hypotension and her temperature was down to 37.5°C (99.5°F). At noon she reported nasal irritation and congestion resembling hay fever, and symptomatic orthostatic hypotension.



Laboratory tests showed modest elevations of the ALT to 81 and AST to 79 U/L (upper limits of normal for both 35 U/L), but blood taken for acute viral hepatitis infection was later reported negative for A, B, and C, and for acute EBV and CMV infections. She still had palpable lymph nodes as before, a normal blood pressure, and some skin rash on her chest. She requested permission to go home, and did so, and reported slight fevers that night between 38.3 and 39.1°C (100.9-102.4°F), for which she took more acetaminophen 1 g , she returned to unit for examination in the morning, feeling well, and was found to have no postural hypotension before maraviroc dosing. But three hours later she was shivering, unable to stand, felt itching in

the face, nausea and vomiting, and developed an urticarial rash on the abdomen, chest, arms, and legs, with fever to 40.1°C (104.2°F). There was no leukocytosis (white count 4,100/ µL) but 8.6% eosinophils and mild platelet reduction to 136,000/ µL. Her ALT had risen a bit to 104 U/L, AST 95 U/L, total bilirubin (TBL) 2.3 mg/dL and INR 1.22. Gastroenterology consultation was requested and was reported as “consistent with drug-induced hepatitis.” Maraviroc was discontinued on 8 June, the [redacted] of treatment.

The next day, 9 June, no further maraviroc was given. She reported feeling better, had no fever or leukocytosis but eosinophils were 10.5% (total white cell count 4,200/ µL). She received intravenous saline and was normotensive, but her ALT rose to 178 and AST to 145 U/L, TBL 2.2 mg/dL and INR 1.16. Later that afternoon AST was 255 U/L and ALT 194 U/L, TBL 2.0 mg/dL, and the next morning even more to AST 504, ALT 393, TBL 1.5 and AST 543, ALT 410, and TBL 1.6. Following those peak values, the elevated serum enzymes declined over the next two weeks, the AST more rapidly than the ALT (has a shorter plasma half-life if the cause of elevation is removed). By 26 June 2007 the ALP and TBL were in the normal range, and the ALT and AST only very slightly elevated. The eosinophilia, fever, and rash had disappeared. All tests for alternative possible causes of the hepatic test abnormalities were negative, including serological markers for acute viral hepatitis A, B, and C, EBV and CMV, although there were IgG antibodies detected for past infections for hepatitis C, EBV, and CMV. There was no history or findings for biliary tract disease, autoimmune hepatitis, excessive alcohol consumption, or notable shock or congestive heart failure. The sponsor did a very thorough job of searching for alternative possible causes, but found negative test results for Mycoplasma pneumoniae, Borrelia burgdorferi, toxoplasmosis, rubella, brucellosis, Q fever, rickettsiae, leptospirosis, malaria, stool ova and parasites, enteroviruses, parvovirus B19, adenovirus, hepatitis E, and HHV-6.

Comment: It is pertinent to review the grading levels upon which the decisions were made.

grade	definition	ALT	AST	ALP	TBL
		all expressed in multiples of ULN (xULN)			
Grade 1 mild	transient or mild discomfort, no disability, no treatment needed	1.25 - 2.5	1.25 - 2.5	1.25 - 2.5	>1 - 1.5
Grade 2 moderate	some limitation in activity, may need assistance, minimal therapy	>2.5 - 5	>2.5 - 5	>2.5 - 5	>1.5 - 2.5
Grade 3 severe	marked limitation, assistance and therapy required, hospitalization	> 5 - 10	> 5 - 10	> 5 - 10	>2.5 - 5
Grade 4 life-threatening	disabled, need much assistance and treatment, threat of death	>10	>10	>10	>5

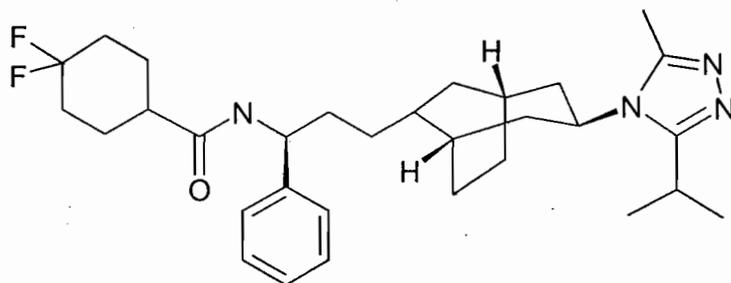
Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase: all in units/L of activity; TBL, total serum bilirubin, in mg/dL; ULN, upper limit of normal range.

The origin of these values and definitions is not well established, but appears to date back to the early 1980s, when panels of experts were convened at the National Cancer Institute to classify and grade both clinical and laboratory abnormalities into the four grades of severity. For serum enzyme elevations, which do not measure any liver function or of themselves cause disease or symptoms, but simply give a rough and unspecific indication of cellular injury causing release of enzymes into plasma, the grading is frankly absurd. However, when grade 2 elevations of both ALT and TBL are seen in a patient with drug-induced hepatocellular (but not cholestatic) injury, the damage to the liver may be extensive enough to predict possible grade 4 clinical outcome of acute liver failure, as observed long ago by the late Hyman Zimmerman

The drug, maraviroc, is the first of several receptor blockers of the CCR5 receptor discovered to be found necessary for binding, in conjunction with CD4, of the HIV-1 virus so it can penetrate target cells. Key observations were reported by Liu, et al. (1996) that absence of a recently discovered cell surface CC-CKR-5 (or CCR5) co-receptor with CD4 appeared to explain the resistance of certain people to infection by HIV-1 (Deng, et al. 1996), despite exposure to the virus. It had been observed that some individuals whose sexual behavior placed them at very high risk of exposure to HIV-1 did not become infected and remained seronegative (Clerici, et al., 1992). In HIV-1 seroconverters who did get infected, the viral phenotype was uniformly macrophage-tropic and non-syctium-inducing (Zhu, et al., 1993). Gambian prostitutes heavily exposed to HIV infection but seronegative for HIV infection by polymerase chain reaction (PCR) testing nevertheless had strong cytolytic T-lymphocyte activity (Rowland-Jones, et al, 1995). Dragic and colleagues (1996) found that entry of HIV-1 into CD4+ T-cells is mediated by the chemokine co-receptor CC-CKR-5 (also abbreviated CCR5). These observations converged in the findings of Paxton et al. (1996), who found that exposed but uninfected individuals had CD4+ lymphocytes that were less susceptible to infection with multiple HIV-1 isolates than lymphocytes from non-resistant control subjects. Further, their CD8+ lymphocytes had greater anti-HIV-1 activity. Resistance of the CD4+ lymphocytes was only to the macrophage-tropic but not T-cell line-adapted HIV strains, was restricted by the viral envelope glycoprotein, and associated with the cell surface co-receptor chemokines of the CCR5 group. When the CCR55 receptor is unavailable for binding, the "R5-tropic" type of HIV cannot engage with a CD4 T-cell to enter and infect the cell. This variant of the virus is common early in HIV infection, but later the virus may adapt to use a CXCR4 receptor and "X4-tropic" strains gradually may become dominant in the disease process.

Huang and colleagues (1996) found a 32-nucleotide deletion within the beta-chemokine receptor gene in subjects who were resistant to infection by HIV-1, with prevalence of about 1 in 12 among Caucasians but not in people of Asian or African ancestry. The seminal report by Liu et al. (1996) described inability of macrophage-tropic HIV-1 isolates to enter CD4+ lymphocytes of two individuals who were homozygous for the genetic defect of the gene CKR-5 that encodes for the CCR5 co-receptor. The genetic defect in the co-receptor CCR5 was then found to protect naturally CCR5-defective but otherwise healthy individuals from HIV-1 infection (Yang, et al. 1997). This led to intense search for antagonists to the CCR5 receptor as a possible novel approach to preventing infection by HIV-1 (Simmons, et al., 1997). Kilby and Eron (1993) described a new set of therapeutic agents in development, based on their effects on HIV-1 cell entry. Several CCR5 antagonists other than maraviroc have been developed, including aplaviroc and vicriviroc (Schering), and others, TAK-220 (Takashima, et al., 2005) and TAK-652 are just beginning clinical study (Castagna, et al., 2005; DeClercq, 2005; Reeves and Piefer, 2005). However, aplaviroc was terminated from further development in 2005 by its sponsor Glaxo SmithKline because of hepatotoxicity (see my consultation of 20 October 2005).

Maraviroc is a compound developed as a novel, small, non-peptide inhibitor of the CC-chemokine receptor-5 (CCR5) that is a principal co-receptor needed for macrophage-tropic entry of the human immunodeficiency virus (HIV-1) into target cells. It was known initially as UK-457857 before its generic name assignment.



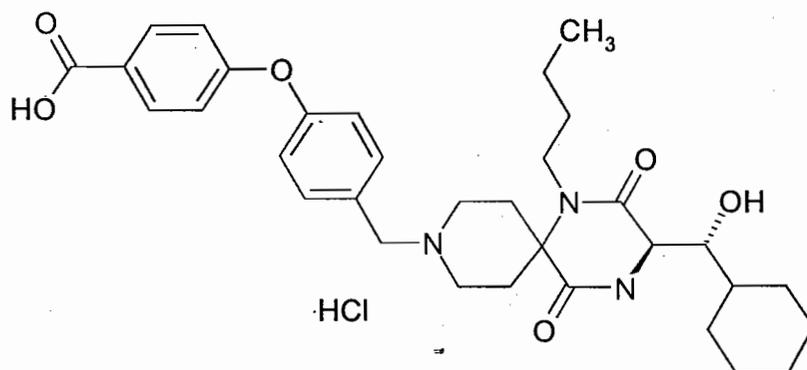
maraviroc
UK-427857, Pfizer

Maraviroc is a substrate of CYP3A4, which may lead to interactions with other drugs used in treating AIDS, especially protease inhibitors (atazanavir, and ritonavir-boosted lopinavir and saquinavir) that compete for CYP3A4 and therefore may raise levels of maraviroc. Its various metabolites are essentially inactive against HIV-1.

After oral administration the absolute bioavailability of a 100-mg dose was 23%, and predicted to be about 33% for a 300-mg dose. It is a substrate for the P-glycoprotein efflux transporter. A single oral dose of 1 to 1200 mg reaches peak plasma concentration in from 0.5 to 4 hours. Once absorbed maraviroc is about 76% bound to plasma proteins, including albumin and glycoproteins.

Maraviroc was scheduled for accelerated approval for patients infected with CCR5-tropic HIV-1 who had been previously treated on other regimens. Its efficacy in reducing the HIV-1 load was demonstrated in clinical trials 1027 and 1028, as summarized in the medical review of Dr. Scott Proestel.

It may be of interest to compare maraviroc with another CCR5 antagonist (aplaviroc, GSK) that was removed from clinical trials under IND on 15 September 2005 because of hepatotoxicity.



aplaviroc
AK602, ONO4128, GW873140

Comment: It is impressive to note that research conducted all over the world has quite rapidly merged to greater understanding of the mechanisms of HIV-1 infection of cells, and to the many avenues of treatment that have revolutionized the treatment of acute immunodeficiency disease (AIDS) using combined multiple approaches (Barbaro, et al., 2005). This approach simulates an experiment of nature, which produced genetically deficient and resistant individuals, by blocking the specific cell surface receptor present in most people but missing in those naturally resistant. Very clever. But not necessarily safe. We now have some instances of possible hepatotoxicity to consider.

There are no reports in the literature of hepatotoxicity or other serious toxicity of aplaviroc or maraviroc, but clinical trials are conducted under confidentiality and results cannot be made public without consent of the sponsor.

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Comment: It is unclear whether occasional hepatotoxicity may or may not be a class effect of viroc drugs, but the issue may require close watching. Even if one agent in a class shows serious hepatotoxicity, it is not necessarily found with other members (as exemplified by troglitazone, which was far more hepatotoxic than rosiglitazone or pioglitazone).

Recommendations:

- 1) Maraviroc appears to have probably caused at least one potentially serious case of acute hepatocellular injury with immunoallergic findings that that did not lead to liver failure. The patient should be followed until complete recovery occurs and is documented.
- 2) Because maraviroc may be the first of its class of novel CCR5 receptor blockers, it will very likely be actively promoted by the sponsor. It will be important for prescribing physicians to be at least aware of potential hepatotoxicity as much larger numbers of patients are exposed to maraviroc. A strong warning is recommended for the labeling.

John R. Senior, M.D.

cc: ODS DDRE PID#D050542
M. Avigan, ODS/DDRE
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CLINICAL REVIEW

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ANTIMICROBIAL PRODUCTS
DIVISION OF ANTIVIRAL PRODUCTS

NDA:	22-128
PRODUCT:	SELZENTRY (maraviroc)
SPONSOR:	Pfizer Global Research and Development
REVIEWER:	Scott Proestel, M.D.
REVIEW DATE:	08-02-2007

The purpose of this memorandum is to provide an update for the events that led up to the issuance of an Approvable letter for NDA 22-128 on June 20, 2007, as well as to provide the basis for the subsequent decision to approve maraviroc for treatment-experienced adult patients infected with CCR5-tropic HIV-1.

On June 11, 2007, FDA was notified of a serious adverse event in a 27-year-old woman during a healthy volunteer study entitled, "A Double Blind (3rd Party Open), Placebo Controlled, Randomized Study to Investigate the Safety and Toleration of Maraviroc 600 mg QD Both Fed and Fasted for a Total of 28 Days in Healthy Subjects." A narrative of this adverse event is provided within the clinical review for NDA 22-128. A brief summary and update are provided here. Slight discrepancies in the laboratory results between the clinical review and this update are due to receipt of additional information. On Day 14 of maraviroc dosing, this subject was noted to have eosinophilia, and developed shivering, pruritus, and a feeling of weakness. She continued to have these symptoms over the next several days, and on Day 16 she had a temperature of 40°C. On Day 17, she developed rhinitis, nasal congestion, and symptomatic orthostatic hypotension approximately 3.5 hours after her dose. At that time, her AST was 79 U/L, ALT 81 U/L, total bilirubin 1.6 mg/dL, and total IgE 259 kU/L (upper limit of normal 120 kU/L). Three hours following her dose on Day 18, she developed shivering, fever (40°C), facial pruritus, vomiting, and a feeling of weakness. Later that day, she developed an urticarial-like rash on her arms, chest, and legs. Laboratory results at that time revealed increasing eosinophilia (8.6%), AST 104 U/L, ALT 95 U/L, total bilirubin 2.3 mg/dL, and INR 1.22. Maraviroc was discontinued on Day 18, and her AST peaked at 543 U/L on Day 20 and ALT peaked at 411 U/L on Day 21. She has subsequently done well with improvement in liver enzymes and normalization of bilirubin and INR. Of note, she had a sore throat 2 days prior to starting maraviroc, but this resolved 12 days prior to her symptoms on Day 14 of drug administration. A throat culture obtained two days after maraviroc discontinuation revealed Group A streptococcus, but there is no report of antibiotic administration before or after this finding. An extensive evaluation for other infectious or autoimmune etiologies for her hepatitis and other symptoms was unremarkable, as was her abdominal ultrasound.

Based on this event during a healthy volunteer trial which met Hy's law, and in the setting of an increase in liver-related adverse events during the maraviroc phase 3 studies,

FDA determined that a Box Warning for hepatotoxicity should be included in the maraviroc label. The Applicant contended that the case was confounded by a streptococcal infection and that the subject's presentation could be consistent with scarlet fever. Due to disagreement regarding the need for a Box Warning, an Approvable letter was issued on June 20. Subsequently, FDA consulted external hepatology experts (William Lee, M.D., The University of Texas Southwestern Medical Center at Dallas, and John Vierling, M.D., Baylor College of Medicine) as did the Applicant. Dr. Lee felt that while an infectious cause could not be completely excluded, all of the findings in this case were consistent with drug-induced hepatotoxicity. Dr. Vierling felt that the subject's presentation was most consistent with scarlet fever given her documented Group A streptococcal infection, fever, and rash.

Following review of all of the external consultants' findings, FDA determined that the subject's presentation was most consistent with drug-induced hepatotoxicity likely due to a hypersensitivity response to maraviroc. The reasons for this include the description of her rash as "urticarial-like," and the findings of eosinophilia and elevated IgE following maraviroc administration. The timing and description of her rash were not felt to be consistent with scarlet fever. In addition, the occurrence of hepatitis in the setting of scarlet fever is rare. After discussion of the consultants' findings with the Applicant, it was agreed that a Box Warning for hepatotoxicity would be added to the label. The Box Warning, subject to final approval, will be as follows:

WARNING: HEPATOTOXICITY

See full prescribing information for complete boxed warning

- Hepatotoxicity has been reported. (5.1)
- May be preceded by evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia or elevated IgE). (5.1)
- Immediately evaluate patients with signs or symptoms of hepatitis or allergic reaction. (5.1)

In light of the concern regarding hepatotoxicity, a Medication Guide is being developed for maraviroc which will describe the symptoms patients should watch for as well as the actions that should be taken should such symptoms occur.

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Acting Office Director Memo

Applicant: Pfizer

NDA #: 22-128

Drug: maraviroc 150 mg and 300 mg tablets

Proposed Trade Name: SELZENTRY

Proposed Indication

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There are no study results demonstrating the effect of SELZENTRY on clinical progression of HIV-1.

This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials of 24 weeks duration in treatment-experienced subjects.

A study in antiretroviral-naïve subjects is ongoing; the benefit-risk assessment for this population is therefore not yet known.

Proposed Dose and Durations

The recommended dose of SELZENTRY differs based on concomitant medications due to drug interactions. SELZENTRY can be taken with or without food. SELZENTRY must be given in combination with other antiretroviral medications.

Table. Recommended Dosing Regimen

Concomitant Medications	SELZENTRY Dose
CYP3A4 inhibitors (with or without a CYP3A4 inducer) including: <ul style="list-style-type: none">• protease inhibitors (except tipranavir/ritonavir)• delavirdine• ketoconazole, itraconazole, clarithromycin,• Other strong CYP3A inhibitors (e.g., nefazadone, telithromycin)	150mg twice daily
Other concomitant medications, including tipranavir/ritonavir, nevirapine, all NRTIs and enfuvirtide	300mg twice daily
CYP3A4 inducers (without a CYP3A4 inhibitor) including: <ul style="list-style-type: none">• efavirenz• rifampin• carbamazepine, phenobarbital, and phenytoin	600mg twice daily

Date of Initial Submission: December 20, 2007

PDUFA Goal Date: June 20, 2007

Regulatory Action: Approvable

- Before the application can be approved it will be necessary for the Applicant to submit final printed labeling identical to the draft labeling affixed to the approvable letter and to submit a draft medication guide

Background

SELZENTRY (maraviroc) is a CCR5 co-receptor antagonist, a new class of antiretroviral agent. Maraviroc will provide an additional option for treatment experienced adult patients with CCR5-tropic HIV who have HIV-1 strains resistant to multiple antiretroviral agents. The application was presented to the Antiviral Drugs Advisory Committee on April 24, 2007. The Committee voted unanimously that the safety and efficacy data supported accelerated approval for treatment experienced HIV-1 infected patients with CCR5-tropic virus. The Committee also voted unanimously in support of the applicant's proposed dosing regimen. The Committee also discussed cardiovascular risk, hepatotoxicity, and the potential risk of malignancy and infection. Also during the discussions, the Committee brought up the limited racial and ethnic diversity of the patient population enrolled in the clinical trials.

The review team has reviewed the issues in detail in their respective disciplines with regards to the safety and efficacy of maraviroc for the treatment of HIV infection in

antiretroviral experienced adult patients. For a detailed discussion of NDA 22-128, the reader is referred to the individual discipline specific reviews. In addition Dr. Laessig's Team Leader's Memo and Dr. Birnkrant's Division Director's Memo summarize key issues in the NDA submission. This memorandum will focus on selected issues from the application.

Chemistry Manufacturing and Controls

The chemistry manufacturing and controls are summarized in the Chemists' review which recommends approval from the standpoint of CMC for maraviroc 150 mg and 300 mg tablets. Facilities inspections were performed for the drug substance and drug product manufacturing facilities and found to be acceptable. The recommendation regarding CMC is for approval.

Pharmacology Toxicology

The recommendation from Dr. Farrelly and Dr. Verma with regards to the pharm/tox studies is for approval from a pharm/tox standpoint. Among the pharm tox studies is a one-month oral toxicity study in rats that found changes related to the liver. These included moderate elevations of ALT, AST, ALP, GGT, and cholesterol in high dose animals. Histopathologic changes involving the liver were also noted that included necrosis in the centrilobular area with occasional extension into the periportal region in the high dose animals. In the 26-week oral toxicology study, in the high dose groups, bile duct vacuolation and hyperplasia and multinucleated hepatocytes were noted. As noted in the product label, no drug-related increases in tumor incidence were found in mice at exposures up to 32 times the exposure in humans and also in rats at exposures up to 11 times those observed in humans. Maraviroc is categorized as Pregnancy Category B.

Microbiology

The microbiologic assessment of maraviroc is discussed in Dr. Naeger's microbiologist's review. Maraviroc is a CCR5 co-receptor antagonist that inhibits the interaction of HIV gp120 of CCR5 tropic HIV-1 to the CCR5 co-receptor on the cell membrane. Studies of serial passage in cell culture in the presence of maraviroc have identified amino acid changes in the envelope glycoprotein associated with maraviroc resistance. As noted in the microbiology review, possible reasons for clinical failure on maraviroc include co-receptor switch from CCR5 to CXCR4 tropic virus, outgrowth of previously undetected CXCR4 subpopulations, outgrowth of CCR5 maraviroc-resistant virus, resistance to other agents in the regimen, or theoretically, a host CCR5 receptor to which maraviroc does not bind efficiently.

Clinical Pharmacology

The clinical pharmacology of maraviroc is discussed in the clinical pharmacology and biopharmaceutics and pharmacometrics reviews. An exposure response analysis shows that antiviral efficacy was associated with C_{min} , baseline CD4+ cell count, baseline viral load, and overall sensitivity score (OSS). The finding of a $C_{min} > 50-75$ ng/mL was associated with a better chance of success. Maraviroc is a CYP 3A substrate as well as a P-gp substrate. Dosage adjustment as listed in the dosage and administration section is needed in the setting of drugs that inhibit CYP 3A or that are CYP 3A inducers. The product label also provides a table with a listing of drug interactions describing the effects on co-administered agents and their effects on maraviroc pharmacokinetics. Maraviroc should not be used with products containing St. John's Wort containing products.

The DSI inspection report notes an issue with sample retention at the clinical site for Study A4001040. The clinical pharmacologists further evaluated this issue and found that Pfizer did retain samples that were identified in a random fashion at an alternative site and therefore found that the data from this study could be relied upon to evaluate the bioequivalence of the maraviroc research tablet with the commercial tablet.

Additional data from studies in patients with renal and hepatic impairment are needed in order to provide dosing recommendations in patients with hepatic or renal impairment.

Efficacy

The results of the clinical trials evaluating the safety and efficacy of maraviroc are discussed in detail in the Medical Officer's Review, the Statistical Review, and also in the reviews prepared by Dr. Laessig and Dr. Birnkrant. The reader is referred to their reviews for a detailed discussion of safety and efficacy.

The doses of maraviroc for the phase 3 studies were based upon information from 2 studies of maraviroc monotherapy in HIV-infected subjects along with data from dose escalation studies. Two doses were evaluated in studies 1027 and 1028. These studies were randomized, double-blind, studies of maraviroc plus optimized background therapy vs. optimized background therapy plus placebo in treatment experienced patients with HIV. The primary efficacy endpoint for the studies was change in HIV-1 RNA from baseline at the 24-week timepoint. The design of the studies was identical and the results of the studies are presented together in the FDA analysis. The results show a statistically significant greater change in HIV RNA at week 24 for the maraviroc QD and BID arms compared to the placebo arm.

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**Primary Efficacy Endpoint (Change in HIV-1 RNA from Baseline to Week 24)*
(Studies 1027 and 1028 Combined, Modified ITT Population)†**

Treatment Group	N	Raw Mean (se)	Raw Median	Adjusted Mean (se)	Treatment Estimate** (99.95% CI)
MVC QD	414	-1.825 (0.070)	-2.229	-1.833 (0.069)	-0.872 (-1.335, -0.409)
MVC BID	426	-1.946 (0.069)	-2.409	-1.950 (0.068)	-0.988 (-1.447, -0.529)
Placebo	209	-0.960 (0.091)	0.000	-0.962 (0.097)	N/A

* If missing at Week 24, baseline value used as the Week 24 result

** Difference between adjusted means for MVC and placebo

† Source: FDA Table 8, from Dr. Proestel's Medical Officer Review

Additional analyses of secondary endpoints and sensitivity analyses support the findings for the primary efficacy endpoints. Although not statistically significant differences, there was a slightly greater virologic response in the in the subset of patients receiving maraviroc dosing BID with increased viral load, decreased CD4+ cell count, or decreased OSS at baseline. The studies provide evidence of efficacy of maraviroc, in combination with other antiretroviral agents, for treatment experienced adult patients infected with CCR5-tropic HIV-1 who have HIV-1 strains resistant to multiple antiretroviral agents based upon the 24-week virologic endpoint, an endpoint appropriate for accelerated approval under subpart H, 21CFR §314.500 in this population.

Safety

A total of 840 patients received maraviroc in studies 1027 and 1028. Of there 840 patients, 426 received maraviroc BID. The most common adverse events were nausea and vomiting.

Cardiovascular adverse events revealed ischemic adverse events (AEs) were noted to occur exclusively in the maraviroc arms. There were 14 ischemic adverse events in 11 patients (8 MVC QD and 6 MVC BID). A slight imbalance of cardiovascular disorders at baseline was noted, but did not appear to explain the differences in ischemic adverse events in the maraviroc arms compared to placebo. Also in the broader category of cardiovascular AEs is the finding from phase I studies of postural hypotension at unit doses of maraviroc of 600 mg and above. The draft labeling contains a statement in the Warnings and Precautions section about cardiovascular AEs describing the ischemic events and postural hypotension.

Analyses of laboratory values for ALT/AST and total bilirubin by degree of elevation revealed similar proportions of subject with elevations of these laboratory analytes across treatment arms. In a food effect study a 27-year old woman on day 14 of dosing developed flu-like symptoms and postural hypotension and was noted to have submaxillary and cervical adenopathy. She was also noted to have a rise in her eosinophil count from 1.1% at baseline to 5.1% on day 14. She went on to develop dizziness,

shivering, pruritis, and weakness. Over the next few days she went on to develop a rash later described as an urticarial like rash. Her total bilirubin became elevated (peak 2.3 mg/dL) and her AST and ALT were also elevated (peak AST 504 U/L and ALT 393 U/L). Her eosinophils peaked at 10.5%. She was also noted to have an elevated IgE level. A gastroenterology consult was obtained and her findings were considered consistent with drug induced hepatitis. Her maraviroc dosing was discontinued. The subject also had a sore throat that began 2 days prior to maraviroc dosing and resolving 12 days prior to her flu-like symptoms.

There was also a case in the treatment naïve study (1026) of a 24 year old woman with HIV and HCV infection who was receiving maraviroc 300 mg QD along with Bactrim and isoniazid that had been started 7 weeks prior to maraviroc. Her baseline AST and ALT were elevated. She developed a pruritic rash 4 days after starting maraviroc followed by fever and dizziness. She became progressively more ill and was hospitalized with rigors, loss of appetite, and fever. During her hospitalization her AST and ALT continued to rise to levels of approximately 2500 U/L along with a rising bilirubin. Her liver biopsy revealed severe acute toxic hepatitis characterized by hepatocellular and canalicular damage. Inflammatory cells including eosinophils, macrophages, and lymphocytes were also noted on the biopsy. She also was noted to have an elevated IgE level. She underwent liver transplantation.

The two cases of what appear to be drug-related hepatitis are of concern. The case from the food effect study was in an otherwise healthy subject. There are some similarities between the two cases (rash, fever, elevated IgE along with hepatitis (although the case from study 1026 was much more severe and required transplantation) and eosinophils either on biopsy or peripherally. Also of note is that the case from study 1026 also was HCV positive and on Bactrim and isoniazid. From the preclinical studies in rats, maraviroc was associated with liver-related abnormalities at the higher dose studied. Given the above information and taking the limited size of the safety database for maraviroc into consideration, healthcare providers and patients should be appropriately informed about the potential for hepatotoxicity. A boxed Warning and a Medication Guide would provide information to convey the potential for hepatotoxicity and also provide patients with information and instructions to seek medical evaluation should symptoms consistent with hepatotoxicity develop.

The development of malignancies was also evaluated based upon data from studies 1027 and 1028. The evaluation was undertaken in part because of the concern for the potential for development of malignancy because maraviroc binds to the human CCR5 co-receptor. Analyses of the data on lymphomas and non-hematologic malignancies did not reveal an increase in frequency associated with maraviroc.

Analyses of the frequency of infections for maraviroc treated patients compared to placebo did not show an increase in the maraviroc arm compared to the placebo group. Within the subsets of infection types, there did appear to be a slightly greater frequency of adverse events classified as herpes simplex infections, upper respiratory tract infections and influenza.

The occurrence of death in the studies in treatment experienced patients (study 1027 and 1028), study 1026 (treatment naïve), and study 1029 (a study in dual or mixed tropic CCR5/CXCR4 tropic HIV infection), did not reveal imbalances in mortality between maraviroc and comparators (note that randomization in these studies was either 2:1 or 4:1).

Study 1029 was a phase 2 study that enrolled patients with CCR5/CXCR4 tropic HIV infection to investigate the effects of maraviroc in a mixed or dual tropic population. The study did not show differences in HIV RNA in the maraviroc plus OBR group compared to the placebo plus OBR group. There was a trend towards slightly higher CD4+ cell counts in the maraviroc group. The data available from the study do not reveal a deleterious effect on disease course or CD4 cell count, but the limited size and duration of the study also need to be considered.

DSI Inspections / DDMAC / DMETS consults

DMETS and DDMAC have consulted on the proprietary name and do not object to the use of the proprietary name SELZENTRY at this time (this may need to be re-reviewed at time of a future action, depending upon when the action occurs).

The Division of Scientific Investigations performed inspections of three clinical sites and found that the data from these sites appeared to be acceptable in support of the maraviroc application.

Risk Benefit Summary

Maraviroc, a CCR5 co-receptor antagonist, is the first in a new class of antiretroviral agent. The data from studies 1027 and 1028 provide evidence of maraviroc's efficacy in the treatment of HIV, in combination with other antiretroviral agents, for treatment experienced adult patients infected with CCR5-tropic HIV-1 who have HIV-1 strains resistant to multiple antiretroviral agents based upon its effect on HIV viral load at 24-weeks, an accepted endpoint for accelerated approval under 314.500 Subpart H for treatment experienced patients. The safety data reveal a disproportionate number of cardiovascular ischemic adverse events. There was also a case in a food effect study of a normal subject who developed what appears to be drug-related hepatitis with eosinophilia and elevated IgE. In study 1026, a study in treatment naïve patients, there was a case of a woman who was on Bactrim, isoniazid, acetaminophen, and maraviroc, who went on to develop toxic hepatitis and went on to liver transplantation. A liver biopsy revealed toxic hepatitis with severe acute toxic hepatitis characterized by hepatocellular and canalicular damage and inflammatory cells including eosinophils, macrophages, and lymphocytes. It will be important for patients and providers to be informed of these risks and the labeling should contain a statement in the Warnings and Precautions section of the label regarding cardiovascular effects and a boxed Warning describing the hepatotoxic potential. In

addition, a Medication Guide should be considered as a means to communicate to patients and mitigate risk. Other information that should be included in the Warnings and Precaution section include information on immune reconstitution syndrome, potential for malignancy, and potential for infection. Given that maraviroc will provide an additional therapeutic option for treatment experienced adult patients with CCR5-tropic HIV-1 who have HIV-1 strains resistant to multiple antiretroviral agents, the benefits of the agent in this population outweigh the risks. At this time the action will be an approvable action as agreement on the product labeling was not reached during this review cycle. Pfizer also seeks additional expert review of the findings regarding hepatic toxicity and that information will not be available until after the action date. It will also be important to consider postmarketing commitments that will accompany any subsequent approval and means for monitoring safety.

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Edward Cox
6/20/2007 04:56:08 PM
MEDICAL OFFICER

Decisional Review for NDA 22-128

Date	June 20, 2007
From	Debra Birnkrant, M.D.
Subject	Division Director's Summary Review
NDA/BLA #	NDA 22-128
Supp #	
Proprietary / Established (USAN) names	Selzentry/maraviroc
Dosage forms / strength	150 mg and 300 mg tablets
Proposed Indication(s)	For use in combination with other antiretroviral agents in treatment-experienced adult patients infected with CCR5 tropic virus who have strains resistant to multiple antiretroviral agents
Action	Approval

1. Introduction to Review: This Division Director's memorandum summarizes salient features of NDA 22-128, Pfizer's New Drug Application (NDA) for maraviroc, a new molecular entity that functions as a CCR5 receptor blocker for treatment of HIV-infected adults who have resistant strains of HIV. This review will cover the following areas in detail: safety and efficacy, virology, including comments related to the tropism assay and clinical pharmacology considerations. Brief comments will cover chemistry/manufacturing and controls and pharmacology/toxicology.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status: Currently, there are more than twenty marketed antiretroviral products for HIV treatment. They fall into four main categories including nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors and fusion inhibitors. As there is an estimated 40,000 new cases of HIV per year in the United States and tens of millions worldwide infected with the virus, there is a clear and present need for additional drugs in the armamentarium. In addition, drug resistance, toxicity and adherence underscore the need for new medications.

Maraviroc is a CCR5 receptor antagonist developed by Pfizer, Inc. It is a unique drug in that its mechanism of action involves inhibition of a host CD4 receptor to prevent HIV entry and thus infection. Candidates for this drug should have CCR5-tropic virus as demonstrated by a tropism assay. Although this CCR5 tropism assay is unapproved, its performance characteristics were reviewed and we are in agreement that a 10% minority population of CXCR4-using clones could be detected with 100% sensitivity, while the presence of a 5% CXCR4-using population could be detected with 83% sensitivity. The assay was used in the clinical trials and plans are underway for the Center for Biologic Evaluation and Research to encourage the company,

Monogram Biosciences to submit an application for review. Currently, regulatory policies are evolving for this type of test.

This NDA was submitted in December 20, 2006 and received a priority review because it meets an unmet medical need. This application was also presented at the Antiviral Products Advisory Committee on April 24, 2007. The advisory committee unanimously recommended approval following presentations by the applicant and DAVP staff. The panel members also recommended that labeling include comments related to the potential development of malignancies and infections as this drug's mechanism of action could impact immune surveillance.

3. **CMC/Microbiology/Device:** There are no notable issues to discuss. Please see review by the CMC Review Team.
4. **Nonclinical Pharmacology/Toxicology:** A thorough pharmacology/toxicology review was performed by Dr. Peter Verma. Per Dr. Verma's review, major pathways of maraviroc metabolism were represented in all species examined in toxicology studies. Key findings in non-clinical studies included: 1) maraviroc was not mutagenic or genotoxic, 2) maraviroc was not tumorigenic in carcinogenicity studies conducted in Sprague-Dawley rats and transgenic mice, 3) QTc increases were seen in dog and monkey studies, however there was no evidence of cardiac arrhythmias; QTc prolongation in dogs and monkeys occurred at exposure multiples of 6X and 12X the human equivalent dose, respectively, 4) toxicology studies in monkeys indicated reductions in blood pressure at doses that were approximately 11-fold higher than the therapeutic dose in man, but studies in dogs indicated no significant changes in blood pressure at plasma concentrations 3-6 fold that of the maximum therapeutic dose, 5) at the highest doses studied in rats, elevations of AST and ALT were seen and accompanied by histopathologic changes, and 6) maraviroc is pregnancy category B based on reproductive toxicology findings.
5. **Clinical Pharmacology/Biopharmaceutics:** Maraviroc is both a CYP3A substrate and a P-gp substrate. Coadministration of maraviroc with drugs that induce CYP3A and P-gp may decrease maraviroc plasma concentrations and hence its therapeutic effect whereas CYP3A and P-gp inhibitors would have the opposite effect, whereby maraviroc plasma concentrations would be increased. Labeling addresses this issue and different doses of maraviroc are recommended depending on concomitant medications.

Dose-finding studies were adequate and based on the totality of the data including results from phase 3 trials, where it was determined that the dose of maraviroc should be 150 mg BID when administered with a CYP 3A inhibitor, plus or minus an inducer, except tipranavir/ritonavir and the dose of maraviroc should be 300 mg BID when used with tipranavir/ritonavir, nevirapine, all nucleoside reverse transcriptase inhibitors and enfuvirtide; the dose of maraviroc is 600 mg BID when given with a CYP 3A inducer such as efavirenz. This will be outlined in the dosage and administration section of the label.

Exposure-response analyses were conducted by Dr. Pravin Jadhav, Pharmacometrics reviewer. He determined that patients with a $C_{min} > 50-75$ ng/mL have a better chance of virologic success, however virologic success was also dependent on baseline CD4 count, baseline viral load, and overall susceptibility score. Dr. Jadhav also determined that doubling the dose in patients with $C_{min} < 75$ ng/mL is predicted, by modeling to only result in a 2% increase in response rate; therefore, dose individualization is not recommended at present. It was also determined that there are no exposure-response safety concerns within the observed concentration range.

6. **Clinical Efficacy/Statistical:** Efficacy and safety were based primarily on phase 2b/3 studies, 1027 and 1028. Study 1029 was conducted in dual/mixed tropic subjects to ensure that there were no safety concerns of administering maraviroc in this setting. Study 1026 was conducted in naïve subjects and was reviewed for safety signals as it is ongoing and blinded.

Briefly, maraviroc was shown to be safe and effective in phase 2b/3 trials based on week 24 results. Both 1027 and 1028 were designed as 48-week multicenter, randomized (2:2:1), placebo-controlled trials that demonstrated that two different doses of maraviroc, 300 mg QD and 300 mg BID or their equivalents, added to optimized background therapy were superior to optimized background based on proportion of patients with viral load < 50 and < 400 as well as mean change from baseline in \log_{10} HIV-1 RNA. Maraviroc arms also showed a greater increase in CD4 count compared to optimized background alone. Analyses were pooled as the trials were identically designed.

Specifically, over 1800 U.S. and Canadian subjects were screened for Study 1027 and 601 were randomized of whom 585 received at least one dose of study drug. This was an advanced population with a median HIV viral load of 4.84 - 4.86 logs, median CD4 count of 150-168, and greater than 40% use of enfuvirtide in OBT. In addition, between 66-76 % of patients had ≤ 2 active drugs in their OBT.

Outcomes in the maraviroc BID and maraviroc QD arms were highly statistically significant compared to placebo for the endpoints of < 50 copies/mL and < 400 copies/mL and mean change from baseline in \log_{10} HIV-1 RNA. Forty-eight percent of patients on the BID arm and 42% on the QD arm achieved < 50 copies/mL of HIV RNA as compared to 24% on the placebo arm. Mean CD4 increase on the maraviroc arms were 107-111 cells/mm³ compared to an increase on the placebo arm of 52 cells/mm³. Baseline characteristics were comparable for Study 1028 in that it was a highly treatment-experienced population. Conducted in the U.S, Europe and Australia, 475 patients were randomized and 464 received study medication. Results showed that virologic and immunologic outcomes were highly statistically significant when maraviroc was compared to OBT. Forty percent of patients on the BID arm and 45% on the QD arm achieved < 50 copies/mL of HIV RNA as compared to 20% on

the placebo arm. Mean CD4 increase on the maraviroc arms were 102-112 cells/mm³ compared to an increase on the placebo arm of 64 cells/mm³.

Of note, in both trials use of enfuvirtide did not affect differences in treatment effect. It is also important to note that when the OSS was ≥ 3 for maraviroc and placebo arms, there was no difference between patient groups. This is not surprising as it represents use of an active regimen with multiple active agents.

To decide on a dose between QD and BID dosing of maraviroc, the BID dosing regimen was selected for the following reasons. Patients with high viral loads and lower CD4 counts had numerically better outcomes on maraviroc BID compared to the QD dosing regimen. For patients with viral loads greater than 200,000 copies/mL, 31% of patients on the BID arm compared to 24% on the QD arm had viral loads < 50 copies/mL at the week 24 time point. With regard to CD4 count, in patients with CD4 counts < 74 (Q1), 21% compared to 12% had HIV RNA < 50 copies/mL for the BID versus QD regimens, respectively whereas when CD4 counts were in the fourth quartile (>284 cells/mm³) there was no difference between maraviroc treatment groups.

Although Studies 1027 and 1028 showed statistical superiority of maraviroc-containing arms compared to OBT, there were two notable deficiencies in the trials. One was that there were an insufficient number of non-Caucasian subjects to make a firm determination as to whether there were racial differences in outcomes. The second deficiency relates to the numbers of women enrolled in the trials. Approximately 10 % of patients were women and therefore it is difficult to draw conclusions based on gender. To begin to address this issue, the applicant has recruited more women and non-Caucasians in the naïve study, 1026.

7. **Safety:** The following safety issues were identified and presented at the Antiviral Drugs Advisory Committee meeting on April 24, 2007: cardiovascular toxicity, hepatotoxicity, potential for malignancies and infections based on maraviroc's mechanism of action, and laboratory abnormalities; mortality was also presented.

Cardiovascular events: There were slightly more baseline cardiovascular disorders in both maraviroc groups as compared to placebo. During studies 1027 and 1028; a total of 11 cardiovascular events occurred only on the maraviroc arms. The majority of events occurred in subjects with risk factors for heart disease including presence of cardiac stents, hypertension, hyperlipidemia, diabetes and history of myocardial infarction. Events on study included angina pectoris, acute myocardial infarction and myocardial ischemia. Days from starting maraviroc to development of a cardiac event ranged from 91-263 days.

It is not surprising to see these events on study as this is an advanced population who had been on multiple HAART regimens. Recently published findings of the DAD Study (Data Collection on Adverse Events of Anti-HIV Drugs) indicate that individuals treated with protease inhibitors had a 16% increased risk of heart attack

for each year of protease inhibitor exposure. The risk declined to 10% per year after adjusting for the effect of lipid elevations (NEJM, April 2007). The authors go on to state that whether this risk translates into an important additional absolute risk depends on preexisting cardiovascular risk profile. It is worth noting here that overall AIDS-related mortality has declined since introduction of protease inhibitors into HAART regimens regardless of cardiovascular risk. Another relevant example of cardiovascular disease in HIV-infected subjects is the SMART study (14th Conference on retroviruses and Opportunistic Infections) where the risk of cardiovascular disease was higher in subjects who interrupted treatment suggesting that viral suppression may reduce short-term cardiovascular risk.

In sum, it is difficult to determine the contribution of maraviroc to cardiovascular patient outcomes as this endpoint is confounded by baseline and on-treatment cardiovascular risk factors. Labeling will contain wording in the Warnings and Precautions section to highlight this finding. In addition, cardiac events will be reported as 15-day expedited reports post-marketing. Review of Study 1029 did not reveal additional cardiovascular concerns.

With regard to QTc prolongation, Pfizer conducted a formal QT study with moxifloxacin as a control. It was reviewed by the FDA's Interdisciplinary Review Team for QT Studies. The team's review stated that they were unable to determine if maraviroc prolonged the QT interval because of a lack of assay sensitivity using moxifloxacin as a control. Upon review of resubmitted data the Interdisciplinary Review Team determined that the drug does not appear to have a clinically relevant effect on QT.

Per Dr. Proestel's review, there were 16 adverse events related to a ventricular arrhythmia. There was no increase detected in the maraviroc arms compared to placebo when unequal randomization was considered.

Hypotension was observed in phase 1 studies at significantly higher doses than those studied in the phase 2b/3 trials. Based on the randomization scheme and longer duration of observation in the maraviroc arms, there does not appear to be a signal for hypotension. However, the label will contain wording that caution should be used when administering maraviroc with concomitant medications known to lower blood pressure.

Hepatotoxicity: Hepatotoxicity was seen with another member of this class that is no longer being developed. Aplaviroc, a GlaxoSmithKline CCR5 antagonist was associated with hepatotoxicity. Consequently, maraviroc was examined closely for liver-related findings.

Per Dr. Proestel's review, there were a total of 130 liver-related adverse events in Studies 1027 and 1028 to date. After accounting for increased duration of observation per subject in the maraviroc arms, there were more hepatic events in the maraviroc arms as compared to placebo. It is also important to note that a significant proportion

of subjects had liver abnormalities at baseline: 59% in maraviroc QD arm, 61% in the maraviroc BID arm and 59% in the OBT arm. There were 85 liver-related adverse events in 56 subjects who were co-infected with hepatitis B or C. It was determined that there was no increase in liver-related adverse events associated with maraviroc in the co-infected population after accounting for the unequal randomization in the trials, however very few patients had detectable HCV RNA and HBV surface antigen.

Review of Study 1029 did not reveal additional hepatotoxicity concerns. However, review of Study 1026 in naïve subjects revealed a 24 year old, Hepatitis C co-infected patient with a CD4 count < 200 and elevated baseline AST and ALT, with a normal bilirubin who developed a rash 4 days after starting maraviroc. On treatment she developed AST/ALT levels of 2452 U/L and 2530 U/L, respectively with an elevated bilirubin. Her liver biopsy revealed severe acute toxic hepatitis; her IgE level was also increased. This case was confounded by use of trimethoprim/sulfamethoxazole and isoniazid 7 weeks prior to receiving maraviroc and administration of paracetamol between study days 6-10. The patient underwent liver transplantation and has done well subsequently. It is difficult to determine the contribution of maraviroc in this case as it was highly confounded by concomitant medications and underlying Hepatitis C infection.

We have recently been made aware of a case of hepatotoxicity in a healthy volunteer in a food-effect study. A 34 year old female subject developed fever with flu-like symptoms, elevated liver enzymes, eosinophilia, and lymphadenopathy following exposure to maraviroc. On day 2 post last dose, AST and ALT were 504 U/L and 393 U/L, respectively with a total bilirubin of 1.5 mg/dL, down from a peak of 2.2 mg/dL. An abdominal ultrasound was normal and the patient continues to improve. Serologic testing ruled out the following potential infectious causes of this patient's condition: hepatitis A, B and C, CMV, EBV. She was subsequently found to have a sore throat caused by Group A beta-hemolytic streptococcus. This case is much less confounded than the one in Study 1029. It appears to be a case of drug-induced liver injury secondary to maraviroc that is resolving upon dechallenge.

The label will contain a boxed warning to address the issue of hepatotoxicity. The boxed warning is based on the following: a case of drug-induced liver injury in a healthy volunteer received on June 11, 2007, a confounded case in the naïve study where the patient underwent a liver transplant and on hepatotoxicity seen with another member of this drug class, as well as findings in non-clinical studies. Although this is a conservative approach, it must be recognized that the databases for accelerated approval are limited. Based on small numbers of enrolled patients with co-infection, no conclusions can be drawn regarding whether they are at increased risk for hepatic adverse events. The label states that caution should be used when administering maraviroc to patients with pre-existing liver disease.

Potential for Malignancies and Infection: Due to the mechanism of action of maraviroc and the potential for the drug to interfere with immune surveillance there is a theoretical concern that there may be an increase in malignancies and infections in

patients taking maraviroc. This concern became more prominent when cases of lymphoma were seen in a clinical trial of another CCR5 antagonist, Schering's vicriviroc.

No clear increase in malignancies was observed in the maraviroc database. There were a total of 7 cases of lymphoma seen in studies 1027 and 1028. Most occurred in patients with very low CD4 counts. There were 3 cases of lymphoma on the maraviroc arms and 2 on placebo; an additional placebo patient developed lymphoma after failing virologically on placebo and subsequently receiving maraviroc during an open-label period. In addition there was another lymphoma on the maraviroc BID arm, but it was a presumed case as no biopsy was performed. Twenty-six non-hematologic malignancies were evenly divided among the three treatment arms of the two studies without adjustment for unequal randomization. The labeling will include wording about the potential to develop malignancies and the applicant will be following patients from 1027 and 1028 for 5 years to assess malignancy rates. In addition, the applicant will be conducting a large simple trial where development of malignancy will be assessed along with cardiovascular events, hepatotoxicity and non-category C infections.

Similarly, we were concerned about development of infections based on the mechanism of action of maraviroc. It was determined that the overall incidence and severity of infection was comparable in the treatment groups in Studies 1027 and 1028, but there was a higher rate of upper respiratory tract infections, not including pneumonia, and herpes infections even after adjustment for exposure compared to placebo. An excess of Candida infections was seen in the maraviroc QD arm only. No overall increase in category C events was seen.

8. **Clinical Microbiology:** Please see extensive review by Dr. Lisa Naeger. A significant concern with this class of drugs was the potential of tropism switching to viral isolates that would use CXCR4 co-receptor. This was a concern because it has been published that patients with naturally occurring CXCR4 isolates have a more rapid progression of their disease. Therefore a comprehensive analysis was undertaken to determine causes of treatment failure. The following mechanisms were explored: viral mutation to CXCR4-using virus, outgrowth of CXCR4-tropic virus not detected at screening, development of resistance to maraviroc while viral isolates remained CCR5-tropic and development of resistance to other drugs in the regimen.

Regardless of the definition of treatment failure, about 50-60% of subjects failed with CXCR4-tropic virus or dual/mixed-tropic virus in the maraviroc arms whereas more than 80% of subjects in the placebo arm failed with CCR5-tropic virus. This supports the mechanism of action of maraviroc. Further, the more susceptible drugs in a patient's OBT, the more likely the patient was to fail with CCR5-tropic virus and conversely, the lower the OSS, the more likely a patient failed with CXCR4-tropic virus.

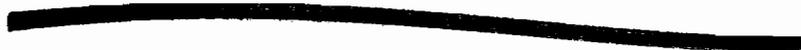
It was important to determine if patients who failed with a CXCR4 virus had a tropism switch versus outgrowth of CXCR4 already present at baseline, but not detected. After extensive analysis, it was determined that failure with X4 virus was a result of an outgrowth of species not detected at screening as opposed to a true tropism switch. Follow-up data on 20 subjects who failed with CXCR4-tropic virus was that two-thirds had changed back to CCR5-tropic virus or dual-mixed. For those subjects who remained CXCR4-tropic, the follow-up time was one month or less. Therefore, more time is needed to see if these subjects revert to virus type detected at screening.

9. Mortality: Prior to receipt of study drug, there were 11 deaths in patients. Causes of death were consistent with an advanced population and there was no specific clustering of causes. Death rates irrespective of time on or off study drug were approximately 1.7% for the maraviroc arms compared to 1.8% on placebo. This is similar to other recent drug development programs for a highly treatment-experienced HIV-infected population.

10. Risk Minimization Considerations: A consult was obtained from the Office of Epidemiology and Surveillance. In addition to consulting on the large simple trial to assess rates of malignancies, infections, cardiovascular events, etc. the OSE review team recommended the submission of a risk minimization action plan that focuses on prescriber education. In addition OSE recommended a pharmacovigilance plan that includes expedited reporting of all liver-related deaths and liver failure, fatal and non-fatal myocardial infarctions and all non-Category C AIDS- defining malignancies.

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Conclusions and Recommendations: I am in agreement with the Maraviroc Review Team that maraviroc should be approved under the accelerated approval regulations based on the totality of the data contained in NDA 22-128. It has been demonstrated that the benefits of using maraviroc in the indicated population exceed the risks of using maraviroc. Labeling and post-marketing commitments address the concerns of the Antiviral Drugs Advisory Committee. A boxed warning for hepatotoxicity will help to inform practitioners about the potential for drug-induced liver injury and ensure that only patients for whom treatment with maraviroc is indicated will receive the drug. Warnings of drug-induced liver injury appear in labels of other antiretroviral agents. As maraviroc is indicated for a highly treatment-experienced population, it has been determined that this is a manageable risk for this population. With the approval of maraviroc, we can now begin to construct highly active treatment regimens for advanced patients.



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MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN
SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH**

DATE: 06-07-07

FROM: Katherine A. Laessig, M.D.
Division of Antiviral Products

TO: Division File

SUBJECT: Medical Team Leader Memo for NDA 22-128, maraviroc 150 and 300 mg tablets (tradename TBD)

1.0 Background

Maraviroc (MVC) is a member of a new class of antiretroviral agents known as CCR5 coreceptor antagonists. The mechanism of action is via inhibition of HIV binding to a coreceptor found on T-lymphocytes known as chemokine receptor CCR5. Inhibition of binding to the coreceptor prevents conformational changes in HIV viral protein gp41 that normally allow fusion and entry of the viral core. The applicant, Pfizer Inc., has submitted NDA 22-128 in support of 150 and 300 mg tablets and proposed a dose of 300 mg bid. The requested indication is treatment-experienced adults infected with CCR5-tropic HIV-1.

Despite the availability of 4 classes of antiretroviral agents, tolerability and resistance remain issues for a significant proportion of the HIV infected patient population. To support the accelerated approval of MVC, the applicant has conducted 2 identical phase 3 trials using a validated surrogate endpoint of change in HIV-1 RNA, which has been used for the accelerated approval of previous antiretroviral agents and is discussed in the Guidance for Industry entitled "Antiretroviral Drugs Using Plasma HIV RNA Measurements-Clinical Considerations for Accelerated and Traditional Approval. This application was granted a priority review based on its demonstrated superiority to placebo when added to an optimized background antiretroviral regimen (OBR) and its unique mechanism of action, which therefore provides a new drug for treatment experienced subjects with limited currently available therapeutic options.

The development program for MVC consisted of numerous clinical pharmacology studies, 2 proof-of-concept 10 day monotherapy studies in HIV infected subjects, 1 Phase 2 study in subjects with dual or mixed CCR5/CXCR4 tropic HIV infection (study 1029), 2 Phase 2b/3 studies in treatment experienced HIV infected subjects with CCR5 tropic virus (studies 1027 and 1028), and 1 Phase 2b/3 study in treatment naïve HIV infected subjects with CCR5 tropic virus (study 1026). Note that study 1026 is ongoing and has not been submitted at this time in support of the indication for treatment experienced subjects.

The development program was agreed upon in multiple meetings and correspondence with the applicant. The program was somewhat unusual in that a traditional independent phase 2b study was not undertaken because of the need to make a promising antiretroviral agent with a new mechanism of action available more rapidly. In order to ensure study participants' safety and to generate additional evidence of safety prior to exposing large numbers of study subjects to MVC, the pivotal trials incorporated a phase 2b run-in period during which time a smaller number of subjects were enrolled, and results of this 16 week period were assessed by an independent DSMB and communicated to DAVP prior to allowing continued enrollment in the trials.

Since MVC represents the first in a new class of antiretroviral agents, and because safety signals of hepatotoxicity and malignancy have been identified with other drugs in development in the same class, the MVC NDA was presented to the Antiviral Products Advisory Committee on April 24, 2007. The AC voted unanimously in favor of approval. The AC also recommended post-approval evaluation of all potential safety signals, including hepatotoxicity, malignancy, infections, and cardiovascular events. They also requested more data for additional populations including viral hepatitis co-infection, pediatrics, women, minorities, and in patients with hepatic and renal impairment.

For detailed discussions of efficacy, safety, clinical pharmacology, virology, pharmacology/toxicology, and chemistry and manufacturing, please refer to the reviews of the relevant disciplines.

2.0 Summary of Clinical Pharmacology

MVC is a substrate of CYP3A4 and P-glycoprotein (P-gp), however it has not been demonstrated to inhibit any of the major cytochrome p450 enzymes. Therefore, MVC requires dose adjustment when coadministered with drugs that inhibit or induce CYP3A4 or P-gp pathways. Multiple drug-drug interaction studies and population PK analyses were conducted to establish the dosing recommendations outlined in Table 1.

Table 1. Maraviroc dose in the presence of certain coadministered drugs

Concomitant Medications	Maraviroc Dose
CYP3A4 inhibitors (with or without a CYP3A4 inducer) including: <ul style="list-style-type: none"> • protease inhibitors (except tipranavir/ritonavir) • delavirdine • ketoconazole, itraconazole, clarithromycin, • Other strong CYP3A inhibitors (e.g., nefazadone, telithromycin) 	150mg twice daily
Other concomitant medications, including tipranavir/ritonavir, nevirapine, all NRTIs and enfuvirtide	300mg twice daily
CYP3A4 inducers (without a CYP3A4 inhibitor) including: <ul style="list-style-type: none"> • efavirenz • rifampin • carbamazepine, phenobarbital, and phenytoin 	600mg twice daily

Source: Proposed U.S. package insert

The rationale for the dose selection for the pivotal trials was generated from the single and multiple ascending dose studies in healthy volunteers, and from the 2 10-d monotherapy studies in subjects with HIV-1 infection. In the dose escalation studies, postural hypotension was identified as the dose limiting toxicity and was noted at unit doses of maraviroc of 600 mg and above. Data from the monotherapy studies indicated that doses ≥ 200 mg total daily dose resulted in similar mean viral load reductions of $> 1 \log_{10}$ copies/mL from baseline at Day 11. Therefore, based on the antiviral activity and the dose limiting toxicity, doses of 300 mg qd and 300 mg bid were chosen for the phase 3 trials. The applicant has selected the 300 mg bid dose as the recommended to-be-marketed dose, based on similar safety profiles of the qd and bid doses, and a slight improvement in efficacy with the 300 mg bid dose noted primarily in subjects with high viral loads or low CD4 counts.

No gender or race effects on PK have been noted, and there were too few patients aged 65 or greater to permit conclusions regarding any age effect. A hepatic impairment study has been completed and submitted, however the applicant submitted this study report at month 5 of the review cycle, which will not allow substantive review of the results prior to the action date. These results will be included in the review of the traditional approval package, which Pfizer plans to submit in July 2007. Since MVC is primarily metabolized by the liver, it is likely that dose adjustment will need to be made for hepatically impaired subjects. A renal impairment study has not been conducted, and will be requested as a PMC, despite the fact that renal impairment is not a major route of elimination ($<25\%$ of total clearance). However for subjects with renal impairment who are coadministered a CYP3A4 inhibitor, dose adjustment of MVC may be necessary therefore the label will recommend not to administer MVC to patients with $\text{CrCl} < 50$. A thorough QT study was conducted and there was no evidence of QT prolongation in subjects receiving MVC.

Exposure-response analyses were conducted by the applicant and the review team to evaluate the relationship between selected pharmacokinetic parameters and outcome. Results of these analyses determined that C_{min} , baseline viral

load, baseline CD4 count, and overall susceptibility score (OSS) at baseline were important predictors of virologic success. In particular, patients with MVC $C_{min} > 50-75$ ng/mL were more likely to achieve an HIV RNA < 400 copies/mL (67%). Modelling of available data indicated that doubling the dose for patients with MVC $C_{min} < 75$ ng/mL would increase their probability of success from 56% to 62%. However, doubling the dose for all subjects would only increase the probability of success by 2% (from 67% to 69%). Additionally, toxicities such as QT prolongation, ALT/AST elevation, and hypotension were not concentration dependent across the observed concentration range.

3.0 Summary of Efficacy

The efficacy of MVC has been demonstrated in two adequate and well-controlled Phase 2b/3 trials, referred to as studies 1027 and 1028, with supportive evidence derived from two 10 day monotherapy studies (studies 1007 and 1015). Studies 1027 and 1028 are identically designed, ongoing, double-blind, randomized, placebo-controlled studies of treatment-experienced adults (>16 y.o.) infected with CCR5 tropic HIV-1 who were failing their current regimens. Study 1027 enrolled 601 subjects in North America while study 1028 enrolled 475 subjects in Europe, Australia, and North America. Tropism of subject's HIV viral variants was identified using the Monogram Biosciences Trofile™ HIV Entry assay at screening. Subjects were randomized 2:2:1 to maraviroc 300 mg qd, maraviroc 300 mg bid, or placebo in addition to their investigator selected optimized background regimen (OBR). Appropriate dose adjustments were made for concomitantly administered protease inhibitors, etc, as previously discussed. This type of study design is similar to that used for other recently approved antiretroviral products including darunavir and tipranavir.

The primary efficacy endpoint for these studies was mean change from baseline to week 24 in HIV-1 RNA. Important secondary analyses included proportion of subjects with HIV-1 RNA <400 copies/mL, proportion of subjects with HIV-1 RNA <50 copies/mL, and change from baseline to week 24 in CD4 cell count. Study subjects were predominantly male, Caucasian, with a mean age of 46, and had known HIV infection > 10 years duration. Most subjects were heavily treatment experienced and ~50% had an overall susceptibility score of 0-1 at baseline.

Table 1 illustrates the results of the primary efficacy analysis which demonstrates the superiority of the qd and bid doses of maraviroc to placebo. Notably, approximately half of the placebo subjects discontinued the study by week 24 due to virologic failure and therefore the baseline value of these subjects' HIV RNA was used as the week 24 result. Multiple sensitivity analyses conducted by the applicant and the review team support the results of the primary analysis (data not shown).

Table 1: Primary Efficacy Endpoint (Change in HIV-1 RNA from Baseline to Week 24)*

(Studies 1027 and 1028 Combined, Modified ITT Population)

Treatment Group	N	Raw Mean (se)	Raw Median	Adjusted Mean (se)	Treatment Estimate** (99.95% CI)
MVC QD	414	-1.825 (0.070)	-2.229	-1.833 (0.069)	-0.872 (-1.335, -0.409)
MVC BID	426	-1.946 (0.069)	-2.409	-1.950 (0.068)	-0.988 (-1.447, -0.529)
Placebo	209	-0.960 (0.091)	0.000	-0.962 (0.097)	N/A

* If missing at Week 24, baseline value used as the Week 24 result

** Difference between adjusted means for MVC and placebo

Source: FDA MO review of Dr. Scott Proestel

Tables 2 depicts the results of selected secondary analyses, and again demonstrates the superiority of the maraviroc qd and bid arms to placebo for the endpoints of proportion BLOQ and mean change from baseline in CD4 cell count.

Table 2. Selected secondary endpoints: Studies 1027 and 1028 combined.

Endpoint	MVC qd (N=414)	MVC bid (N=426)	Placebo (N=209)
% < 50 copies/mL	44	45	23
% < 400 copies/mL	55	61	28
Mean Δ from baseline in CD4 cells	+109	+106	+57

Source: NDA 22128 Clinical Overview, pg 24

In summary, the applicant has convincingly demonstrated the efficacy of MVC qd and bid compared to placebo for the endpoints of HIV RNA and CD4 count at 24 weeks, when combined with OBR in treatment experienced subjects. There were small numbers of women and minorities which did not permit definitive conclusions regarding any difference of treatment effect of MVC in these groups; however study 1026 includes more women and minorities and therefore will provide more robust data for these important subgroups.

4.0 Summary of Safety

As mentioned above, a number of safety issues have arisen during the course of development of CCR5 coreceptor antagonists in general, and during the review of the maraviroc NDA. Safety signals that have been identified during the

development of other CCR5 coreceptor antagonists include hepatotoxicity (development of GSK's aplaviroc was terminated for this reason), QT prolongation (development of Schering C was terminated for this reason), and a possible increase in AIDS-associated lymphomas (occurred in a single Phase 2 trial of Schering's vicriviroc). Additional safety concerns related to the mechanism of action of maraviroc include a risk for increased rates of infection due to inhibition of lymphocyte trafficking, and a risk for more rapid progression to AIDS and CD4 count decline if inhibition of CCR5 viral variants by maraviroc leads to outgrowth of or tropism switch to CXCR4 using HIV. CXCR4 variants are more common in late stage HIV infection, although the actual cause and effect relationship is not well understood.

The review team and the applicant reviewed the safety database for all of these issues. For complete details, please see the medical officer review by Dr. Scott Proestel, as well as FDA and Pfizer AC presentations and background documents. A total of 964 subjects received at least one dose of MVC in the phase 2b/3 studies, including 840 subjects from 1027 and 1028. The median exposure (days) for 1027 and 1028 was 237 for the MVC arms combined and 145 for the placebo arm, and the total exposure in patient-years was ~260 for the MVC arms combined compared to 99 for the placebo group. No increased rates of infection, hepatotoxicity, or malignancy were identified. There were no cases of hepatotoxicity that meet the criteria for Hy's law in studies 1027 and 1028. One case of fulminant liver failure requiring transplant has occurred in the treatment naïve study 1026. This case was confounded by the administration of isoniazid and trimethoprim/sulfamethoxazole 6 weeks prior to initiation of maraviroc such that transaminases were already beginning to rise from normal values at screening by the first day of MVC dosing. In addition, the subject received IV paracetamol when she first presented to the hospital with acute hepatitis as well as multiple other antiretroviral medications. Therefore the contribution of MVC to this SAE is uncertain.

Quite late in the review cycle on Monday, June 11, 2007, Pfizer submitted an IND safety report of a 27 y.o. healthy white female subject in an ongoing food effect study that described an apparent case of drug-induced hepatitis with a hypersensitivity component. The case is fairly convincing for drug-related toxicity, as the subject was a healthy volunteer on no concomitant medications. During the 7 day placebo run-in phase of the study, the subject had streptococcal pharyngitis with associated leukocytosis, however she had improved by the time she began receiving MVC at a dose of 600 mg qd. She had allergic symptoms including rash, fever, pruritis, and dizziness that occurred beginning on the 14th day of active drug dosing with MVC, and these symptoms recurred every day after dosing for the next 5 days until she was finally discontinued from MVC. Oddly, her bilirubin increased more markedly initially to 1.6 with a peak of 2.2, followed later by the transaminases which peaked at 400-450. The subject's symptoms and laboratory abnormalities have all improved and she is still being monitored. A GI consultant concluded that these findings were consistent with

drug-induced hepatitis. Although additional information about this case is expected from Pfizer, at this time it is the opinion of the review team that this case is consistent with drug-induced hepatitis related to MVC and that a boxed warning describing the potential for liver toxicity is warranted. Given the small size of the safety database, the limited duration of exposure, liver findings in animals, and the aplaviroc experience, even this one case that meets Hy's Law is highly concerning. A boxed warning may ensure that only highly treatment experienced subjects who require new treatment options receive MVC. In addition, language describing the case will be added section 5.2 Hepatotoxicity in Warnings/Precautions section of the label. We have requested that Pfizer review their clinical trials database for a like analysis, and submit all cases of hepatotoxicity as 15-day reports. Events of hepatotoxicity will continue to be evaluated in ongoing clinical trials and in a proposed large simple phase 4 study. Evaluation of the 48 week data from studies 1027, 1028, and 1026 may permit a better estimate of the frequency of this adverse reaction in the near future.

Although the overall rate of infections was not increased in the MVC arms compared to the placebo arm, there was a higher rate of herpes and upper respiratory tract infections in both the qd and bid MVC arms, and increased rates of Candida infections and influenza in the qd arm. The absence of a clear dose-response relationship for the Candida and influenza infections makes determination of a true association with MVC problematic.

With respect to the risk of more rapid HIV disease progression with tropism switches, the applicant conducted a phase 2 study of OBR plus MVC compared to OBR with placebo in subjects with dual/mixed R5/X4 HIV. Although no treatment effect on HIV RNA levels was demonstrated, a trend toward improved CD4 counts compared to placebo was noted at 24 weeks. This study is continuing, although there has been discontinuation of subjects from all arms due to virologic failure and other reasons, so numbers of remaining subjects by 48 weeks is likely to be small. Therefore, at this time there is no evidence to suggest that maraviroc use in patients with dual/mixed tropic virus has a deleterious effect on CD4 counts or disease course, although this will continue to be assessed in additional studies and with long term follow-up.

A concerning signal that has been identified during the course of the NDA review is an increased rate of cardiovascular events in subjects receiving MVC compared to those receiving placebo. There were 14 CV events occurring in 11 subjects, all of whom were receiving MVC either qd or bid. These MedRA terms for these events included acute MI, angina pectoris, unstable angina, arterial occlusive disease, coronary artery disease, coronary artery occlusion, MI, myocardial ischemia, and Prinzmetal's angina. A review of the baseline medical history of all subjects revealed an imbalance in the presence of CV risk factors at baseline, i.e. more subjects randomized to the MVC arms had known risk factors at baseline. An additional FDA analysis of other reported thrombotic events did not reveal a similar increased rate for the MVC arms compared to the placebo.

arm nor did there appear to be a greater risk of hypotensive events in the MVC arms that could have been contributory. The package insert will include information about the cardiovascular events, and further assessment of this potential signal will be performed with the 48 week data from studies 1027 and 1028 at the time of traditional approval, as well as for the 48 week data from the treatment naïve study 1026, and in postmarketing studies.

In general, MVC was well tolerated and the most common adverse events that occurred at incidences of $\geq 2\%$ and at a higher rate than placebo included pyrexia, cough, upper respiratory tract infection, rash, herpes simplex, myalgia, dysuria, dyspnoea, ALT increased, AST increased, blood CPK increased, and influenza. Changes in laboratory abnormalities of the MVC arms were similar to the placebo group, with the exception of CPK for which mild increases were more common in the MVC arms.

There were 18 deaths in studies 1027 and 1028. When corrected for the increased period of observation for the MVC arms (more placebo subjects d/ced study early for virologic failure) and the 4:1 randomization scheme, there does not appear to be an increased risk of mortality with MVC use compared to placebo. Nor was there any consistent cause of death; however many were related to complications of AIDS. The study population was fairly advanced at study entry, as illustrated by the 11 deaths that occurred during the 6 week period between screening and randomization, which was prior to any study drug administration.

A total of 162 subjects reported SAEs during the phase 3 trials, including 56 subjects with at least 1 SAE on MVC qd, 70 subjects on MVC bid, and 36 on placebo. No pattern of SAE was noted, and when corrected for the 2:2:1 randomization scheme, the number of SAEs per treatment group was fairly similar.

Despite several safety concerns that have been identified for the CCR5 coreceptor antagonist class, the safety profile of MVC based on this NDA package is acceptable and the applicant has provided substantive evidence of the safety of MVC 300 mg bid, given the proposed indication of treatment experienced HIV infected subjects in need of new options. These safety issues will be further addressed in product labeling, and pursued in the ongoing clinical trials and in the post approval setting.

5.0 Summary of Virology

The aspect of tropism for this class of product added another layer of complexity to an already extensive virology review. For complete details of the virology and resistance of MVC, please see Dr. Lisa Näeger's review. In order to be eligible for enrollment in studies 1027 and 1028, subjects' HIV had to be identified as!

CCR5 tropic, using the Trofile HIV Entry Tropism assay. Notably, the assay has a lower limit of sensitivity of 1000 copies/mL of HIV RNA, and cannot reliably detect minority populations of viral clones using X4 of <10%. All subjects also had phenotypic and genotypic resistance testing at baseline, which was used to assist in selection of OBR, as well as for other assessments of treatment response. The most important aspect of the virology review from a clinical perspective is the analyses of the reasons for treatment failure on MVC compared to placebo (excluding noncompliance or AEs, etc). The possibilities include: co-receptor switch, outgrowth of non-CCR5 tropic virus that wasn't detected at baseline, outgrowth of CCR5 tropic virus resistant to MVC, resistance to OBR, or some aspect of the host CCR5 genotype (not identified at this point). An analysis of the percentage of virologic failures by tropism at time of failure found that ~50-60% of subjects failed with X4 dual/mixed tropic virus in the MVC arms, compared to only 20% of subjects in the placebo arms.

The applicant conducted substudies of 1027 and 1028 to ascertain if subjects who experienced a change in their tropism resulted from undetected X4 tropic virus at screening, or as a result of mutations in a CCR5 tropic virus. This evaluation included clonal analysis of the virus at baseline and on-treatment, nucleotide sequence analysis of the gp120 region, phylogenetic analysis, and nucleotide sequence analysis of the protease and reverse transcriptase to assess resistance to the OBR. The results of these analyses demonstrated that most subjects who failed maraviroc had outgrowth of X4 virus that was present at baseline but not detected, while some subjects developed genotypic (changes in the V3 loop at amino acid position 308 or 323) and phenotypic resistance to MVC while retaining R5 tropism, and others developed resistance to their OBR. The applicant has agreed to a PMC to investigate the role of host CCR5 genotype in MVC treatment failure.

6.0 Recommendation

I concur with the findings and recommendations of the MVC review team. At this time, the applicant has provide substantive evidence of the efficacy and safety of maraviroc 150 and 300 mg tablets for treatment-experienced HIV-1 infected adults with CCR5 tropic virus. Therefore, this application for the accelerated approval of MVC should be approved under 21 CFR 314.500. However, because we have been unable to come to agreement with Pfizer regarding the boxed warning for hepatotoxicity in the label, this application will receive an approvable, pending agreement on the boxed warning and submission of outstanding laboratory results and consults from ID and hepatology experts regarding the healthy subject with the liver event.

Katherine A. Laessig, M.D.

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CLINICAL REVIEW

Application Type NDA
Submission Number 22-128

Letter Date December 19, 2006
Stamp Date December 20, 2006
PDUFA Goal Date June 20, 2007

Reviewer Name Scott Proestel, M.D.
Review Completion Date June 18, 2007

Established Name Maraviroc
Proposed Trade Name Selzentry
Therapeutic Class CCR5 co-receptor antagonist
Applicant Pfizer Global Research and
Development

Priority Designation P

Formulation Tablets (150 and 300 mg)
Dosing Regimen 150 or 300 mg, twice daily
Proposed Indication Maraviroc in combination with
other antiretroviral agents, is
indicated for treatment-
experienced adult patients infected
with CCR5-tropic HIV-1

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Accelerated approval of maraviroc (MVC) is recommended for the management of treatment-experienced adults infected with CCR5-tropic HIV-1. This recommendation is based on the finding of virologic suppression in a patient population with few remaining treatment options.

The efficacy of MVC was demonstrated with the 24-week results of two large, randomized, placebo-controlled trials (Studies 1027 and 1028, see Section 4.2 and 6.1.3 for further description of these trials). Median viral load reduction at Week 24 was greater with MVC than in the placebo arm, and decrease in viral load to undetectable levels (<50 copies/mL) at Week 24 was also more common with MVC. Please see Section 6.1.4 for a detailed description of the efficacy findings.

Important safety concerns during the clinical development of MVC have been the possibility of an increased risk of infection or malignancy, due to its blockade of CCR5 co-receptors on immune cells. However, no increase in malignancy has been observed during the MVC clinical development program, and there was no overall increase in infections. A possible increase in Candida, herpes, influenza, and upper respiratory infections was observed. Another significant concern has been the possibility of hepatotoxicity based on experience with another investigational CCR5 co-receptor antagonist (see Section 2.4). While there have been no cases of severe hepatotoxicity that could be clearly attributed to MVC during the phase 2b/3 program, there was one significant case following MVC exposure during a healthy volunteer trial (see Section 7.1.3 for details). This case has strengthened concern regarding the potential of MVC to cause hepatotoxicity, and a Black Box Warning is recommended. Finally, an increase in cardiac ischemic events was observed during Studies 1027 and 1028. Due to the small number of cases, and the significant cardiac risk factors and cardiac diseases at baseline of the subjects who had these events, a causal relationship with MVC cannot be concluded at this time. However, additional data will be available when the 48-week results are submitted for these studies. Please see Section 7.1.3 for additional information regarding the MVC safety data.

In summary, based on the demonstrated virologic efficacy of MVC in treatment-experienced adults with CCR5-tropic HIV-1 and the appropriate supporting safety data, accelerated approval under 21 CFR 312 subpart H is recommended.

1.2 Recommendation on Postmarketing Actions

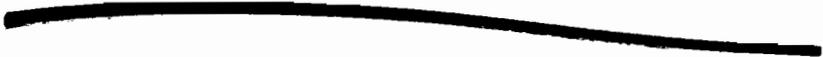
1.2.1 Risk Management Activity

The FDA Office of Surveillance and Epidemiology (OSE) was consulted regarding the appropriate risk management activities that should be pursued based on the safety issues that

have been raised during the development of MVC. OSE provided the following recommendations, and discussion with the Applicant is ongoing regarding these plans:

Regarding the Pharmacovigilance Plan

- Expedited (15-day) reporting of the following events during the postmarketing period:
 - Liver-related deaths and liver failure
 - Fatal and non-fatal myocardial infarctions
 - All non-AIDS defining malignancies
- The long term safety protocol to be submitted by the Applicant should include, as described by the FDA pharmacovigilance guidance, the study objectives, plans for recruitment and follow-up, and methods for data collection, management, and analysis. The study should include a control group and should be extended up to 10 years to adequately capture any potential increase in malignancies.



1.2.2 Required Phase 4 Commitments

The following postmarketing commitments (PMCs) have been proposed and are under negotiation with the Applicant. Following discussions with OSE, it was determined that for the long-term safety study (PMC #4 listed below), a total of 5 years of follow-up would be appropriate due to the likelihood of significant subject dropout over a 10-year follow-up period. The Clinical Pharmacology PMCs, as well as other PMCs, are currently under development. Of note, the Applicant has also agreed to participate in the Antiretroviral Pregnancy Registry.

1. Submit Week 48 and Week 96 reports and datasets for Studies 1027 and 1028. Subjects in these studies will also be followed for at least 5 years for mortality, liver

failure, malignancy, myocardial ischemia or infarction, and rhabdomyolysis, as well as for infections considered at least moderate in severity or qualify as a CDC Category C event.

2. Deferred pediatric substudy under PREA for the treatment of HIV in pediatric subjects from [redacted] years of age. This study will determine the maraviroc exposure (pharmacokinetics profile) for pediatric subjects from [redacted] years of age to support dose selection for the efficacy and safety assessment.
3. Deferred pediatric study under PREA for the treatment of HIV in pediatric subjects from [redacted] years of age. Using doses selected based on the substudy listed in item #2 above, conduct a pediatric safety and efficacy study of maraviroc with efficacy based on viral load reduction through 48 weeks of dosing, and safety monitored over 96 weeks.
4. Conduct and submit a final report for a non-randomized, controlled clinical trial to provide additional safety data regarding the incidence of mortality, liver failure, malignancy, myocardial ischemia or infarction, and rhabdomyolysis, as well as for infections considered at least moderate in severity or qualify as a CDC Category C event. Follow-up of subjects will be at least every 6 months for a total of 5 years.
5. Conduct and submit a final report for a study in subjects with HIV-1 who are co-infected with hepatitis C and/or B, including some subjects with a Child-Pugh score of C.
6. Submit Week 48 and Week 96 reports for Study 1026. Subjects in this study will also be followed for at least 5 years for mortality, liver failure, malignancy, myocardial ischemia or infarction, and rhabdomyolysis, as well as for infections considered at least moderate in severity or qualify as a CDC Category C event.
7. Perform cell culture combination activity assessments of maraviroc with darunavir and tipranavir, and submit a complete study report of these assessments by December 2007.

8.

[redacted]

9.

[redacted]

1.2.3 Other Phase 4 Requests

There are no other phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

MVC is a selective, slowly reversible, small molecule CCR5 co-receptor antagonist intended to inhibit entry of CCR5-tropic HIV-1 into cells. It is a new molecular entity, and the Applicant has proposed that it be indicated, in combination with other antiretroviral agents, for treatment-experienced adult patients infected with CCR5-tropic HIV-1.

Data from Studies 1027 and 1028 formed the principal basis for characterizing the safety and efficacy of MVC in treatment-experienced patients with HIV infection. Please see Section 6.1.3 for a detailed description of these studies. As Study 1027 was moderately larger and contained a higher proportion of subjects from the United States, the review focused somewhat more on the results of that trial and commented on Study 1028 where substantive differences existed. Pooled analyses of the study data from these two trials were a prominent component of this review as the trials had identical designs. Study 1029 was performed in subjects with CXCR4- or dual/mixed-tropism and the results were also submitted with this application. The primary purpose of Study 1029 was to evaluate whether exposure to MVC in these subjects caused unanticipated safety concerns. Please see Section 4 for additional details regarding the clinical development program of MVC.

1.3.2 Efficacy

MVC was demonstrated to be superior to placebo with respect to virologic suppression in treatment-experienced subjects with CCR5-tropic HIV-1 using multiple endpoints and sensitivity analyses. An approximate 1.0 log₁₀ decrease in HIV-1 copies/mL was observed with MVC compared to placebo at Week 24. In addition, a modest increase in CD4+ cell count was observed with MVC. Subjects with a baseline overall susceptibility score (OSS) ≥ 3 were the one subgroup that did not appear to achieve a benefit with MVC. OSS is a measure of the number of drugs to which a patient's HIV is considered sensitive. As these subjects had multiple available treatment options based on their OSS score, it is not surprising that there was no apparent benefit with MVC. It should be noted that there were few women and non-Caucasians enrolled in Studies 1027 and 1028, which hinders the ability to assess potential differences in efficacy in these groups. Please see Section 6.1.4 for a complete description of the efficacy findings.

1.3.3 Safety

The possibility that MVC might increase the rate of malignancy has been a theoretical concern for CCR5 co-receptor antagonists based on their mechanism of action. However, at this time no such increase has been observed with MVC during clinical trials. In addition, no overall increase

in infections has been observed. However, it should be noted that a possible increase in Candida, herpes, influenza, and upper respiratory tract infections was reported.

There was a slight increase in mortality with MVC in one of the phase 2b/3 trials, but this finding was not observed in the other trials. It should be noted that the types of deaths were consistent with the population studied, and this was a sick population with 11 deaths observed during the approximately 6 week time period between screening and enrollment. Finally, there was no clustering of causes of death in the MVC arms to suggest a drug etiology. Taken as a whole, there is no evidence of an increase in mortality in association with MVC based on the available clinical data.

There was no clear evidence of hepatotoxicity during the phase 2b/3 program, but this was a complicated patient population with a high rate of liver abnormalities at baseline. There was an increase in hepatic AEs in the MVC arms, but similar proportions of subjects in the MVC and placebo arms had at least one hepatic AE. An episode of hepatotoxicity in association with MVC during a healthy volunteer study occurred after the initial NDA filing and 3-month Safety Update (see Section 7.1.3). This episode has strengthened the concern that MVC could potentially be hepatotoxic, and a Black Box Warning is recommended.

There were 11 subjects in the MVC arms with cardiac ischemic AEs during the double-blind period of Studies 1027 and 1028, and no such events in the placebo arm. This has raised concern that MVC could cause cardiac ischemia. However, no imbalance was observed in the dual/mixed-tropism trial (Study 1029), and no imbalance was observed during the open-label period of these studies. Additional data will be available when the 48-week results are submitted for Studies 1027 and 1028, as well as when the treatment-naïve study results are submitted (Study 1026). However, based on the available data it is possible that MVC use could result in an increase in cardiac ischemic events.

The laboratory data revealed an increase in the proportion of subjects with a mild increase in CPK levels with MVC compared to placebo, as well as mild increases in total cholesterol, LDL, and triglyceride levels.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen for MVC is 300 mg twice daily in adults, but a dose adjustment is required for certain concomitant medications due to drug interactions (see Section 8.1 for specific dosing information).

1.3.5 Drug-Drug Interactions

MVC is considered unlikely to alter the metabolism of co-administered drugs that are metabolized by cytochrome P450 enzymes because it does not affect CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4 at clinically relevant concentrations in vitro.

MVC is a substrate of CYP3A4 and P-gp. Therefore, its pharmacokinetics are likely to be altered by inhibitors and inducers of these enzymes/transporters. The CYP3A4/P-gp inhibitors ketoconazole, lopinavir/ritonavir, ritonavir, saquinavir and atazanavir were all found to increase the C_{max} and AUC of MVC. The CYP3A4 inducers rifampin and efavirenz decreased the C_{max} and AUC of MVC. Tipranavir/ritonavir (overall CYP3A4 inhibitor/P-gp inducer) did not affect the steady state pharmacokinetics of MVC. Substrates and inhibitors of renal clearance (co-trimoxazole and tenofovir) did not affect MVC pharmacokinetics. Please see Section 8.1 for the proposed MVC dose adjustments based on concomitant medication use.

1.3.6 Special Populations

MVC was only studied in individuals at least 16 years of age, so no pediatric information is available at this time. In addition, there were insufficient numbers of subjects age 65 and older in the clinical studies to determine whether this population responds differently from younger patients. However, caution should be used when administering MVC in elderly patients in light of the greater frequency of decreased hepatic and renal function, concomitant disease, and other drug therapies.

The incidence of fetal malformations was not increased during pre-clinical studies performed with MVC in rats at exposures higher than that anticipated with the proposed human doses. However, no adequate studies have been performed in pregnant women. Because animal reproduction studies are not necessarily predictive of human response, MVC should be used during pregnancy only if clearly needed.

The pharmacokinetics of MVC have not been studied in patients with renal impairment. However, renal clearance constitutes less than 25% of the total MVC clearance. Therefore, the impact of renal impairment on MVC elimination is likely to be small. A postmarketing commitment is being developed with the Applicant to assess the pharmacokinetics of MVC in the setting of significant renal impairment.

The pharmacokinetics of MVC have not been sufficiently studied in patients with hepatic impairment. As MVC is metabolized by the liver, concentrations are likely to be increased in these patients.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

MVC is a selective, slowly reversible, small molecule CCR5 co-receptor antagonist intended to inhibit entry of CCR5-tropic HIV-1 into cells. It is a new molecular entity, and chemically described as 4,4-difluoro-*N*-{(1*S*)-3-[*exo*-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclohexanecarboxamide.

2.2 Currently Available Treatment for Indications

Four classes of antiretroviral drugs have been approved for the treatment of HIV: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and a fusion inhibitor. The use of antiretroviral drugs in combination has decreased the morbidity and mortality associated with HIV infection. However, these medications are associated with important toxicities including fat redistribution, hyperglycemia, pancreatitis, lactic acidosis, and the development of resistance. Therefore, the development of new therapies for HIV has been a priority for the U.S. Food and Drug Administration (FDA).

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient is not available in the United States or elsewhere.

2.4 Important Issues With Pharmacologically Related Products

There are no products pharmacologically related to MVC that have received marketing approval. However, two other CCR5 co-receptor antagonists have been evaluated during clinical trials, vicriviroc and aplaviroc. A possible association of vicriviroc with lymphoma has been reported,¹ although the finding is uncertain and clinical development of this drug continues. With respect to aplaviroc, clinical development of this drug was discontinued due to an increased incidence of severe hepatotoxicity.² Based on these findings, the potential for MVC to cause lymphoma or hepatotoxicity has been an important safety concern, and the relevant clinical safety data are discussed in detail in Section 7.1.3.

2.5 Presubmission Regulatory Activity

The phase 2b/3 development program for MVC was discussed with FDA during a Clinical Development Meeting with the Applicant on June 7, 2004, and during a subsequent teleconference on July 12, 2004. During these meetings, the following points were made:

¹ Schering-Plough Provides Update on Phase II Study of Vicriviroc. Press release, March 3, 2006.

² GlaxoSmithKline Terminates Patient Enrollment for Phase 3 Studies of Investigational HIV Entry Inhibitor Aplaviroc. Press release, October 25, 2005.

- For accelerated approval, 24-week data from two adequate and well-controlled trials would be needed.
- A general indication for use in treatment-experienced patients (i.e., without regard to CXCR4-tropism status) would not be possible without evidence of MVC efficacy in the mixed/dual-tropic study (Study 1029). However, the indication could be limited to patients with CCR5-tropic virus if a tropism assay were clinically available.
- FDA stated that 48-week data would be needed for approval of a treatment-naïve indication.

An additional teleconference was held on November 8, 2004, to discuss the FDA statistical reviewer comments. During this meeting, it was agreed that the primary efficacy endpoint would be the change in viral load from baseline to Week 24. However, FDA noted that additional endpoints such as the proportion of subjects with undetectable virus would likely be emphasized in the label should MVC be approved.

On December 15, 2005, the Applicant proposed increasing the sample size of Study 1027 from 500 to 600 subjects in order to compensate for slower enrollment in Study 1028. The Applicant confirmed that they remained blinded to treatment allocation, and that the primary efficacy analyses would not be changed. FDA notified the Applicant on January 6, 2006, that the proposal was acceptable.

The End of Phase 2 meeting was held on April 11, 2006. During this meeting, the Applicant summarized the Data Safety Monitoring Board recommendations to discontinue the once daily dosing arm of the treatment-naïve study (Study 1026) due inadequate efficacy. In addition, the Week 24 results from the mixed/dual tropic study (Study 1029) were also presented. The Applicant proposed that as neither superiority nor non-inferiority of MVC QD or BID dosing could be concluded, Study 1029 should be continued to completion at Week 48. FDA agreed with this proposal. The Applicant also reiterated their plan to initiate pediatric studies in children only after the safety and efficacy of MVC in adults had been established. FDA agreed with this proposal.

The Pre-NDA meeting was held on November 28, 2006, and the following was discussed:

- FDA requested datasets that would allow reviewers to pool safety data from the open-label and double-blind periods of Studies 1027 and 1028.
- FDA requested a 3-month instead of 4-month Safety Update in order to have adequate time to review in anticipation of an Advisory Committee meeting for MVC.
- FDA stated that data from Studies 1027 and 1028 would need to be reviewed before agreement could be reached on the design of the Expanded Access Program for MVC.

2.6 Other Relevant Background Information

There is no additional relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

There have not been any CMC issues identified that would preclude approval of MVC. Please refer to the FDA CMC Review of MVC for additional information.

3.2 Animal Pharmacology/Toxicology

Due to the mechanism of action of MVC in blocking a receptor on immune cells, there has been concern regarding the possibility that use of this drug could lead to an increased risk of malignancy or infection. Carcinogenicity studies in transgenic mice and Sprague Dawley (S-D) rats were conducted in conformance with the International Conference on Harmonization (ICH) as well as Good Laboratory Practices (GLP). Overall, these studies did not reveal evidence of carcinogenicity. However, it should be noted that cholangiocarcinoma was observed in two S-D rats at the highest dose tested (900 mg/kg/day for 104 weeks). While this is an uncommon tumor in S-D rats, the finding was not considered sufficient to clearly implicate MVC. With respect to infection, no increased risk was observed in association with MVC during pre-clinical testing.

As previously noted in Section 2.4, the potential for hepatotoxicity has been a concern in light of the experience with a different CCR5 co-receptor antagonist. Bile duct vacuolation was observed in rats, but no evidence of liver toxicity was observed in mice, dogs, or monkeys. The changes in rat bile ducts were considered possibly a response to biliary excretion of MVC or a metabolite.

With respect to QT prolongation, non-clinical studies demonstrated the potential of MVC to prolong ventricular repolarization at doses approximately 6 times the projected human dose. Please see Sections 7.1.3 and 7.1.9 for information regarding how this finding was addressed during the clinical assessment of MVC.

The incidence of fetal malformations was not increased during pre-clinical studies performed with MVC in rats at exposures approximately 20-fold higher and in rabbits 5-fold higher than the human exposure anticipated for MVC at the proposed doses.

Please refer to the FDA Pre-Clinical Review of MVC for additional information.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Data from Studies 1027 and 1028 formed the principal basis for characterizing the safety and efficacy of MVC in treatment-experienced patients with CCR5-tropic HIV-1 infection. As Study 1027 was moderately larger and contained a higher proportion of subjects from the United

States, the review focused somewhat more on the results of that trial and commented on Study 1028 where substantive differences existed. In addition, the combined results from Studies 1027 and 1028 were extensively analyzed and are presented in this review. Study 1029 was performed in subjects with mixed/dual tropism and the results also submitted with this application. The primary purpose of this trial was to evaluate whether exposure to MVC in these subjects caused unanticipated safety concerns.

4.2 Tables of Clinical Studies

FDA Table 1: Clinical Studies Analyzed in this Review

Study Number	Study Title	Phase	Participating Countries	Subjects Randomized
1027	A multicentre, randomised, double-blind, placebo-controlled trial of a novel CCR5 antagonist, maraviroc, in combination with optimized background therapy versus optimized background therapy alone for the treatment of antiretroviral-experienced HIV-1 infected subjects	2b/3	United States, Canada	601
1028	A multicentre, randomised, double-blind, placebo-controlled trial of a novel CCR5 antagonist, maraviroc, in combination with optimized background therapy versus optimized background therapy alone for the treatment of antiretroviral-experienced HIV-1 infected subjects	2b/3	Europe, Australia, North America	475
1029	A multicentre, randomised, double-blind, placebo-controlled trial of a novel CCR5 antagonist, maraviroc, in combination with optimized background therapy versus optimized background therapy alone for the treatment of antiretroviral-experienced, non-CCR5 tropic HIV-1 infected subjects	2b	Australia, Belgium, Canada, Germany, Netherlands, Spain, Switzerland, United Kingdom, United States	190

4.3 Review Strategy

The results from two phase 2b/3 trials conducted in treatment-experienced subjects infected with CCR5-tropic HIV-1 (Studies 1027 and 1028) were evaluated in support of the proposed indication. The FDA clinical and statistical reviewers collaborated extensively during the review process, and a number of the efficacy analyses in this review are the result of work performed by the FDA statistician. In addition, there was significant interaction with the FDA clinical pharmacology, toxicology, and product evaluation groups. Their assessments are summarized in

this document, but complete descriptions of their findings are available in their respective reviews.

4.4 Data Quality and Integrity

A routine consult was submitted to the Division of Scientific Investigations on February 7, 2007, in response to the submission of the MVC New Drug Application (NDA). Three clinical sites were inspected (Table 2). For Site #1048, a minor deviation from the protocol was observed for one subject, and non-reporting of prior antiretroviral medications was observed for two subjects. However, these deviations were considered minor, and in general the records that were reviewed were accurate and without problems that would impact the study results. In addition, the inspections of Sites #1022 and #1023 did not reveal any significant issues. Therefore, the data from all three sites were considered acceptable in support of the MVC NDA.

FDA Table 2: Listing of DSI Inspection Sites

Name of Primary Investigator	Site #	Location	Inspection Date
Frederick Cruickshank	1022	Huntersville, NC	03-08-2007
Jacob Lalezari	1023	San Francisco, CA	03-12-2007
Michael Wohlfeiler	1048	North Miami Beach, FL	03-05-2007

4.5 Compliance with Good Clinical Practices

The protocol and informed consent documents were reviewed and approved by the Institutional Review Boards and Independent Ethics Committees for each of the investigational centers that participated in Studies 1027 and 1028. The Applicant certified that these studies were conducted in compliance with the ethical principles described in the Declaration of Helsinki, and in compliance with International Conference on Harmonisation Good Clinical Practice guidelines.

In addition, the FDA Division of Scientific Investigations inspected three clinical sites, and data from all three were considered acceptable (see Section 4.4)

4.6 Financial Disclosures

The Applicant examined financial data regarding significant payments and equity for all of the investigators. A total of 2357 investigators participated in Studies 1026, 1027, 1028, and 1029. A certification was provided for 2331 (99%) of the 2357 investigators, which indicated that 2328 (99%) had no financial arrangement as defined by 21 CFR 54.2. Of the 26 investigators who had financial information to disclose, 25 had significant payments, and 1 investigator disclosed ownership of equity. This investigator worked at [REDACTED] and as part of his benefits, had stock-options and profit-sharing. Since leaving [REDACTED], he

confirmed that he is not participating in profit-sharing and does not own any stock options or other interest in Pfizer.

Based on the low proportion of investigators with a financial interest and the double-blind nature of the trial designs, the likelihood that study results were substantively biased based on financial interests is low.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

This Section provides a brief summary of the pharmacokinetics of MVC. Please refer to the FDA Clinical Pharmacology Review for additional information.

Absorption

Peak MVC plasma concentrations were attained 0.5 to 4 hours following single oral doses of 1-1200 mg administered to healthy volunteers. The pharmacokinetics of oral MVC were not dose proportional over the dose range. The absolute bioavailability of a 100 mg dose was 23% and is predicted to be 33% at 300 mg. MVC is a substrate for the efflux transporter P-glycoprotein (P-gp).

Distribution

MVC is bound (approximately 76%) to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. The volume of distribution of MVC is approximately 194 liters.

Metabolism

Studies in humans and in vitro studies using human liver microsomes and expressed enzymes demonstrated that MVC is principally metabolized by the cytochrome P450 system to metabolites that are essentially inactive against HIV-1. In vitro studies indicate that CYP3A4 is the major enzyme responsible for MVC metabolism, and that CYP2C9, CYP2D6 and CYP2C19 do not contribute significantly.

MVC is the major circulating component (~42% drug-related radioactivity) following a single oral dose of 300 mg [¹⁴C]-MVC. The most significant circulating metabolite in humans is a secondary amine formed by N-dealkylation. This polar metabolite has no significant pharmacological activity. Other metabolites are products of mono-oxidation and are only minor components of plasma drug-related radioactivity.

Elimination

A mass balance/excretion study was conducted using a single 300 mg dose of ¹⁴C-labeled MVC. Approximately 20% of the radiolabel was recovered in the urine and 76% was recovered in the feces over 168 hours. MVC was the major component present in urine (mean of 8% dose) and feces (mean of 26% dose). The remainder was excreted as metabolites.

Drug-drug interactions

MVC is unlikely to inhibit the metabolism of co-administered drugs metabolized by cytochrome P450 enzymes because it does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4 at clinically relevant concentrations in vitro.

Drug interaction studies were performed with MVC and other drugs likely to be co-administered or commonly used as probes for pharmacokinetic interactions. MVC had no effect on the pharmacokinetics of zidovudine or lamivudine, suggesting no interactions with renal clearance or non-P450 metabolism. MVC had no clinically relevant effect on the pharmacokinetics of midazolam, the oral contraceptives ethinylloestradiol and levonorgestrel, and no effect on the urinary 6 β -hydroxycortisol/cortisol ratio, suggesting no induction of CYP3A4 in vivo. MVC had no effect on the debrisoquine metabolic ratio (MR) at 300 mg BID or less in vivo. However, there was a 234% increase in debrisoquine MR on treatment compared to baseline at 600 mg QD, suggesting a potential inhibition of CYP2D6 at higher doses.

MVC is a substrate of CYP3A4 and P-gp, and hence its pharmacokinetics are likely to be modulated by inhibitors and inducers of these enzymes/transporters. The CYP3A4/P-gp inhibitors ketoconazole, lopinavir/ritonavir, ritonavir, saquinavir and atazanavir all increased the C_{max} and AUC of MVC. The CYP3A4 inducers rifampin and efavirenz decreased the C_{max} and AUC of MVC. Tipranavir/ritonavir (net CYP3A4 inhibitor/P-gp inducer) did not affect the steady state pharmacokinetics of MVC. Co-trimoxazole and tenofovir did not affect the pharmacokinetics of MVC.

5.2 Pharmacodynamics

Please see Section 5.3.

5.3 Exposure-Response Relationships

This Section provides a brief summary of the FDA Pharmacometric Review. Please refer to that Review for additional information.

The relationship between plasma trough concentration of MVC (C_{min}) and virologic response in treatment-experienced subjects infected with CCR5-tropic HIV-1 was evaluated. Several virologic efficacy endpoints were investigated, including viral load <50 copies/mL at 24 weeks and viral load <400 copies/mL at 24 weeks.

Subjects with a C_{min} greater than 50-75 ng/mL were observed to have a greater probability of virologic success. In addition to C_{min}, success also appeared to be influenced by other subject

With respect to secondary efficacy analyses, the collection of CD4+ cell count data and clinical endpoints such as CDC Class C events are recommended by the Guidance, and were submitted as part of the current application.

6.1.3 Study Design

Studies 1027 and 1028 are 48-week, multicenter, double-blind, randomized, placebo-controlled, phase 2b/3 clinical trials intended to compare the safety and efficacy of two MVC regimens in the treatment of subjects with CCR5-tropic HIV-1. Subjects were randomized 2:2:1 to 300 mg dose equivalent once daily, 300 mg dose equivalent twice daily, or placebo. All subjects also received optimized background therapy (OBT). Study 1027 was originally intended to enroll 500 subjects, but enrollment was increased to 600 subjects following protocol amendment 2 on December 20, 2005. This was in response to slower than expected enrollment in Study 1028. Investigators optimized the open-label OBT regimen, with 3 to 6 approved antiretroviral agents (excluding low-dose ritonavir) on the basis of resistance testing, treatment history, and safety considerations. The primary efficacy endpoint was the mean decrease in viral load at Week 24, and this data was submitted in support of the current application. However, these studies are ongoing and will be unblinded to investigators and subjects following the last subject visit at Week 48.

The major eligibility criteria for enrollment were the following:

- Men or women at least 16 years of age
- Infected with CCR5-tropic HIV-1
- No evidence of CXCR4- or dual/mixed-tropic virus
- At least 6 months of prior treatment with at least 1 agent (at least 2 for PIs) from 3 of the 4 antiretroviral drug classes, or documented resistance to members from 3 of 4 classes
- Stable antiretroviral regimen for at least 4 weeks prior to randomization and a plasma viral load $\geq 5,000$ copies/mL

MVC is a substrate for cytochrome P450 3A4. Therefore, the dose of MVC required adjustment based on the concomitant antiretroviral medications administered (Table 3).

Sponsor Table 3: Recommended MVC Dose for Studies 1027 and 1028

Concomitant Antiretrovirals	MVC Dose
≥ 1 PI (excluding tipranavir) and/or delavirdine	150 mg
All other regimens	300 mg

The schedule of subject monitoring procedures performed during Studies 1027 and 1028 are presented in Table 4.

Sponsor Table 4: Timetable of Study Procedures for Studies 1027 and 1028

Procedures	Screening (Day -42 to -28)	Randomization (Day -7 to -4)	Baseline ^a Day 1	Week 2 ^b	Weeks 4, 8, 12, 16, 20, 32, 40 ^b	Weeks 24 and 48 or Early Termination ^{b,c}
Informed Consent and Eligibility Check	X					
Medical History			X			
Physical Exam/Vital Signs			X			X
Targeted Physical Exam/Vital Signs					X	
Body Weight/Height ^f			X	X	X	X
Selection/confirmation of OBT Regimen		X				
Adverse Events			X	X	X	X
Concomitant Medications			X	X	X	X
Chemistry, Hematology	X	X ^q	X	X	X	X
Fasting Metabolic Assessment (total cholesterol, HDL/LDL, triglycerides, glucose, glycosylated hemoglobin)			X			X
12-lead Electrocardiogram			X			X
Orthostatic BP Monitoring	X		X ^d	X		X
PK Sampling ^e				X	X	X
Urinalysis			X			X
Hepatitis screen (B core Ab, sAg, sAb, C Ab)	X					
Hepatitis C Virus RNA ^f			X		X	X
CD4/CD8	X		X	X	X	X
Plasma HIV-1 RNA	X	X	X	X	X	X
Pregnancy Test ^g	X		X		X	X
Plasma/PBMC/Proviral DNA Storage ^h			X		X	X
Viral Resistance (Phenotype, Genotype) ⁱ	X				X ^j	X ^o
Co-receptor tropism (Phenotype, Genotype ^k)	X		X		X ^{j,l}	X ^o
Host Genotyping			X ^p			
Free T4, TSH			X			X
Dispense Study Medication			X	X ^m	X	X ⁿ
Assess Dosing Compliance				X	X	X

a. Day 1, prior to dosing.

- b. All visits must occur within ± 4 days.
- c. Subjects who discontinue study drug due to treatment failure or for other reasons must be followed per protocol until Week 48.
- d. Patients with asymptomatic postural hypotension at the Baseline visit will be monitored for 4 hours following the first dose of study drug.
- e. Two 5 ml PK samples are required at Weeks 2 and 24 and must be at least 30 minutes apart. One 5 ml PK sample required at other visits. Through Week 24 only.
- f. If Hepatitis C antibody is positive at Screening Visit, to be performed at Baseline, Weeks 12, 24 and 48 or Early Termination.
- g. For Women of Child Bearing Potential. Serum pregnancy at Screening and Urine Tests at the following visits. A positive Urine test must be confirmed with a serum test.
- h. Plasma aliquots (2 of 1 mL each) at all time points. PBMCs, and proviral DNA will be stored at Baseline and at Weeks 24 and 48 or upon treatment failure only.
- i. Reverse transcriptase, protease and fusion inhibitor resistance testing at screening to determine background regimen and at Week 24/48 if viral load >500 copies/mL or upon treatment failure.
- j. Upon treatment failure as defined in the protocol (this sample is to be drawn when the confirmatory plasma HIV-1 RNA sample is collected).
- k. Genotype (V3 loop alone or as part of gp 160 sequencing) at Baseline, Weeks 24 and 48 and at treatment failure only.
- l. Weeks 4, 8, 16, 32 and 40 only.
- m. Container from previous visit.
- n. At Week 48 or Early Termination, medication will be dispensed to subjects who have completed 48 weeks of therapy and for whom it is medically appropriate to continue or begin therapy with UK-427,857
- o. Except at Early Termination if a treatment failure (sample should be drawn when confirmatory HIV-1 RNA is collected)
- p. Unless prohibited by local regulations
- q. Chemistry only
- r. Height recorded once. Weight through Week 24 only

Subjects who experienced virologic failure during Studies 1027 and 1028 were unblinded to treatment assignment and allowed to have their medications adjusted as needed. This allowed them to obtain appropriate revisions to their regimen in a timely manner. The following criteria were used to determine virologic failure:

- An increase to at least 3 times the baseline (mean of all 3 values before start of dosing) plasma HIV-1 RNA level at the Week 2 visit or thereafter (confirmed by a second measurement taken no more than 14 days after the first measurement);
- HIV-1 RNA $<0.5 \log_{10}$ decrease from baseline (mean of all 3 values before start of dosing) on two consecutive measurements starting at Week 8 (second measurement taken no more than 14 days after the first measurement);
- HIV-1 RNA $<1.0 \log_{10}$ decrease from baseline (mean of all 3 values before start of dosing) on two consecutive measurements starting at Week 8 (second measurement taken no more than 14 days after the first measurement), in a subject who had previously achieved a $\geq 2.0 \log_{10}$ decrease from baseline; or
- An increase in HIV-1 RNA to $\geq 5,000$ copies/mL on two consecutive measurements taken no more than 14 days apart, in subjects previously confirmed to have undetectable levels of <400 copies/mL on 2 consecutive visits.

6.1.4 Efficacy Findings

A total of 1816 subjects were screened during Study 1027, of whom 601 were randomized and 585 received at least one dose of study agent (232 received MVC QD, 235 received MVC BID, and 118 received placebo). Treatment groups were well-matched with respect to baseline characteristics (Table 5). The vast majority of subjects were male (90%) and Caucasian (83%), and the mean age was 46 years. The most common risk factor for HIV was male to male sexual contact (75%). Heterosexual contact was the next most common risk factor (17%), and injection drug use and blood product exposure were risk factors for 6% of subjects. A total of 81% of subjects had a diagnosis of HIV for greater than 10 years at the time of enrollment. The baseline characteristics for subjects in Study 1028 were quite similar overall to Study 1027. The only substantive difference was that while the United States was the highest enrolling country in Study 1028 at 32%, the proportion of subjects from the United States was less than in Study 1027 (89%). The only other country that enrolled subjects in Study 1027 was Canada (11%). Other high enrolling countries in Study 1028 included Germany (14%), France (10%), Spain (10%), and Australia (9%).

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FDA Table 5: Baseline Characteristics (Study 1027, Modified ITT Population)

Baseline Characteristics	Treatment Group		
	MVC QD (n=232)	MVC BID (n=235)	Placebo (n=118)
Gender			
Male	210 (91%)	212 (90%)	106 (90%)
Female	22 (9%)	23 (10%)	12 (10%)
Race			
Caucasian	187 (81%)	197 (84%)	99 (84%)
African-American	39 (17%)	33 (14%)	15 (13%)
Asian	3 (1%)	2 (1%)	0 (0%)
Other/unspecified	3 (1%)	3 (1%)	4 (3%)
Age, mean (years)	46.0	45.8	46.1
Weight, median (kg) ¹	74.3	75.9	79.1
Country			
United States	201 (87%)	212 (90%)	107 (91%)
Canada	31 (13%)	23 (10%)	11 (9%)
HCV RNA present	7 (3%)	14 (6%)	8 (7%)
HBsAg present	9 (4%)	16 (7%)	9 (8%)
Duration of HIV (years)			
<5	5 (2%)	4 (2%)	4 (3%)
5-10	41 (18%)	34 (14%)	21 (18%)
>10	186 (80%)	197 (84%)	93 (79%)
HIV exposure			
Male to male sexual contact	174 (75%)	170 (72%)	87 (74%)
Heterosexual contact	42 (18%)	40 (17%)	16 (14%)
Other ²	16 (7%)	25 (11%)	15 (12%)
CCR5 Δ32 mutation			
CCR5+/CCR5+	200 (86%)	207 (88%)	101 (86%)
Deletion/CCR5+	17 (7%)	13 (6%)	11 (9%)
Missing	15 (7%)	15 (6%)	6 (5%)
CCR5 promoter haplotype			
P1/other	107 (46%)	103 (44%)	57 (48%)
P1/P4	73 (31%)	82 (35%)	39 (33%)
P4/other	31 (13%)	29 (12%)	13 (11%)
Missing	15 (6%)	15 (6%)	6 (5%)
Other	6 (3%)	6 (3%)	3 (3%)
Viral load, median (log ₁₀ copies/mL)	4.88	4.88	4.93
CD4+ cell count, median	168	150	163
Clade			
B	228 (98%)	230 (98%)	116 (98%)
Non-B/undetermined	4 (2%)	5 (2%)	2 (2%)
OSS			
0	30 (13%)	27 (12%)	19 (16%)
1	78 (34%)	86 (37%)	21 (18%)
2	51 (22%)	65 (28%)	38 (32%)

≥3	69 (30%)	54 (23%)	37 (31%)
Missing	4 (2%)	3 (1%)	3 (3%)
Fusion inhibitor use	100 (43%)	107 (46%)	50 (42%)

¹ Baseline weights were not obtained until protocol amendment #3 on March 2, 2006. The weight data in this table represent the 152 subjects (26% of the entire study) who had a baseline weight obtained within 30 days of the first dose of study agent.

² The category "Other" includes in descending order of frequency: injection drug use, blood product exposure, individuals with multiple risk factors, and perinatal exposure.

The protocol deviations reported during Study 1027 are provided in Table 6. The most common deviations involved procedures or tests (59.0%), with the second most common deviation involving the investigational product (10.5%). Investigational product deviations included decreased compliance (most common), incorrect initial dosing instructions, and dosing errors.

Sponsor Table 6: Summary of Protocol Deviations During Study 1027

Deviation Category	Number of Deviations Total = 553
Procedure/test	326 (59.0%)
Investigational product ^a	58 (10.5%)
Laboratory ^b	46 (8.3%)
Inclusion/exclusion	44 (8.0%)
Visit schedule	35 (6.3%)
Concomitant medication	13 (2.4%)
Project specific discontinuation criteria	12 (2.2%)
Safety reporting ^c	8 (1.4%)
Other	8 (1.4%)
Multiple reasons	3 (0.5%)

^a Investigational product included: subjects <80% compliant with study drug (24 cases); incorrect initial dosing instructions given by sites (7 cases), dosing errors

^b Laboratory included: pharmacokinetic, urinalysis, pregnancy tests not done (28 cases); blood samples clotted on receipt (8 cases); incorrect sample times

^c Safety reporting included: serious adverse events not reported to sponsor within specified timeline and 1 case of an unreported pre-randomization serious adverse event

The concomitant optimized background therapy (OBT) medications administered during Study 1027 are provided in Table 7. The most common OBT was low dose-ritonavir, which the majority of study subjects received (86-88%). Other commonly used medications were tenofovir, enfuvirtide, emtricitabine, and lamivudine. Use of the various medications for OBT appeared to be balanced across the three treatment arms.

Sponsor Table 7: Summary of Concomitant OBT Drug Treatments During Study 1027

Drug Treatments	MVC QD N=232	MVC BID N=235	Placebo N=118
	n	n	n
Ritonavir low-dose	204	202	101
Tenofovir	183	207	107
Enfuvirtide	100	107	50
Emtricitabine	87	114	53
Lamivudine	101	90	43
Lopinavir	80	92	39
Abacavir	78	60	39
Didanosine	57	45	38
Amprenavir ^a	52	52	34
Zidovudine	49	37	22
Atazanavir	50	36	20
Saquinavir	31	22	12
Tipranavir	22	24	13
Stavudine	20	18	6
Efavirenz	12	18	7
Nevirapine	8	14	2
Indinavir	7	9	4
Delavirdine	8	5	4
Nelfinavir	3	4	1
T-1249	3	0	0
Ritonavir	2	0	0
TMC-114 (darunavir)	0	0	1

^a Includes fosamprenavir.

Change in HIV viral load from baseline to Week 24 was the primary endpoint of Studies 1027 and 1028. Due to the identical trial designs and patient populations studied, the viral load results of these two trials were pooled (Table 8). Superiority to placebo was evident in both MVC arms, with the MVC BID arm having slightly greater viral load reduction than that observed with MVC QD.

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FDA Table 8: Primary Efficacy Endpoint (Change in HIV-1 RNA from Baseline to Week 24)*
 (Studies 1027 and 1028 Combined, Modified ITT Population)

Treatment Group	N	Raw Mean (se)	Raw Median	Adjusted Mean (se)	Treatment Estimate** (99.95% CI)
MVC QD	414	-1.825 (0.070)	-2.229	-1.833 (0.069)	-0.872 (-1.335, -0.409)
MVC BID	426	-1.946 (0.069)	-2.409	-1.950 (0.068)	-0.988 (-1.447, -0.529)
Placebo	209	-0.960 (0.091)	0.000	-0.962 (0.097)	N/A

* If missing at Week 24, baseline value used as the Week 24 result

** Difference between adjusted means for MVC and placebo

Several sensitivity analyses of the primary efficacy endpoint were performed, and all 99.95% confidence intervals supported superiority of MVC over placebo. One sensitivity analysis assessed all subjects with Week 24 viral load data regardless of whether they remained on their originally assigned treatment. Treatment efficacy (i.e., the degree of viral load suppression observed beyond that seen in the placebo arm) was -0.50 and -0.49 log₁₀ copies/mL in the MVC QD and BID arms, respectively. A second sensitivity analysis evaluated only treatment completers through Week 24, and treatment efficacy was -0.48 and -0.54 log₁₀ copies/mL in the MVC QD and BID arms, respectively. Finally, a third analysis imputed multiple single values as the missing value (-0.4 to 0.3 by increments of 0.1) and the treatment efficacy was -0.79~0.97 and -0.88~1.06 in the MVC QD and BID arms, respectively.

An assessment of viral load undetectability, as defined by HIV-1 RNA <50 copies/mL at 24 weeks, was performed with respect to multiple baseline characteristics for Study 1027 (Table 9). Overall, the MVC arms were superior to placebo (42%, 49%, and 25% in the MVC QD, MVC BID, and placebo arms, respectively). The MVC arms appeared to be superior to placebo across all of the subgroups examined, except for subjects with an overall susceptibility score (OSS) ≥3. As these subjects had multiple available treatment options as reflected by their OSS score, it is not surprising that any incremental benefit potentially provided by an additional therapy such as MVC would be less apparent.

Across all treatment arms, there was a decrease in virologic success with increasing baseline viral load, decreasing CD4+ cell count, and decreasing OSS. With respect to race, there appeared to be a decrease in virologic success in blacks compared with Caucasians, but this finding is uncertain due to the low enrollment of blacks. Likewise, no firm conclusions can be reached regarding potential efficacy differences with other races due to very small subject numbers. Due to the limited variability in ages of the enrolled subjects, and the low enrollment of women, conclusions regarding potential efficacy differences based on age or gender also cannot be reached. Finally, subject baseline weights were not routinely collected initially, resulting in insufficient data to comment regarding the potential for differences in efficacy based on weight.

FDA Table 9: Proportion of Subjects with HIV RNA <50 copies/mL at 24 Weeks ¹
 (Study 1027, Modified ITT Population)

Baseline Characteristics	Proportion of Subjects with HIV RNA <50 copies/mL at Week 24		
	MVC QD (n=232)	MVC BID (n=235)	Placebo (n=118)
All subjects	98 (42%)	114 (49%)	29 (25%)
Gender			
Male	88 (42%)	104 (49%)	26 (25%)
Female	10 (45%)	10 (43%)	3 (25%)
Race			
Caucasian	85 (45%)	102 (52%)	26 (26%)
Black	10 (26%)	11 (33%)	3 (20%)
Country			
United States	82 (41%)	98 (46%)	26 (24%)
Canada	16 (52%)	16 (70%)	3 (27%)
Age (years)			
Q ₁ (<41)	21 (38%)	19 (37%)	8 (32%)
Q ₂ (≥ 41- <45)	24 (45%)	23 (36%)	8 (29%)
Q ₃ (≥45 - <51)	26 (39%)	35 (59%)	6 (17%)
Q ₄ (≥51)	27 (47%)	37 (61%)	7 (23%)
Weight (kg) ²			
<76	20 (54%)	16 (48%)	2 (15%)
≥76	15 (65%)	16 (53%)	7 (44%)
Duration of HIV (years)			
<5	1 (20%)	2 (50%)	1 (25%)
5-10	17 (41%)	13 (38%)	7 (33%)
>10	80 (43%)	99 (50%)	21 (23%)
Viral load (copies/mL)			
Q ₁ (<30767)	34 (55%)	36 (65%)	12 (41%)
Q ₂ (≥30767-<82367)	34 (61%)	37 (58%)	8 (30%)
Q ₃ (≥82367-<189667)	18 (32%)	24 (42%)	8 (23%)
Q ₄ (≥189667)	12 (21%)	17 (29%)	1 (4%)
CD4+ cell count (cells/uL)			
Q ₁ (<60)	4 (7%)	13 (20%)	1 (4%)
Q ₂ (≥60 - <159)	25 (45%)	33 (58%)	10 (29%)
Q ₃ (≥159 - <279)	32 (53%)	26 (51%)	8 (22%)
Q ₄ (≥279)	37 (62%)	42 (68%)	10 (43%)
OSS			
0	2 (7%)	10 (37%)	0 (0%)
1	36 (46%)	36 (42%)	1 (5%)
2	22 (43%)	37 (57%)	8 (21%)
≥3	37 (54%)	29 (54%)	20 (54%)
Enfuvirtide use			
Yes	46 (46%)	49 (46%)	14 (28%)

No	52 (39%)	65 (51%)	15 (22%)
CCR5 promoter haplotype			
P1/other	45 (42%)	53 (51%)	14 (25%)
P1/P4	33 (45%)	40 (49%)	11 (28%)
P4/other	16 (52%)	16 (55%)	1 (8%)

¹ Missing = failure

² Due to the small number of baseline weights that were obtained, efficacy results with respect to baseline weight were analyzed as \geq median weight vs. $<$ median weight.

Due to the relatively small numbers of subjects within individual subgroups for Study 1027, a similar analysis was performed that combined all subjects in Studies 1027 and 1028 (Table 10). The findings originally noted in Study 1027 were confirmed in this analysis. There appeared to be a trend towards increased virologic benefit with MVC BID over MVC QD in subjects with increased viral load, decreased CD4+ cell count, or decreased OSS at baseline.

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FDA Table 10: Proportion of Subjects with HIV RNA <50 copies/mL at 24 Weeks¹
 (Studies 1027 and 1028 Combined, Modified ITT Population)

Baseline Characteristics	Proportion of Subjects with HIV RNA <50 copies/mL at Week 24		
	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
All subjects	181 (44%)	192 (45%)	48 (23%)
Gender			
Male	158 (44%)	173 (45%)	41 (22%)
Female	23 (45%)	19 (43%)	7 (29%)
Race			
Caucasian	154 (46%)	173 (48%)	42 (24%)
African-American	23 (33%)	15 (29%)	6 (23%)
Country			
United States	106 (41%)	119 (43%)	28 (21%)
Non-United States	75 (48%)	73 (49%)	20 (27%)
Age (years)			
Q ₁ (<41)	46 (40%)	34 (36%)	15 (29%)
Q ₂ (≥41 - <45)	40 (45%)	39 (39%)	12 (26%)
Q ₃ (≥45 - <51)	46 (41%)	54 (51%)	10 (17%)
Q ₄ (≥51)	49 (49%)	65 (52%)	11 (22%)
Weight (kg) ²			
<75	30 (45%)	38 (58%)	8 (24%)
≥75	39 (64%)	36 (46%)	10 (34%)
Duration of HIV (years)			
<5	1 (20%)	4 (50%)	1 (20%)
5-10	28 (42%)	28 (39%)	10 (30%)
>10	152 (44%)	160 (46%)	37 (22%)
Viral load (copies/mL)			
Q ₁ (<28650)	62 (60%)	58 (59%)	18 (32%)
Q ₂ (≥28650 - <80367)	62 (63%)	63 (54%)	14 (31%)
Q ₃ (≥80367 - <211167)	33 (31%)	38 (40%)	13 (23%)
Q ₄ (≥211167)	24 (24%)	33 (31%)	3 (6%)
CD4+ cell count (cells/uL)			
Q ₁ (<74)	12 (12%)	23 (21%)	1 (2%)
Q ₂ (≥74 - <169)	50 (49%)	51 (49%)	16 (29%)
Q ₃ (≥169 - <284)	56 (54%)	51 (50%)	15 (25%)
Q ₄ (≥284)	63 (60%)	67 (61%)	15 (32%)
OSS			
0	9 (17%)	16 (28%)	1 (3%)
1	52 (39%)	56 (41%)	4 (9%)
2	43 (49%)	54 (52%)	10 (17%)
≥3	75 (56%)	64 (51%)	33 (50%)
Enfuvirtide use			
Yes	79 (47%)	79 (43%)	21 (23%)

No	102 (41%)	113 (46%)	27 (23%)
CCR5 Δ32 mutation			
CCR5+/CCR5+	162 (45%)	171 (46%)	38 (22%)
Deletion/CCR5+	12 (38%)	15 (54%)	6 (38%)
CCR5 promoter haplotype			
P1/other	85 (44%)	85 (45%)	26 (26%)
P1/P4	57 (45%)	66 (46%)	16 (25%)
P4/other	29 (53%)	33 (57%)	2 (9%)
CXCR4 tropic ³			
Yes	12 (12%)	10 (10%)	4 (11%)
No	169 (53%)	182 (57%)	44 (26%)

¹ Missing = failure

² Due to the small number of baseline weights that were obtained, efficacy results with respect to baseline weight were analyzed as \geq median weight vs. $<$ median weight.

³ This category does not represent a baseline characteristic, as subjects determined to have CXCR4-tropic HIV during screening were to be excluded from the trial. "Yes" indicates subjects found to have CXCR4-tropic HIV at any time during the study. Efficacy by CXCR4-tropism status at Week 24 was not assessed as only 46 of the 702 subjects who had tropism results at Week 24 were CXCR4-tropic.

The Δ32 mutation has previously been associated with a marked decrease in the likelihood of acquiring HIV due to alteration of the CCR5 co-receptor. However, protection has only been associated with homozygosity, not heterozygosity. As MVC inhibits the receptor which is altered by the Δ32 mutation, an exploratory analysis was performed to assess whether there was evidence of a decrease in virologic response to MVC in subjects with this mutation. As might have been expected, none of the subjects in Studies 1027 and 1028 were homozygous for the Δ32 mutation. However, there were 41 (7%) subjects who were heterozygous. Of the 17 heterozygous subjects who received MVC QD and 13 who received MVC BID, an HIV RNA viral load of less than 50 copies/mL at Week 24 was achieved in 5 (29%) and 9 (69%), respectively. Of the 11 heterozygous subjects who received placebo, 5 (45%) achieved an HIV RNA viral load of less than 50 copies/mL. Due to the small numbers of subjects, substantive conclusions regarding this data cannot be reached.

A secondary efficacy endpoint was change in CD4+ cell count from baseline to Week 24. Assessments were made of all completers through Week 24 as well as using the last observation carried forward for all subjects, and there was a modest increase in CD4+ cell count in the MVC arms compared with placebo (Tables 11 and 12).

FDA Table 11: Mean CD4 Count at 24 Weeks by Treatment Group
 (Studies 1027 and 1028, Modified ITT Population, Completers through Week 24)

Treatment Group	N	Mean CD4 Count (se)	Treatment Effect (99.95% CI)
MVC QD	283	137.8 (7.7)	41.1 (-5.0, 87.3)
MVC BID	296	123.6 (6.2)	26.9 (-18.9, 66.3)
Placebo	93	96.7 (10.8)	N/A

FDA Table 12: Mean CD4 Count at 24 Weeks by Treatment Group
 (Studies 1027 and 1028, Modified ITT Population, LOCF* through Week 24)

Treatment Group	N	Mean CD4 Count (se)	Treatment Effect (99.95% CI)
MVC QD	408	113.5 (6.1)	58.8 (26.5, 91.1)
MVC BID	418	105.9 (5.1)	51.2 (21.0, 81.4)
Placebo	207	54.7 (7.0)	N/A

* Last observation carried forward

6.1.5 Clinical Microbiology

This Section provides a brief summary of the FDA Microbiology Review. Please refer to that Review for additional information.

A concern with the use of CCR5 co-receptor antagonists has been that they might increase the likelihood of HIV-1 switching from CCR5- to CXCR4-tropism through mutation and selection. Evolution to a CXCR4-utilizing HIV-1 has been proposed to result in a more virulent virus and is associated with more rapid progression to AIDS.

Therefore, the percentage of virologic failures that had CCR5-tropic and CXCR4-tropic virus at the time of failure was determined. The analysis was done using two definitions of treatment failure: (1) protocol-defined treatment failure (PDTF, defined in Section 6.1.3) and (2) subjects with PDTF plus subjects with >400 copies/mL at Week 24. Regardless of the definition of treatment failure, a higher proportion of subjects in the MVC arms failed with CXCR4- or dual/mixed-tropic virus in the MVC arms compared with placebo (Tables 13 and 14). A high percentage of treatment failure on MVC appears to be driven by tropism change from CCR5-tropic to CXCR4- or dual/mixed-tropic virus.

FDA Table 13: Viral Tropism of Protocol-Defined Treatment Failures
 (Studies 1027 and 1028 Combined, As Treated Population)

Tropism	MVC QD (n=81)	MVC BID (n=91)	Placebo (n=109)
CCR5	25 (31%)	24 (26%)	96 (88%)
CXCR4	10 (12%)	14 (15%)	1 (1%)
Dual/mixed	35 (43%)	42 (46%)	6 (5.5%)
NR/NP*	11 (14%)	11 (12%)	6 (5.5%)

*Not reported/non-phenotypable

FDA Table 14: Viral Tropism of Treatment Failures (PDTF or >400 copies/mL at Week 24)
 (Studies 1027 and 1028 Combined, As Treated Population)

Tropism	MVC QD (n=154)	MVC BID (n=143)	Placebo (n=146)
CCR5	72 (47%)	48 (34%)	122 (84%)
CXCR4	18 (12%)	20 (14%)	1 (0.7%)
Dual/mixed	48 (31%)	61 (43%)	11 (7.5%)
NR/NP*	16 (10%)	14 (10%)	12 (8%)

*Not reported/non-phenotypable

Of the 204 treatment failure subjects who were CCR5-tropic at baseline, 34% of MVC QD and 32% of MVC BID subjects switched to dual/mixed-tropism, while only 4% of the placebo subjects who failed experienced a similar tropism switch (Table 15). A switch from CCR5 to CXCR4-tropism was less common among the treatment failures, but again was more frequent with MVC (12%, 9%, and 0% in the MVC QD, MVC BID, and placebo arms, respectively). In the placebo arm, 82% of treatment failures had HIV-1 that remained CCR5-tropic compared to 22-26% of treatment failures in the MVC arms. Overall, these results again suggest that a high percentage of treatment failures on MVC are driven by tropism change.

FDA Table 15: Tropism Change of Treatment Failures on Treatment
 (Studies 1027 and 1028 Combined, As Treated Population)

	MVC QD (n=68)	MVC BID (n=77)	Placebo (n=97)
CCR5 to CCR5	18 (26%)	17 (22%)	80 (82%)
CCR5 to Dual/mixed	23 (34%)	25 (32%)	4 (4%)
CCR5 to CXCR4	8 (12%)	7 (9%)	0 (0%)
CCR5 to NR/NP/BLQ/missing*	8 (12%)	9 (12%)	5 (5%)
Non-CCR5 to all	11 (16%)	19 (25%)	8 (8%)

*Not-reported, non-phenotypable, below the level of quantitation or missing

Approximately 70% of subjects who had dual/mixed-tropic virus at baseline (changing from CCR5-tropic virus at screening) were treatment failures (PDTF or >400 copies/mL at Week 24) (Table 16). Tropism remained dual/mixed in the majority of the MVC failures who had dual/mixed-tropic virus at baseline, but 24% and 30% of such subjects in the MVC QD and BID arms, respectively, changed to CXCR4-tropic virus. In comparison, only 9% of such subjects in the placebo group switched to CXCR4-tropism. The majority of failures in the placebo group had CCR5-using virus at failure reflecting either normal changes in tropism or a shortcoming of the tropism assay.

FDA Table 16: Subjects with Dual/mixed Tropic Virus at Baseline
 (Studies 1027 and 1028 Combined, As Treated Population)

	MVC QD (n=33)	MVC BID (n=32)	Placebo (n=16)
Failures (PDTF or >400 copies/mL)	21 (70%)	23 (72%)	11 (69%)
Tropism at Failure			
CCR5	1 (5%)	0 (0%)	7 (64%)
Dual/mixed	13 (62%)	13 (57%)	3 (27%)
CXCR4	5 (24%)	7 (30%)	1 (9%)
NR/NP*	2 (9%)	3 (13%)	0 (0%)

*Not reported/non-phenotypable

6.1.6 Efficacy Conclusions

MVC was demonstrated to be superior to placebo with respect to virologic suppression using multiple endpoints and sensitivity analyses. In addition, a modest increase in CD4+ cell count was observed with MVC. Subjects with an OSS ≥ 3 constituted the one subgroup that did not appear to achieve a benefit with MVC. It should be noted that there were few women and non-Caucasians enrolled in the pivotal studies, which hindered the ability to assess potential differences in efficacy in these groups.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

All adverse events (AEs) reported during Studies 1027 and 1028 were combined to increase the probability of detecting AEs potentially associated with MVC administration. Additionally, safety signals of particular concern were further evaluated in Studies 1026 and 1029 as needed (Study 1026 is an ongoing trial investigating the use of MVC in treatment-naïve subjects infected with CCR5-tropic HIV-1, and a description of Study 1029 is provided in Sections 4.1 and 4.2). AEs that occurred while receiving study drug or within 7 days of study drug discontinuation were considered to be during the double-blind period, and all AEs that occurred following this period were considered to have occurred during the open-label period. Serious adverse events (SAEs) were included within the double-blind period if they occurred while receiving study drug or within 28 days of study drug discontinuation. AEs and SAEs occurring during the open-label period were considered separately as these subjects had already experienced either treatment failure or an AE necessitating study agent discontinuation, and were therefore considered a potentially biased subset of subjects.

During the double-blind period, there were a total of 2242, 2292, and 936 distinct AEs in the MVC QD, MVC BID, and placebo groups, respectively (Table 17). The total duration of observed time was substantially different in the MVC and placebo groups during the double-blind period (259, 267, and 99 years of observed time in the MVC QD, MVC BID, and placebo

groups, respectively). Therefore, the AEs were also assessed by events per 100 subject-years of observation.

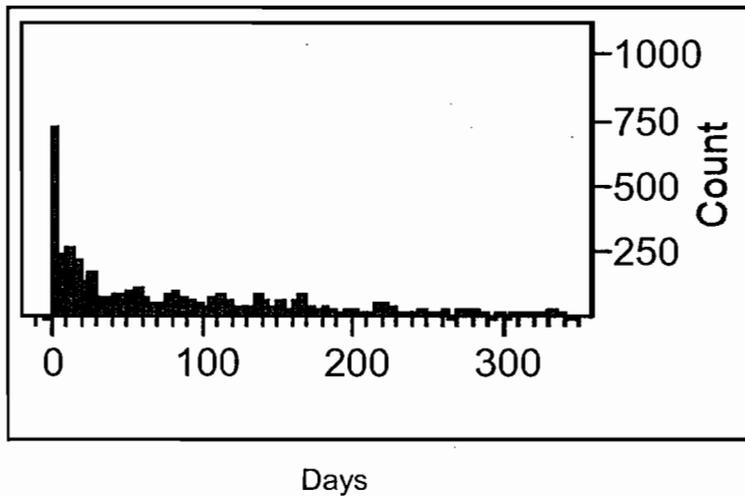
FDA Table 17: Summary of AE Findings During the Double-Blind Period
 (Studies 1027 and 1028 Combined, As Treated Population)

Event	MVC QD N=414	MVC BID N=426	Placebo N=209
Total AEs	2242	2292	936
Total Grade 3/4 AEs	192	227	94
Total SAEs	108	125	64
Avg. # of AEs/subject	5.42	5.38	4.48
Avg. # of Grade 3/4 AEs/subject	0.46	0.53	0.45
Avg. # of SAEs/subject	0.26	0.29	0.31
AEs/100 subject-years	2.09	2.01	4.51
Grade 3/4 AEs/100 subject-years	0.18	0.20	0.45
SAEs/100 subject-years	0.10	0.11	0.31

There was a greater than two-fold increase in total AEs, Grade 3/4 AEs, and SAEs in the placebo arm compared to the MVC arms when evaluated by subject-years of observation. This appears to be due to the shorter duration of time that placebo subjects were monitored during the double-blind period of the trials, in light of the fact that AEs were much more common in all treatment arms during the first 25 days of these two trials (Figure 1). Therefore, a treatment arm that had a shorter duration of follow-up would be enriched with AEs when analyzed by AEs per unit of time observed. This appears to have been the case for the placebo group. There may be multiple reasons for the greater frequency of AEs early in the trial. Optimization of the background regimen at the time of study entry may have led to an increase in early events. In addition, there are fewer subjects available with longer durations of monitoring to have AEs. It is also possible that patients who are experiencing a recent increase in medical problems are more likely to enroll in a clinical trial in the first place.

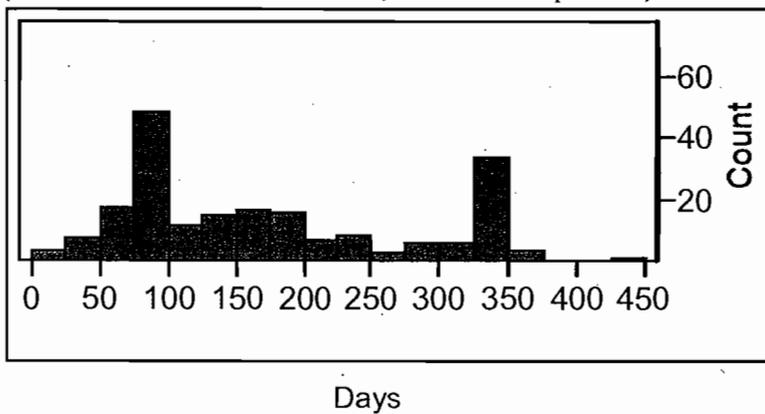
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FDA Figure 1: Days to Individual AEs During the Double-Blind Period in the MVC Groups
(Studies 1027 and 1028 Combined, As Treated Population)

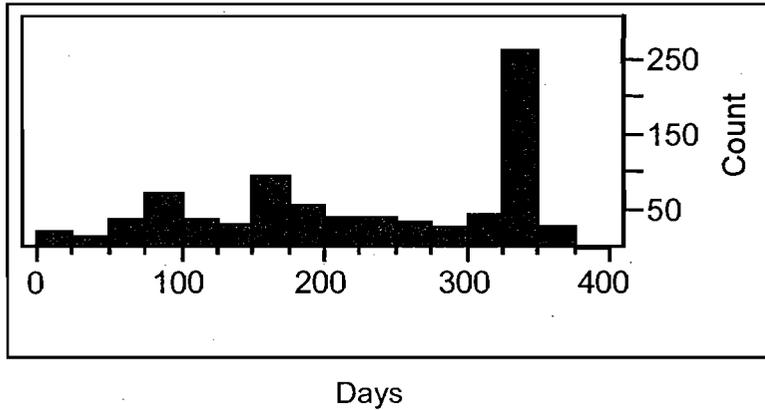


An additional analysis was performed to determine if the observed increase in early AEs was simply a reflection of more subjects being present early in the trials (Figures 2 and 3). However, substantial subject drop-out occurred considerably after the observed decrease in AEs. Therefore, a decrease in subject number over the course of the trials does not appear to explain the increased frequency of AEs during the first 25 days of the studies, which may have been related to exposure to multiple new drugs at the beginning of the study during the optimization of the background regimen.

FDA Figure 2: Days to Subject Discontinuation During the Double-Blind Period in the Placebo Group
(Studies 1027 and 1028 Combined, As Treated Population)



FDA Figure 3: Days to Subject Discontinuation During the Double-Blind Period
in the MVC Groups
(Studies 1027 and 1028 Combined, As Treated Population)



An analysis was performed comparing the most common AEs reported during the first 25 days of Studies 1027 and 1028 versus the remainder of these trials (Table 18). The two most common AEs during both time frames were diarrhea and nausea. While there were some differences between the two time frames, no clear pattern was apparent.

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FDA Table 18: 20 Most Common AEs During Early Versus Late Timeframes of the Double-blind Period by Decreasing Order of Frequency for all Treatment Groups (Studies 1027 and 1028 Combined, As Treated Population)

Study Days 0-25	Study Days > 25
1. Diarrhea	1. Diarrhea
2. Nausea	2. Nausea
3. Headache	3. Pyrexia
4. Fatigue	4. Upper respiratory tract infection
5. Dizziness	5. Headache
6. Injection site reaction	6. Cough
7. Vomiting	7. Fatigue
8. Pyrexia	8. Nasopharyngitis
9. Rash	9. Vomiting
10. Insomnia	10. Bronchitis
11. Constipation	11. Herpes simplex
12. Flatulence	12. Rash
13. Upper respiratory tract infection	13. Sinusitis
14. Abdominal pain upper	14. Back pain
15. Abdominal pain	15. Arthralgia
16. Cough	16. Depression
17. Decreased appetite	17. Insomnia
18. Night sweats	18. Abdominal pain
19. Abdominal distension	19. Dizziness
20. Anorexia	20. Anorexia

7.1.1 Deaths

All deaths from the phase 2b/3 trials investigating the use of MVC were reviewed and are summarized in Table 19. After correcting for the uneven randomizations of MVC to the control arms for these trials (2:1, 4:1, 4:1, and 2:1 for Studies 1026, 1027, 1028, and 1029, respectively) there was no evidence of an overall mortality imbalance with respect to MVC use. It should be noted that the types of deaths observed are consistent with what might be expected in the study population, and there was no apparent clustering of causes of death. Additionally, there were 11 other subjects who died during the approximately 6-week time period between screening and randomization, reflecting the advanced stage of disease of the study population.

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FDA Table 19: All Deaths by Treatment Group
 (Studies 1026, 1027, 1028, and 1029 Combined, As Treated Population)

Subject #	Treatment	Cause of Death	Total Days on Therapy	Days Post-Therapy to Death
Study 1026				
11310006	MVC QD	Suicide	34	7
11270003	MVC QD	Non-Hodgkin's lymphoma	35	92
10830006	MVC BID	Liver failure, pneumonia	11	120
10400002	Efavirenz	Castleman's disease	30	15
11160006	Efavirenz	Hodgkin's lymphoma	11	180
Study 1027				
10230010	MVC QD	Cerebrovascular hemorrhage	11	2
11110011	MVC QD	Respiratory failure	84	19
10310007	MVC BID	Cerebrovascular accident	142	2
10050022	MVC BID ¹	HIV disease progression	153	73
10210002	MVC BID ²	Large B-cell lymphoma	143	39
10680006	MVC BID ¹	HIV progression/giardiasis	82	>6 months
10460007	Placebo	Pneumonia	88	On Treatment
10210001	Placebo	Large cell lymphoma	298	84
Study 1028				
10440002	MVC QD	Anorexia	198	26
10510032	MVC QD	Septic shock, lymphoma ³	79	2
10820018	MVC QD	Myocardial infarction	206	On Treatment
11940011	MVC QD	Bacterial pneumonia	63	25
11150001	MVC QD	HIV disease progression	56	249
10440012	MVC BID	Cause unknown	62	1
11130004	MVC BID	Pneumonia/endocarditis	190	18
11230001	MVC BID	HIV disease progression	18	1
12160009	MVC BID	Cause unknown ³	35	On Treatment
12050011	MVC BID	CNS lymphoma ⁴	62	48
Study 1029				
10790001	MVC QD	Pneumonia	63	6
12130003	MVC QD	HIV progression/AIDS infection	195	19
12240005	MVC BID	Pneumocystis carinii pneumonia	31	23
10990002	MVC BID	Bacterial pneumonia	88	29
10870001	Placebo	HIV progression, renal failure	92	On Treatment
11810004	Placebo	Multiple cerebral lesions	Unknown	Unknown
11260003	Placebo	Multifocal leukoencephalopathy	36	29

¹ Death occurred during open-label period, subject originally randomized to MVC BID

² Death occurred during open-label period, subject originally randomized to placebo

³ Cause of death assessment by the FDA reviewer if it differs from the Investigator

⁴ Presumed cause of death as no biopsy was performed

There was disagreement between the FDA reviewer and study investigators for two of the causes of death, and narratives for these subjects are provided below. For Subject #10510032, lymphoma was included by the FDA reviewer for the cause of death as it appeared to be the underlying cause for septic shock. For Subject #12160009, the FDA reviewer concluded that the

cause of death was unknown as no worsening of respiratory symptoms was observed to support chronic obstructive pulmonary disease (COPD) as the cause.

Subject #10510032

FDA Reviewer Assessment: Lymphoma, septic shock

Investigator Assessment: Septic shock

This 57-year-old man with HIV infection received MVC once daily ~~for a total of 79 days~~ for a total of 79 days. On Days 47 and 56, his ultrasound and CT scans revealed lymphadenopathy. On Day 75, his biopsy report revealed non-Hodgkin's lymphoma and he was hospitalized for therapy on the same day. On Day 79, he experienced septic shock and MVC was permanently discontinued. On Post-Therapy Day 2, he died with the cause of death reported as septic shock. Illnesses present at the onset of the lymphoma and septic shock and other relevant medical history included hepatitis B, myocardial infarction, peripheral neuropathy, and dyslipidemia. Concomitant therapy taken within 2 weeks before the onset of lymphoma included fosamprenavir, ritonavir, zidovudine, atorvastatin, lisinopril, metoprolol, omeprazole, acetylsalicylic acid, dopamine and levofloxacin. In the opinion of the investigator, septic shock was probably due to lymphoma, and both lymphoma and septic shock were considered not related to MVC.

Subject #12160009

FDA Reviewer Assessment: Cause of death unknown

Investigator Assessment: Worsening COPD

This 45-year-old man with HIV infection received MVC twice daily ~~for a total of 35 days~~ for a total of 35 days. On Post-Therapy Day 3, he was reported to have been found dead, slumped over a chair in the kitchen. He had a history of near end-stage chronic obstructive pulmonary disease (COPD), which was reported to be the cause of death. Prior to this event, he was tolerating his anti-retrovirals, including study medications without problems. Two days prior to the reported death, he missed his visit to the clinic and was called by the clinic with no response. MVC continued unchanged until the time of his death. The death was reported to be on Day 35. No autopsy was performed. Other medical history included panic attacks and depression. Concomitant therapy taken within 2 weeks of his death included valproate, lorazepam, escitalopram, salbutamol, fluticasone, salmeterol, tiotropium, enfuvirtide, tenofovir, emtricitabine and lopinavir/ritonavir. In the opinion of the investigator, the death was due to worsening of COPD secondary to tobacco abuse, and was not related to MVC.

7.1.2 Other Serious Adverse Events

A total of 56, 70, and 36 subjects reported at least one SAE during the double-blind period of Studies 1027 and 1028 in the MVC QD, MVC BID, and placebo arms, respectively. Please see Section 7.1.3 for detailed discussions regarding AEs of potential concern for CCR5 co-receptor antagonists in general as well as those specific to MVC.

7.1.3 Dropouts and Other Significant Adverse Events

A total of 414 subjects permanently discontinued their participation during Studies 1027 and 1028. The majority of these were due to lack of efficacy (81 [20%], 91 [21%], and 106 [51%] in the MVC QD, MVC BID, and placebo arms, respectively). A much smaller proportion of subjects discontinued due to an AE, and no increase in such discontinuations was observed in the MVC arms (16 [4%], 16 [4%], and 8 [4%] in the MVC QD, MVC BID, and placebo arms, respectively). There were several types of AEs of particular concern in light of the mechanism

of action of MVC, pre-clinical data for MVC, or previous experience with other CCR5 receptor antagonists. Each of these categories is considered in detail in this section.

Malignancy

The following MedDRA preferred terms were pooled during a search of the MVC adverse event database:

- Lymphoma (*B-cell lymphoma, Central nervous system lymphoma, Diffuse large B-cell lymphoma, Lymphoma*)
- Solid tumor malignancies (*Basal cell carcinoma, Anal cancer, Squamous cell carcinoma, Squamous cell carcinoma of skin, Kaposi's sarcoma, Metastases to liver, Esophageal carcinoma, Skin cancer, Tongue neoplasm malignant stage unspecified, Bowen's disease*)
- Tumors (*Neoplasm, Neoplasm skin, Abdominal neoplasm, Benign neoplasm of orbit, Benign esophageal neoplasm, Conjunctival neoplasm, Upper extremity mass, Testicular neoplasm, Vocal cord polyp, Skin papilloma, Hemangioma, Hemangioma of liver, Lung neoplasm, Skin lesion, Skin nodule, Lipoma, Sweat gland tumor*)

All lymphomas reported during the double-blind and open-label periods of Studies 1027 and 1028 were assessed (Table 20). In light of the approximately twice as many subjects in both the MVC QD and MVC BID arms in comparison with the placebo group, there was no increased frequency of lymphoma observed in association with MVC.

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FDA Table 20: All Lymphomas by Treatment Group
 (Studies 1027 and 1028 Combined, As Treated Analysis)

Subject #	Treatment	AE	Period	Baseline CD4	Outcome	Days From First Dose of MVC to AE
A4001027 10170010	MVC QD	Large B-cell lymphoma	Double-blind	45	Recovered	50
A4001028 10510032	MVC QD	Non-Hodgkin's lymphoma	Double-blind	85	Died from other causes	26
A4001028 10040009	MVC BID	B-cell lymphoma	Double-blind	26	Not Recovered	0
A4001027 10210001	Placebo	Lymphoma	Double-blind	164	Not Recovered	N/A
A4001027 11190008	Placebo	Large B-cell lymphoma	Double-blind	214	Not Recovered	N/A
A4001027 10210002	Placebo ¹	B-cell lymphoma	Open-label	167	Died due to this AE	145
A4001028 12050011	MVC BID	Central nervous system lymphoma ²	Open-label	3	Died due to this AE	101

¹ Received placebo during the double-blind period, but subsequently received MVC during the open-label period prior to malignancy diagnosis

² Presumed diagnosis as no biopsy was performed

There were 26 non-hematological malignancies during the double-blind period of Studies 1027 and 1028 (Table 21). The most common were **anal cancer (9), Kaposi's sarcoma (6), and squamous cell carcinoma (4)**. The malignancies occurred in 10, 9, and 7 of the MVC QD, MVC BID, and placebo subjects. Therefore, in light of the randomization scheme there was no evidence of an increase in non-hematological malignancies with MVC use.

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FDA Table 21: Non-Hematological Malignancies During the Double-Blind Period
 (Studies 1027 and 1028 Combined, As Treated Population)

Malignancy	Numbers of Subjects with an AE*		
	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
Anal cancer	3	3	3
Kaposi's sarcoma	1	2	3
Squamous cell carcinoma	3	1	1
Basal cell carcinoma	1	1	0
Esophageal carcinoma	1	0	0
Liver metastases	1	0	0
Skin cancer	0	1	0
Bowen's disease	0	1	0
TOTAL	10	9	7

* A subject could have more than one type of adverse event.

Hepatotoxicity

An assessment for hepatotoxicity was performed due to the observation of significant liver toxicity in association with a different CCR5 co-receptor antagonist, aplaviroc. The following MedDRA preferred terms were pooled in this analysis: *Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood bilirubin increased, Blood bilirubin, Gamma-glutamyltransferase increased, Gamma-glutamyltransferase, Hepatic failure, Hepatomegaly, Hepatosplenomegaly, Hyperbilirubinemia, Jaundice, Liver function test abnormal, Hepatic enzyme increased, Transaminases increased, and Ocular icterus.*

There were a total of 128 hepatic AEs reported during the double-blind period of Studies 1027 and 1028 (Table 22). Within the MVC QD arm, 30 subjects experienced 53 AEs. Of these AEs, 31 (58%) were considered Grade 3/4, and 2 (4%) were SAEs. Within the MVC BID arm, a total of 39 subjects experienced 61 AEs. Of these AEs, 39 (64%) were considered Grade 3/4, and 9 (15%) were SAEs. Within the placebo arm, 13 subjects experienced 14 AEs. Of these AEs, 11 (79%) were considered Grade 3/4, and 2 (14%) were SAEs. Even after accounting for the increased number of subjects and duration of observation in the MVC arms, there appears to be a modest increase in the number of hepatic AEs with MVC compared to placebo. However, the proportion of subjects who experienced at least one hepatic AE during the studies was similar across treatment arms (7%, 9%, and 6% for MVC QD, MVC BID, and placebo, respectively). Of note, the majority of hepatic AEs involved liver enzyme elevation (58%) or increased bilirubin (30%).

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FDA Table 22: Liver-Related AEs During the Double-Blind Period
(Studies 1027 and 1028 Combined, As Treated Population)

	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)	Placebo Time-Adjusted (Placebo x 2.6)
Subjects	30 (7%)	39 (9%)	13 (6%)	34
Total AEs	53	61	14	36
Grade 3/4	31	39	11	29
SAE	2	9	2	5

There were 85 hepatic AEs in 56 subjects with evidence of prior or current infection with hepatitis B or C (17 MVC QD, 28 MVC BID, 11 placebo). After accounting for the randomization scheme, no increase in hepatic AEs was observed with MVC in subjects with viral hepatitis. However, the finding is uncertain due to the small number of subjects.

In addition, an analysis was conducted in subjects who reported alcohol consumption at baseline. There were 30/197 (15%) hepatic AEs in the MVC QD arm, 39/207 (19%) in the MVC BID arm, and 13/99 (13%) in the placebo arm. After adjusting for the difference in total time of observation, there did not appear to be an increase in hepatic AEs in association with MVC in this group compared to placebo. However, once again the number of subjects was small making the finding uncertain.

An analysis was performed to assess all subjects who met “Hy’s Law” during Studies 1027 and 1028. In 1978, Hyman Zimmerman first made the observation that a combination of hepatocellular injury and jaundice caused by a drug led to death from acute liver failure in 10-50% of patients.³ Due to advances in transplantation, this definition was subsequently revised to include liver transplantation or death. The definition excludes episodes of hepatotoxicity where a non-drug cause is implicated. For the purposes of this review, “Hy’s Law” was defined as having an AST or ALT greater than 3 times the upper limit of normal (ULN) in combination with a total bilirubin greater than 2 times ULN, in the absence of an alternative explanation for the liver toxicity.

A total of 8, 8, and 2 subjects met the liver enzyme and bilirubin criteria for Hy’s Law in the MVC QD, MVC BID, and placebo arms, respectively. After adjusting for differences in subject number and time of observation between the MVC and placebo arms, these results do not provide any clear evidence of an increase with MVC, particularly in light of the small number of events. Adjustment of the placebo arm for differences in subject number and observation time results in a total of 5.2 events, compared with the 8 events in both MVC arms. However, no Hy’s Law cases were observed in Studies 1027 and 1028 as all of the subjects who met the criteria based on liver enzyme and bilirubin levels had other reasons for hepatotoxicity, such as the presence of viral hepatitis or alcohol abuse. Many of the subjects who met the bilirubin

³ Zimmerman HJ. Hepatotoxicity. The Adverse Effects of Drugs and Other Chemicals on the Liver. 1st ed. New York: Appleton-Century-Crofts, 1978. Chapter 16: Drug-induced liver disease.

criteria had an indirect hyperbilirubinemia secondary to atazanavir. It should be noted that the study population overall was medically complicated, with a substantial proportion having AST or ALT elevation prior to receiving study agent (246 [59%], 258 [61%], and 124 [59%] in the MVC QD, MVC BID, and placebo arms, respectively).

The following case summary is for a subject who required liver transplantation following use of MVC during the treatment-naïve HIV trial (Study 1026). As was true of all of the significant hepatic adverse events during the phase 2b/3 program, she had alternative explanations for her liver disease and in fact had evidence of worsening liver inflammation at the time of starting MVC.

Subject #10650005

The subject is a 24-year-old woman, diagnosed with HIV _____, who was enrolled in Study 1026 for treatment-naïve individuals. She had started trimethoprim-sulfamethoxazole and isoniazid approximately 7 weeks prior to starting MVC 150 mg daily, and was noted to have antibodies to hepatitis C virus at screening, but with undetectable HCV RNA. She developed a pruritic rash 4 days after starting on MVC and zidovudine/lamivudine. The next day she presented to medical attention with dizziness and high fever (40.4°C), in addition to a continued pruritic rash. MVC was stopped at this time (received a total of 5 doses), but zidovudine/lamivudine, isoniazid, and trimethoprim/sulfamethoxazole were continued for several more days and lopinavir/ritonavir was started. A dermatology consultant noted a pronounced maculopapular rash over the thorax, back, arms and face, but without mucosal involvement. She declined to be hospitalized, and was treated with cetirizine, betamethasone cream, and paracetamol. Later the same day, she developed additional symptoms including rigors and loss of appetite, and was hospitalized. At the time of admission, she had an AST of 924 U/L, ALT of 1103 U/L, and normal bilirubin. Her IgE level was 2420 kU/L (ULN 100 kU/L). Her liver enzymes increased steadily, and peaked with an AST of 2452 U/L on Day 10 and ALT of 3167 U/L on Day 13. Her total bilirubin peaked at 31 mg/dL on Day 14. Her liver biopsy revealed severe acute toxic hepatitis characterized by hepatocellular and bile canalicular damage. Of note, during the 7 weeks prior to receiving MVC, her ALT had risen from 19 to 102 U/L, and AST had risen from 36 to 79 U/L. Bilirubin level had been normal at baseline. Due to progressive hepatic decompensation with worsening coagulopathy, she underwent a liver transplant on Day 16. She subsequently did well following transplant and was discharged from the hospital approximately 4 weeks later. Further assessment revealed that she possessed the NAT2 alleles associated with a slow acetylation phenotype and increased risk of isoniazid induced hepatitis, and a CYP2E1 genotype that has also been associated with an increased susceptibility to hepatotoxicity in slow acetylators.

The following additional case summary is of an hepatic SAE that met Hy's Law following MVC exposure during a healthy volunteer trial (Study 1066). This event occurred late in the review of this application (June 2007), and is included due to its clinical importance and the absence of identifiable alternative explanations other than MVC for hepatotoxicity. Due to the presence of eosinophilia, increased IgE, and rash, the etiology of hepatotoxicity appears to have been allergic in nature. Based primarily on this most recent report in a healthy volunteer, MVC should be considered potentially hepatotoxic and a Black Box Warning is recommended.

Subject #34

The subject is a 27-year-old healthy volunteer Caucasian woman who enrolled in a trial in Brussels entitled, "A Double Blind (3rd Party Open), Placebo Controlled, Randomized Study to Investigate the Safety and Tolerantion of Maraviroc 600 mg QD Both Fed and Fasted for a Total of 28 Days in Healthy Subjects." On Day 14 of MVC dosing, the eosinophil percentage increased from 1.1% at screening to 5.1%. Her liver

enzymes were normal at that time. She complained of flu-like symptoms and postural dizziness, and was noted to have submaxillary and cervical adenopathy. The next day, she had dizziness 1 hour following the MVC dose, and shivering, pruritus, and a feeling of weakness 2 hours after the dose. She continued to have similar symptoms during the next 2 days, but on Day 17 of dosing reported feeling better than the previous 2 days. Approximately 3.5 hours following dosing on Day 17 she developed rhinitis, nasal congestion, and symptomatic orthostatic hypotension by report. At that time she had mild thrombocytopenia (144,000/mm³, decreased from 199,000/mm³ at screening), CRP 2.3 mg/dL, AST 79 U/L, ALT 81 U/L, total bilirubin 1.6 mg/dL, and total IgE 259 kU/L (ULN 120 kU/L). A rash was noted on her chest. She subsequently felt well on Day 18, and received another dose of MVC. Three hours following this dose, she again developed shivering, facial pruritus, vomiting, and a feeling of weakness and dizziness (unable to stand). Later that day she developed an urticarial-like rash on her arms, chest, and legs. At this time, she had 8.6% eosinophils, persistent mild thrombocytopenia, CRP 3.8 mg/dL, AST 104 U/L, ALT 95 U/L, and a total bilirubin of 2.3 mg/dL. The clotting time was 27 seconds, PTT 66%, and INR 1.22 (ULN 1.15). By report, a gastroenterology consult felt that her presentation was consistent with drug-induced hepatitis. Dosing was discontinued at that time. One day following MVC discontinuation, she had some abdominal discomfort and episodes of feeling weak. Her eosinophil percentage increased to 10.5%, and AST and ALT increased to 238 and 195 U/L, respectively. Two days following dose discontinuation, she had an episode of emesis and some abdominal discomfort. Her AST was 504 U/L, ALT 393 U/L, and total bilirubin 1.5 mg/dL. Three days following MVC discontinuation, the subject was felt to be improving and had the following laboratory results: CRP was 0.8 mg/dL, AST 342 U/L, ALT 411 U/L, total bilirubin 1.1 mg/dL, and INR 1.05. An abdominal ultrasound was normal. An extensive evaluation for infectious or autoimmune cause for this event has been negative so far. Of note, she had a sore throat 2 days prior to starting MVC, but this resolved 12 days prior to her subsequent flu-like illness on Day 14 of MVC administration. In addition, she had come back from a one week trip to Turkey 16 days prior to starting MVC.

Infection

There were a total of 897 infection-related AEs during the double-blind period of Studies 1027 and 1028. Of these, 43%, 41%, and 16% occurred in the MVC QD, MVC BID, and placebo arms, respectively. It should be noted that there was a longer duration of follow-up per subject within the double-blind period in the MVC arms compared to placebo. Therefore, instead of the anticipated 2:1 difference in monitored time that might have been expected based on the randomization scheme, there was an approximately 2.6:1 difference in monitored time. When this is taken into account, there is no overall difference between the MVC and placebo arms with respect to infection-related AEs.

An additional analysis of all Grade 3/4 infection-related AEs during the double-blind period was performed. Of the 75 such AEs, 30 (40%), 27 (36%), and 18 (24%) occurred in the MVC QD, MVC BID, and placebo arms, respectively. Of the 69 infection-related SAEs that occurred during the double-blind period, 23 (33%), 28 (41%), and 18 (26%) occurred in the MVC QD, MVC BID, and placebo arms, respectively. In light of the increased number of subjects and observation time in the MVC arms, there is no evidence of an increased proportion of infection-related Grade 3/4 AEs or SAEs in association with MVC.

The most common infection-related AEs during the double-blind period are presented in Table 23. After adjusting the placebo arm for differences in subject number and observation time, there was an excess of influenza and influenza-like illnesses as well as herpes infections in the MVC arms. An increase in Candida infections was observed in the MVC QD arm only.

FDA Table 23: Most Common Infection-Related AEs During the Double-Blind Period by Treatment Group (Studies 1027 and 1028 Combined, As Treated Population)

Infectious AEs	Numbers of AEs			
	MVC QD	MVC BID	Placebo	Time-Adjusted Placebo (Placebo x 2.6)
Upper respiratory tract infection ¹	142	131	50	130
Candida infection ²	41	18	11	29
Herpes simplex infection ³	25	32	8	21
Influenza ⁴	19	7	1	3

¹ Also includes the terms Bronchitis, Bronchitis acute, Bronchitis bacterial, Laryngopharyngitis, Nasopharyngitis, Laryngitis, Pharyngitis, Respiratory tract infection, Viral upper respiratory tract infection, Rhinitis, Sinusitis, Acute sinusitis, and Sinobronchitis

² Also includes the terms Candidiasis, Oral fungal infection, Oropharyngeal candidiasis, Pharyngeal candidiasis, Oesophageal candidiasis, Worsening of candidiasis, Vaginal candidiasis, Balanitis Candida

³ Includes the term Herpes virus infection

⁴ Includes the term Influenza-like illness

The distribution of herpes AEs is provided in Table 24. Most commonly, no location of the herpes AE was reported. When a location was provided, anal/rectal and labial were the most common. An adjustment for differences in subject number and observation time is provided to allow direct comparison of the placebo arm with the MVC arms. However, dividing the AEs by location decreases the power to detect differences by treatment arm, and no firm conclusions can be reached regarding an association of MVC with a specific herpes AE location.

FDA Table 24: Herpes AEs During the Double-Blind Period (Studies 1027 and 1028 Combined, As Treated Population)

Adverse Event	Numbers of Subjects with an AE*			
	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)	Time-Adjusted Placebo (Placebo x 2.6)
Herpes simplex	10	8	2	5
Herpes virus	3	2	2	5
Anal/rectal herpes	3	8	1	3
Labial herpes	3	8	0	0
Oral herpes	0	3	0	0
Genital herpes	1	2	3	8
TOTAL	20	31	8	21

* A subject could have more than one type of adverse event.

The distribution of types of Candidal AEs is provided in Table 25. The most commonly reported locations were oral and esophageal. An adjustment for differences in subject number and observation time is provided to allow direct comparison of the placebo arm with the MVC arms. However, dividing the Candidal AEs by location decreases the power to detect differences by treatment arm, and no firm conclusions can be reached regarding an association of MVC with a specific Candidal AE location.

FDA Table 25: Candidiasis AEs During the Double-Blind Period*
 (Studies 1027 and 1028 Combined, As Treated Population)

Adverse Event	Numbers of Subjects with an AE			
	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)	Time-Adjusted Placebo (Placebo x 2.6)
Oral candidiasis	16	13	8	21
Oesophageal candidiasis	12	2	2	5
Oropharyngeal candidiasis	2	0	1	3
Pharyngeal candidiasis	1	0	0	0
Vaginal candidiasis	2	0	0	0
Worsening candidiasis	1	0	0	0
Candidiasis	1	2	0	0
Balanitis candida	1	0	0	0
Nail candida	0	1	0	0
TOTAL	36	18	11	29

* A subject could have more than one type of adverse event.

Pneumonia, sepsis, and abscess formation were analyzed due to their clinical significance. There were a total of 42 AEs of pneumonia, of which 18 (43%), 11 (26%), and 13 (31%) occurred in the MVC QD, MVC BID, and placebo arms. Two cases of *Pneumocystis jiroveci* pneumonia, both of which occurred in association with MVC BID, were excluded due to differences in pathophysiology from bacterial pneumonia. However, inclusion of these cases would not have altered the overall findings. With respect to sepsis or bacteremia, there were a total of 6 AEs: 2, 3, and 1 in the MVC QD, MVC BID, and placebo arms, respectively. Finally, with respect to abscess formation, there were a total of 27 AEs: 11, 7, and 9 in the MVC QD, MVC BID, and placebo arms, respectively. In light of the total duration of observation for the treatment groups, there was no evidence of an excess of pneumonia, sepsis, or abscess formation in association with MVC.

Category C Events

A total of 80 Category C AEs occurred in 66 subjects following administration of study agent during Studies 1027 and 1028. Of these, 66 events occurred during the double-blind period and 14 occurred during the open-label period. During the double-blind period, there were 31, 19, and 16 AEs in the MVC QD, MVC BID, and placebo arms (Table 26). After adjusting the placebo

arm for differences in subject number and observation time, no overall increase in Category C events was observed with MVC.

FDA Table 26: Category C AEs During the Double-Blind Period by Treatment Group (Studies 1027 and 1028 Combined, As Treated Population)

Category C AEs	Numbers of AEs			
	MVC QD	MVC BID	Placebo	Time-Adjusted Placebo (Placebo x 2.6)
Candidiasis	14	3	2	5
Herpes virus infection	11	6	2	5
Kaposi's sarcoma	1	2	3	8
Lymphoma	2	1	2	5
Cytomegalovirus infection	2	2	0	0
MAC	0	1	3	8
Pneumonia	1	0	3	8
Pneumocystis jiroveci pneumonia	0	2	0	0
Cryptosporidial gastroenteritis	0	0	1	3
PML	0	1	0	0
Mycobacterial infection	0	1	0	0
TOTAL	31	19	16	42

There appeared to be an increase in candidiasis and herpes virus infection Category C events associated with MVC based on the results in Table 26. Therefore, additional analyses were performed for these types of events. With respect to Category C herpes virus infections, a total of 16 MVC subjects (10 MVC QD, 6 MVC BID) had 17 herpes virus AEs. One was considered a Grade 3 event, and 2 were considered SAEs. Nine had experienced a Category C event prior to enrollment, and the median baseline CD4 count was 144 cells/mL. The median time from beginning MVC to experiencing a candidiasis Category C event was 86 days. The 2 placebo subjects who experienced a Category C candidiasis event had baseline CD4 counts of 13 and 77 cells/ μ L, and 1 had experienced a Category C event prior to enrollment. One of the events was considered an SAE, although neither was considered Grade 3 or 4 in severity. There were no open-label herpes virus AEs considered Category C. Based on the imbalance of events between the MVC and placebo arms, it is possible that MVC use may be associated with an increase in herpes virus infections.

With respect to candidiasis, a total of 15 MVC subjects (13 MVC QD, 2 MVC BID) had 17 candidiasis AEs that were classified as Category C. Four of these events were considered Grade 3 or 4, and 2 were considered SAEs. All but one of these subjects had experienced a Category C event prior to enrollment, and their median baseline CD4 count was 35 cells/ μ L. The median time from beginning MVC to a candidiasis Category C event was 56 days. Both of the placebo subjects who had a candidiasis Category C event had previous Category C events prior to

enrollment, and their CD4 counts were 4 and 103 at baseline. One of the events was considered Grade 3 as well as an SAE.

Category C candidiasis events during the open-label period were also considered. Interpretation of these AEs is complicated as such subjects are in this period due to either virologic failure or an adverse event considered significant enough to end double-blind participation. A total of 6 subjects experienced 6 candidiasis AEs during the open-label period, of whom two had previously received MVC at any time before the event. Therefore, there was insufficient data from the open-label period to allow substantive interpretation.

Based on the imbalance of events between the MVC and placebo arms, it is possible that MVC may be associated with an increase in candidiasis. However, it should be noted that the imbalance was only in the lower dose MVC arm.

Influenza

An increase in cases of influenza was observed in the MVC arms during Studies 1027 and 1028. There were 18 subjects with at least one episode of influenza in the MVC QD arm, 7 in the MVC BID arm, and 1 with placebo. As the lower dose of MVC was associated with a higher incidence of influenza, the results are somewhat less convincing than they would be in the presence of a dose response. However, taken as a whole there was a considerably higher rate of influenza in the MVC arms, and the increase remained even after adjustment for the differences in subject number and observation time.

Upper Respiratory Tract Infections

Multiple MedDRA preferred terms consistent with upper respiratory infection were pooled in order to increase the power of detecting a potential increase in association with MVC (see footnote 1 of Table 23 for the terms that were pooled). When this was done, there were 130 (31%) subjects in the MVC QD arm, 149 (35%) in the MVC BID arm, and 43 (21%) in the placebo arm who experienced at least one upper respiratory tract infection. Even after adjustment for the differences in subject number and time of observation, an increase in the MVC arms over placebo was observed.

Hypotension

An assessment of hypotensive AEs was performed as postural hypotension was the dose-limiting AE during phase 1 investigations of MVC. The MedDRA preferred terms included in this analysis were the following: *Dizziness, Dizziness postural, Hypotension, Orthostatic hypotension, and Syncope.*

There were 117 hypotensive AEs during the double-blind period in 109 subjects (51 [12%] MVC QD, 39 [9%] MVC BID, and 19 [9%] placebo). In light of the randomization scheme and longer duration of observation in the MVC arms, there was no imbalance with respect to hypotensive

AEs. Of note, hypotension was observed in the phase I studies at significantly higher doses (1200 mg daily) than was given during the phase 2b/3 studies.

Immunologic Reactions

While there were no AEs in Studies 1027 or 1028 with the MedDRA preferred terms *Stevens-Johnson Syndrome* or *toxic epidermal necrolysis*, two episodes of severe hepatotoxicity which were potentially immunologically mediated were reported in other trials of MVC and are presented in the Hepatotoxicity section of this review (see Section 7.1.3). Additionally, there was one episode of Stevens-Johnson Syndrome reported in a subject receiving MVC 300 mg once daily during Study 1026. It is possible that MVC contributed to the event, although the subject had received other medications capable of causing this AE as well. The following is a narrative of the AE:

Subject #1065006

This is a 35-year-old woman with HIV infection who received MVC and zidovudine/lamivudine during Study 1026. She received MVC from October 28, 2005, to December 21, 2005 (150 mg daily for the first 45 days, followed by MVC at a total daily dose of 300 mg for an additional 10 days). Zidovudine/lamivudine was administered at a total daily dose of 600/300 mg over the same time period as MVC. She had received trimethoprim/sulfamethoxazole since September 23, 2005, for *Pneumocystis jirovecii* pneumonia prophylaxis, which was changed to dapsone November 14, 2005. At that time, cetirizine was also started. [REDACTED], she presented with mouth pain, swollen lips and complaints of vaginal discharge [REDACTED] she was hospitalized with severe swollen lips, stomatitis, red swollen vulva, tremor and loss of appetite, and was diagnosed with Stevens-Johnson Syndrome. Her skin biopsy revealed variable thickness of the epidermis which was covered with lamellar orthokeratotic cornification with some focal parakeratosis, a clear basal pigmentation, basal vacuolary alteration and infiltration by inflammatory cells, focal epidermal necrosis, superficial plexus of vessels surrounded by inflammatory cell infiltrate, and occasional neutrophils without any remarkable lesions in the deeper stroma. These biopsy results were compatible with the diagnosis of erythema exudativum multiforme. In response to the event, MVC and zidovudine/lamivudine treatments were permanently discontinued. [REDACTED] she was considered recovered from the event and was discharged from the hospital.

Cardiovascular Events

An assessment of cardiovascular AEs was performed due to their clinical importance, as well as the concern that hypotension induced by MVC might predispose individuals to ischemic events. The MedDRA preferred terms pooled in this analysis were the following: *Acute myocardial infarction, Angina pectoris, Angina unstable, Arterial occlusive disease, Coronary artery disease, Coronary artery occlusion, Myocardial infarction, Myocardial ischemia, and Prinzmetal angina.*

There were 14 cardiovascular AEs during the double-blind period in 11 subjects, all of which occurred in the MVC arms (6 MVC QD and 8 MVC BID) (Table 27). No additional cardiovascular AEs were reported during the open-label period. As the AEs occurred only with MVC, and to a similar degree in the QD and BID arms, the finding is concerning.

As all but two of the subjects had reported cardiac disease or important risk factors for cardiac disease at baseline, an additional analysis was performed to assess whether there was an imbalance by treatment group at baseline with respect to cardiovascular disease. When the medical history information was analyzed by MedDRA system organ class, there were 122 cardiovascular disorders in 95 subjects (40 [10%] MVC QD, 40 [9%] MVC BID, and 15 [7%] placebo). An additional analysis of the medical history data was performed to assess terms more directly relevant to cardiovascular ischemic events by pooling the following MedDRA preferred terms: *Acute myocardial infarction, Angina pectoris, Arteriosclerosis coronary artery, Coronary artery disease, Myocardial infarction, and Myocardial ischemia*. Using these, 57 medical history terms were identified in 45 subjects (21 [5%] MVC QD, 17 [4%] MVC BID, and 7 [3%] placebo). Therefore, there is a slight increase at baseline in the MVC arms with respect to cardiovascular disorders overall as well as cardiovascular ischemic disorders more specifically. However, this slight increase does not completely explain the degree of imbalance observed in cardiovascular events.

As postural hypotension was the dose-limiting event observed during phase 1 studies of MVC, this raised the concern that the cardiovascular AEs observed in the MVC arms of Studies 1027 and 1028 might be due to an interaction between MVC and a phosphodiesterase type 5 (PDE5) inhibitor such as sildenafil citrate. However, none of the subjects with cardiovascular AEs had received that class of medication during the trials.

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FDA Table 27: Cardiovascular AEs During Double-Blind Period¹
 (Studies 1027 and 1028 Combined, As Treated Population)

Subject ID	Treatment Group	Age	Gender	Relevant Medical History	Adverse Event	Days From Starting MVC to Event
10670024	MVC QD	54	Male	MI ² , coronary artery stent placement	Angina pectoris	144
10420011	MVC QD	54	Male	None	Angina pectoris	171
10260013	MVC QD	53	Male	HTN ³ , hyperlipidemia	Coronary artery disease	137
10510030	MVC QD	52	Male	MI	Coronary artery occlusion	98
10610009	MVC QD	48	Male	None	MI	285
10110002	MVC QD	43	Male	HTN, DM ⁴ , sleep apnea, obesity, hyperlipidemia	Acute MI	246
10440002	MVC QD	70	Male	Arteriosclerosis	Coronary artery disease	150
					Coronary artery occlusion	149
11170002	MVC BID	52	Female	Hyperlipidemia, DM	Angina pectoris	224
					Angina unstable	162
					Myocardial ischaemia	91
10690035	MVC BID	49	Male	Coronary artery stent placement	Arterial occlusive disease	106
11140020	MVC BID	54	Male	Hyperlipidemia, HTN	Myocardial ischaemia	263
11010018	MVC BID	43	Male	MI, coronary angioplasty	Prinzmetal angina	153

¹ A subject could have more than one type of adverse event.

² Myocardial infarction

³ Hypertension

⁴ Diabetes mellitus

Thrombotic Events

Due to the possible association of cardiovascular events with MVC, an additional analysis was performed with respect to AEs consistent with thrombotic events. The MedDRA preferred terms pooled in this analysis were the following: *Acute myocardial infarction, Angina pectoris, Angina unstable, Antiphospholipid syndrome, Arterial occlusive disease, Cavernous sinus thrombosis, Cerebral infarction, Coronary artery disease, Coronary artery occlusion, Iliac artery stenosis, Intermittent claudication, Mesenteric artery stenosis, Myocardial ischemia, Peripheral*

embolism, Portal vein thrombosis, Pulmonary embolism, Thrombophlebitis, Transient ischemic attack, and Venous thrombosis.

There were 27 AEs consistent with thrombosis during the double-blind period in 22 subjects (10 MVC QD, 7 MVC BID, and 5 placebo) (Table 28). One additional thrombotic event of cerebral infarction occurred during the open-label period in a subject who was previously on placebo but started on MVC 37 days prior to the AE. In light of the randomization scheme, there was no evidence of an increase in thrombotic events in association with MVC.

FDA Table 28: Thrombotic AEs During the Double-Blind Period*
 (Studies 1027 and 1028 Combined, As Treated Population)

Adverse Event	Numbers of Subjects with an AE		
	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
Transient ischemic attack	0	0	3
Angina pectoris	2	1	0
Unstable angina	1	1	0
Myocardial ischemia	0	2	0
Myocardial infarction	2	0	0
Coronary artery disease	3	1	0
Antiphospholipid syndrome	1	0	0
Mesenteric artery thrombosis	0	0	1
Peripheral embolism	0	1	0
Portal vein thrombosis	0	1	0
Pulmonary embolism	0	1	0
Venous thrombosis	0	1	0
Thrombophlebitis	0	0	1
Cavernous sinus thrombosis	1	0	0
Iliac artery stenosis	0	0	1
Intermittent claudication	1	0	0
TOTAL	11	9	6

* A subject could have more than one type of adverse event.

Cerebrovascular Events

An assessment of cerebrovascular AEs was performed due to their clinical importance, and the concern that hypotension induced by MVC might predispose individuals to ischemic events. The MedDRA preferred terms pooled in this analysis were the following: *Cerebrovascular haemorrhage, Cerebrovascular accident, and Transient ischaemic attack.*

There were 6 cerebrovascular AEs during the double-blind period in 6 subjects (2 MVC QD, 1 MVC BID, and 3 placebo). Therefore, there was no evidence of an increase in cerebrovascular AEs in association with MVC.

QT Prolongation

An assessment of ventricular arrhythmias was performed due to the finding of QT prolongation during the phase I studies of MVC, and the potential for QT prolongation observed during preclinical testing. In addition, a previous CCR5 antagonist (“Schering C”) was found to cause QT prolongation. The MedDRA preferred terms pooled in this analysis were the following: *Arrhythmia, Palpitations, Syncope and Tachycardia*. Bradyarrhythmias and supraventricular tachyarrhythmias were excluded.

There were 16 AEs potentially related to a ventricular arrhythmia during the double-blind period reported in 14 subjects (4 [1.0%] MVC QD, 7 [1.6%] MVC BID, and 3 [1.4%] placebo). Therefore, there was no evidence of an increase in AEs potentially related to ventricular arrhythmias with MVC.

Please see Section 7.1.9 for the results of the Thorough QT study.

Thyroid Disease

An assessment of thyroid AEs was performed due to the finding of thyroid follicular cell hypertrophy during a 6-month rat study, which was shown to be reversible when MVC was withdrawn. The MedDRA preferred terms pooled in this analysis were the following: *Basedow’s disease, Blood thyroid stimulating hormone increased, Hypothyroidism, and Thyroxine free decreased*.

There were 9 thyroid AEs during the double-blind period in 8 subjects (4 MVC QD, 1 MVC BID, and 3 placebo). The AEs were all related to hypothyroidism except for one case of worsening Graves disease in a subject in the MVC QD arm. There was no evidence of an increase in thyroid AEs in association with MVC.

Renal Disease

Due to a modest increase in creatinine observed in a small number of subjects who received MVC in a phase I study, an assessment of AEs related to renal function was performed. The MedDRA preferred terms pooled in this analysis were the following: *Blood creatinine increased, Renal failure, Renal failure acute, and Renal impairment*.

There were 32 renal AEs during the double-blind period in 26 subjects (9 MVC QD, 12 MVC BID, and 5 placebo). In light of the randomization scheme, there was no evidence of an increase in renal AEs in association with MVC. An additional analysis was performed to assess all Grade 3/4 renal AEs or AEs with the MedDRA preferred term of *Renal failure* or *Renal failure acute*. There were 14 such events in 13 subjects (4 MVC QD, 6 MVC BID, and 3 placebo). In light of the randomization scheme, there was no evidence of an increase in severe renal AEs in association with MVC.

Myositis

An assessment of myositis was performed as a modest increase in CPK levels was observed in the MVC arms during analysis of the laboratory results (see Section 7.1.7). The following MedDRA preferred terms were pooled in this analysis: *Blood creatine phosphokinase increased, Myositis, and Rhabdomyolysis*.

Using the above terms, there were 24 AEs identified during the double-blind period in 19 subjects (7 [1.7%] MVC QD, 11 [2.6%] MVC BID, and 1 [0.5%] placebo). All 4 AEs with the MedDRA preferred term *Rhabdomyolysis* were in the MVC arms (1 MVC QD, 3 MVC BID). However, review of the case narratives for these 4 subjects revealed that all had potential alternative explanations for CPK elevation. In addition, one subject had only mild CPK elevation despite being reported as having rhabdomyolysis, and CPK levels for the other subject were not significantly above the level noted at baseline. There were 12 Grade 3/4 AEs in 9 subjects (2 MVC QD, 6 MVC BID, and 1 placebo). During the open-label period, there was 1 additional AE of increased CPK in a subject who received placebo during the double-blind period but started on MVC 67 days prior to the AE. The modest overall increase of the pooled terms in the MVC arms was primarily due to laboratory reports of blood creatine phosphokinase being reported as an AE. When the more clinically relevant terms rhabdomyolysis and myositis were pooled, there were few events and no evidence of an increase with MVC.

7.1.4 Other Search Strategies

All search strategies conducted during the safety analyses of the Studies 1027 and 1028 are described in Section 7.1.3.

7.1.5 Common Adverse Events

AEs during Studies 1027 and 1028 were reported by MedDRA preferred term, and the most common are presented in Table 29. Some discrepancies compared with the AE numbers presented in Section 7.1.3 exist as no pooling of terms was used in Table 29, which presents all AEs reported at least 10 times within any of the treatment groups. They are provided by decreasing order of frequency in the MVC BID arm, as this is the dose regimen being sought for approval.

The most commonly reported AEs in the MVC BID arm were diarrhea, nausea, pyrexia and headache. These AEs were also among the most common in the other two treatment arms. While more rashes were reported in the MVC BID arm compared with placebo, an additional analysis of rashes suggestive of a drug-related etiology (maculopapular or diffuse in nature) showed no evidence of increase in the MVC BID arm. The MVC QD and placebo arms were well-matched with respect to reports of rash. Due to the increase in reports of dysuria in the MVC arms, an assessment using the pooled terms *urinary tract infection, cystitis, and pyelonephritis* was performed. This revealed 10, 5, and 3 subjects with any of these terms in the MVC QD, MVC BID, and placebo arms, respectively. After accounting for differences in subject number and time of observation, no increase in the MVC arms compared with placebo is

apparent. All other AEs of concern due to their clinical significance or increase in observed frequency with MVC are characterized in greater detail in Section 7.1.3.

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FDA Table 29: AEs Occurring ≥ 10 Times in Any Treatment Group During the Double-Blind Period (Studies 1027 and 1028 Combined, As Treated Analysis)

Adverse Event Preferred MedDRA Term	MVC QD	MVC BID	Placebo	Time-Adjusted Placebo (Placebo x 2.6)
Diarrhea	113	104	52	135
Nausea	84	80	44	114
Pyrexia	33	60	20	52
Headache	77	59	33	86
Fatigue	50	55	33	86
Upper respiratory tract infection	42	51	13	34
Cough	38	51	11	29
Rash	28	40	11	29
Dizziness	40	34	14	36
Vomiting	48	33	25	65
Nasopharyngitis	36	31	9	23
Injection site reaction	29	31	18	47
Sinusitis	16	30	9	23
Insomnia	23	29	9	23
Herpes simplex	21	29	6	16
Bronchitis	23	27	10	26
Constipation	21	24	6	16
Arthralgia	18	24	6	16
Abdominal pain	19	22	7	18
Back pain	22	21	6	16
Abdominal pain upper	22	17	7	18
AST increased	7	17	1	3
Anorexia	21	16	8	21
Flatulence	16	16	9	23
Night sweats	15	16	7	18
Pruritus	11	15	3	8
Decreased appetite	10	15	5	13
Myalgia	19	14	2	5
Depression	14	14	6	16
Anemia	11	14	6	16
Folliculitis	7	14	4	10
Weight decreased	17	13	4	10
Nasal congestion	10	13	5	13
Hypertension	9	13	4	10
Blood CPK increased	5	13	1	3
Asthenia	18	12	5	13
Hypoaesthesia	10	12	2	5
Anxiety	8	12	5	13
Dysgeusia	3	12	2	5
Edema peripheral	15	11	6	16
Abdominal distension	14	11	6	16

Dyspnea	13	11	2	5
Pain in extremity	12	11	5	13
Paresthesia	12	11	5	13
Dyspepsia	10	11	5	13
Dysuria	7	11	1	3
Oral candidiasis	17	10	7	18
Pharyngolaryngeal pain	17	10	6	16
Muscle spasms	13	10	9	23
ALT increased	10	10	1	3
Skin papilloma	11	9	3	8
Influenza	15	6	0	0
Pneumonia	12	6	7	18
Sleep disorder	10	6	3	8
Rhinitis	10	4	2	5
Esophageal candidiasis	13	2	2	5

7.1.6 Less Common Adverse Events

All AEs that were considered clinically important, appeared to occur with a greater frequency with MVC, or were of concern based on pre-clinical or prior clinical observation are considered in Section 7.1.3.

7.1.7 Laboratory Findings

Laboratory results pertinent to the concerns that have been raised during the clinical development of MVC, or that were observed to have a higher frequency of abnormalities in the MVC arms, are provided in this Section.

No increase in LFT or total bilirubin abnormalities was observed in the MVC arms compared to placebo during Studies 1027 and 1028 (Tables 30 and 31). In light of the prior finding of a modest increase in hepatic AEs with MVC (Section 7.1.3), these laboratory results are somewhat reassuring.

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FDA Table 30: AST/ALT Elevation¹ by Treatment Group During the Double-Blind Period
 (Studies 1027 and 1028 Combined, As Treated Population)

AST/ALT Level	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
> ULN ²	249 (60%)	269 (63%)	139 (67%)
> 3 x ULN	43 (10%)	56 (13%)	21 (10%)
> 5 x ULN	21 (5%)	21 (5%)	10 (5%)
> 10 x ULN	3 (1%)	6 (1%)	1 (<1%)

¹ Subjects with an elevation of either AST or ALT

² ULN = upper limit of normal

FDA Table 31: Total Bilirubin Elevation by Treatment Group During the Double-Blind Period
 (Studies 1027 and 1028 Combined, As Treated Population)

Total Bilirubin Level	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
> ULN ¹	99 (24%)	90 (21%)	50 (24%)
> 2 x ULN	46 (11%)	33 (8%)	20 (10%)
> 5 x ULN	4 (1%)	3 (1%)	3 (1%)
> 10 x ULN	0 (0%)	1 (<1%)	0 (0%)

¹ ULN = upper limit of normal

Due to an increase in creatinine observed in a small number of subjects who received MVC during a phase 1 study, creatinine levels for all subjects during Studies 1027 and 1028 were assessed (Table 32). No increase in creatinine levels was observed with MVC compared with placebo.

FDA Table 32: Creatinine Elevation by Treatment Group During the Double-Blind Period
 (Studies 1027 and 1028 Combined, As Treated Population)

Creatinine Level	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
> ULN ¹	86 (21%)	93 (22%)	33 (16%)
> 2 x ULN	4 (1%)	7 (2%)	2 (1%)
> 5 x ULN	1 (<1%)	1 (<1%) ²	0 (0%)
> 10 x ULN	0 (0%)	1 (<1%) ²	0 (0%)

¹ ULN = upper limit of normal

² Subject 11360002 had a creatinine level >10 x ULN at baseline

Creatine phosphokinase (CPK) levels were analyzed due to an apparent increase in AEs associated with myositis during Studies 1027 and 1028 (see Section 7.1.3). An increase in subjects with elevated CPK levels was observed in the MVC arms (Table 33). However, there was no increase in markedly elevated levels (i.e., >5 or >10 times ULN) with MVC.

FDA Table 33: CPK Elevation by Treatment Group During the Double-Blind Period (Studies 1027 and 1028 Combined, As Treated Population)

CPK Level	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
> ULN ¹	227 (55%)	236 (55%)	92 (44%)
> 2 x ULN	121 (29%)	121 (28%)	42 (20%)
> 5 x ULN	38 (9%)	40 (9%)	18 (9%)
> 10 x ULN	19 (5%)	25 (6%)	10 (5%)

¹ ULN = upper limit of normal

Amylase and lipase elevation was assessed as pancreatitis is a common drug-related toxicity. No evidence of an increase in amylase or lipase levels was observed in the MVC arms compared with placebo (Table 34).

FDA Table 34: Amylase/Lipase Elevation¹ by Treatment Group During the Double-Blind Period (Studies 1027 and 1028 Combined, As Treated Population)

Amylase/Lipase Level	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
> ULN ²	162 (39%)	155 (36%)	88 (42%)
> 2 x ULN	33 (8%)	28 (7%)	15 (7%)
> 5 x ULN	4 (1%)	2 (<1%)	0 (0%)
> 10 x ULN	2 (<1%)	0 (0%)	0 (0%)

¹ Subjects with an elevation of either amylase or lipase

² ULN = upper limit of normal

During pre-clinical testing of MVC, thyroid follicular cell hypertrophy was noted in a 6-month rat study which was shown to be reversible when MVC was withdrawn. Therefore, thyroid hormone levels were of concern during the MVC clinical development program. However, assessment of TSH and free thyroxine levels in Studies 1027 and 1028 did not reveal an increase in abnormal levels with MVC compared to placebo (Table 35).

FDA Table 35: TSH and Free Thyroxine Levels by Treatment Group During the Double-Blind Period (Studies 1027 and 1028 Combined, As Treated Population)

TSH/Free Thyroxine Levels	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
TSH			
Low	3 (1%)	2 (<1%)	0 (0%)
High	11 (3%)	13 (3%)	6 (3%)
Free thyroxine			
Low	32 (8%)	39 (9%)	25 (12%)
High	0 (0%)	1 (<1%)	0 (0%)

There was no evidence of an increase in fasting total cholesterol levels in the MVC arms compared to placebo when subjects were assessed by degrees of elevation above the ULN (Table 36). However, the median upper limit of normal for fasting cholesterol for the reporting laboratories appeared high (280 mg/dL). Therefore, relatively few subjects were abnormal with respect to total cholesterol, and the ability to detect a difference by treatment arm was limited. In light of this, an additional analysis was performed to assess the proportions of subjects with elevation above their baseline cholesterol greater than 15%, 30%, and 50% at any time during the study. This analysis revealed an increase in total cholesterol levels in both MVC arms over placebo (Table 37).

FDA Table 36: Fasting Total Cholesterol During the Double-Blind Period Using Elevation Above ULN¹ Thresholds (Studies 1027 and 1028 Combined, As Treated Population)

Fasting Total Cholesterol Level	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
> ULN	21 (5%)	20 (5%)	8 (4%)
> 1.15 x ULN	9 (2%)	6 (1%)	2 (1%)
> 1.30 x ULN	4 (1%)	2 (<1%)	2 (1%)
> 1.50 x ULN	3 (1%)	1 (<1%)	1 (<1%)

¹ ULN = upper limit of normal

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FDA Table 37: Fasting Total Cholesterol During the Double-Blind Period Using Elevation Above Baseline Thresholds (Studies 1027 and 1028 Combined, As Treated Population)

Fasting Total Cholesterol Level	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
> 1.15 x Baseline	163 (39%)	161 (38%)	50 (24%)
> 1.30 x Baseline	97 (23%)	94 (22%)	21 (10%)
> 1.50 x Baseline	48 (12%)	38 (9%)	7 (3%)

However, it is possible that the increase in total cholesterol with MVC might have been due to an increased duration of exposure to protease inhibitors, as MVC subjects tended to remain in the trial longer. Therefore, an analysis of total cholesterol was performed which included only subjects who completed 24 weeks of study participation (Table 38). The increase in total cholesterol with MVC remained, suggesting that an increased exposure to other agents such as protease inhibitors was not a cause for the difference.

FDA Table 38: Fasting Total Cholesterol at Week 24 (+/- 2 Weeks) Using Elevation Above Baseline Thresholds (Studies 1027 and 1028 Combined, As Treated Population)

Fasting Total Cholesterol Level	MVC QD (n=287)	MVC BID (n=307)	Placebo (n=94)
> 1.15 x Baseline	130 (45%)	131 (43%)	29 (31%)
> 1.30 x Baseline	76 (26%)	76 (25%)	13 (14%)
> 1.50 x Baseline	37 (13%)	27 (9%)	5 (5%)

A less sensitive but more clinically important analysis was performed using criteria from the National Cholesterol Education Program (NCEP). Based on these criteria, no increase in total cholesterol levels was observed with MVC compared to placebo (Table 39).

FDA Table 39: Fasting Total Cholesterol During the Double-Blind Period Using NCEP¹ Criteria (Studies 1027 and 1028 Combined, As Treated Population)

Fasting Total Cholesterol Level (mg/dL)	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
≥ 200 - 239	99 (24%)	94 (22%)	42 (20%)
≥ 240	47 (11%)	67 (16%)	23 (11%)

¹ National Cholesterol Education Program

There was no evidence of a difference in LDL levels by treatment arm when assessed by degrees of elevation above ULN (Table 40). However, the median upper limit of normal for the reference ranges of the reporting laboratories appeared to be high for LDL (197 mg/dL). Therefore, relatively few subjects were abnormal with respect to LDL, and the ability to detect a difference by treatment arm was limited. In light of this, an additional analysis was performed to assess the proportions of subjects with elevation of their baseline LDL greater than 15%, 30%, and 50% at any time during the study. This analysis revealed a modest increase in LDL levels in both MVC arms over placebo (Table 41).

FDA Table 40: LDL Cholesterol Level¹ During the Double-Blind Period Using Elevation Above ULN² Thresholds (Studies 1027 and 1028 Combined, As Treated Population)

LDL Level	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
> ULN	4 (1%)	6 (1%)	4 (2%)
> 1.15 x ULN	2 (<1%)	2 (<1%)	2 (1%)
> 1.30 x ULN	0 (0%)	0 (0%)	0 (0%)
> 1.50 x ULN	0 (0%)	0 (0%)	0 (0%)

¹ Friedewald Estimation.

² ULN = upper limit of normal

FDA Table 41: LDL Cholesterol Level¹ During the Double-Blind Period Using Elevation Above Baseline Thresholds (Studies 1027 and 1028 Combined, As Treated Population)

LDL Level	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
> 1.15 x Baseline	127 (31%)	124 (29%)	45 (22%)
> 1.30 x Baseline	85 (21%)	76 (18%)	30 (14%)
> 1.50 x Baseline	52 (13%)	43 (10%)	15 (7%)

¹ Friedewald Estimation

A less sensitive but more clinically important analysis was performed using criteria from the National Cholesterol Education Program. Based on these criteria, no increase in LDL levels was observed with MVC compared to placebo (Table 42).

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FDA Table 42: LDL Cholesterol During the Double-Blind Period Using NCEP¹ Criteria (Studies 1027 and 1028 Combined, As Treated Population)

LDL Level (mg/dL)	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
≥ 100 - 129	89 (21%)	92 (22%)	49 (23%)
130 - 159	45 (11%)	59 (14%)	25 (12%)
160 - 189	10 (2%)	15 (4%)	9 (4%)
≥ 190	5 (1%)	7 (2%)	3 (1%)

¹ National Cholesterol Education Program

Fasting triglyceride levels were also assessed, and revealed increases above the ULN with both MVC arms compared to placebo (Table 43). An additional analysis used NCEP triglyceride elevation criteria, and revealed a modest increase in the proportion of subjects with triglyceride levels ≥ 500 mg/dL in the MVC arms compared to placebo (Table 44).

FDA Table 43: Fasting Triglyceride Level During the Double-Blind Period Using Elevation Above ULN¹ Thresholds (Studies 1027 and 1028 Combined, As Treated Population)

Fasting Triglyceride Level	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
> ULN	111 (27%)	140 (33%)	43 (21%)
> 1.15 x ULN	94 (23%)	112 (26%)	32 (15%)
> 1.30 x ULN	78 (19%)	92 (22%)	28 (13%)
> 1.50 x ULN	60 (14%)	71 (17%)	20 (10%)

¹ ULN = upper limit of normal

FDA Table 44: Fasting Triglyceride Level During the Double-Blind Period Using NCEP¹ Criteria (Studies 1027 and 1028 Combined, As Treated Population)

Fasting Triglyceride Level (mg/dL)	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
< 150	135 (33%)	123 (29%)	57 (27%)
150 - 199	72 (17%)	79 (19%)	42 (20%)
200 - 499	160 (39%)	181 (42%)	76 (36%)
≥ 500	51 (12%)	65 (15%)	15 (7%)

¹ National Cholesterol Education Program

7.1.8 Vital Signs

Vital signs were routinely monitored in all subjects during Studies 1027 and 1028, and no significant differences were observed in the MVC arms compared with placebo. However, based on early clinical testing of MVC which revealed postural hypotension to be the dose-limiting toxicity, postural blood pressure measurements were also obtained during the phase 2b/3 studies. Measurements of blood pressure and pulse were obtained supine and standing at screening, Day 1, and Weeks 2, 24, and 48, or at the time of early termination. Supine measurements were obtained following 5 minutes in the supine position. Subjects subsequently sat for 2 minutes and then stood for an additional 2 minutes prior to measurements being obtained. Postural hypotension was defined as a decrease in blood pressure on standing of greater than 20 mm Hg systolic or 10 mm Hg diastolic, and was observed at a slightly higher frequency in the MVC arms compared with placebo (Table 45).

Sponsor Table 45: Subjects with Postural Hypotension in the Phase 2b/3 Studies (Studies 1027, 1028 and 1029 Combined, All Treated Population)

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

7.1.9 Electrocardiograms (ECGs)

Non-clinical studies demonstrated the potential of MVC to prolong ventricular repolarization at doses approximately six times the projected human dose. In addition, another investigational CCR5 co-receptor antagonist (“Schering C”) was previously found to cause QT prolongation. Therefore, there has been some concern regarding the potential for MVC to prolong the QT interval and induce ventricular arrhythmias during clinical use.

During the treatment-experienced phase 2b/3 trials (Studies 1027, 1028, and 1029), ECGs were obtained at baseline, Weeks 24 and 48, and at the time of early termination. Two subjects in the MVC BID arm had QTc prolongation ≥ 60 msec, while none in the MVC QD and placebo arms had this degree of prolongation. With respect to a less severe degree of prolongation (≥ 30 to < 60 msec), no increased incidence was observed with MVC (7.4%, 5.0%, and 6.7% in the MVC QD, MVC BID, and placebo arms, respectively).

A Thorough QT study was performed to further assess MVC. This was a randomized, single-dose, placebo and active controlled crossover study that enrolled 61 subjects. Three doses of MVC (100, 300, and 900 mg) were assessed in addition to an active comparator (moxifloxacin

400 mg) and placebo. No MVC or placebo subjects had a QTcI value ≥ 450 ms (males) or ≥ 470 ms (females). The results were analyzed by the FDA Center for Drug Evaluation and Research (CDER) Thorough QT Team who determined that the moxifloxacin arm had a prolonged QT at all time points which is not consistent with prior experience with this drug. As serum moxifloxacin concentrations were not obtained during the study, the cause of this finding was unclear and the results were not considered adequate. While the ECG interpreters were blinded to treatment, they were not blinded to time of ECG acquisition relative to study agent dosing. As it is possible that such knowledge may have biased the ECG interpretations, a reanalysis of the ECGs was performed in which the readers were blinded to subject, treatment group, and ECG timing. The FDA CDER Thorough QT Team analyzed the results of this reanalysis, and determined that the data showed no evidence of clinically meaningful QT prolongation in association with MVC.

7.1.10 Immunogenicity

As MVC is a small molecule and not a peptide, development of immunogenicity directed against this drug was not specifically evaluated. While there was no evidence of an overall increase in AEs associated with allergic-type reactions during the MVC phase 2b/3 development program, two cases of hepatotoxicity had features suggestive of allergic reactions during other trials with MVC, and there was a case of Stevens-Johnson Syndrome in association with MVC during Study 1026 (treatment-naïve trial). Please see the *Hepatotoxicity* and *Immunologic Reactions* sections of this document (Section 7.1.3) for the narratives of these events.

7.1.11 Human Carcinogenicity

Due to a theoretical concern that inhibition of the CCR5 co-receptor could result in decreased immune surveillance, and the observation of a potential increase in lymphoma in association with another investigational CCR5 inhibitor (i.e., vicriviroc), there has been concern regarding the carcinogenic potential of MVC. Carcinogenicity studies in transgenic mice and Sprague Dawley (S-D) rats were conducted in conformance with the International Conference on Harmonization (ICH) as well as Good Laboratory Practices (GLP). Overall, these pre-clinical studies did not reveal evidence of carcinogenicity. However, it should be noted that cholangiocarcinoma was observed in two S-D rats at the highest dose tested (900 mg/kg/day for 104 weeks), and one subject in the MVC BID arm of Study 1028 developed cholangiocarcinoma after receiving MVC for 250 days (reported in the Safety Update, Section 7.2.9). While this is an uncommon tumor in S-D rats, the findings were not considered sufficient to clearly implicate MVC. As there was only a single episode of cholangiocarcinoma during the phase 2b/3 clinical studies, the relative contribution of MVC to this event is not known. Overall, there was no evidence of an increase in malignancies in general or of lymphoma in particular with MVC use (see Section 7.1.3).

7.1.12 Special Safety Studies

Study 1029 was a 48-week, multicenter, double-blind, randomized, placebo-controlled, phase 2b study intended to assess the safety and antiviral activity of two MVC dosing regimens compared

with placebo in subjects with dual/mixed-tropic, CXCR4-tropic, or non-reportable/non-phenotypable HIV-1. Subjects were randomized 1:1:1 to MVC 300 mg dose equivalent QD, MVC 300 mg dose equivalent BID, or placebo. All subjects also received OBT.

As MVC is a CYP3A4 substrate, dose adjustments were required based on the concomitant antiretroviral medications (Table 46).

FDA Table 46: Recommended MVC Dose During Study 1029

Concomitant Antiretrovirals	MVC Dose
≥1 Protease inhibitor and/or delavirdine	150 mg
All other regimens	300 mg

Study 1029 Major Eligibility Criteria

- ≥16 years of age
- Infected with dual/mixed-tropic, CXCR4-tropic, or non-reportable/non-phenotypable HIV-1
- At least 3 months of prior treatment with at least one drug from 3 of the 4 antiretroviral drug classes, or demonstrated resistance to 3 of the 4 classes
- Stable antiretroviral regimen for at least 4 weeks
- Plasma HIV-1 viral load ≥5,000 copies/mL

Study 1029 Results

A total of 186 subjects received at least one dose of study agent (63 MVC QD, 61 MVC BID, and 62 placebo). A total of 70% of subjects were Caucasian, and 87% were male.

No evidence of antiviral activity was observed in the MVC arms (adjusted mean changes in viral load from baseline to Week 48 were -0.615, -1.106, and -0.844 log₁₀ copies/mL for the MVC QD, MVC BID, and placebo arms, respectively). There was a slight increase in CD4 count in the MVC arms compared to placebo (adjusted mean changes in CD4 count from baseline to Week 48 were 65, 79, and 51 cells/μL for the MVC QD, MVC BID, and placebo arms, respectively). Given the small number of subjects in this trial and the absence of improvement in viral load, the significance of the CD4 findings is uncertain.

With respect to safety, the percentage of subjects with an AE of any cause was similar across treatment arms (87%, 93%, and 94% in the MVC QD, MVC BID, and placebo arms, respectively). In addition, the percentage of subjects with an SAE of any cause was also similar across treatment arms (16%, 16%, and 18% in the MVC QD, MVC BID, and placebo arms, respectively).

With respect to specific AEs of concern based on the mechanism of drug action or data from pre-clinical or phase 1 studies, there were no reports of orthostatic hypotension during this trial. Of note, two subjects in the MVC BID arm had Grade 1/2 syncope, but both continued in the study. Two subjects during the trial had myocardial infarctions, one in the MVC BID arm and the other in the placebo arm. There was a slight increase in Category C AIDS-defining illnesses in the MVC arms (8%, 7%, and 3% in the MVC QD, MVC BID, and placebo arms, respectively). In light of the small number of subjects, the significance of this finding is uncertain. Similar numbers of subjects had Grade 3/4 liver function test abnormalities (3, 1, and 2 in the MVC QD, MVC BID, and placebo arms, respectively). There were no occurrences of lymphoma during the trial, but 3 subjects developed malignancies (1 MVC QD subject developed anal carcinoma, 1 MVC BID subject developed Bowenoid papulosis, and 1 placebo subject developed basal cell carcinoma).

There were five deaths during the study or within 28 days of end of treatment (2 MVC QD, 1 MVC BID, and 2 placebo) (Table 47). There was no evidence of a difference in mortality between the 3 study arms.

FDA Table 47: Causes of Death During Study 1029 (As Treated Population)

Subject	Treatment	Cause of Death	Days from Starting Study Agent to Death
10790001	MVC QD	Pneumonia, possible chest mass	69
12130003	MVC QD	Advanced HIV disease	214
12240005	MVC BID	HIV disease progression	54
10870001	Placebo	Worsening renal failure, hemothorax, and HIV disease progression	92
11810004	Placebo	Reported as "brain damage"	85

Overall, there was no evidence of viral suppression with MVC use in subjects with mixed/dual-tropic or CXCR4-tropic HIV-1. The results of this study do not raise any new safety concerns with respect to MVC.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No evidence of withdrawal phenomena or abuse potential has been observed during the clinical development of MVC.

7.1.14 Human Reproduction and Pregnancy Data

Pregnancy was an exclusion criterion during the clinical development program for MVC, and subjects who became pregnant were to discontinue MVC immediately. Five subjects became pregnant during the phase 2b/3 studies. Three underwent induced abortions, one had a healthy

delivery, and the outcome for one pregnancy is unknown. Therefore, there is little human data regarding the effect of in utero MVC exposure.

7.1.15 Assessment of Effect on Growth

MVC has only been administered in adults, and therefore no clinical assessment of effects on growth has been performed.

7.1.16 Overdose Experience

There were no reported episodes of MVC overdose during the clinical development program.

7.1.17 Postmarketing Experience

MVC has not yet been approved in any country and therefore there is no postmarketing experience at this time.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Please see Sections 4.1 and 4.2 for descriptions of the studies used in the assessment of safety, and Section 6.1.4 for a description of the subject baseline characteristics. A total of 840 treatment-experienced subjects infected with CCR5-tropic HIV-1 received at least one dose of MVC during Studies 1027 and 1028. Including information contained in the Safety Update (Section 7.2.9), there has been a cumulative exposure to MVC during the double-blind phase of Studies 1027 and 1028 of 284.4 and 291.3 subject-years within the MVC QD and MVC BID arms, respectively.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

See Section 7.1.12 for a description of Study 1029, which was primarily conducted to determine the safety of MVC administration in patients infected with mixed/dual-tropic or CXCR4-tropic HIV-1.

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects and duration of drug exposure was obtained during the MVC phase 2b/3 development program, in light of the life-threatening nature of the disease and few remaining treatment options for the patient population under study. In addition, the study designs were of a high-quality (i.e., randomized and placebo-controlled).

However, few women and non-Caucasians were assessed during Studies 1027 and 1028 and therefore a comprehensive assessment of the safety and efficacy of MVC in these groups is not possible at this time. Additional information on these groups will be available when the 48 Week data are submitted from Studies 1027 and 1028, as well as the data from Study 1026 (treatment-naïve trial) which has had a more balanced distribution of subject demographics.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Appropriate pre-clinical testing was performed. Concerns particular to this drug class were addressed, including the potential for infection, malignancy, and hepatotoxicity. No increase in infection or evidence of carcinogenicity was observed. Bile duct vacuolation was observed in rats, but no evidence of liver toxicity was observed in mice, dogs, or monkeys. The changes in rat bile ducts were considered possibly a response to biliary excretion of MVC or a metabolite. Please see the FDA Pre-Clinical Review of MVC for further details.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing performed during Studies 1027 and 1028 were adequate and are summarized in Section 6.1.3. The evaluations occurred approximately every 4 weeks and included routine chemistry and hematology measurements, adverse event assessments, and targeted physical examinations including vital signs.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolic, clearance, and interaction workup was adequate. Please see Section 5 for details.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

As noted in Section 7.1.3, there are a number of special concerns for the CCR5 co-receptor drug class including the potential for an increased risk of infection, malignancy, or hepatotoxicity. In light of the life-threatening nature of HIV and few remaining treatment options for treatment-experienced patients with detectable virus despite antiretroviral therapy, the evaluation for these types of AEs has been appropriate. Additional information regarding these events will be available when 48 Week data are submitted. A prolonged duration of observation may be necessary to detect an association of some of these types of AEs with MVC, particularly with respect to malignancy. The need for more prolonged observation of subjects is being addressed as a postmarketing commitment (see Section 9.3.2).

7.2.8 Assessment of Quality and Completeness of Data

The overall quality of the clinical data was acceptable, and was obtained from high-quality trial designs (randomized, blinded, with placebo-control). The frequency of clinical assessments was

also appropriate. While there was a substantial amount of missing data in the placebo arm at 24 weeks, this was primarily due to virologic failure in this group and was to be expected based on the trial designs which specified termination of the blinded phase in the event of virologic failure.

7.2.9 Additional Submissions, Including Safety Update

A 3-month instead of the typical 4-month Safety Update was submitted in order to allow adequate time for FDA review prior to the Antiviral Products Advisory Committee meeting held to discuss MVC on April 24, 2007. The data cut-off date for this Safety Update was November 30, 2006. Additional clinical events of particular relevance to MVC are reviewed in this section.

There were 2 new cases of lymphoma, both in the MVC BID arm (T-cell lymphoma and large B-cell lymphoma). Overall, in Studies 1027 and 1028 there have now been 7 cases of lymphoma in the MVC arms and 2 in the placebo arms. In light of the 4:1 randomization scheme, there is no evidence of an increase in lymphoma with MVC at this time.

Cumulative liver-related and infectious AEs were reviewed and the results did not alter the findings from the initial NDA filing. With respect to cardiovascular disease, there were no additional cardiac ischemic events during the double-blind period of Studies 1027 and 1028. Therefore, the increase in such events in association with MVC described in Section 7.1.3 remains unchanged. Cardiovascular AEs in Study 1029 are discussed in Section 7.1.12.

There were 4 additional deaths reported during Studies 1027 and 1028 in the MVC BID arm, and 1 additional death in the placebo arm. The causes of death in the MVC BID arm were T-cell lymphoma, cholangiocarcinoma, suicide, and cause unknown. The one placebo subject died of progressive multifocal leukoencephalopathy and subsequent pulmonary edema. In light of the 4:1 randomization scheme, this information does not alter the findings based on data from the initial NDA filing.

In conclusion, analysis of the additional data contained in the Safety Update did not reveal new safety concerns with respect to MVC.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Potentially drug-related AEs during the phase 2b/3 development program have included cardiovascular ischemic events, liver-related events, and several types of infection (Candida, herpes simplex, influenza, and upper respiratory tract infection). Analyses of these AEs and conclusions are described in Section 7.1.3.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Studies 1027 and 1028 had identical trial designs including the same eligibility criteria. Therefore, the safety data from these trials were pooled to increase the power to detect AEs potentially associated with MVC use. Given the identical trial designs, no weighting of data was considered necessary.

7.4.2 Explorations for Predictive Factors

With respect to baseline characteristics, there was little variability in age among subjects, and as previously discussed, the large majority of subjects were male and Caucasian. Therefore, while there was no evidence of differences in safety based on these characteristics, there was little power to detect differences if they existed.

7.4.3 Causality Determination

All AEs potentially caused by MVC are considered in detail in Section 7.1.3.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimen for MVC is 300 mg twice daily in adults, but a dose adjustment is required for certain concomitant medications due to drug interactions (Table 48).

FDA Table 48: Proposed MVC Dosing Regimen

Concomitant Medications	MVC Dose
CYP3A4 inhibitors including: <ul style="list-style-type: none">• protease inhibitors (except tipranavir/ritonavir)• delavirdine• ketoconazole, itraconazole, clarithromycin, nefazadone, telithromycin CYP3A4 inhibitor in combination with a CYP3A4 inducer	150 mg twice daily
Other concomitant medications, including all other antiretrovirals	300mg twice daily
CYP3A4 inducers (without a CYP3A4 inhibitor) including: <ul style="list-style-type: none">• efavirenz and nevirapine	600 mg twice daily

8.2 Drug-Drug Interactions

MVC is considered unlikely to alter the metabolism of co-administered drugs that are metabolized by cytochrome P450 enzymes because it does not affect CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4 at clinically relevant concentrations in vitro.

MVC is a substrate of CYP3A4 and P-gp. Therefore, its pharmacokinetics are likely to be altered by inhibitors and inducers of these enzymes/transporters. The CYP3A4/P-gp inhibitors ketoconazole, lopinavir/ritonavir, ritonavir, saquinavir and atazanavir all increased the C_{max} and AUC of MVC. The CYP3A4 inducers rifampin and efavirenz decreased the C_{max} and AUC of MVC. Tipranavir/ritonavir (overall CYP3A4 inhibitor/P-gp inducer) did not affect the steady state pharmacokinetics of MVC. Substrates and inhibitors of renal clearance (co-trimoxazole and tenofovir) did not affect MVC pharmacokinetics. Please see Section 8.1 for the proposed MVC dosing adjustments based on concomitant medication use.

8.3 Special Populations

The incidence of fetal malformations was not increased during pre-clinical studies performed with MVC in rats at exposures approximately 20-fold higher and in rabbits 5-fold higher than the human exposure anticipated at the proposed doses. However, no adequate studies have been performed in pregnant women. Because animal reproduction studies are not necessarily predictive of human response, MVC should be used during pregnancy only if clearly needed.

The pharmacokinetics of MVC have not been studied in patients with renal impairment. However, renal clearance constitutes less than 25% of the total MVC clearance. Therefore, the impact of renal impairment on MVC elimination is likely to be small.

The pharmacokinetics of MVC have not been sufficiently studied in patients with hepatic impairment. As MVC is metabolized by the liver, concentrations are likely to be increased in these patients.

There were insufficient numbers of subjects age 65 and older in the clinical studies to determine whether this population responds differently from younger patients. However, caution should be used when administering MVC in elderly patients in light of the greater frequency of decreased hepatic and renal function, concomitant disease, and other drug therapies.

8.4 Pediatrics

A Written Request (WR) for pediatric studies was issued to the Applicant in December 2006. The WR asked that the following two studies be conducted to determine the pharmacokinetic and safety profile of MVC in pediatric patients, identify appropriate dosing in HIV-infected pediatric patients and HIV exposed neonates, and to evaluate the activity of the dose in treatment and/or prophylaxis:

1. A multiple-dose pharmacokinetic, safety and activity study of maraviroc in combination with other antiretroviral agents in HIV-infected pediatric patients
2. A multiple-dose pharmacokinetic and safety study of maraviroc in HIV-exposed neonates (born to HIV-infected mothers)

In the Applicant's response to the WR on May 31, 2007, a staged approach to the studies was proposed. Study #1 would be conducted first, and enroll subjects 2-18 years of age. Study #2 in neonates would be initiated when additional safety data in adults and older children have been obtained. The Applicant's rationale for this approach was based on the concern that CCR5 co-receptor inhibition could adversely affect the developing nervous system in children less than 2 years of age by altering neuronal maturation and migration. CCR5 expression has been observed on neuronal cells, including microglial cells, astrocytes, and cerebral and hippocampal neurons. Negotiations with the Applicant regarding the pediatric study program are ongoing.

8.5 Advisory Committee Meeting

A meeting of the Antiviral Products Advisory Committee was held on April 24, 2007. The Committee discussed the safety, efficacy, pharmacokinetic, and viral tropism data for MVC, and addressed questions posed by the FDA. The questions posed by FDA during the meeting are listed below, followed by a summary of the Committee's responses:

1. **Do the safety and efficacy data presented support accelerated approval of maraviroc for treatment-experienced HIV-1 infected patients with CCR5-tropic virus? If not, please discuss what additional data are needed to provide sufficient evidence of efficacy and safety. If so, please comment on additional data (e.g., patient subgroups, longer term follow-up etc.) that Pfizer should provide post-marketing to further characterize the safety and efficacy profile of maraviroc.**

The Committee voted unanimously that the data supports accelerated approval with the caveat that future study designs include increased representation of women and minorities. The Committee also recommended postmarketing data collection on patients with viral hepatitis co-infection, pediatrics, immunologic signals, and malignancies.

2. **There have been several safety concerns during the development of all the CCR5 co-receptor antagonists including risk of lymphomas and infection, hepatotoxicity, and tropism switching. Please discuss each of these issues with respect to maraviroc specifically, and provide recommendations for possible product labeling, post-marketing studies or post-marketing risk management strategies.**

The Committee recommended including cardiovascular risk and hemodynamic instability as additional issues. The Committee felt that there was no evidence of an increased risk of lymphoma and suggested that it be categorized as a theoretical risk. Infection was not discussed in detail but was considered by the Committee a potential risk. Hepatotoxicity was also considered a potential risk and the Committee agreed that data are relevant but that the cases presented are not necessarily an indication of this potential risk. Additional

monitoring of patients receiving concomitant hepatotoxic drugs was also recommended. Hemodynamic instability was discussed as an important concern and included as a potential risk, and postural hypotension was discussed as a dose limiting toxicity with need for language to be included in product labeling.

3. Do the data support the Applicant's proposed dosing? Please consider the recommended dose in light of the exposure-response modeling.

The Committee voted unanimously in favor of the proposed dosing. The Committee recommended conducting a study to investigate optimization of dose specifically for individuals with low MVC concentrations. There was also concern that the current exposure-response did not include sufficient numbers of historically relevant populations.

4. The Monogram Trofile assay was used to screen subjects for enrollment and to monitor subjects for tropism switching. Please discuss how you would recommend assays for tropism testing be used for the management of subjects who might receive maraviroc in clinical practice.

The Committee was unable to provide a specific recommendation regarding assays for tropism testing. However, it was agreed that tropism testing was needed to select patients for treatment with MVC and some members recommended testing at the time of virologic failure.

5. Please discuss the impact of the availability of maraviroc on the design of future Phase 3 trials for new antiretroviral agents in the treatment-experienced population and provide recommendations for how those trials should be designed accordingly.

The Committee was unable to recommend any specific trial designs.

8.6 Literature Review

Literature citations are provided as footnotes in the relevant sections of this document.

8.7 Postmarketing Risk Management Plan

Please see Section 9.3 for a detailed description of all of the postmarketing activities currently being discussed with the Applicant.

8.8 Other Relevant Materials

No other materials were used during this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

The efficacy of MVC in the management of treatment-experienced adults infected with CCR5-tropic HIV-1 was demonstrated with the 24-week results of Studies 1027 and 1028. Median viral load reduction at Week 24 was greater with MVC than in the placebo arm, as well as decreases in viral load to <50 copies/mL at Week 24. Please see Section 6.1.4 for a detailed description of the efficacy findings.

With respect to safety, no increase in malignancy has been observed in association with MVC. While no overall increase in infections was observed, a possible increase was noted in Candida, herpes, influenza, and upper respiratory tract infections.

There was a slight increase in mortality with MVC in one of the phase 2b/3 trials, but this finding was not observed in the other phase 2b/3 trials. However, the types of deaths were consistent with the population studied, and this was a sick population with 11 deaths observed during the approximately 6-week time period between screening and enrollment. In addition, there was no clustering of causes of death in the MVC arms to suggest a drug etiology.

There was no clear evidence of hepatotoxicity during the phase 2b/3 program. However, an episode of hepatotoxicity in association with MVC during a healthy volunteer study was reported after the initial NDA filing and 3-month Safety Update (see Section 7.1.3). This episode has strengthened the concern that MVC could be hepatotoxic.

There were 11 subjects in the MVC arms with cardiac ischemic AEs during the double-blind period of Studies 1027 and 1028, and no such events in the placebo arm. This has raised concern that MVC could cause cardiac ischemia. However, no imbalance was observed in the non-CCR5-tropic trial (Study 1029), and few cardiac events have occurred during the open-label period of these studies. It should also be noted that an analysis of thrombotic events did not reveal an increase with MVC compared to placebo. Additional data will be available when the 48-week results are submitted for Studies 1027 and 1028, as well as the results of the treatment naïve study (Study 1026), but at this time it is possible that MVC use could result in an increase in cardiac ischemia.

With respect to the laboratory data, there was an increased proportion of subjects with mild elevation of CPK in the MVC arms, as well as mild increases in total cholesterol, LDL, and triglyceride levels.

9.2 Recommendation on Regulatory Action

Accelerated approval of MVC is recommended for the management of treatment-experienced adults infected with CCR5-tropic HIV-1. This recommendation is based on the demonstration of virologic suppression in a patient population with few remaining treatment options.

9.3 Recommendation on Postmarketing Actions

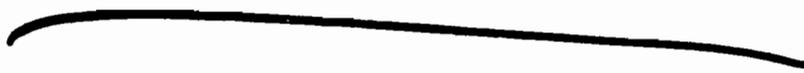
9.3.1 Risk Management Activity

The FDA Office of Surveillance and Epidemiology (OSE) was consulted regarding the appropriate risk management activities that should be pursued based on the safety issues that have been raised during the development of MVC. OSE provided the following recommendations, and discussion with the Applicant is ongoing regarding these plans:

Regarding the Pharmacovigilance Plan

- Expedited (15-day) reporting of the following events during the postmarketing period:
 - Liver-related deaths and liver failure
 - Fatal and non-fatal myocardial infarctions
 - All non-AIDS defining malignancies
- The long term safety protocol to be submitted by the Applicant should include, as described by the FDA pharmacovigilance guidance, the study objectives, plans for recruitment and follow-up, and methods for data collection, management, and analysis. The study should include a control group and should be extended up to 10 years to adequately capture any potential increase in malignancies.

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9.3.2 Required Phase 4 Commitments

The following postmarketing commitments (PMCs) have been proposed and are under negotiation with the Applicant. Additional PMCs are also under development. Of note, the Applicant has committed to participate in the Antiretroviral Pregnancy Registry.

1. Submit Week 48 and Week 96 reports and datasets for Studies 1027 and 1028. Subjects in these studies will also be followed for at least 5 years for mortality, liver failure, malignancy, myocardial ischemia or infarction, and rhabdomyolysis, as well as for infections considered at least moderate in severity or qualify as a CDC Category C event.
2. Deferred pediatric substudy under PREA for the treatment of HIV in pediatric subjects from _____ years of age. This study will determine the maraviroc exposure (pharmacokinetics profile) for pediatric subjects from birth _____ years of age to support dose selection for the efficacy and safety assessment.
3. Deferred pediatric study under PREA for the treatment of HIV in pediatric subjects from _____ years of age. Using doses selected based on the substudy listed in item #2 above, conduct a pediatric safety and efficacy study of maraviroc with efficacy based on viral load reduction through 48 weeks of dosing, and safety monitored over 96 weeks.
4. Conduct and submit a final report for a non-randomized, controlled clinical trial to provide additional safety data regarding the incidence of mortality, liver failure, malignancy, myocardial ischemia or infarction, and rhabdomyolysis, as well as for infections considered at least moderate in severity or qualify as a CDC Category C event. Follow-up of subjects will be at least every 6 months for a total of 5 years.
5. Conduct and submit a final report for a study in subjects with HIV-1 who are co-infected with hepatitis C and/or B, including some subjects with a Child-Pugh score of C.
6. Submit Week 48 and Week 96 reports for Study 1026. Subjects in this study will also be followed for at least 5 years for mortality, liver failure, malignancy, myocardial ischemia or infarction, and rhabdomyolysis, as well as for infections considered at least moderate in severity or qualify as a CDC Category C event.
7. Perform cell culture combination activity assessments of maraviroc with darunavir and tipranavir, and submit a complete study report of these assessments by December 2007.

8.

9.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

9.4 Labeling Review

The most significant changes to the Applicant's proposed label involve the Warnings Section, with the following additional warnings recommended:

Clinical Review
Scott Proestel, M.D.
NDA 22-128
Maraviroc

9.5 Comments to Applicant

Comments were provided to the Applicant throughout the review, and there are no additional comments at this time.

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/s/

Scott Proestel
6/20/2007 11:51:25 AM
MEDICAL OFFICER

Kathrine Laessig
6/20/2007 12:01:22 PM
MEDICAL OFFICER

**Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: QT Study Review**

IND or NDA	22128
Brand Name	NA
Generic Name	Maraviroc
Sponsor	Pfizer Inc.
Indication	Treatment-experienced patients infected with CCR5-trophic HIV-1, in combination with other antiretroviral agents
Dosage Form	150 and 300 mg tablets
Therapeutic Dose	150 mg BID (with protease inhibitor) or 300 mg (without protease inhibitor)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	1200 mg qd (maximum dose tested)
Application Submission Date	20 December 2006
Review Classification	Priority NDA
Date Consult Received	23 January 2007
Date Consult Due	06 April 2007
Clinical Division	Division of Antiviral products
PDUFA Date	June 6, 2007

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

In nonclinical studies, Maraviroc demonstrated the potential to prolong ventricular repolarization. While Maraviroc is not a potent inhibitor of hERG, it appears to be sufficiently potent to prolong QT interval in vivo in animals at approximately 8 times the projected human therapeutic concentration.

The sponsor only assessed ECGs for 12 hours following a single dose of maraviroc. We generally recommend that the QTc is measured for at least 24 hours to allow exploration of possible delayed pharmacodynamic effects on the QTc interval.

The change in QTc after administration of moxifloxacin minus the baseline QTc after placebo as a function of time is unusual. The change is near maximal at 1 hour and remains unusually elevated at 12 hours. This unusual result means that assay sensitivity has not been demonstrated in this study; i.e., it is unclear that had product administration prolonged the QTc, it could have been detected. Therefore, we are uncertain whether administration of maraviroc prolongs the QTc above the threshold established in the ICH E14 guideline.

1.2 RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION

None.

1.3 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

None.

2 PROPOSED LABEL

3 BACKGROUND

3.2 DRUG CLASS

Maraviroc is a selective, slowly reversible, small molecule antagonist of the human chemokine co-receptor CCR5 that inhibits viral entry into cells, an essential step in the replication of HIV-1. Maraviroc is chemically described as 4,4-difluoro-*N*-{(1*S*)-3-[*exo*-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclohexanecarboxamide.

3.3 MARKET APPROVAL STATUS

Maraviroc is a new chemical entity.

3.4 PRECLINICAL INFORMATION

Maraviroc tested positive nonclinically for the potential to prolong ventricular repolarization in a series of in vitro and in vivo cardiovascular safety pharmacology studies.

In vitro

- Maraviroc (10 μ M) inhibited hERG current when evaluated in a whole cell voltage clamp study, with hERG expressed in a mammalian cell line (HEK293). While dofetilide was utilized as a positive control, only a supratherapeutic concentration (1 μ M) was evaluated. Therefore, assay sensitivity was not clearly demonstrated.

- Maraviroc (10 μM) displaced [^3H] dofetilide binding to hERG expressed in HEK293 cells. The positive control, unlabeled dofetilide, displaced [^3H] dofetilide binding with an IC_{50} of 9.65 nM. Therefore, the assay was demonstrated to be sensitive.
- Maraviroc (3 and 10 μM) lengthened cardiac action potential duration in canine Purkinje fibers. An internal positive control was not utilized.

In vitro effects were concentration related and internally consistent, e.g. 19% inhibition of hERG current and 43% inhibition of hERG binding at 10 μM are within assay variability. Based on the concentrations needed for effects, Maraviroc is not considered to be a potent inhibitor of hERG.

In vivo

- An in vivo QT study in conscious telemeterized dogs was negative when Maraviroc was given orally at a single dose of 1.5 mg/kg, which resulted in a C_{max} (free) of 179 ng/ml.
- An in vivo QT study in conscious restrained dogs given a constant intravenous infusion that resulted in a higher free plasma concentration of Maraviroc increased QT over vehicle without altering heart rate. The free plasma concentration associated with QT prolongation was approximately 8 times the human free C_{max} at a therapeutic dose of 300 mg BID.

It should be noted that while an internal positive control was not evaluated in these in vivo QT studies, an approximately 10% increase (or about 25-30 ms) is typically needed to capture a drug related effect on QT in these models. Results of these in vivo cardiovascular safety pharmacology studies are consistent with QT prolongation observed in repeat dose dog and monkey toxicology studies at similar multiples of the human therapeutic concentration (not discussed in this review) and the in vitro effects on hERG and action potential duration described above.

Study Type	Study	Finding	Concentration or Dose	Free plasma concentration	Human Multiple [^]
Safety Pharmacology	hERG Inhibition (whole cell voltage clamp assay)	19% inhibition	10 μM	NA	NA
	hERG Binding Assay	43% inhibition	10 μM	NA	NA
	Action Potential Duration (APD90) Canine Purkinje fiber	9.6 \pm 2.4%	3 μM	NA	NA
		30.6 \pm 6.7%	10 μM		
	QT in vivo (conscious telemeterized dogs)	No effect	1.5 mg/kg, po	179 ng/l	1 fold
QT in vivo (conscious restrained dogs)	24 ms increase (maximum) over vehicle	3.5 mg/kg/hr constant infusion (2-3 hr infusion)	1310 ng/ml	8 fold	

[^] Human multiples are based on a human C_{max} (free) of 155 ng/mg at 300 mg BID.
NA, not applicable

While Maraviroc is not a potent inhibitor of hERG, it appears to be sufficiently potent to prolong QT interval in vivo in animals at approximately 8 times the projected human therapeutic concentration. In summary, Maraviroc tested positive nonclinically for the potential to prolong ventricular repolarization.

3.5 PREVIOUS CLINICAL EXPERIENCE

Marovic is not marketed in the USA so no clinical experience has been reported.

3.6 CLINICAL PHARMACOLOGY

Table 1 summarizes the key features of maraviroc clinical pharmacology.

Table 1: Highlights of Clinical Pharmacology

Therapeutic dose	The recommended dose of maraviroc is 300 mg BID in adults but a dose adjustment may be needed due to the potential for drug interactions. 150 mg BID if administered with CYP3A4 inhibitors including: protease inhibitors (except tipranavir/ritonavir) delavirdine, ketoconazole, itraconazole, clarithromycin, nefazadone, telithromycin 600 mg BID if administered with CYP3A4 inducers (without a CYP3A4 inhibitor) including: efavirenz and nevirapine rifampin and rifabutin. 300 mg BID if administered with other concomitant medications, including all other antiretrovirals including tipranavir/ritonavir	
Maximum tolerated dose	Not reported.	
Principal adverse events	None so far. Other CCR-5 inhibitors have been discontinued to hepatotoxicity. However, no indication of abnormal increase in ALT or AST was seen in registration trials. Postural hypotension was observed at 1200 mg doses in early phase studies.	
Maximum dose tested	Single Dose	1200 mg
	Multiple Dose	1200 mg QD
Exposures Achieved at Maximum Tested Dose Mean (range)	Single Dose (A40001001)	2807 (1980-3960) Cmax and 11300 (8790-17700) AUC
	Multiple Dose At day 14 (A40001019)	2988 (1850-3720) Cmax and 10394 (7520-14000) AUC
Range of linear PK	Maraviroc pharmacokinetics are not dose proportional over the dose range 50 to 600 mg (A40001003- a single dose study). The dose proportionality constant for AUC _{inf} was estimated as 1.18.	
Accumulation at steady state	The mean accumulation ratios on day 12, for 300 mg BID and 600 mg QD were 1.7 and 1.2, respectively.	
Metabolites	In a radio labeled study, unchanged maraviroc was the major circulating component in plasma, accounting for 42% of the circulating radioactivity. UK-408,027, which resulted from N dealkylation and an analogue of this amine involving oxidation of the methyl group of the triazole moiety, was also identified, accounting for 22% and 11% of the circulating radioactivity respectively. The major metabolite pathways involved oxidation	

	<p>in the difluorocyclohexane ring, oxidation in the triazole group and N-dealkylation adjacent to the tropane moiety. The major excreted components were unchanged maraviroc (33% of total radioactive dose), four metabolites involving mono-oxidation in the difluorocyclohexane ring (each accounting for between 5 and 9%), a metabolite which resulted from oxidation in the triazole group (10%) and a secondary amine (UK-408,027) resulting from N-dealkylation adjacent to the tropane moiety (7%). The N-dealkylation also yielded an unlabelled carboxylic acid (UK-463,977; ~ 3%).</p> <p>Total mean recovery of radioactivity was 96%. Most radioactivity was excreted via the feces (76.4%) whilst 19.6% was recovered in urine. Intersubject variability was low in terms of relative quantities of maraviroc and its metabolites in both plasma and excreta.</p>	
Absorption	Absolute/Relative Bioavailability	100 mg oral tablet – absolute F= 23 % (CI 19.2,27.8)
	Tmax	• 1.64 (0.3- 4) hr at 300 mg single dose for parent
Distribution	Vd/F or Vd	194 L (IV administration) (118-319)
	% bound	75%
Elimination	Route	<ul style="list-style-type: none"> • Unchanged; 42% • CYP metabolism
	Terminal t _{1/2}	• 13.2 (10.3-18.3) hr for parent
	CL/F or CL	44 L/hr (IV administration) (37.4-57.8)
Intrinsic Factors	Age	There were no significant age effects on maraviroc pharmacokinetic parameters as assessed in the population pharmacokinetic analysis of pooled Phase 1/2a data.
	Sex	There were no significant gender effects on maraviroc pharmacokinetic parameters as assessed in the population pharmacokinetic analysis of pooled Phase 1/2a data.
	Race	The population pharmacokinetic analysis of pooled Phase 1/2a data found the typical Asian subject to have a 26.5% increase in AUC compared to the typical non-Asian subject, independent of dose. This 0.265 fold higher maraviroc exposure is not considered clinically significant and no dose adjustment would be recommended for this difference.
	Hepatic & Renal Impairment	The pharmacokinetics of maraviroc have not been studied in patients with hepatic and renal impairment.
Extrinsic Factors	Drug interactions	See 6.1 (Effect of co-administered agents on the pharmacokinetics of maraviroc)
	Food Effects	Specify mean changes in C _{max} and AUC and meal type (i.e., high-fat, standard, low-

	fat)
Expected High Clinical Exposure Scenario	When maraviroc was administered in healthy volunteer studies at doses higher than the recommended dose, cases of symptomatic postural hypotension were seen at a greater frequency than placebo. However, when maraviroc was given at the recommended dose in HIV patients in Phase 3 studies, postural hypotension was seen at a similar rate compared to placebo (approximately 0.5%). Caution should be used when administering maraviroc in patients with a history of postural hypotension or on concomitant medication known to lower blood pressure.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted a 'thorough QT study' (TQT).

4.2 TQT

4.2.1 Title

A randomized single dose, placebo and active controlled five-period crossover study to investigate the effect of three oral doses of maraviroc on QTc interval in healthy subjects

4.2.2 Protocol Number

A4001016

4.2.3 Dates

Conducted from 29 April 2003 to 18 August 2003. Study report dated 19 December 2003.

4.2.4 Objectives

The study objectives were to assess the effect of therapeutic and suprathreshold doses of maraviroc on the QTc interval and to evaluate its safety and tolerability in healthy subjects.

4.2.5 Design

4.2.5.1 Description

This was a randomized, single dose, placebo and active controlled five way crossover study to investigate the effect of three oral doses of maraviroc (100, 300 and 900mg) and an active comparator (oral moxifloxacin 400mg) on QTc interval in healthy subjects.

A run-in day was performed in study period 3 (of 5). A placebo (for maraviroc) was administered during the run-in day.

4.2.5.2 Sponsor's Justification for Design

No justification provided.

4.2.5.3 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.4 Blinding

Moxifloxacin was administered open label during one study period. During the other four study periods, either one of the three doses of Maraviroc or placebo was administered double blind.

4.2.6 Study Subjects

A sample size of 51 subjects was estimated to give 80% power of concluding non-inferiority between an active dose and placebo, using a one-sided 5% level test, where non-inferiority was based on a ≤ 10 ms increase in QTc in the active group.

4.2.7 Dosing Regimens

4.2.7.1 Treatment Arms

Single doses of placebo, maraviroc 100 mg, 300 mg and 900 mg and moxifloxacin 400 mg

4.2.7.2 Sponsor's Justification for Doses

The proposed therapeutic dose is 300 mg po bid. The sponsor states, "Single doses of UK-427,857 up to 900mg have been well tolerated in healthy male subjects. At 1200mg, a clinically significant dose limiting adverse event (postural hypotension) was noted in 4/9 subjects. The onset of symptoms tended to coincide with C_{max} and lasted between 2.8-5.8h....the highest dose for (this) study (900mg) is likely to achieve plasma concentrations 2-3-fold high than steady state concentrations observed for UK-427,857 (100 mg BID) co-administered with a potent CYP3A4 / P-gp inhibitor."

4.2.7.3 Instructions with regard to meals

Subjects fasted (except water) from 00:00 hours on the evening prior to dosing until after the four hour post-dose assessments. Fluid was restricted from one hour prior to dosing until one hour post-dose. A light lunch was served following the four hour post-dose assessments. Further meals were served after the eight hour post-dose assessments; however, these had to be completed at least one hour and 30 minutes prior to the next ECG measurement. Subjects were restricted to drinking room temperature fluids until after the four hour post-dose ECG and thereafter subjects were to avoid hot or cold drinks for one hour prior to each ECG recording.

4.2.7.4 Study Assessments

Pharmacokinetic sampling

Blood samples (5ml) for maraviroc assay were taken to provide 2 ml plasma at the following times, relative to the morning dose: Run-in day (study period 3 only) and Day

1 (all study periods): pre-dose and at 1, 2, 3, 4, 8 and 12 hours post-dose. Blood was not sampled during the study period in which moxifloxacin was administered.

ECG measurements

The ECG measurements were recorded at the exact protocol times before the pharmacokinetic blood samples were collected (within 5 minutes of the ECG), after subjects had been resting semi-recumbent for at least 30 minutes. ECGs were recorded at the following times: Run-in day (study period 3 only) and Day 1 (all study periods): 1h 15min, 45 min and immediately pre-dose, and at 1, 2, 3, 4, 8 and 12 hours post-dose.

4.2.7.5 Sponsor's justification for sampling schedule

Not provided.

4.2.7.6 Baseline

The run-in day during study period 3 was used as baseline by the sponsor.

4.2.8 ECG Collection

From the protocol:

"The positions of the ECG leads will be marked on the subject's torso with indelible ink prior to dosing...Subjects must rest semi-recumbent for at least 30 minutes prior to any ECG measurement."

From the study report:

"The ECG measurements were recorded at the exact protocol times before the pharmacokinetic blood samples were collected (within 5 minutes of the ECG), after subjects had been resting semi-recumbent for at least 30 minutes...The ECG print outs were reviewed immediately to ensure they were of suitable quality for QTc assessment. If they were of insufficient quality then the ECG was repeated immediately."

"All ECGs were sent for independent central analysis by Hertford Medical International Ltd."

Reviewer's comments:

1. *Neither the protocol nor the study report indicate that the ECGs were interpreted in accordance with the ICH E14 guideline; i.e., that the readers were blinded to time, treatment, and subject identifier and that one reader should read all the ECGs from a given subject.*
2. *Only a single ECG was recorded at each timepoint. Given the intrinsic variability in measuring QT, a single measurement is likely to result in "noisy" data.*

4.2.9 Sponsor's Results

4.2.9.1 Study Subjects

Sixty-one subjects were randomized. The number of subjects in each evaluation group is shown in the following table:

Table 2: Disposition of study subjects

	UK-427,857			Moxifloxacin 400mg	Placebo	Placebo <i>Run-in</i>
	100mg	300mg	900mg			
Entered study period	61	59	58	58	59	59
Completed study period	58	58	58	58	59	59
Discontinued from study period	3	1	0	0	0	0
Evaluated for PK	60	59	58	0	0	0
Evaluated for PD	60	59	58	58	59	59
Assessed for safety:						
Adverse events	61	59	58	58	59	59
Laboratory data	61	59	58	58	59	1*

Source: Table 1.1

*Subject 46 had repeat laboratory tests which occurred on the placebo *run-in* day.

Key: PK=pharmacokinetics; PD=pharmacodynamics.

(Sponsor's Table, page 30 of a4001016 study report)

A demographic summary of all subjects randomized to treatment is presented below:

Table 3: Demographics of patients

Variable		Male Subjects N=30	Female Subjects N=31	All Subjects N=61
Age (years)	Mean	29	31	30
	Range	19 - 42	19 - 44	19 - 44
Race	White	29	29	58
	Black	0	1	1
	Asian	1	1	2
Weight (kg)	Mean	72	61	66
	Range	60 - 85	50 - 80	50 - 85
Height (cm)	Mean	175	165	170
	Range	164 - 186	157 - 176	157 - 186

(Sponsor's Table, page 30 of a4001016 study report)

4.2.9.2 Statistical Analyses

4.2.9.2.1 Primary Analysis

Comparisons against placebo were carried out for all three primary endpoints. The primary endpoints were: 1) QTcI at median Tmax for UK-427,857/moxifloxacin; 2) maximum increase from baseline in QTcI over the ECG assessments collected until four hours post-dose; 3) average QTcI over the ECG assessments collected until four hours post-dose (Protocol Amendment, 11 June 2003).

A separate analysis of variance (ANOVA) was conducted for each of the pairwise comparisons of interest. The comparisons of interest were UK-427,857 100mg versus placebo, UK-427,857 300mg versus placebo, UK-427,857 900mg versus placebo and moxifloxacin 400mg versus placebo. The ANOVA allowed for variation due to sequence, subject within sequence (random effect), period and treatment. Baseline was used as a covariate. It was split into two variables, the average for subjects over the two study periods and the deviation of each study period baseline from this average. Satterthwaite's approximation for the denominator degrees of freedom was used. The treatment means

and the differences between the active treatments and placebo were calculated along with 90% confidence intervals (CIs). These CIs were presented graphically. Only subjects who had QTc data recorded for both treatments in the pairwise comparison of interest were used in the statistical analysis (Protocol Amendment, 11 June 2003). For the analysis of median Tmax, the comparison was made against the placebo value at the corresponding median Tmax for the UK-427,857/moxifloxacin dose. For endpoint 1), if median Tmax occurred at a half hour interval, then the analysis was produced for both time points. The Tmax which occurred the most frequently was taken as primary and the other as secondary. If both time points were just as frequent then the first timepoint was used as primary and the second timepoint as secondary. Should any of the assumptions of the analysis methods presented above not be adequately met, an alternative procedure would be used and fully documented (Protocol Amendment, 11 June 2003).

The following table displays a comparison of the active treatments against placebo for the three primary endpoints.

Table 4: QTcI analysis results for active treatment against placebo (from the sponsor)

Endpoint	Comparison	N	Adjusted Means		Mean Diff	90% CI
			Active	Placebo		
1) QTcI at median Tmax	UK-427,857 100mg vs Placebo	59	399.67	400.39	-0.72	(-3.03, 1.59)
	UK-427,857 300mg vs Placebo	58	400.84	400.59	0.24	(-1.85, 2.34)
	UK-427,857 900mg vs Placebo	58	402.76	399.15	3.61	(1.01, 6.21)
	Moxifloxacin 400mg vs Placebo	58	412.67	398.71	13.96	(11.49, 16.44)
2) Maximum increase in QTcI from 1 - 4h post-dose	UK-427,857 100mg vs Placebo	59	5.00	7.33	-2.33	(-4.44, -0.22)
	UK-427,857 300mg vs Placebo	58	6.87	7.46	-0.59	(-2.55, 1.37)
	UK-427,857 900mg vs Placebo	58	8.68	7.70	0.98	(-0.85, 2.80)
	Moxifloxacin 400mg vs Placebo	58	21.11	8.18	12.93	(10.88, 14.97)
3) Average QTcI from 1 - 4h post-dose	UK-427,857 100mg vs Placebo	59	399.44	401.12	-1.68	(-3.29, -0.06)
	UK-427,857 300mg vs Placebo	58	401.46	401.38	0.08	(-1.35, 1.50)
	UK-427,857 900mg vs Placebo	58	401.95	400.76	1.19	(-0.30, 2.68)
	Moxifloxacin 400mg vs Placebo	58	412.44	400.32	12.11	(10.68, 13.55)

4.2.9.2.2 Categorical Analysis

Plan

The Committee for Proprietary Medicinal Products Points to Consider document suggests the use of categories for both absolute values and changes from baseline, using QTcB.7 As the QT:RR is known to vary between subjects, QTcI was regarded as the primary QTc measurement. The number of subjects with absolute QTcI values in the following categories were tabulated by treatment for the endpoints; 1) maximum post-dose QTcI; 2) QTcI at median Tmax for each dose (for UK- 427,857 and placebo only); 3) QTcI at two hours post-dose, the assumed Tmax for moxifloxacin [for moxifloxacin and placebo only (Protocol Amendment, 11 June 2003)]:

Table 5: Three categories used for the categorical analysis by gender

Adult Males	Adult Females
QTc < 430ms	QTc < 450ms
430ms ≤ QTc < 450ms	450ms ≤ QTc < 470ms
QTc ≥ 450ms	QTc ≥ 470ms

Results

No subjects receiving UK-427,857 or placebo had a maximum QTcI value ≥450ms (males) or ≥470ms (females). Two subjects receiving moxifloxacin 400mg had maximum QTcI values at 3 hours post-dose above these limits (Tables 5.5.1 and 5.5.2 and Section 13, Table 19.3). One male subject had a maximum QTcI value ≥450ms (455ms) and one female subject had a maximum QTcI value ≥470ms (482ms). There were a similar number of subjects in each treatment group who had a maximum QTcI of between 430 and 449ms (males) and between 450 and 469ms (females) for all treatment groups. No subjects had maximum increases in QTcI value ≥60ms from baseline at any timepoint. However, there was a greater incidence of subjects with maximum increases from baseline of between 30 and 59 ms for the moxifloxacin 400mg treatment group

4.2.9.3 Safety Analysis

None of the following events were observed during the trial: torsades de pointes, sudden death ventricular tachycardia or fibrillation, syncope or seizures (Appendix 3.6 “Adverse Events”). No deaths or serious adverse events occurred. 3 subjects withdrew from the study due to an adverse event; one of these events was a miscarriage and the other two were infections.

No significant changes in vital signs were noted but the sponsor notes that postural hypotension and dizziness was reported more frequently after administration of the highest dose of maraviroc.

4.2.9.4 Clinical Pharmacology

4.2.9.4.1 Pharmacokinetic Analysis

Maraviroc was rapidly absorbed with T_{max} occurring in general between 1.0 and 4.0 hours. C_{max} and AUC_{last} increased with increasing dose and median T_{max} was three hours for maraviroc 100mg and 300mg and two hours for maraviroc 900mg. The variability was moderate, with coefficients of variation of 29 to 56%. The mean maraviroc plasma pharmacokinetic parameters are summarised in the following table:

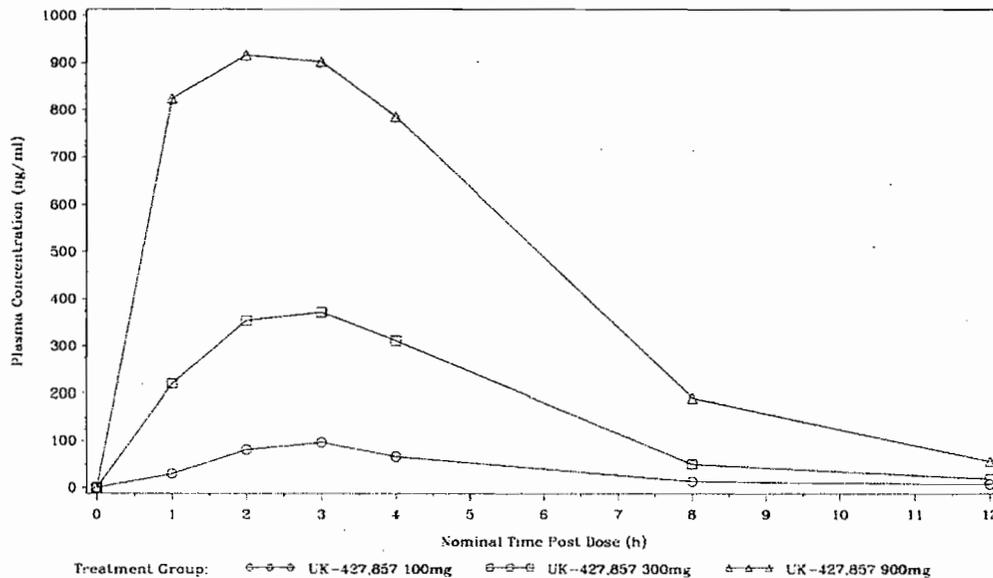
Table 6: Maraviroc pharmacokinetic parameters

Parameter (units)	UK-427,857 100mg N=60	UK-427,857 300mg N=59	UK-427,857 900mg N=58
AUC _{last} (ng.h/ml)	396	1840	5259
C _{max} (ng/ml)	111	464	1148
T _{max} (h)	2.8	2.6	2.2

(Sponsor’s table, page 34 of a4001016 study report)

Mean plasma concentration profiles are presented in the figure below.

Figure 1 Plasma concentration time profile for maraviroc



(Sponsor's Figure 1.1, page 135 of a4001016 study report)

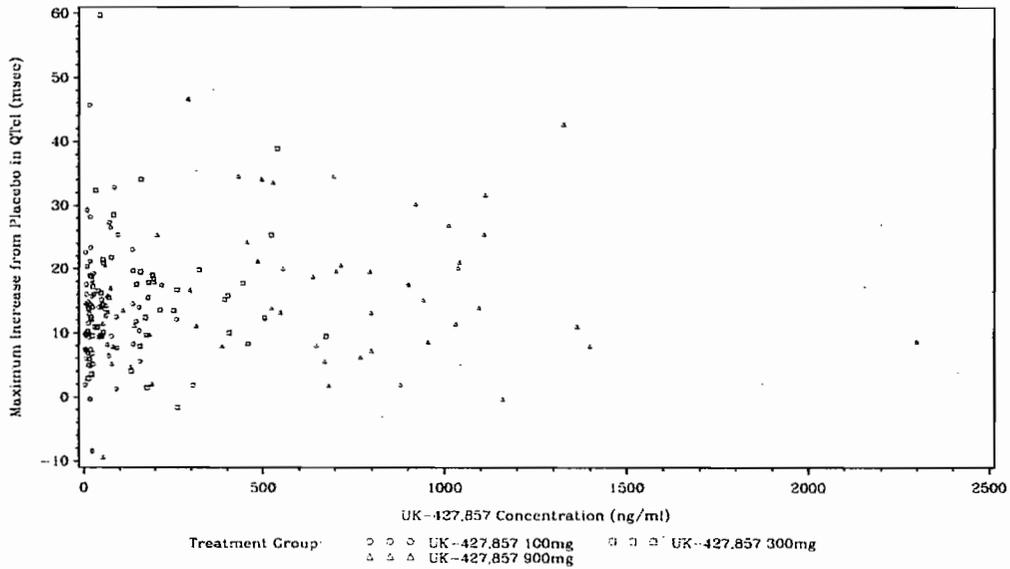
4.2.9.4.2 Exposure-Response Analysis

For each subject, the QT: RR relationship was evaluated from measurements made pre-dose in the five study periods and on the run-in day of study period 3. A non-linear mixed effect model was used to estimate the correction factor for each subject (bs). QTcI was calculated using these correction factors, $QTcI_s = QT/(RR)^{bs}$. The QTc interval corrected for heart rate using Bazett's formula [$QTcB = QT/(RR)^{1/2}$ where $RR=60/HR$] and Fridericia's formula [$QTcF = QT/(RR)^{1/3}$ where $RR=60/HR$] were also calculated.

There was no clear relationship between the maximum increases from baseline in QTcI versus the maraviroc plasma concentrations at the time of the maximum increase from placebo (Figure 2). Similarly, there was no clear relationship between the change from placebo in QTcI versus the maraviroc plasma concentrations at an individual's T_{max} (Figure 3). The change from placebo in QTcI is plotted against the maraviroc plasma concentrations and time in Figure 4.

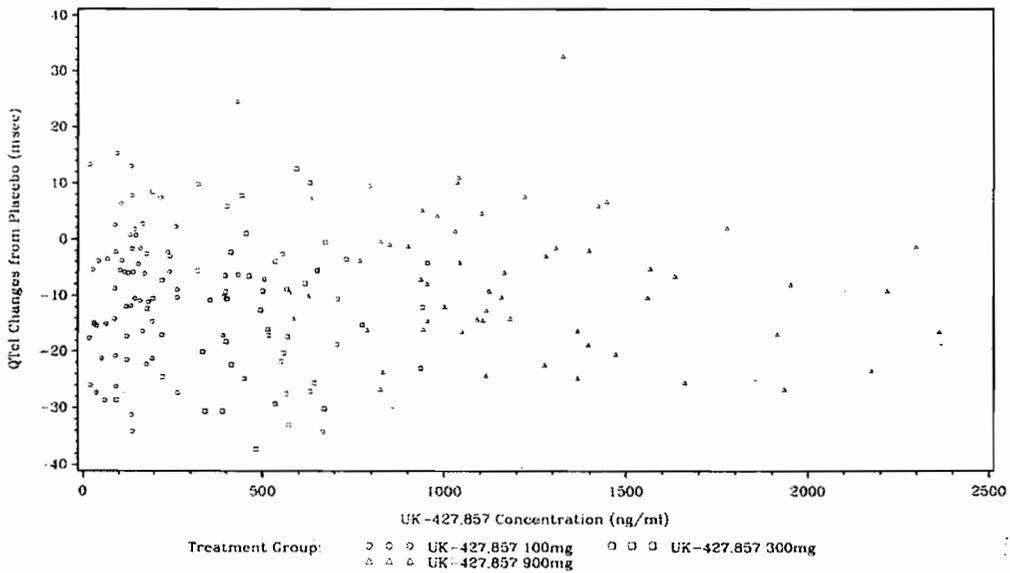
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Figure 2: The relationship between the maximum increase from baseline in QTcI versus the maraviroc plasma concentration at the time of the maximum increase from placebo



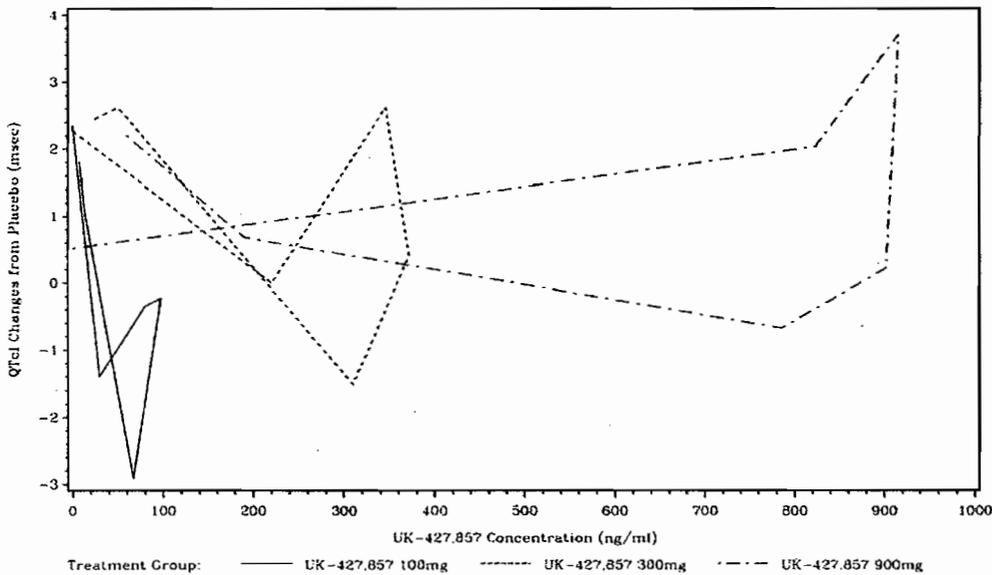
(Sponsor's Figure 4.1.1, page 154 of a4001016 study report)

Figure 3: The relationship between the change from placebo in QTcI versus the maraviroc plasma concentrations at an individuals Tmax



(Sponsor's Figure 4.1.2, page 155 of a4001016 study report)

Figure 4: The change from placebo in QTcI is plotted against the maraviroc plasma concentrations and time



(Sponsor's Figure 4.1.3, page 156 of a4001016 study report)

The results indicate that maraviroc at single doses up to and including 900 mg does not have any clinically relevant effect on QTcI. The mean difference from placebo in QTcI for all the primary endpoints was less than 4 ms for all three doses of maraviroc (100, 300 and 900mg). Furthermore, the upper limits of the 90% CI were below 7 ms for all endpoints. For the active comparator, moxifloxacin, the mean difference in QTcI for all three endpoints was between 12 and 14 ms. There did not appear to be any differences in the magnitude of the effects of maraviroc and moxifloxacin between male and female subjects.

No clear relationship between maraviroc plasma concentration and maximum increase in QTcI was observed at the time of the maximum increase from placebo. Similarly, there was no clear relationship between the change from placebo in QTcI versus the maraviroc plasma concentrations at an individuals Tmax.

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

The statistical reviewer's evaluation is based on the sponsor's data and in accordance with **E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs**.

Data set EVAL1.xpt was used by the statistical reviewer in the statistical evaluation. The statistical reviewer performed independent analyses based on **mean change in QTcI from baseline at each time point post-dose** to verify the sponsor's findings. Note that the results the statistical reviewer got are slightly different from those of the sponsor. This can due to: (1) The data set EVAL might not be exactly the data set the sponsor used

in its analyses. (2) Some data manipulations might be done by the sponsor for the analyses. (3) The statistical model the sponsor used was different from that of the statistical reviewer.

5.2 STATISTICAL ASSESSMENTS

Table 7 through Table 9 describe characteristics of the subjects in the study.

Table 7: Number of subjects by sex

Sex	N	%
Male	30	49.18
Female	31	50.82
Total	61	100.00

Source: DEMOG

Table 8: Number of subjects by race

Race	N	%
Asian	2	3.28
Black	1	1.64
White	58	95.08
Total	61	100.00

Source: DEMOG

Table 9: Analysis of ages of the subjects

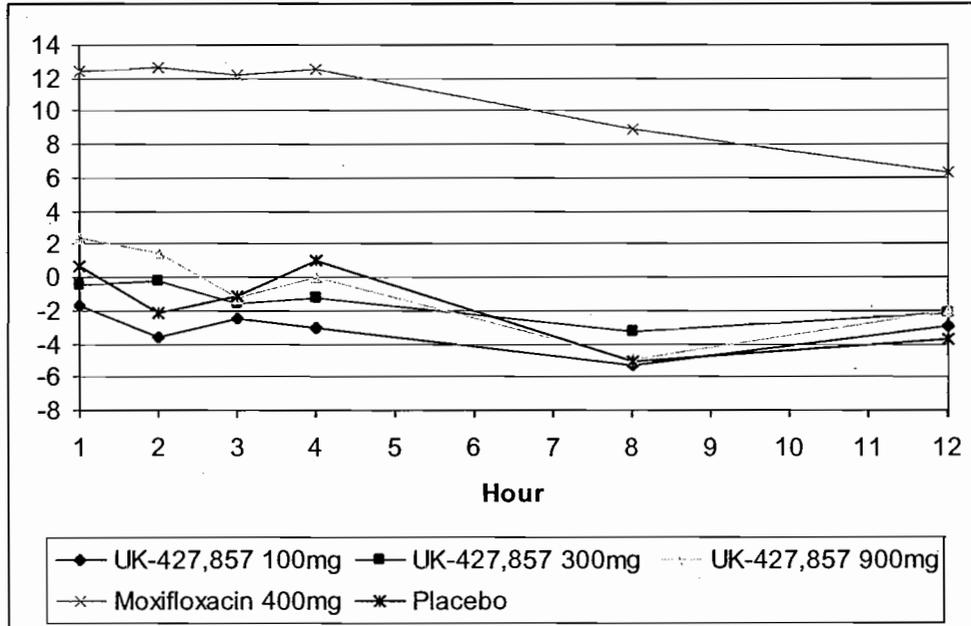
Treatment	
Number of subjects	61
Mean	30
Minimum	19
Maximum	44

Source: DEMOG

Figure 5 shows a graph depicting raw mean QTcI changes from baseline by time.

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Figure 5: Raw mean QTcF changes from baseline by time



Source: EGEL1

Table 10: Number of subjects included in the study

TREATMENT	#SUBJECT
UK-427,857 100 mg	59
UK-427,857 300 mg	58
UK-427,857 900 mg	58
Placebo	59
Moxifloxacin 400mg	58

Source: EGEL1

The statistical reviewer used SAS Proc Univariate procedure to calculate the 2-side 90% confidence interval of Delta-delta QTcI Mean Change. ($\Delta\Delta\text{QTcI} \pm 1.64 \text{ Stderr}$), which is more conservative than the sponsor's Mixed Model. Statistical Analysis results are shown in Table 11 below.

Table 11 Reviewer's Analysis of Delta-delta QTcI Mean Change at Each Time Point

Treatment Group	Hour	N	Estimate	Standard error	Lower	Upper
UK-427,857 100 mg	1	59	-1.40	1.81	-4.38	1.58
	2	59	-0.35	1.60	-2.98	2.29
	3	59	-0.22	1.48	-2.65	2.21
	4	59	-2.92	1.56	-5.48	-0.35
	8	59	1.03	1.64	-1.67	3.74
	12	59	1.81	1.28	-0.30	3.92
UK-427,857 300 mg	1	58	-0.01	1.55	-2.56	2.55
	2	58	2.63	1.75	-0.25	5.50

	3	58	0.41	1.29	-1.71	2.53
	4	58	-1.52	1.47	-3.94	0.90
	8	58	2.62	1.68	-0.15	5.39
	12	58	2.41	1.48	-0.03	4.85
UK-427,857 900 mg	1	58	2.03	1.65	-0.68	4.74
	2	58	3.71	1.57	1.13	6.28
	3	58	0.22	1.55	-2.33	2.77
	4	58	-0.67	2.01	-3.97	2.63
	8	58	0.68	1.66	-2.06	3.41
	12	58	2.23	1.51	-0.25	4.72
Moxifloxacin 400mg	1	58	10.17	1.51	6.56	13.78
	2	58	13.09	1.66	9.11	13.09
	3	58	11.79	1.78	7.53	35.90
	4	58	10.04	1.65	6.09	10.04
	8	57	12.29	1.81	7.96	17.17
	12	58	8.79	1.54	5.10	8.79

Source: EGEL1

For all three doses of UK-427,857 (100 mg, 300 mg, and 500 mg) and all the different Hours, the upper limit of the 2 sided 90% Confidence Intervals for the UK-427,857 vs. placebo differences after baseline adjustments were below the 10 ms threshold. The maximum upper limit for UK-427,857 100 mg was 3.92 and observed at Hour 12. The maximum upper limit for UK-427,857 300 mg was 5.39 and observed at Hour 6. The maximum upper limit for UK-427,857 900 mg was 6.28 and observed at Hour 2.

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Figure 6 through Figure 9 depicts the CIs for mean change from baseline at each time point post-dose for all four treatment groups.

Figure 6: 90% 2-sided CIs for mean change from baseline at each time point post-dose for UK-427,857 100 mg

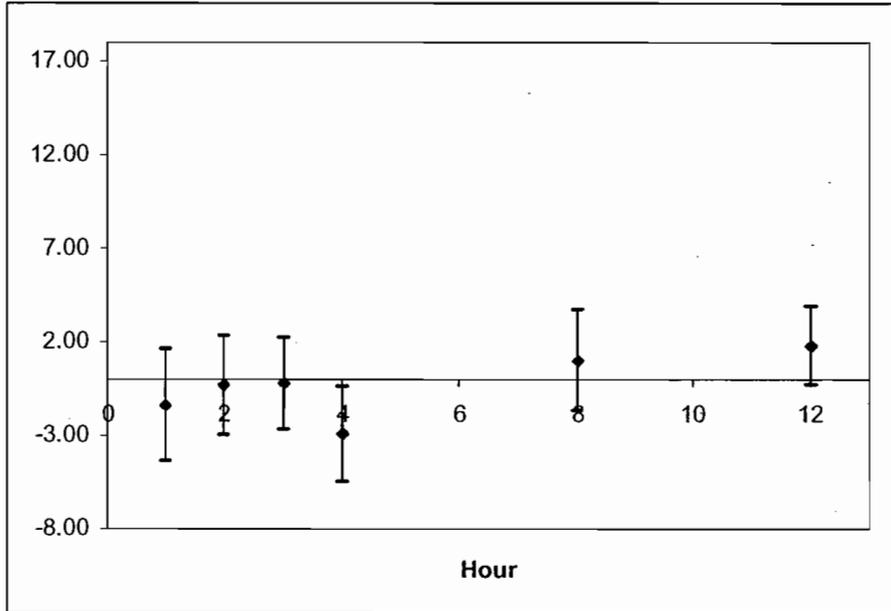


Figure 7: 90% 2-sided CIs for mean change from baseline at each time point post-dose for UK-427,857 300 mg

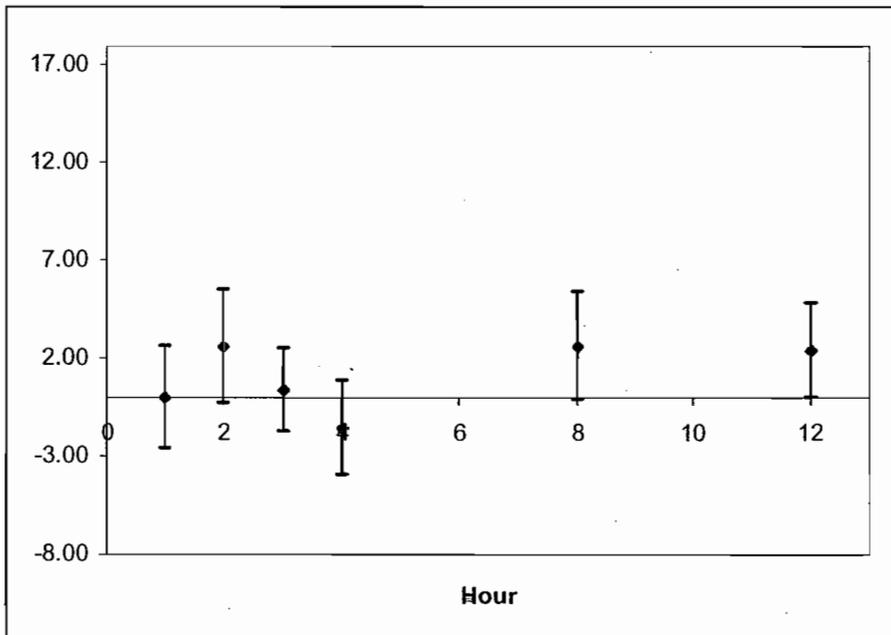


Figure 8: 90% 2-sided CIs for mean change from baseline at each time point post-dose for UK-427,857 900 mg

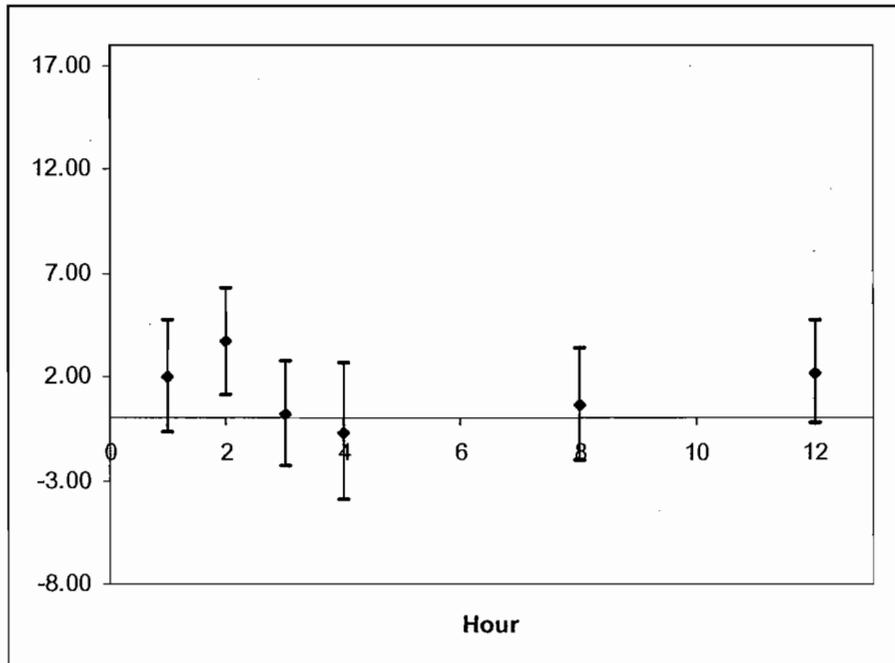
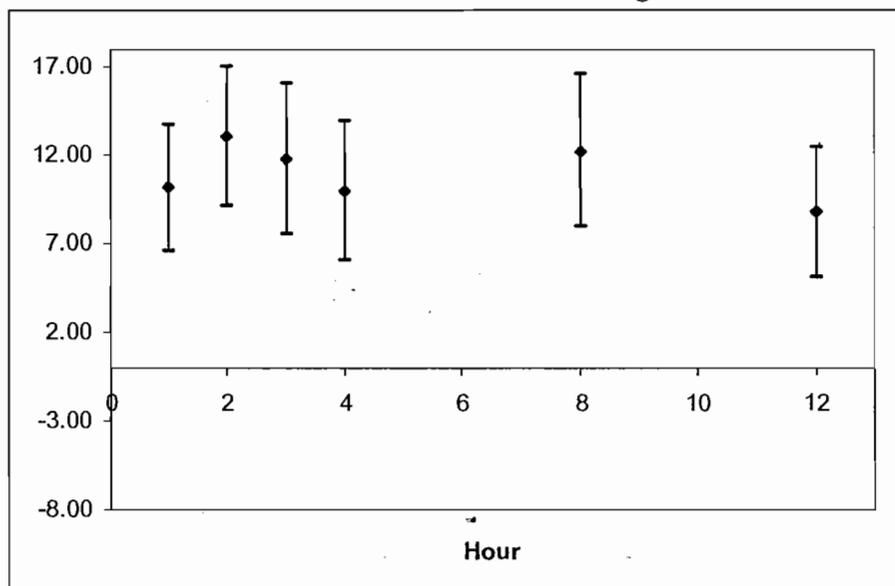


Figure 9: 90% 2-sided CLs for mean change from baseline at each time point post-dose for Moxifloxacin 400 mg



5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

5.3.1 Concentration-QTc Analysis

Plasma concentration- time profile presented by the sponsor in Figure 1 was revised to include 95% CI (Figure 10). The concentration-QTc relationship presented by the sponsor in Figure 2 and Figure 3 was revised to include all concentration points and differentiate between dose groups (Figure 11). The hysteresis investigated by the sponsor in Figure 4 was revised to include 95% CI (Figure 12).

Overall, we agree with the sponsor's conclusion that (1) there is minimal or no observable hysteresis in concentration-QTc relationship (2) within the concentration studies, maraviroc seem not to prolong QTc based on the concentration-dQTc relationship.

Additionally, the time course of QT, RR, QTc, dQTc was investigated (Figure 13 - Figure 17). Two types of baseline/placebo adjustments were investigated. Since the placebo was administered on the run-in day of period 3, theoretically, there are two placebo occasions were available per patient. The change from baseline QTc (dQTc) represents the use of run-in day as a placebo adjustment and the change from placebo QTc (dQTc) represents the use of data from placebo period as an adjustment (Figure 16 and Figure 17).

The results from the moxifloxacin arm are unusual because moxifloxacin appears to prolong QT at all time points reported (dQT_{C95%} lower confidence limit > 5 msec). Blood was not collected to assay moxifloxacin concentration; therefore, the source of these unusual findings is not resolved.

Figure 10: FDA Analysis: The plasma concentration (ng/mL)-time (hr) profile of maraviroc by dose groups (mean \pm 95% CI)

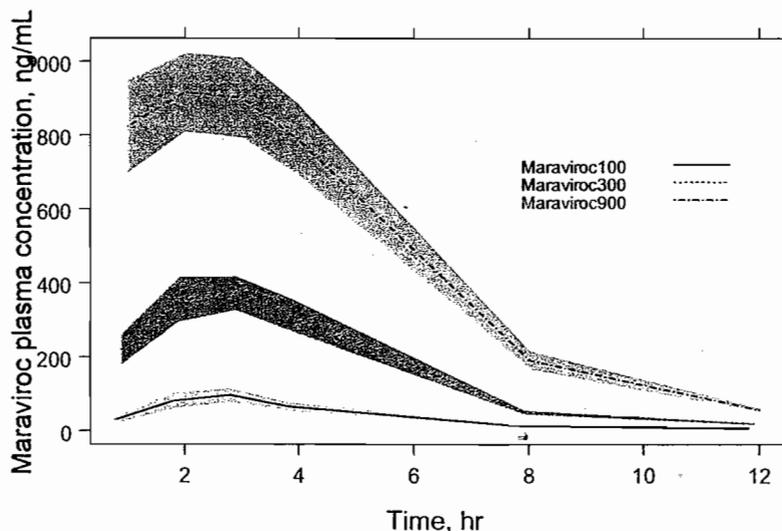


Figure 11: FDA Analysis: The scatter plot for relationship between change from placebo QTc (dQTc), msec and mean plasma concentration (ng/mL) by dose groups

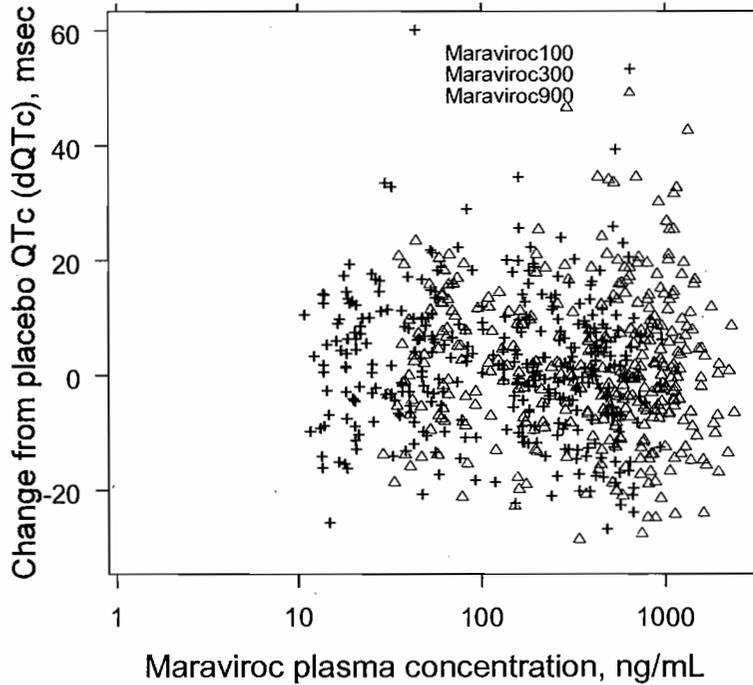


Figure 12: FDA Analysis: The relationship between change from placebo QTc (dQTc), msec and mean plasma concentration (ng/mL) by time and dose groups (mean \pm 95% CI with one sided error bars plotted for clarity)

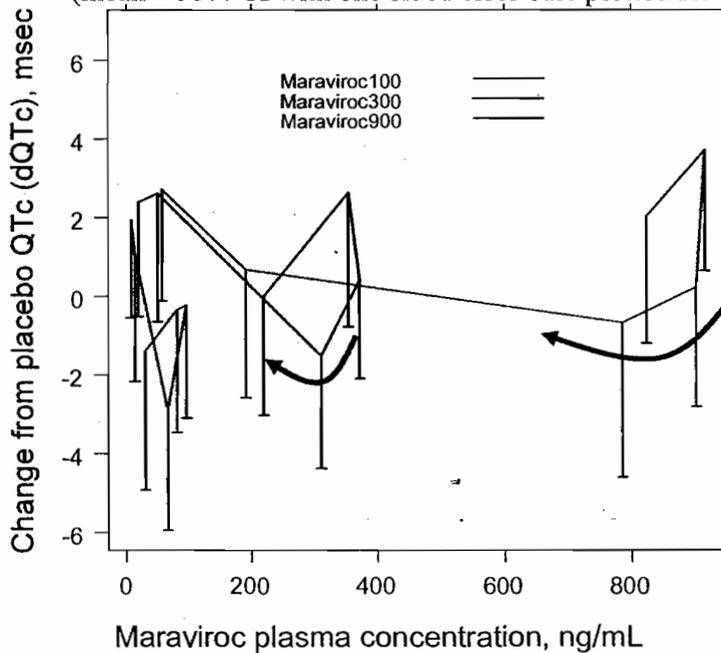


Figure 13: FDA Analysis: The relationship between raw QT, msec and time, hr by dose groups (mean \pm 95% CI with error bars offset for clarity)

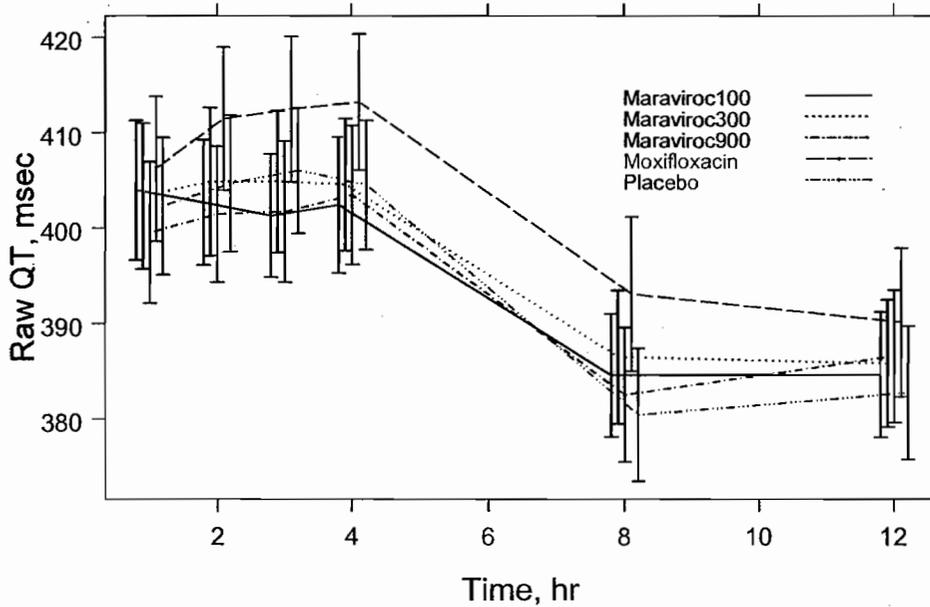


Figure 14: FDA Analysis: The relationship between RR, msec and time, hr by dose groups (mean \pm 95% CI with error bars offset for clarity)

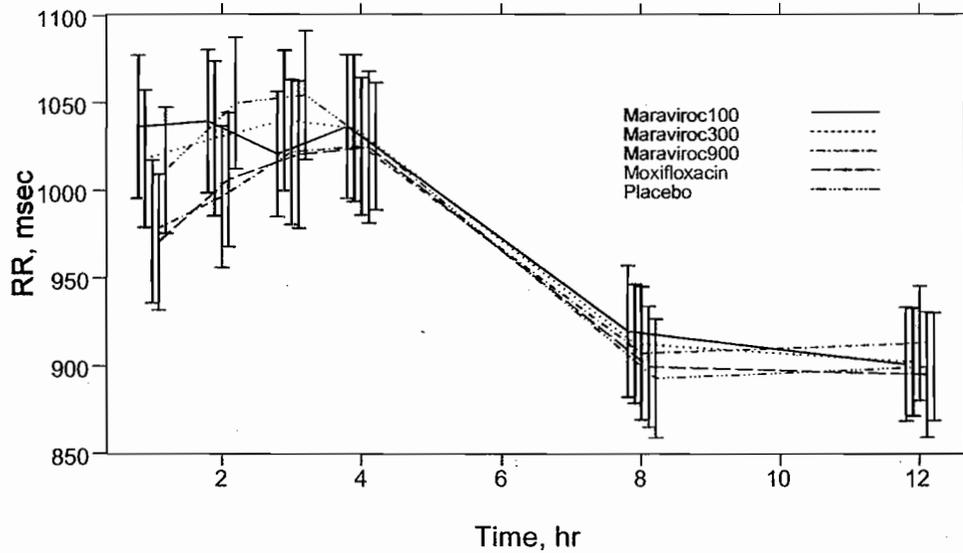


Figure 15: FDA Analysis: The relationship between individual corrected QT (QTc), msec and time, hr by dose groups (mean \pm 95% CI with error bars offset for clarity)

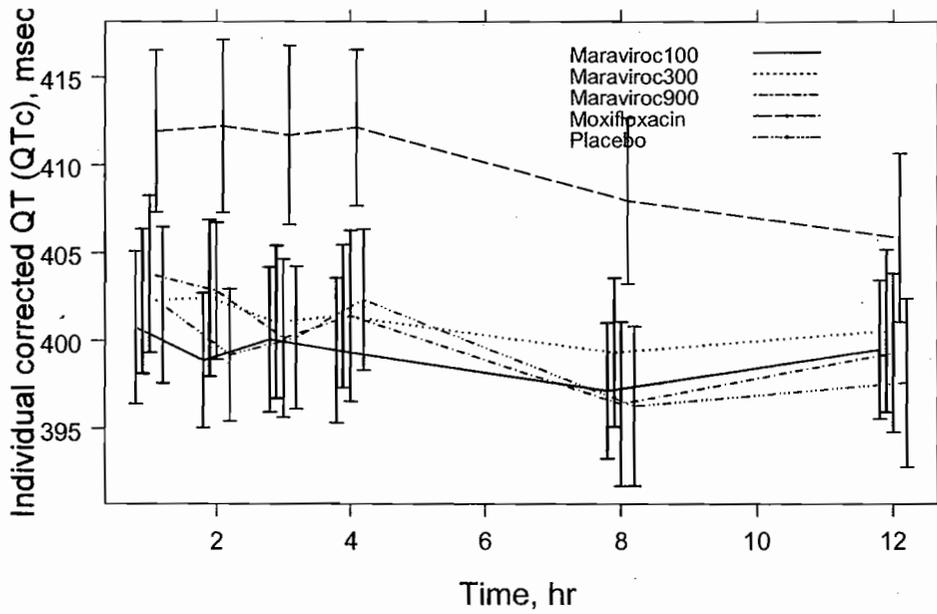


Figure 16: FDA Analysis: The relationship between change from baseline QTc (dQTc), msec and time, hr by dose groups (mean \pm 95% CI with error bars offset for clarity)

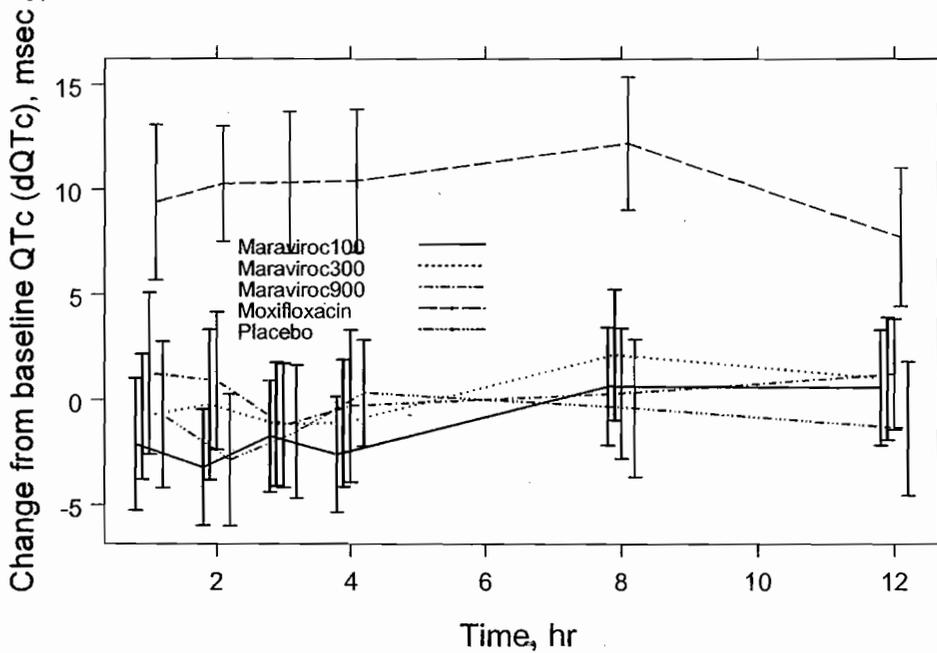
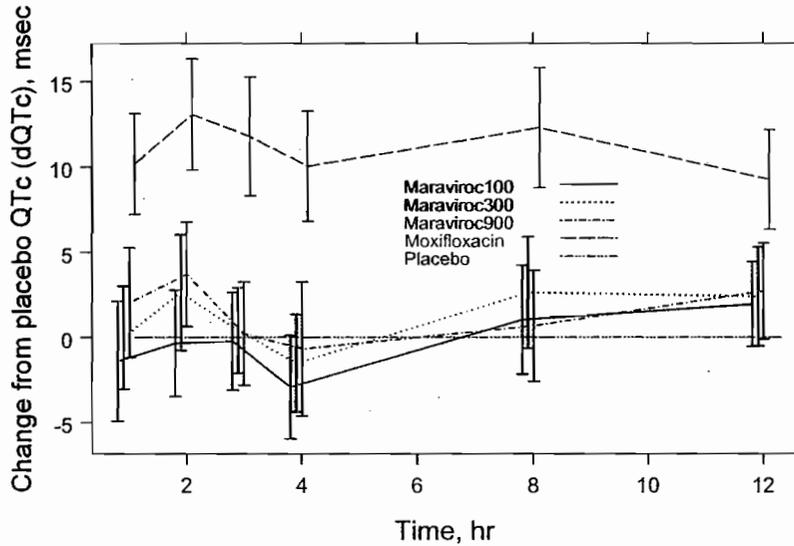


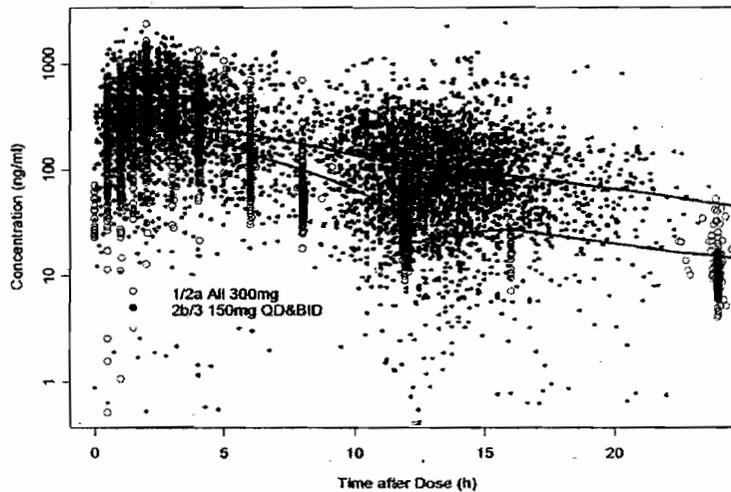
Figure 17: FDA Analysis: The relationship between change from placebo QTc (dQTc), msec and time, hr by dose groups (mean \pm 95% CI with error bars offset for clarity)



5.3.2 Adequacy of Dose

Figure 18 displays maraviroc concentration versus time after dose: 150 mg QD and BID data from combined phase 2b/3 overlaid with all 300 mg phase 1/2a data. Figure 10 to Figure 11 illustrate the range of concentration observed in the QT study with single doses of 100, 300 and 900 mg maraviroc. The doses used in the current QT study yield concentrations similar to the range of concentrations observed in the phase 2b/3 studies.

Figure 18: Maraviroc concentration versus time after dose: 150 mg QD and BID data from combined phase 2b/3 overlaid with all 300 mg phase 1/2a data. (lines=lowest smooth)



(Sponsor's Figure 9, page 47 of Final population pharmacokinetic analysis; amendment 036)

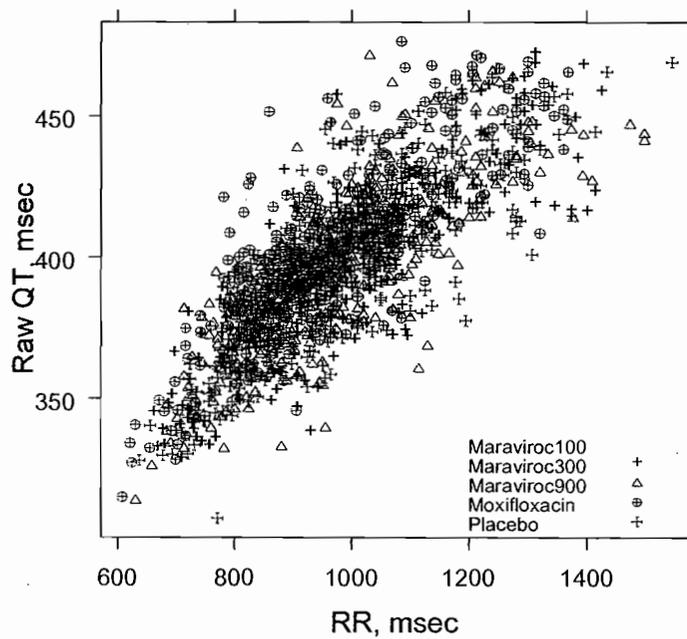
5.3.3 Adequacy of Sampling Times

The sampling times and study duration are adequate for exploring effects on the QTc that correlate directly with serum concentration of maraviroc. The T_{max} is ~2 hrs and the major fraction of drug is eliminated within 12 hrs. Generally the QTc should be measured at 24 hours at least to allow exploration of possible delayed pharmacodynamic effects on the QTc interval.

5.3.4 Adequacy of QT Correction Factor

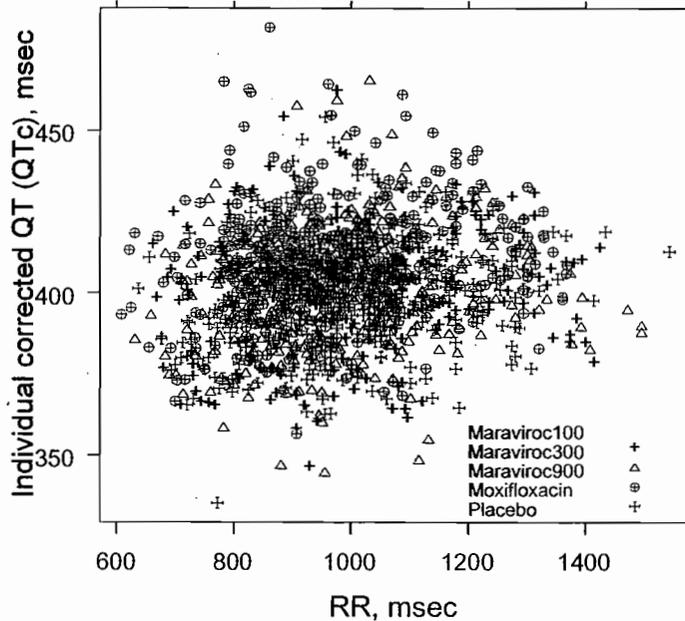
Figure 19 illustrate relationship between raw QT (msec) and RR (msec), The individualized correction factor seem to perform well based on the relationship presented in Figure 20.

Figure 19 FDA Analysis: The scatter plot for relationship between raw QT and RR intervals by dose groups



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Figure 20 FDA Analysis: The scatter plot for relationship between QTc and RR intervals by dose groups



5.3.5 Conclusion

- With the concentration range studied, maraviroc does not to prolong QTc based on the concentration-dQTc relationship.
- Individualized correction factor adequately corrects for the QT-RR relationship.
- The results from the moxifloxacin arm are slightly unusual. It seems that moxifloxacin prolongs QT at all time points (dQTc_{95%} lower confidence limit > 5 msec). Moxifloxacin concentrations were not collected; therefore, the source of these unusual findings is not resolved.

5.4 CLINICAL ASSESSMENTS

5.4.1 ADVERSE EVENTS

None of the adverse events identified s significant in the ICH E14 guidelines were observed during the trial.

5.4.2 ECG WAREHOUSE

ECGs from this study were not provided to the ECG warehouse.

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