MEMORANDUM

DATE:	April 24, 2007
TO:	FDA Antiviral Products' Advisory Committee Members/Guests
FROM:	Maraviroc Review Team
THROUGH:	Edward Cox, MD, MPH Acting Director, Office of Antimicrobial Products Debra Birnkrant, MD Director, Division of Antiviral Products
DRUG:	CELSENTRI® (maraviroc) 150 or 300 mg tablets
APPLICANT'S PROPOSED INDICATION:	CELSENTRI (maraviroc), in combination with other antiretroviral agents, is indicated for treatment-experienced adult patients infected with CCR5-tropic HIV-1

1.0 INTRODUCTION

The purpose of this document is to provide the Antiviral Products' Advisory Committee with a summary of FDA analyses of data submitted in support of a request for accelerated approval of maraviroc, the first in a new class of antiretroviral drugs called CCR5 receptor antagonists. During the Advisory Committee meeting to be held on April 24, 2007, the Committee will be asked to consider the safety and efficacy data and provide comments regarding the following issues:

1. Potential safety issues

   Due to the mechanism of action of maraviroc, a concern during clinical development has been the possibility of an increase in infection or malignancy with its use. Of note, a possible association of lymphoma with a different CCR5 co-receptor antagonist, vicriviroc, has been reported. [1] In addition, the clinical development of another drug in the same class, aplaviroc, has been terminated due to concerns of hepatotoxicity. [2] These safety issues and other safety concerns related to the development of CCR5 receptor antagonists were discussed at a

[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

collaborative meeting of FDA and the Forum for Collaborative HIV Research (a Draft report of this meeting is included in FDA's background package as an attachment). Lastly, the potential of maraviroc to cause QT prolongation was raised during pre-clinical development. The Committee will be asked to provide recommendations regarding the possible need for special labeling as well as whether additional clinical trials should be performed to address particular safety issues.

2. Additional clinical data in patient subgroups

   As 90% of subjects in the two pivotal phase 2b/3 trials (Studies 1027 and 1028) were men and 83% were Caucasian, there was little data provided in women and African-Americans to allow substantive evaluation of safety and efficacy in these groups. The Committee will be asked to comment on any additional data that should be obtained in these groups, and to recommend an appropriate timeframe for when the additional information should be obtained and provided to the Agency for review.

3. Potential for use of therapeutic drug monitoring

   Exposure-response analyses suggest that virologic success is associated with maraviroc trough concentrations. Subjects with lower maraviroc trough concentrations appeared to experience a decrease in efficacy. This finding suggests that dose adjustments based on therapeutic drug monitoring may be beneficial. However, such a treatment strategy was not directly assessed during the phase 2b/3 clinical program. The Committee will be asked to comment on whether the use of a maraviroc dosing algorithm that incorporates both a pharmacokinetic measure and virologic response would be appropriate.

4. View on the risk of tropism changes

   There appeared to be an increase in CXCR4-tropism shifts associated with maraviroc use. In addition, an association between CXCR4-tropism status and more advanced HIV disease has previously been described. In light of some of the concerns with tropism testing (i.e., whether suppression of CCR5-tropic virus may lead to unmasking of CXCR4-tropic virus that was already present), the Committee will be asked to comment on the risk that these apparent tropism shifts may represent. The Committee will also be asked how the tropism test should be used in the clinic for initiating treatment and for monitoring for tropism changes.

Four classes of antiretroviral drugs have been approved for the treatment of HIV: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), 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, and lactic acidosis and

emergence of resistance can sometimes limit their efficacy. Therefore, an important goal has been the development of new medications for the treatment of HIV in order to provide additional treatment options for those patients who are intolerant or develop resistance to currently available options.

Maraviroc is a reversible CCR5 co-receptor antagonist. The CCR5 co-receptor is located on T-cells and macrophages, among other cells. Maraviroc blocks the interaction of CCR5 tropic HIV-1 gp120 with the CCR5 co-receptor, an essential step in viral entry. Site-directed mutagenesis and computer modeling studies have determined that the likely binding site of maraviroc is a pocket within the transmembrane region of CCR5. As a consequence of this binding, maraviroc is thought to alter the structure of CCR5 such that the viral envelope glycoprotein, gp120, is unable to recognize and bind to the co-receptor. The active ingredient of maraviroc is not approved in the United States or elsewhere, and there are no pharmacologically related products that have received marketing approval.

2.0 PRECLINICAL DATA

2.1 General Toxicology

Single dose studies

Single dose oral administration of maraviroc to mice and rats produced no effects of treatment at 2000 mg/kg. These studies were conducted in compliance with GLP regulations. These data were broadly consistent with those observed in safety pharmacology studies in rats, in which there were mild effects on appearance and behavior at an oral dose of 1000 mg/kg and adverse effects characterized by decreased activity, respiratory changes and vocalization at 2000 mg/kg.

Repeat dose studies

Repeat-dose oral toxicity studies were conducted in rats and dogs for up to 6 months, in mice for up to 3 months, and in monkeys for up to 9 months; these species are routinely used in the safety evaluation of new chemical entities. All pivotal studies were conducted in conformance with appropriate ICH guidelines and GLP regulations. The results of repeated dose toxicology studies indicated that the applicant's proposed dose of 300 mg bid is supported by the no observed effect levels/no observed adverse effect levels (NOELs/NOAELs) achieved in the studies and because maraviroc exposure multiples at the NOELs/NOAELs are higher than that of the proposed clinical dose. The following principal target organs/tissues in animal studies were identified:

Liver
Repeat-dose toxicology studies in mice, rats, dogs and monkeys identified the liver as a target organ in rats only. Bile duct vacuolation was present from 100 mg/kg and was associated with minimal bile duct hyperplasia from 300 mg/kg. At higher dose levels, while the incidence of bile duct changes increased, there was no increase in the severity. In male rats, bile duct hyperplasia was still present 3 months after withdrawing the treatment, but was fully reversed in female rats. These changes are possibly a mild response to the biliary excretion of maraviroc or its metabolite.

Blood pressure and Heart rate
Toxicology studies in monkeys indicated reductions in blood pressure at daily doses of 200 and 400 mg/kg, accompanied at 400 mg/kg by lower heart rates. The doses of 200 mg/kg (1-month study) and 400 mg/kg (9-month study) were associated with similar unbound plasma concentrations (1815 ng/mL and 1718 ng/mL, respectively) and were approximately 11-fold higher than that observed in humans with the applicant's proposed dose of 300 mg twice daily. No effects on blood pressure or heart rate were observed at 120 mg/kg in the 9-month study, with a plasma concentration 5-fold that observed in humans with the applicant's proposed.

Studies in dogs indicated no significant changes in blood pressure at plasma concentrations 3-6-fold that observed in humans with the applicant's proposed dose and only inconsistent reductions in blood pressure in individual animals at concentrations 5- and 9-fold that at the applicant's proposed dose. Maraviroc produced a slight impairment of normal reflex control of blood pressure in the dog during the change to the upright position at plasma concentrations 3-6 fold the concentrations at the applicant's proposed dose. However once the upright position had been established, blood pressure control was maintained at a normal level. While maraviroc produced no obvious postural hypotension in the conscious dog, the effects on the initial reflex response might be sufficient to cause symptoms of postural dizziness in humans.

QT interval prolongation
In vitro studies showed that maraviroc inhibited dofetilide binding. Maraviroc was active at the human cardiac hERG channel and prolonged the action potential of the dog Purkinje fiber at concentrations ≥3 μM or 1541 ng/mL. These results indicated that maraviroc has the potential to block the I_{Kr} current and affect cardiac repolarization in vivo at unbound plasma concentrations greater than 3 μM, which was approximately 10-fold the Cmax observed in humans with the applicant's proposed dose.

These changes were consistent with findings from toxicology studies in which maraviroc increased QTc interval at doses of ≥15 mg/kg in dogs and ≥200 mg/kg in monkeys. The unbound plasma concentrations at these lowest effect doses (899 and 1815 ng/mL) represent exposure multiples of 6- and 12-fold, respectively. In these two species, doses of 5 mg/kg and 120 mg/kg, respectively, had no effect on QTc interval at plasma concentrations 2- and 5-fold the Cmax observed in humans with the applicant's proposed dose. The blockade of cardiac potassium channels can cause prolongation of action potential duration, thereby delaying ventricular repolarization, lengthening QT interval and increasing the risk of serious arrhythmias, such as Torsade de pointes. This activity

of maraviroc was considered to represent a low risk to humans given that the ion channel effects occur at a plasma concentration that was 10-fold the maximum concentration observed during clinical testing (155 ng/mL) with the applicant's proposed dose. Furthermore concentrations in dogs and monkeys have been explored up to 23- and 43-fold, respectively, those seen at the therapeutic dose, with no evidence of cardiac arrhythmias.

In conclusion, in vitro studies and animal data from dogs and monkeys indicated that maraviroc had potential for QT interval prolongation in human patients and provided a cautionary signal to investigators throughout the clinical program. Cardiovascular testing in these species has confirmed no arrhythmogenic activity at plasma exposures several times greater than those expected in humans at the therapeutic dose.

Thyroid gland

In rats only, thyroid follicular cell hypertrophy was noted in the 6-month study from 300 mg/kg, and was shown to be reversible when treatment was withdrawn. Pituitary vacuolation was observed in the 1-month study at 1500 mg/kg. The interdependence of thyroid and liver changes was established in an investigative study in rats. The thyroid of rats is particularly sensitive to disturbances in thyroid hormone metabolism as they lack thyroxine-binding globulin, resulting in a shorter half-life of T4 than in humans. The hepatic changes were consistent with an adaptive response to treatment and were associated with an increase in the activity of hepatic xenobiotic metabolism. Activation of hepatic uridine 5-diphosphate glucuronyl transferase (UDPGT) brought about an increased thyroxine clearance, resulting in a reduction in circulating concentrations of this hormone. Hepatic UDPGT was responsible for conjugation of thyroxine prior to excretion into the bile. Lower plasma concentrations of thyroxine stimulate the pituitary, through a negative feed-back mechanism, to release thyroid stimulating hormone (TSH), resulting in a hypertrophic response on the thyroid epithelium and eventually to proliferative changes of thyroid follicular cells.

Immunotoxicity

The compound has no activity against a number of in vitro human immune function assays, including activity against a number of related chemokine receptor assays. In repeat-dose toxicology studies in mice, rats, dogs (up to 6 months duration) or monkeys (up to 9 months duration), maraviroc produced no alterations in circulating white blood cell parameters, serum globulins, or noteworthy changes to organ weights or histology of the bone marrow, lymph nodes, spleen or thymus. Similarly there was no increase in the incidence of infections during these studies to suggest impairment of the immune system.

A specific study to investigate the potential of maraviroc to impair the immune system in monkeys showed that treatment for 1-month at daily doses of up to 300 mg/kg induced no changes in lymphocyte subset distribution, NK cell activity, phagocytosis activity or oxidative burst. The daily dose of 300 mg/kg was shown to achieve 100% occupancy of CCR5 co-receptors over 24 hours. There was no adverse effect of maraviroc on the immune system in monkeys at plasma exposures (AUC_{0-24}) producing complete and continuous blockade of CCR5 co-receptors and with an exposure multiple 16-fold greater than observed at 300 mg BID.

2.2 Genetic toxicology

The genotoxic potential of maraviroc was evaluated in a battery of well established and validated in vitro and in vivo test systems. The scope of the overall battery of tests and the individual study designs were in conformance with applicable ICH guidelines. Maraviroc did not display mutagenic activity in a bacterial test system when tested up to cytotoxic concentrations in either the absence or presence of exogenous metabolic activation. Chromosomal damage was not observed in human lymphocytes when maraviroc was tested up to cytotoxic concentrations in both the absence and presence of metabolic activation. Chromosomal damage was also absent in the bone marrow of male and female mice treated orally with maraviroc at a maximum practical dose of 2000 mg/kg/day for 3 days. Thus, maraviroc did not display mutagenic activity in bacterial and mammalian cells in vitro or clastogenic activity in vitro or in vivo.

Carcinogenicity
Carcinogenicity studies in transgenic mice and Sprague Dawley rats were conducted in conformance with ICH Guidelines and in compliance with GLP regulations. Transgenic mice and Sprague-Dawley rats are routinely used in carcinogenicity studies, and were the same strains utilized in pivotal repeat-dose toxicity studies with maraviroc. The carcinogenicity studies were adequately designed, and included verification of exposure at all dosage levels. Dose selection for the carcinogenicity studies was based on ICH guidelines.

The oncogenicity potential of maraviroc was investigated in S-D rats with oral gavage dosages of 50 (low), 100 (mid), 500 (high) or 900 (highest) mg/kg/day in comparison with vehicle controls for a period of 104 weeks in males and 96 weeks in females. All female groups were terminated early when survival in the female control group dropped to 33% (20 of 60 rats surviving to 96 weeks). The systemic exposures were 13 and 18 times that in humans (300 mg bid) in male and female rat at the high dose level, respectively.

No significant increase in neoplasms was noted in male or female animals, although, an increased incidence of follicular cell adenoma of the thyroid was noted in males and females at 900 mg/kg/day. This was accompanied by a dose-related increase in follicular cell hyperplasia and hypertrophy at doses from 100 mg/kg/day in males and from 500 mg/kg/day in females. The tumor incidence was within the historical control range of this strain of rat and no follicular cell carcinomas were found in the thyroid gland.

Cholangiocarcinoma of the liver were found in two males (highest dose). As for the cholangiocarcinomas, apparently rare in the S-D rat, absence of a statistically significant difference between the incidences observed in the high dose and vehicle control groups, rendered the finding less than sufficient to clearly implicate the drug.

The oncogenic potential of maraviroc was investigated in male and female transgenic mice at oral gavage dosages of 0 (vehicle control), MNU = 75 mg/kg ip (positive control), 200 (low), 800 (mid) or 1500 mg/kg/day (high) in comparison with the controls

for a period of 26 weeks. The systemic exposures were 33 and 59 times that in humans (300 mg bid) in male and female mice at the high dose level, respectively.

No drug-related malignant neoplasms or non-neoplastic changes were seen in transgenic mice.

Maraviroc was not found to be a carcinogen in rodents.

2.3 Reproductive and Developmental Toxicology

A complete battery of reproductive toxicity studies was conducted with maraviroc. All pivotal studies were conducted in compliance with GLP regulations, were adequately designed, and met ICH guidelines. Reproduction toxicology studies indicate no effects on fertility at 1000 mg/kg. In addition, there was no effect on reproduction parameters or embryo-fetal development at 1000 mg/kg in rats and 200 mg/kg in rabbits. In the pre-and postnatal study in rats, there was no effect on the reproductive function of treated females up to the dose of 1000 mg/kg. This dose produced a slight increase in motor activity in male F1 offspring. Based on this finding, the NOAEL for development toxicity in the offspring of maraviroc-treated female rats was 300 mg/kg.

2.4 Overall Preclinical Conclusions

To support clinical use, the nonclinical toxicity profile of maraviroc was characterized in an extensive battery of in vitro and in vivo studies including carcinogenicity studies in rats and mice. The pivotal toxicology studies supporting the safety of maraviroc were appropriately designed and conducted in compliance with Good Laboratory Practice (GLP) regulations. Pharmacodynamic studies have adequately demonstrated the high potency and selectivity of maraviroc as a CCR5 antagonist agent for the treatment of HIV-1 infection. Pharmacokinetic analysis has established the absorption, metabolism, distribution and elimination profile of maraviroc. The pathways of maraviroc metabolism in humans were all represented in toxicology species. A toxicology program was completed involving repeat-dose studies, which identified toxicological end-points, together with doses of maraviroc without adverse effects. Maraviroc had no adverse effects on fertility and has no teratogenic potential. Similarly, maraviroc was shown not to be mutagenic or clastogenic in appropriate genetic toxicology assays. Carcinogenicity studies in rats and transgenic mice indicated no carcinogenic potential for humans. In conclusion, the results of extensive nonclinical toxicology and pharmacokinetic evaluation programs support the proposed use of maraviroc in humans. There are no unresolved toxicology issues.

3.0 CLINICAL DATA

3.1 Clinical Pharmacology Results

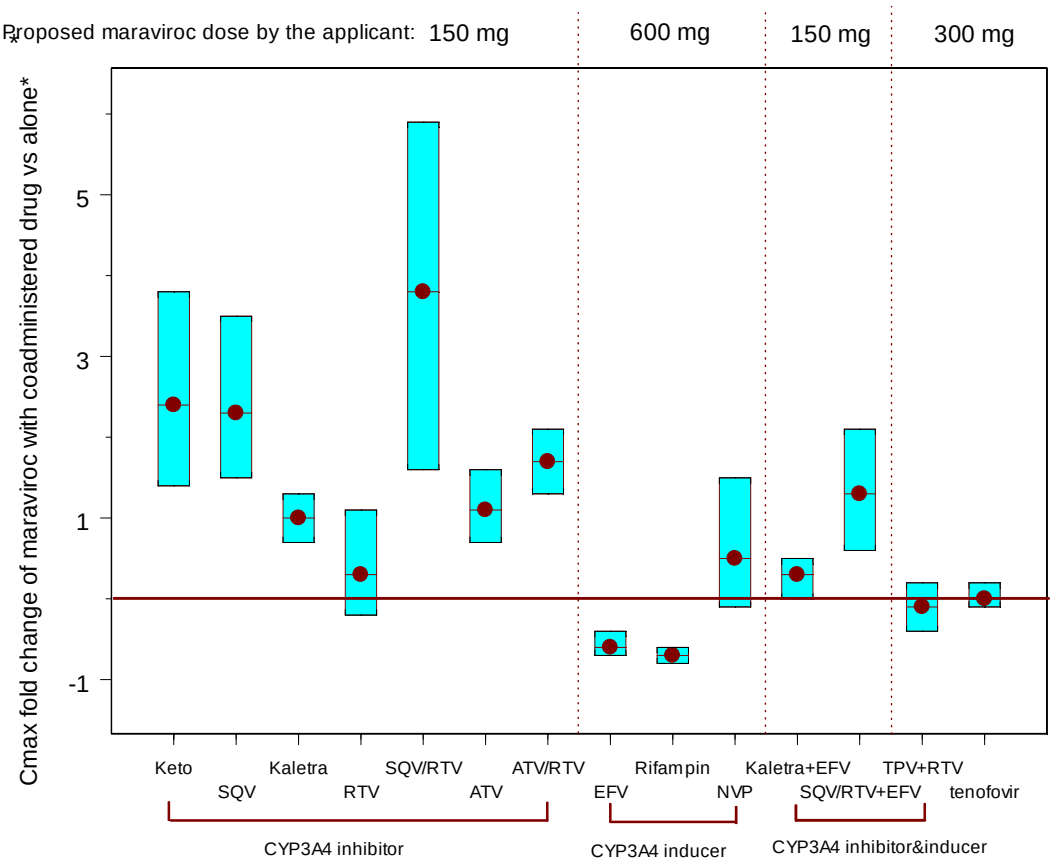
<u>Management of Drug-Drug Interactions</u>

The management of drug-drug interactions is an important issue for maraviroc. The metabolic interaction potential for maraviroc is summarized below. Maraviroc does not affect the pharmacokinetics of drugs primarily eliminated by renal pathways, nor is it affected by the inhibitors of renal transporters.

A. Effects of Other Drugs on Maraviroc

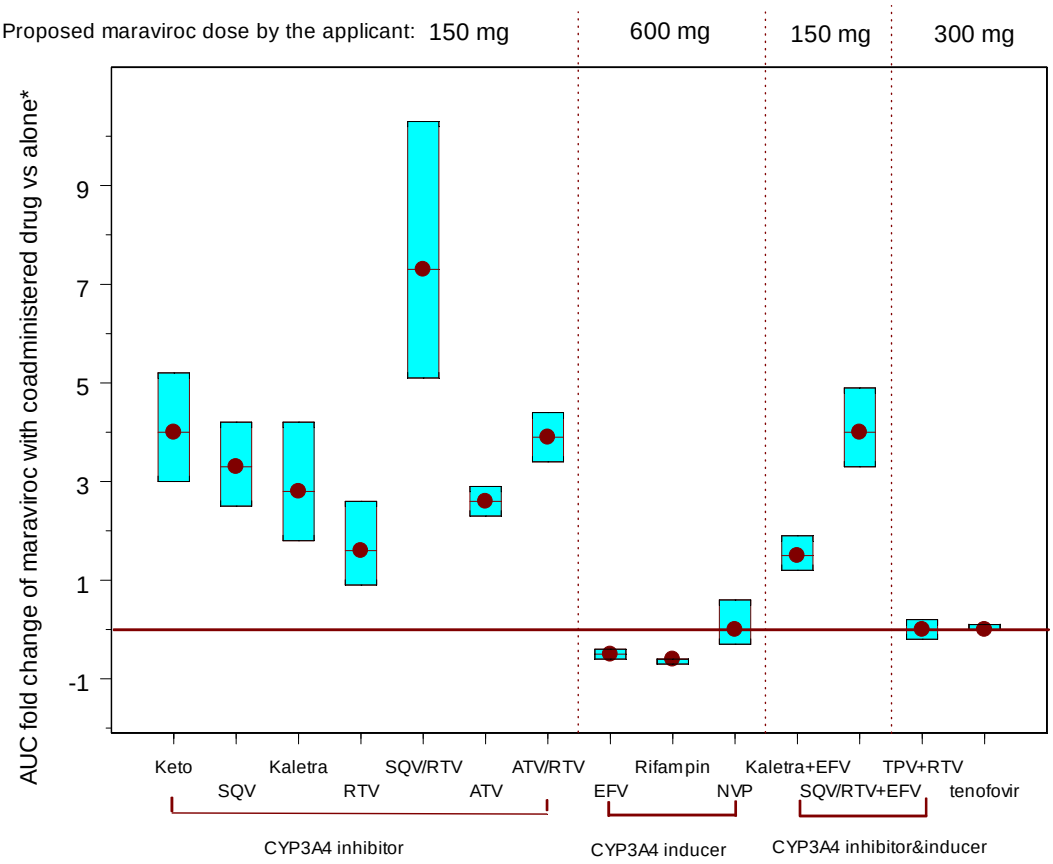
Maraviroc is a CYP3A and P-gp substrate. Since maraviroc will be coadministered with drugs that affect CYP3A and P-gp activity, such as protease inhibitors, the effects of drugs on maraviroc pharmacokinetics were studied in Phase I clinical trials. **Figures 1 and 2** show the effect of CYP3A inhibitors or inducers (some are P-gp inhibitors or inducers as well) on the pharmacokinetics of maraviroc. Tenofovir is also included in the figure, although it does not affect CYP3A or P-gp. The applicant proposes to reduce maraviroc dose to half (eg, 150 mg BID) when it is coadministered with a CYP3A inhibitor with or without a CYP3A inducer, and increase maraviroc dose to 600 mg BID when it is coadministered with CYP3A inducer without a CYP3A inhibitor. The goal of the proposed dose reduction for maraviroc when coadministered with CYP3A inhibitor is to reduce the Cmax to the value obtained with maraviroc 300 mg monotherapy. The proposed regimens are the same as those used in the Phase 3 studies, except for maraviroc when given with a CYP3A inducer (e.g. nevirapine, efavirenz), where maraviroc 300 mg QD or BID was used in Phase 3 studies.

Figure 1: The effect of other drugs on Cmax of maraviroc (from Phase I drug interaction studies)



* Fold change is the ratio of Cmax of maraviroc when combined with other drug to the Cmax of maraviroc when administered alone at the same dose minus 1. The box is the 90% confidence interval (CI) for the fold change.

Figure 2: The effect of other drugs on AUC of maraviroc (From Phase 1 drug interaction studies)



*Fold change is the ratio of AUC of maraviroc when combined with other drug to the AUC of maraviroc when administered alone at the same dose minus 1. The box is the 90% confidence interval (CI) for the fold change.

The data from Phase 3 Studies 1027 and 1028 (**Table 1**) show that when maraviroc 300 mg bid is taken with nevirapine without a protease inhibitor (n=10), AUC (or Cmin) was similar to the AUC (or Cmin) for maraviroc at the same dose when given with efavirenz without a protease inhibitor (n=9), and the AUC (or Cmin) for other 300 mg bid dose group (n=71). Most of the patients in the 300 mg bid dose group had tipranavir/ritonavir in their background therapy. In contrast to other protease inhibitors, a maraviroc dose adjustment (to 150 mg bid) is not needed when tipranavir/ritonavir is part of the background therapy, based on Phase 1 drug interaction results. Based on data from the Phase 3 studies, it is not clear that an increase in the MVC dose from 300 mg bid to 600 mg bid is needed when co-administered with nevirapine or efavirenz without a protease inhibitor.

Table 1: Pharmacokinetics of Maraviroc coadministered with nevirapine and efavirenz (Studies 1027 and 1028, pooled analysis)

	N	AUC (ng.h/mL)			Cmin (ng/mL)		
		Geometric Mean (CV%)	Mean (SD)	Median (Range)	Geometric Mean (CV%)	Mean (SD)	Median (Range)
300 mg maraviroc +nevirapine BID	10	1358 (80%)	1692 (1164)	1283 (613 – 3936)	33.2 (128%)	50.2 (46.9)	34.5 (9.2 -155.8)
300 mg maraviroc +efavirenz BID	9	1375 (74%)	1662 (1061)	1080 (505 – 3296)	34.1 (102%)	46.2 (36.9)	27.3 (9.6 – 106.4)
Other 300 mg maraviroc (no PI, except tipranavir)	71	1304 (118%)	1681 (1025)	1548 (7 - 5225)	33.6 (152%)	49.0 (40.2)	37.4 (0.1 - 204.7)

B. Effects of Maraviroc on Other Drugs

Maraviroc is unlikely to inhibit the metabolism of co-administered drugs that are metabolized by cytochrome P450 enzymes because it does not inhibit the seven major cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) at clinically relevant concentrations in vitro (IC_{50} > 30μM).

Drug interaction studies were performed with maraviroc and other drugs likely to be co-administered or commonly used as probes for pharmacokinetic interactions. Maraviroc had no effect on the pharmacokinetics of zidovudine or lamivudine, suggesting no interactions with drugs eliminated through renal pathways or non-P450 metabolism. Maraviroc had no clinically relevant effect on the pharmacokinetics of midazolam, the oral contraceptives ethinyloestradiol and levonorgestrel and had no effect on the urinary 6β-hydroxycortisol/cortisol ratio, suggesting no induction of CYP3A in vivo. Maraviroc had no effect on the debrisoquine metabolic ratio (MR) at 300 mg BID or less in vivo. However, there was a 2.3-fold increase in debrisoquine MR on treatment at a MVC dose of 600 mg QD compared to baseline, suggesting potential inhibition of CYP2D6 at higher doses.

Food Effect

Phase 1 food effect studies indicate there is a dose dependent and time dependent effect of food when maraviroc is administered with a high fat meal, which was independent of dosage form, as shown in **Table 2**.

Table 2: Summary of the Effect of Food on Maraviroc Pharmacokinetics

Study	Maraviroc Dose	Formulation	Timing of Food	Change of Cmax with food	Change of AUC_{inf} with food
1001	100 mg	Solution	With food	↓88%	↓63%
1004	100 mg	Research Tablet	1h before food	↑3%	↓20%
1004	100 mg	Research Tablet	With food	↓68%	↓52%
1004	100 mg	Research Tablet	1h after food	↓70%	↓49%
1004	100 mg	Research Tablet	2h after food	↓67%	↓42%
1004	100 mg	Research Tablet	4h after food	↓13%	↓21%
1043	300 mg	Commercial Tablet	With food	↓33%	↓33%
1003	600 mg	Research Tablet (4 x 150 tablets)	With food	↓36%	↓33%

Study 1043 showed that food reduced the exposure of maraviroc 300 mg by 33%. The food effect of maraviroc was also assessed in a 10-day Phase 2a study, 1015, to determine whether these effects translated into an effect on antiviral activity. The results of this study showed that although food reduced the Cmax and AUC of maraviroc by approximately 60% and 50% at 150 mg BID, respectively, there was little effect of food on the short-term antiviral activity (change from baseline in viral load $\log_{10}$ copies/mL) of maraviroc, with a -0.103 (90% CI -0.390, 0.185) difference between maraviroc 150 mg fasted and fed treatment groups on Day 11. Consequently, there were no food restrictions in Phase 3 studies.

Other Clinical Pharmacology Findings

After single and multiple oral dosing, maraviroc Cmax generally occurs between 0.5 to 4 hours in both healthy subjects and HIV-1 infected patients. Maraviroc is a substrate of P-gp. The absolute bioavailability of maraviroc increases with dose, probably due to the saturation of P-gp with increased maraviroc concentrations in the gut, which results in more than a dose proportional increase in maraviroc exposure. The absolute bioavailability of a 100 mg dose is 23% and is predicted to be 33% at 300 mg. Intravenous (IV) administration showed approximately linear pharmacokinetics.

Coadministration of a 300mg tablet with a high fat breakfast reduced maraviroc C_{max} and AUC by 33% in healthy volunteers. However, there was little effect of food on antiviral activity in a 10-day maraviroc monotherapy study. Therefore, there were no food restrictions in the Phase 3 studies.

Maraviroc accumulation was approximately 20% for BID dosing and 9% for QD dosing and steady state is observed within 7 days.

Maraviroc is approximately 76% bound to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. The volume of distribution of maraviroc is approximately 194L.

A mass balance study was conducted using a single 300mg dose of ^{14}C-labeled maraviroc in healthy volunteers. Approximately 20% of the radiolabel was recovered in the urine and 76% was recovered in the feces over 168 hours. Maraviroc was the major component present in urine (mean: 8% of dose) and feces (mean: 26% of dose). The remainder was excreted as metabolites. The major metabolites presented were UK-408,027 (22%), an amine analogue (11%) and UK-463,977 (5%). UK-408,027 and UK-463,977 have been evaluated in vitro and show no antiviral activity. All human metabolites have been identified as circulating metabolites in one or more toxicology species tested. In vitro studies indicate CYP3A is the major enzyme responsible for maraviroc metabolism. In clinical studies, CYP3A inhibitors and inducers were shown to modulate the kinetics of maraviroc.

The pharmacokinetics of maraviroc have not been evaluated in subjects with impaired renal function. Renal clearance accounts for about 25% of the total clearance when 300 mg maraviroc is administered alone. However, when maraviroc is coadministered with CYP3A inhibitors, total maraviroc clearance will be reduced while maraviroc renal clearance remains at a similar level as when maraviroc is administered alone; thus the percent of maraviroc clearance due to the renal route will increase with coadministration of CYP3A inhibitors.

A single dose study in subjects with mild or moderate hepatic impairment is currently ongoing. Since maraviroc is metabolized by the liver, concentrations are likely to be increased in these subjects.

The effect of HIV-1 infection on maraviroc pharmacokinetics was assessed in the population pharmacokinetic analysis of pooled Phase 1/2a data. This analysis included 365 healthy subjects and 48 HIV-1 infected patients. The results indicate HIV status (i.e. whether a subject was infected with HIV-1 or not) does not affect maraviroc pharmacokinetic parameters.

The effects of age, gender, and race on maraviroc pharmacokinetics were also assessed in the population pharmacokinetic analysis of pooled Phase 1/2a data. The analysis appeared to indicate that age and gender did not have an impact on maraviroc exposure. However, the results need to be interpreted with caution because no subjects over the age of 65 years were enrolled. Exposure appeared to be slightly increased in Asians (N=95). In addition, a specific study designed to evaluate PK differences between Caucasians and Singaporeans showed no difference between these two populations.

3.2 Clinical Efficacy Results

Studies 1027 and 1028 are 48-week, multicenter, double-blind, randomized, placebo-controlled, phase 2b/3 clinical trials comparing 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 a 300 mg dose equivalent once daily, a 300 mg dose equivalent twice daily, or placebo. All subjects also received optimized background therapy (OBT).

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. Changes to the OBT regimen following the baseline visit were only allowed for protocol-defined virologic failure or in response to an adverse event. These studies are ongoing and will be unblinded to investigators and subjects following the last subject visit at Week 48. However, the Week 24 data are now available and have been submitted in support of this application.

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 dual- or 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 ≥5,000 copies/mL

The demographics and baseline characteristics for the 1049 subjects have been presented by the Applicant. Note that about 41% (430/1049) of the subjects had screening HIV-1 viral load ≥100,000 copies/mL, and 42% (441) were ENF-users. All the baseline characteristics appeared to be well balanced among the three regimens.

Analysis of Primary Endpoint and Sensitivity Analyses

The primary efficacy endpoint was change from baseline in $\log_{10}$ HIV-1 RNA at Weeks 24 and 48. Plasma HIV-1 RNA was determined at screening, randomization, Day 1, Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and at the time of early termination, using the RT-PCR Roche Amplicor v1.5 standard and ultra-sensitive assays. These are superiority trials and if the two-sided 97.5% confidence intervals for each are completely to the left side and completely exclude 0, the superiority of maraviroc over placebo will be concluded.

Of note, 50.7% (106/209) of the subjects in the placebo arms in both studies combined discontinued study treatment by week 24, significantly more (Chi-square test, $p<0.0001$) than from the maraviroc arms, with 29.4% of subjects discontinuing (172/585). Sensitivity analyses were conducted to the investigate time course and pattern of discontinuation using the Kaplan-Meier approach. **Figures 3 and 4** show the results.

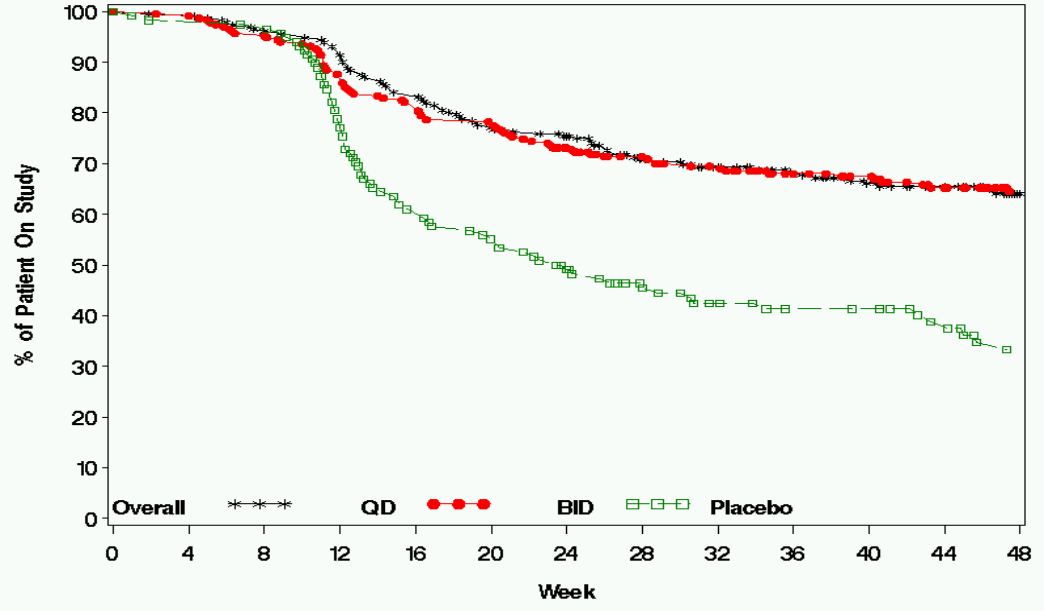


Figure 3. Study 1027: Time to Discontinuation

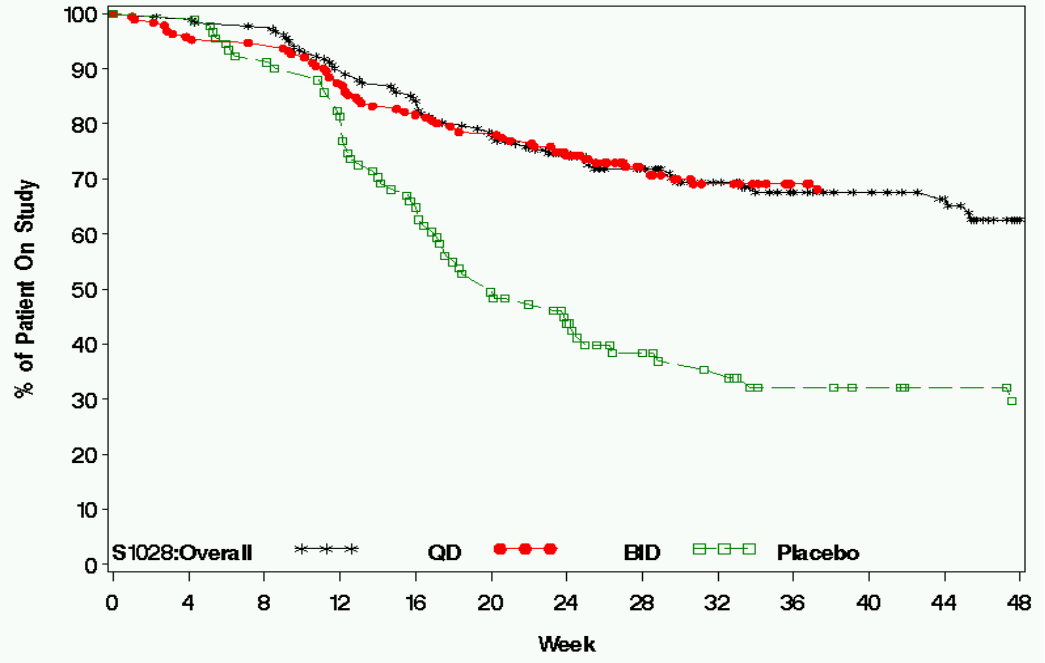


Figure 4. Study 1028: Time to Discontinuation

Overall, the subjects in the two maraviroc regimens had similar patterns in discontinuation, except for the early phase (up to Week 8) of Study 1028.
In Study 1027, the percentage of subjects in placebo regimen who discontinued was 10% at Week 10 and 40% at Week 16. A similar pattern is seen in Study 1028.

Overall, FDA analyses of primary and secondary efficacy endpoints yielded findings that were consistent with the applicant's analyses. We will discuss a number of sensitivity analyses that we have conducted. Because the applicant used a mean of 3 pretreatment HIV-1 RNA values to calculate a baseline value, we conducted a sensitivity analysis using only the Day 1 HIV-1 RNA as the baseline value. We chose this analysis because the data showed that there was a time window (mean of -16 days, and range of -105 to 1 days) between screening and Day 1, during which time the HIV-1 VL may have changed due to effects of a participant's ongoing treatment regimen prior to Day 1.

Table 3 shows the results of the sensitivity analyses using day 1 viral load as baseline. Results include basic statistical analyses and an ANCOVA model which included treatment regimen, screening HIV-1 VL stratum, and enfuvirtide use in the OBT.

Table 3. Primary Endpoint: Change from Baseline to Week 24 in Viral Load

	Mean	Se	Treatment difference and 97.5% CI
Study 1027			
Results Using the Sponsor's Baseline HIV-1 VL[1]			
Maraviroc QD (n=232)	-1.821	0.092	-0.773 (-1.115,-0.430)
Maraviroc BID (n=235)	-1.971	0.095	-0.923 (-1.269,-0.577)
Placebo (n=118)	-1.048	0.122	
Results Using Day 1 HIV-1 VL as Baseline[1]			
Maraviroc QD (n=232)	-1.841	0.092	-0.793 (-1.135,-0.451)
Maraviroc BID (n=235)	-1.971	0.095	-0.923 (-1.269,-0.577)
Placebo (n=118)	-1.048	0.122	
ANCOVA Results Using Day 1 HIV-1 VL as Baseline[2]			
Maraviroc QD (n=232)	-1.636	0.130	-0.798 (-1.259,-0.336)
Maraviroc BID (n=235)	-1.762	0.132	-0.923 (-1.378,-0.459)
Placebo (n=118)	-0.839	0.160	
Study 1028			
Results Using the Sponsor's Baseline HIV-1 VL[1]			
Maraviroc QD (n=182)	-1.924	0.105	-1.022 (-1.413,-0.631)
Maraviroc BID (n=191)	-1.957	0.102	-1.054 (-1.441,-0.667)
Placebo (n=91)	-0.903	0.139	
Results Using Day 1 HIV-1 VL as Baseline[1]			
Maraviroc QD (n=182)	-1.921	0.106	-1.007 (-1.400,-0.614)
Maraviroc BID (n=191)	-1.952	0.103	-1.038 (-1.426,-0.649)
Placebo (n=91)	-0.914	0.139	
ANCOVA Results Using Day 1 HIV-1 VL as Baseline[2]			
Maraviroc QD (n=182)	-1.863	0.142	-1.019 (-1.533,-0.505)
Maraviroc BID (n=191)	-1.889	0.141	-1.045 (-1.558,-0.531)
Placebo (n=91)	-0.844	0.180	

1. Basic statistics: mean, standard error (se) and confidence interval (CI).
2. ANCOVA model includes treatment, screening HIV-1 VL, and enfuvirtide use.

Table 4 summarizes the results for mean change in viral load for Studies 1027 and 1028 combined. The differences in mean viral load decreases between maraviroc arms and the placebo arms (combined) ranged between 0.8 and 1.0 $\log_{10}$ copies/mL.. Results from fitting an ANCOVA model do not affect the applicant's results appreciably.

Table 4. Change from Baseline to Week 24 in Viral Load: Studies 1027 and 1028, Combined

	Mean	Se	Treatment difference And 97.5% CI
ANCOVA Results Using Day 1 HIV-1 VL as Baseline[1]			
Maraviroc QD (n=414)	-1.740	0.096	-0.893 (-1.236,-0.550)
Maraviroc BID (n=426)	-1.822	0.096	-0.975 (-1.319,-0.632)
Placebo (n=209)	-0.847	0.119	
Sponsor's ANCOVA Results (Treatment Failure and Missing as No Change)[2]			
Maraviroc QD (n=414)	-1.876	0.069	-0.888 (-1.153,-0.623)
Maraviroc BID (n=426)	-1.960	0.068	-0.973 (-1.237,-0.709)
Placebo (n=209)	-0.987	0.097	

1. Model includes treatment, screening HIV-1 VL, and enfuvirtide use.
2. Source: Table 9, Antiviral drugs advisory committee briefing document.

Proportion of Subjects Achieving <50 copies/ml HIV-RNA

The proportion of subjects who achieved a viral load of less than 50 copies/mL at Week 24 is presented by treatment group in **Table 5**. Lower baseline viral load, higher baseline CD4 count, and greater OSS score appeared to be predictors of improved response.

Table 5: Proportion of Subjects with HIV RNA <50 copies/mL at 24 Weeks [1] (Protocols 1027 and 1028 Combined, Modified ITT Population)

Baseline Characteristics	Proportion of Subjects with HIV RNA <50 copies/mL at Week 24		
	Maraviroc QD (n=414)	Maraviroc 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%)
Black	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/P1	85 (44%)	85 (45%)	26 (26%)
P1/P4	57 (45%)	66 (46%)	16 (25%)
P4/P4	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 ≥ median weight vs. < median weight.
[3] This category does not represent a baseline characteristic, as subjects infected with CXCR4-tropic HIV at baseline 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.

We conclude the following regarding analyses of efficacy:

1. Sensitivity analyses support the applicant's results in evaluation of primary and important secondary efficacy endpoints. There was a greater mean decrease in HIV-1 RNA from baseline to Week 24 in both maraviroc treatment groups compared with placebo. Both dosing regimens of maraviroc demonstrated superiority compared with placebo.

2. It appears that the Week 24 mean reduction from baseline in $\log_{10}$ VL was statistically greater ($p<0.001$ by the Wald t-test) in the maraviroc regimens than those in the OBT alone regimen (placebo regimen), regardless of screening VL level and enfuvirtide use in the OBT.

3. Study 1028 showed slightly greater decreases in HIV-1 RNA in the two maraviroc arms compared to placebo, compared to that observed in Study 1027.

Changes from Baseline to Week 24 in CD4+ Cell Count (cells/µL)

Sensitivity analyses were conducted for mean changes in CD4 cell counts from baseline to week 24 for both studies combined. **Table 6** shows two analyses of mean changes in CD4 cell count from baseline: in the first analysis no values were imputed for missing CD4 data. In the second analysis, the last CD4 cell count value was carried forward (LOCF) when CD4 data was not available.

Table 6. Change from Baseline to Week 24 in CD4+ Cell Count (cells/μL): Studies 1027 and 1028 Combined

	n	mean	se	Median	min	Max
No imputation						
MVC-QD	332	124.5	7.0	97	-329	782
MVC-BID	356	116.5	6.0	99	-277	740
Placebo	171	85.1	7.5	66	-101	460
Total	859	113.3	4.0	91	-329	782
LOCF						
MVC-QD	414	106.2	6.1	81.0	-329.0	782.0
MVC-BID	426	101.4	5.3	83.5	-277.0	599.5
Placebo	209	71.0	6.7	51.0	-101.0	460.0
Total	1049	97.2	3.5	74.0	-329.0	782.0

Table 7 summarizes changes from baseline to Week 24 in CD4+ cell count using an ANCOVA model with treatment regimen and randomized strata in the model. Mean CD4 increases for the MVC regimens were 30-35 cells/μL greater than the CD4 cell increase for placebo.

Table 7. Change from Baseline to Week 24 in CD4+ Cell Count (cells/μL): ANCOVA, Studies 1027 and 1028 Combined

	Mean	SE	Treatment difference (97.5% CI)
ANCOVA Results Using Day 1 CD4+ as Baseline[1]			
Maraviroc QD (n=414)	115.6	7.736	30.0 (2.350,57.650)
Maraviroc BID (n=426)	120.2	7.704	34.6 (6.995,62.205)
Placebo (n=209)	85.6	9.609	
Sponsor's ANCOVA Results (Treatment Failure and Missing as No Change)[2]			
Maraviroc QD (n=414)	115.6	7.736	** (2.350,57.650)
Maraviroc BID (n=426)	120.2	7.704	** (6.995,62.205)
Placebo (n=209)	85.6	9.609	

1. Model includes treatment, screening HIV-1 VL, and ENF use
2. Source: Table *, Antiviral drugs advisory committee briefing document

3.3 Clinical Pharmacology Modeling Results

The relationship between plasma trough concentration of maraviroc (Cmin) and change from baseline viral load at week 24 in treatment-experienced HIV-1-infected patients with optimized background therapy (OBT) was established. Several binary endpoints indicating virologic success, such as protocol defined failure at week 24, viral load <50 copies/mL at 24 weeks, and viral load <400 copies/mL at 24 weeks were investigated. The Cmin, baseline viral load, baseline CD4+ count and overall sensitivity score (OSS) at baseline were found to be important predictors of virologic success. The relationship was consistent across all endpoints. This summary focuses on findings derived from the

analyses of one clinically relevant endpoint, viral load <400 copies/mL at 24 weeks. We find:

1. Patients with Cmin >75 ng/mL have a better chance of virologic success.
    a. A majority of patients with Cmin <75 ng/mL fail to achieve <400 copies with the sponsor's proposed dosing.
    b. Concomitant drugs or demographic factors were not the source of Cmin values <75 ng/mL.
2. Toxicity (QT prolongation, ALT/AST elevation, hypotension) was not dose/concentration dependent within the therapeutic concentration range.
3. Virologic success may be improved by doubling the dose for patients with Cmin <75 ng/mL. The proposed dose adjustment does not increase concentrations greater than the range in phase 2b/3 studies.

Exposure response analysis

The data from two placebo controlled phase 2b/3 studies (1027 and 1028) of maraviroc and optimized background therapy (OBT) in treatment experienced patients infected with CCR5-tropic HIV-1 were used in this analysis. These trials used 150 mg QD and 150 mg BID of maraviroc when administered with PIs (except tipranavir/ritonavir) or delavirdine (CYP3A4/P-gp inhibitors) or 300 mg QD and 300 mg BID when administered in the absence of PIs/delavirdine. Several binary endpoints indicating virologic success, such as protocol defined failure at week 24, viral load <50 copies/mL at 24 weeks, and viral load <400 copies/mL at 24 weeks were investigated. A total of 970 subjects (775 maraviroc treated and 195 placebo treated) were included in the analyses. A total of 79 subjects were excluded due to unavailability of covariate information. Plasma trough concentrations (Cmin) were used as an exposure variable. The following covariates that could impact the Cmin-virologic success relationship were also evaluated in the generalized additive (logistic) regression analysis:

<u>Patient disease information</u>

- Time since diagnosis, years
- Baseline viral load
- Baseline CD4+ count
- Tropism at baseline

<u>Patient medication information</u>

- Time since first treatment, years
- Overall sensitivity score (OSS)
- Number of sensitive NRTIs
- Number of sensitive NNRTIs
- NNRTI in the OBT
- Presence and sensitivity to protease inhibitors
- Presence and sensitivity to T20

- Previous treatment with T20
- Presence of ritonavir/Kaletra

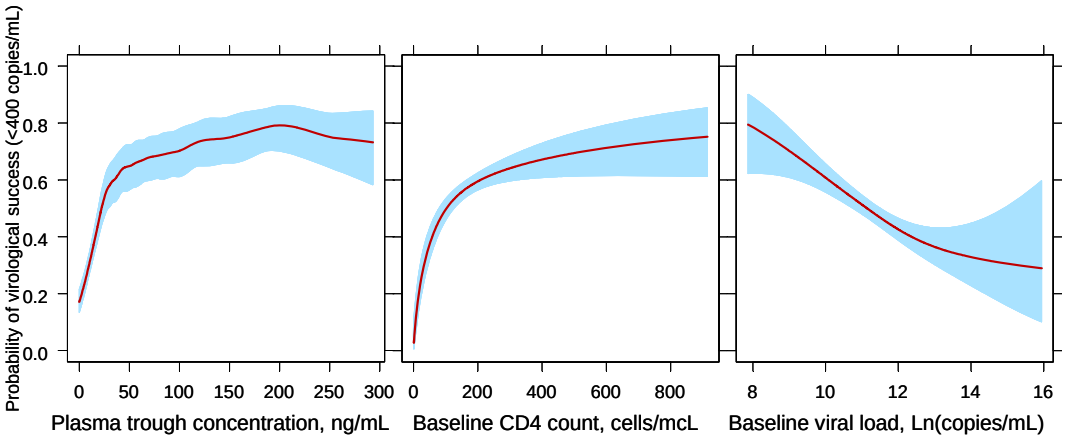
Patient demographic information

- Age
- Sex
- Race

Baseline CD4+ count, baseline viral load, OSS and Cmin were the most important predictors of virologic success. This summary focuses on findings derived from analyses of the clinically relevant endpoint, viral load <400 copies/mL at 24 weeks.

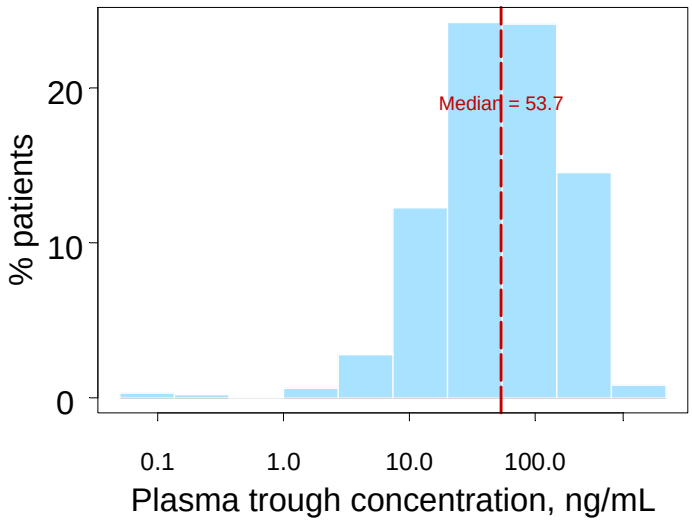
Figure 5 illustrates the relationship between the probability of virologic success (<400 copies/mL) and Cmin, baseline CD4+ count and baseline viral load. The baseline tropism, time since diagnosis, time since the first treatment, NRTIS, PIS, T20S and T20H were also found to impact the virologic success. The probability of virologic success is higher at higher Cmin and/or higher baseline CD4+ count and/or lower baseline viral load.

Figure 5: Cmin (left panel), baseline CD4+ count (middle panel) and baseline viral load (right panel) are important predictors of the virologic success. The shaded area represents twice standard error region.



The variability in Cmin is high, with a range of 0.1 to 560 ng/mL. **Figure 6** illustrates distribution of Cmin across all dose groups in the phase 2b/3 studies.

Figure 6: Distribution of plasma trough concentrations across all dose groups



For the proposed market doses, the proportion of patients with Cmin <50 ng/mL was higher for 300 mg BID (no PIs [except tipranavir/ritonavir] or delavirdine) group than 150 mg BID (with PIs [except tipranavir/ritonavir] or delavirdine) group as shown in **Table 8**.

Table 8: Distribution of concentrations for 150 and 300 mg BID

Dose group	Number of patients	Concentration range	% patients <25 ng/mL	% patients <50 ng/mL	% patients <75 ng/mL	% patients <100 ng/mL
150 mg BID	307	0.08-561.7	7.2	16.9	27.0	41.4
300 mg BID	89	0.12-204.7	32.6	65.2	77.5	89.9

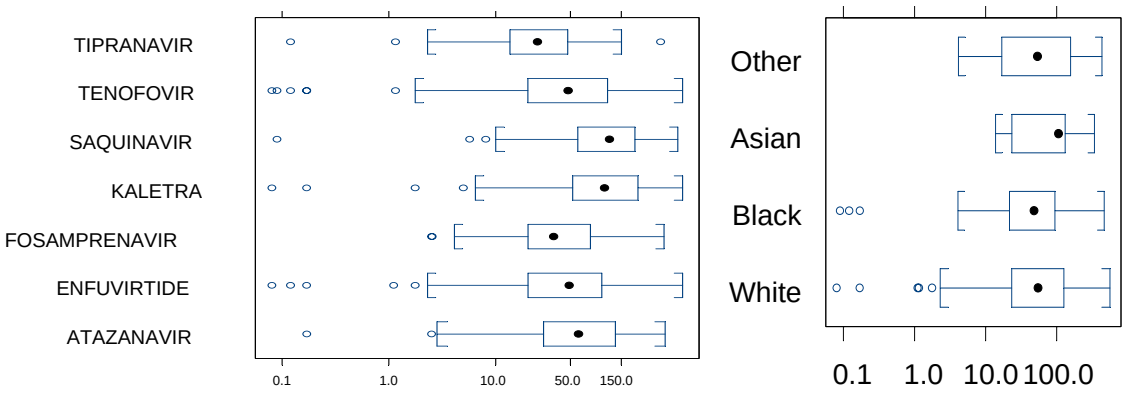
An attempt was made to understand the factors leading to lower Cmin. The box plots in **Figure 7** illustrate that the distribution of Cmin is not affected by concomitant drugs and race groups. Other covariates (listed above) were also investigated and were not found to be explanatory of the lower Cmin.

The proposed dosing does not allow good control over pharmacokinetic variability in maraviroc concentrations. To understand the intrinsic source of variability (inter-patient vs. within patient variability) in Cmin, data from naïve patients were analyzed (Study 1015). In this study, weekly Cmin measurements were available from week 6 to week 10. A random effect approach was used to estimate inter-patient and within patient variability. The inter-patient variability (%CV=50%) was greater than within patient variability (%CV=33%).

Since Cmin is a major predictor of virologic success, and a single trough measurement is a good predictor of the concentrations (inter-patient variability > within patient

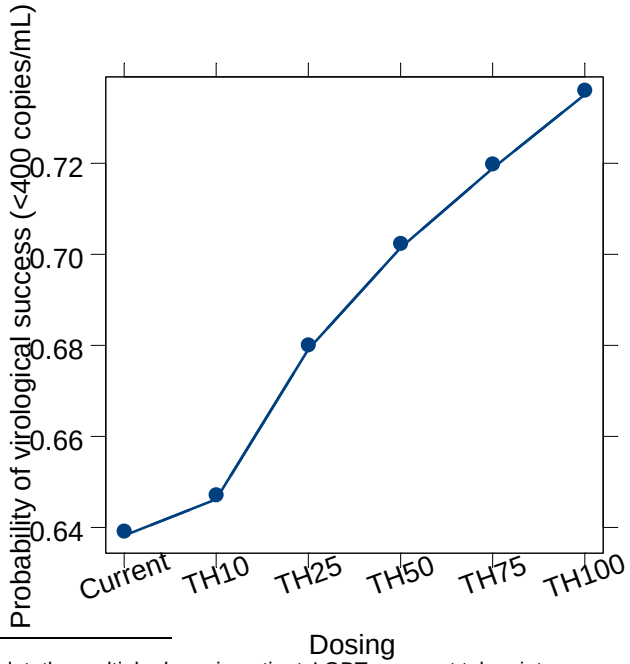
variability), a threshold-based simulation was conducted to understand the advantage of doubling the dose for patients with 'below threshold' concentrations. As shown in **Figure 5**, Cmin above ~75 ng/mL offers minimal/no additional benefit.

Figure 7: Concomitant drugs (left panel) [3] and race[4] (right panel) do not explain lower Cmin levels



The Cmin-virological relationship was employed to investigate the advantage of increasing maraviroc doses in patients with Cmin lower than a certain threshold Cmin. Five different threshold Cmins, 10, 25, 50, 75 and 100 ng/mL, were studied. To simulate Cmin, a factor of 2.5 (to account for more than a proportional dose-concentration relationship) was applied to the original values, if the Cmin was below the defined threshold. If the Cmin was above the defined threshold, the original value was retained. **Figure 8** illustrates the predicted virologic success for threshold-based simulation.

Figure 8: The virologic success can be increased up to 72% (vs. original 64%) by doubling the dose in patients with Cmin <75 ng/mL. THxx represents threshold Cmin (ng/mL) used in simulation



[3] For drug interaction plot, the multiple drugs in patients' OBT were not taken into account. The aim was to highlight if any concomitant medication might stand out as a predictor of lower concentrations

[4] For plot by race group, N= 647 (Caucasian) 109 (Black), 12 (Asian) and 7 (others)

With the dosing used in phase 2b/3 studies, the virologic success on maraviroc with OBT was shown to be 64%. The virologic success can be increased to 72% by doubling the dose in patients with Cmin <75 ng/mL. Therefore, the virologic success can be increased by 8% (12.5% relative increase) using a threshold of 75 ng/mL. As seen from **Table 8**, 75 ng/mL as a threshold will require 27% (150mg BID group) and 77% (300 mg BID group) to have dosing adjustments post Cmin assessment.-

In conclusion,

1. Patients with Cmin values >75 ng/mL have a better chance of virologic success.
    a. Majority of patients with Cmin <75 ng/mL fail to achieve <400 copies with the sponsor's proposed dosing.
    b. Concomitant drugs or demographic factors were not the source of Cmin <75 ng/mL.
2. Toxicity (QT prolongation, ALT/AST elevation, hypotension) was not dose/concentration dependent within the therapeutic concentration range.
3. The virologic success may be improved by doubling the dose for patients with Cmin <75 ng/mL. The proposed dose adjustment is not predicted to increase concentrations greater than the range in phase 2b/3 studies.

3.4 Tropism and Resistance Results

A potential concern with using a CCR5 co-receptor antagonist is that it will increase the chances of HIV switching to the use of the CXCR4 co-receptor through mutation and selection. The evolution to a CXCR4-utilizing HIV has been proposed to result in a more virulent virus and more rapid progression to AIDS. The potential for co-receptor switching as a mechanism of escape from CCR5 co-receptor antagonists concerned the Division and thus we requested sponsors of CCR5 inhibitors to vigilantly monitor co-receptor tropism changes and resistance in clinical trials. We requested tropism reports on a monthly basis to monitor tropism switching, viral load and $CD4^+$ cell counts in all clinical trials.

In addition, a comprehensive analysis of subjects who experienced treatment failure in clinical studies was requested in order to determine whether:

a. Viral isolates mutated to use the CXCR4 co-receptor rather than the CCR5 co-receptor (co-receptor tropism switch)
b. There was outgrowth of CXCR4-tropic HIV not detected at screening
c. Viral isolates remained CCR5-tropic but became resistant to maraviroc
d. Viral isolates developed resistance to OBT

The analyses were extensive and included:

If virus was CCR5-tropic at failure:

- Determining the susceptibility to MVC in cell culture

- Nucleotide sequence analysis of the gp120 region to identify amino acid substitutions that may contribute to resistance to MVC (Potential amino acid changes should be verified, *e.g.* site-directed mutagenesis)
- Nucleotide sequence analysis of PR and RT

If virus was CXCR4-tropic at failure:

- A clonal evaluation of virus at baseline and subsequent time points to determine the relative number of CXCR4-tropic and CCR5-tropic viral isolates.
- Nucleotide sequence analysis of the gp120 region to identify amino acid changes that may contribute to a co-receptor switch to CXCR4
- Phylogenetic analysis to determine the relationship of emerging CXCR4-tropic virus to the CCR5-tropic virus at baseline
- Nucleotide sequence analysis of PR and RT
- Long term follow-up on the subjects viral loads, $CD4^+$ cell counts, HIV co-receptor usage and AIDS defining events

Given the complexity and exploratory nature of the above analyses, substudies from Clinical Studies 1027 and 1028 were proposed. A subset of subjects failing with CCR5-tropic virus were analyzed to identify possible phenotypic and genotypic markers associated with MVC resistance in vivo, and a subset of subjects failing with CXCR4-tropic virus were analyzed to determine whether the CXCR4-using virus emerged from a pre-treatment CXCR4-using reservoir or as a result of mutation from a CCR5-tropic progenitor ("tropism switch") while on MVC. See "**VIROLOGY SUBSTUDIES**" below. In addition, there is documented variation in the human CCR5 gene. Since CCR5 antagonists target this host protein and the activity may vary depending on the individual's CCR5 genotype, we requested that a baseline sample be stored for retrospective analysis of CCR5 genotype for subjects with CCR5 tropic virus who did not respond to MVC in order to determine if MVC is not effective against certain CCR5 genotypes.

Analysis of Subjects Who Failed on MVC Therapy in Studies 1027 and 1028

For resistance and tropism analyses, as-treated analyses were performed. Subjects were censored from the analysis if they discontinued with ≤400 copies/mL, if they discontinued with >400 copies/mL between Baseline and Week 4, or if they discontinued between Baseline and Week 8 with at least 0.5 $\log_{10}$ decrease and no rebound (previous ≥2 $\log_{10}$ decrease with 1 $\log_{10}$ increase). Forty-nine and thirty-nine subjects were censored from the analysis of studies 1027 and 1028, respectively, giving a dataset of 962 subjects.

We determined the percentage of virologic failures that had CCR5-tropic and CXCR4-tropic virus at time of failure. This analysis was done using two definitions of treatment failure: (1) the protocol-defined treatment failure (PDTF) definition (**Table 9**), and (2) subjects with PDTF plus subjects with >400 copies/mL at Week 24 (**Table 10**). Regardless of the definition of treatment failure ~50-60% of subjects failed with CXCR4-

or dual/mixed-tropic virus in the MVC arms, whereas >80% of the subjects in the placebo arm failed with CCR5-tropic virus. A high percentage of treatment failure on MVC was associated with emergence of CXCR4- or dual/mixed-tropic virus, which supports the mechanism of action of MVC.

Table 9. Studies 1027 and 1028: Tropism of Protocol-Defined Treatment Failures (n=281)

Tropism	QD (n=81)	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%)

NR/NP = non-reportable/non-phenotypable

Table 10. Studies 1027 and 1028: Tropism of PDTF + >400 copies/mL Week 24 (n=443)

Tropism	QD (n=154)	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%)

NR/NP- non-reportable/non-phenotypable

For the subjects who switched from CCR5-tropic to CXCR4- or dual-mixed tropic between Baseline and Week 24, the mean and median times to tropism change for each treatment group were similar with a mean of 47-51 days and median of 28-30 days.

Change in $CD4^{\pm}$ Cell Counts Corresponding with Tropism Changes

Overall, there was a greater increase in $CD4^{\pm}$ cell count from baseline to Week 24 for both MVC arms (106-109 cells/μL) compared to placebo (57 cells/μL). The change in $CD4^{\pm}$ counts (from baseline to Week 24 using the last observation carried forward at Week 24 (LOCF24) was examined in the treatment failures (PDTF+>400 copies/mL Week 24) by tropism at failure time point. Subjects in the MVC arms failing with CXCR4- or dual-mixed tropic virus had less of an increase in $CD4^{\pm}$ cell counts than those subjects failing with CCR5-tropic virus (**Table 11**). This difference was not seen in the placebo arm.

Table 11. Mean (median) Change in CD4± Cell Counts from Baseline to LOCF24 by Tropism at Treatment Failure (PDTF+ >400 copies/mL)

Tropism at Failure	QD N=154	BID N=143	Placebo N=146
CCR5	123 (93) N=72	128 (110) N=48	38 (11) N=122
CXCR4	60 (33) N=18	52 (31) N=20	76 N=1
Dual-Mixed	47 (25) N=48	63 (58) N=61	43 (14) N=11
NR/NP	70 (70) N=16	99 (103) N=14	63 (29) N=12

Failure of Optimized Background Therapy

As indicated above, another reason for treatment failure could be resistance to the other drugs in the OBT. Most subjects typically had low genotypic susceptibility score/phenotypic susceptibility score (GSS/PSS) at screening, indicating reduced susceptibility to their OBT. The mean GSS and PSS scores (baseline susceptibility to OBT) in subjects who responded was higher than the scores in subjects who failed therapy.

The susceptibility to drugs in the OBT at baseline and treatment failure was analyzed in detail in the subjects who failed treatment (PDTF + >400 copies/mL Week 24). Twenty-eight percent of treatment failure subjects had no susceptible drugs in the OBT at baseline and 43% of treatment failure subjects lost susceptibility to drugs in their OBT on treatment. There was no difference between the MVC and placebo treatment arms.

Δ32 Deletion/WT or CCR5 Promoter Haplotype

It has previously been observed that a 32-base pair deletion mutation in the gene that encodes the CCR5 co-receptor (CCR5Δ32) results in a decrease in cell-surface expression of CCR5. Individuals who are CCR5 Δ32/Δ32 homozygotes have been found to be significantly less likely to become infected with HIV-1. However, individuals who are heterozygotes have not been observed to have significant protection from infection, although once infected they appear to progress more slowly to AIDS than those without the mutation. More recently, polymorphisms in the CCR5 promoter region have been associated with differences in the rate of progression to AIDS. As both the Δ32 mutation and promoter polymorphisms may alter CCR5 expression, the potential for such baseline genetic differences between patients to affect treatment response to a CCR5 inhibitor was of interest. The percentage of subjects heterozygous for the Δ32 genotype (wildtype CCR5/Δ32 deletion) at baseline ranged from 5% to 9% in studies 1027 and 1028 and was comparable between arms. An examination of subjects who failed treatment showed that there was no difference between treatment arms in the percentage of subjects who were heterozygous for the Δ32 deletion or had CCR5 promoter haplotypes P1/P1, P4/P4, and P1/P4. The majority of treatment failures (>80%) were homozygous wildtype CCR5. Approximately 40% of treatment failures had the P1/P1 promoter haplotype and a third had the P1/P4 haplotype.

VIROLOGY SUBSTUDIES

Virology substudies from Clinical Studies 1027 and 1028 were conducted. Subjects were selected on a blinded basis for more detailed analysis from a pool of 267 subjects from Studies 1027 and 1028 who had the potential to reach Week 24 by December 1, 2005. Two hundred thirteen of these subjects received MVC and 54 received placebo. Thirty-eight subjects were identified as failing blinded therapy and having CCR5-tropic virus. Viral isolates from these subjects were examined to identify possible phenotypic and genotypic markers associated with MVC resistance in vivo.
A second virology substudy analyzed viruses from 20 of the subjects in whom CXCR4-using virus emerged during the blinded phase of treatment. The objective of this study was to understand whether the CXCR4-using virus emerges from a pre-treatment CXCR4-using reservoir or as a result of mutation from a CCR5-tropic progenitor ("tropism switch").

Subjects Who Failed Treatment with CCR5-Tropic Virus

The susceptibility to MVC and ENF of Env recombinant pseudoviruses was analyzed from 38 subjects who failed blinded therapy with a CCR5-tropic virus; 13 subjects were randomized to receive MVC (6 BID: 7 QD) and 25 subjects were on placebo. The results support previous findings from selection of MVC-resistant virus in cell culture and isolates from Phase 2 MVC studies that lower plateaus in the maximum percentage inhibition (MPI) to MVC were associated with subjects failing a MVC-containing regimen rather than changes in EC_{50} values. MVC dose response curves demonstrating lower plateaus in MPI (<95%) were observed in 4 subjects following failure of a MVC-containing regimen during the blinded study period and from a fifth subject who failed in the placebo arm and developed a lower plateau in MPI following open-label MVC (**Table 12**). Lower plateaus in MPI in the PhenoSense™ HIV Entry assay correlated with data obtained with Env clones and in PBL assays.

The entire Env (gp160) sequence was obtained for all clones and time points from 10 subjects in an attempt to determine genotypes associated with decreased MVC susceptibility. Genotypic analysis focused primarily on the V3 region (amino acids 300-350) of gp160. Changes in the V3 loop region of the viral Env appeared to correlate with the presence of lower plateaus in MPI and MVC resistance. Although there is heterogeneity of the envelope protein and likely multiple pathways to MVC resistance, substitutions at amino acid positions P13 or V26 occurred in the V3 loop of the five MVC treatment failure isolates that demonstrated lower plateaus in MPI (**Table 12**). Additionally, a P13S amino acid substitution was also seen in Subject 10050022 who had a shift in MVC EC_{50} value from baseline. Changes outside the V3 loop were observed in some subject viruses and the impact of these is not understood.

Fold changes in EC_{50} values to MVC were not generally associated with failure to a MVC-containing regimen. However, virus from two subjects had approximately a 3-fold shift in MVC susceptibility between baseline and treatment failure. Each of these subjects' failure isolates had one V3 loop amino acid change in K18R or P13S.

Seven subjects receiving MVC during their blinded phase of treatment did not show phenotypic markers of MVC resistance in the PhenoSense assay (**Table 12**). However, the majority of subjects (5/7) had evidence of reduced susceptibility to one or more drugs within their OBT at screening and/or failure.

Site-directed mutagenesis (SDM) was performed on representative Env clones from baseline and failure time points from four of the subjects who had MVC-associated plateaus in MPI and confirmed the role of the V3 loop amino acid substitutions in contributing to MVC resistance. In three subjects, mutating the V3 loop amino acids of the Day 1 clones resulted in a MVC-resistant phenotype (i.e., <95% MPI) and back-mutation of the amino acid changes in the V3 loop of the failure clones resulted in a MVC-sensitive phenotype (>95% MPI). In another subject, the V3 amino acids (S11G and V26I) were necessary, but not sufficient for the MVC resistant phenotype. Perhaps the other substitutions (T2I, V33A and R48Q) that developed in the V3 loop on MVC treatment and were not examined in this study played a role in MVC resistance.

Enfuvirtide-resistant viruses were not cross-resistant to MVC and MVC-resistance did not result in cross-resistance to enfuvirtide.

Table 12. Analysis of MVC Treatment Failure Subjects with CCR5-Tropic Virus

PID	Study	Arm	Failure Week	MPI Monogram assay (MPI PBL data)	EC_{50} FC from BL	ENF in OBT (y/n)	gp160 Substitutions in V3 LOOP	OBT
10070008	1027	QD	E term	30% (-27%)	ND	y	P13S/A16ins/S42G	No susc drugs in OBT at BL ENF^R
10460014	1027	QD	WK24	84% (75%)	1.21	y	I20F/A25D/I26V	
10950001	1027	QD	WK8	80% (70%)	1.05	y	N13H/T22A	Change in OBT ENF^R
10290004	1028	BID MVC +OL	WK32	57% (46%)	0.59	y	T2I/**G11S/I26V**/V33A/R48Q	No susc drugs in OBT at BL ENF^R
10680001	1027	PLC +OL MVC	WK48	41%	ND	n	S13H/A19T/I26V and P16A/A19S [1]	
10800003	1028	BID	WK24	100%	**3.1**	n	K18R	ENF^R
10050022	1027	BID	WK16	(92%)	**3.22**		P13S	No change
10350010	1027	BID	WK24	97%	0.79	n		Change in OBT
10470002	1027	BID	WK20	99%	0.91	n		No change
10930011	1027	BID	WK32	99%	1.34	y		No susc drugs in OBT at BL ENF^R
10220001	1027	QD	WK8	100%	0.81	n		No change
10300002	1027	QD	WK20	98%	1.92	y		ENF^R
10690003	1028	QD	E term	100%	1.28	y		No susc drugs in OBT at BL ENF^R
11000002	1028	QD	WK8	96%	0.89	y		Change in OBT ENF^R
10350001	1027	PLC	WK12	98%	0.82	n	L4P/Q13H/M14I/D25E/I26V/K32Q	
10460003 [2]	1027	PLC	E term	98%	1.06	n	No changes	
10460013	1027	PLC	WK8	97%	1.02	n	No changes	

MPI = maximum percentage inhibition; ND = EC_{50} values could not be determined because MPI did not reach 50%; OL = open-label; Susc = susceptible; ENF^R = enfuvirtide resistant

[1] two pathways to MVC resistance

[2] EC_{50} values 2.65 and 2.82 at baseline and E term, respectively.

Origin of CXCR4 or Dual-tropic Virus that Emerged on Treatment

Of the 20 subjects selected in whom CXCR4-using virus was detected during treatment, 16 were in a MVC treatment group and 4 in the placebo group. The nucleotide sequence of approximately 290 bases from the envelope gene encompassing the V3 loop was determined from 192 pre-treatment and 48 on-treatment clones from each of the 20 subjects. Phylogenetic trees were generated using these sequences in order to investigate

possible ancestry of the CXCR4-using clones. Finally, twelve clones from each time point (*i.e.* 24 clones per subject) were selected and tropism was confirmed in the validated format of the PhenoSense™ HIV tropism Assay (Trofile™).

CXCR4-using *env* clones in the 'on-treatment' samples from 14 subjects (11 MVC: 3 PLC) shared a common ancestor with a pre-treatment virus that was phenotypically and/or genotypically classified as CXCR4-using. The applicant states that the CXCR4-using *env* clones identified in the 'on-treatment' samples from the remaining 6 subjects (30%) (5 MVC: 1 PLC) were genetically distinct from both the 'pre-treatment' and 'on-treatment' CCR5 population based on phylogenetic tree analysis. The V3 loop sequences of the on-treatment CXCR4-using clones differed by 7-17 amino acid residues from the V3 loop of the nearest CCR5 sequence on the phylogenetic tree. Although a MVC-associated tropism switch (CXCR4 to CCR5) resulting from these 7-17 amino acid substitutions in the CCR5 precursor cannot be ruled out, the data suggest that the CXCR4-tropic virus originated from a pre-existing CXCR4-using virus not detected by the assay at day 1.

The primary findings from this substudy were that CXCR4-using virus, detected during blinded treatment of these subjects, originated from a pre-existing CXCR4-using virus reservoir, regardless of treatment arm (MVC or placebo) or time of onset of virology failure. In addition, the baseline (Day 1) samples from subjects whose virus was classified as CCR5-tropic at baseline had a low (≤7%) frequency of CXCR4-using e*nv* clones. This supports the 10% sensitivity performance assessment of the Monogram tropism assay.

Summary of Why Subjects Failed MVC Treatment in Studies 1027 and 1028

Given the novel mechanism of action of this new drug, the reasons for treatment failure could include a co-receptor "tropism switch" from CCR5-using virus to dual-mixed/CXCR4-using virus, outgrowth of minor populations of CXCR4-using virus not detected at screening, resistance of CCR5-tropic virus to MVC, and/or emergence of resistance to OBT. Most (~50-60%) subjects failed with CXCR4- or dual/mixed-tropic virus in the MVC arms. The most prominent reason for failure in these studies was outgrowth of CXCR4-using viruses not detected at screening. Treatment failure on MVC with CCR5-tropic virus also occurred and resulted from phenotypic and genotypic resistance to MVC and resistance to OBT.

The results of Studies 1027 and 1028 were further supported by results from Studies 1026 (Phase 3 study in treatment-naïve subjects) and 1029 (Phase 2 study in dual/mixed-tropic treatment-experienced subjects).

Study 1026 in Treatment-Naïve Subjects (ongoing)

Analysis of three subjects who failed on 300 mg MVC QD with CXCR4-tropic virus from this treatment-naïve study showed that the CXCR4-tropic virus clones were present at baseline. The proportion of CCR5-tropic viruses was reduced during MVC treatment and was reversed after MVC treatment was stopped. In all three subjects, the LAM-resistance M184V mutation was detected at failure and the viruses at failure were dual-mixed tropic. In one subject, the AZT-resistance RT mutations M41M/L and K70R/K

were also detected. When treatment with MVC and AZT/LAM was stopped, CCR5-tropic virus was again detected and the RT mutations were not detected in the post-treatment samples. These results suggest that the RT mutations are on the CXCR4-tropic virus, not the CCR5-tropic virus, although this cannot be proven with the existing PhenoSenseGT and Trofile assays because they separately amplify regions of the virus.

Study 1029

The main findings of a post-hoc analysis of viral tropism and $CD4^+$ cell counts at Week 24 in this study of treatment-experienced subjects with non-CCR5-tropic virus were:

- Approximately 50% of the subjects discontinued (failed) treatment by Week 24 and about 25% had ≤500 copies/mL HIV RNA at Week 24. There was no difference between the MVC and placebo arms.
- Subjects who experienced treatment failure or had >500 HIV RNA copies/mL at Week 24 on MVC were more likely to have CXCR4-tropic virus at failure than subjects failing on placebo. Specifically, 45% (24/53) subjects had a CXCR4-tropic virus at failure in MVC arms compared to 9% (2/22) subjects in placebo.
- Increases in $CD4^+$ and $CD8^+$ cell counts were higher for both MVC treatment arms compared to placebo ($p<0.05$).
- For subjects on MVC whose virus was dual/mixed at screening, changes from baseline in $CD4^+$ cell counts were greater for those responding to MVC treatment at Week 24 (median +80-98) than those who experienced treatment failure (median +15-19).
- Changes in $CD4^+$ cell counts from baseline to time of treatment failure were similar for subjects on MVC whose virus was CXCR4-tropic at failure to those whose virus remained dual-mixed tropic at failure.

3.5 Clinical Safety Results

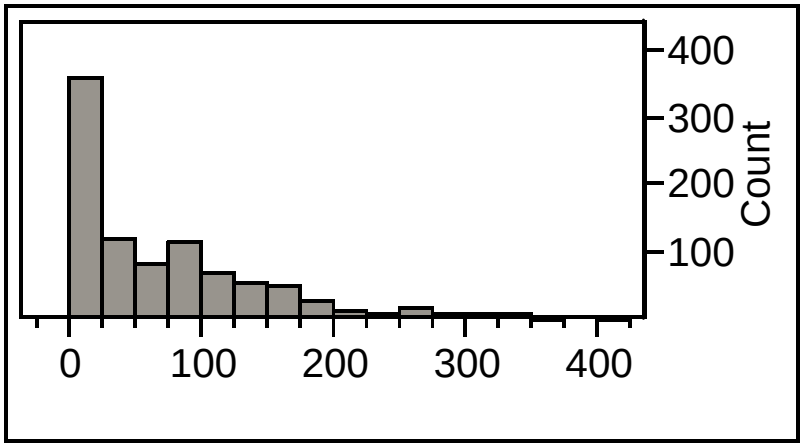
All adverse events (AEs) reported during Studies 1027 and 1028 were combined to increase the probability of detecting AEs potentially associated with MVC administration. AEs that occurred while receiving study drug or within 7 days of study drug discontinuation were considered to be during the "active" (double-blind) treatment period, and all AEs that occurred following the "active" period were considered to have occurred during the "post" (open-label) treatment period. AEs occurring during the "post" 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 "active" period, there was a total of 2242, 2292, and 936 distinct AEs in the MVC QD, BID, and placebo groups, respectively (**Table 13**). The total duration of observed time was substantially different in the MVC and placebo groups during the "active" 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 13: Summary of AE Findings for Studies 1027 and 1028 Combined During the Active Treatment Phase (As Treated Population)

Event	Maraviroc QD N=414	Maraviroc 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 as 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 "active" period of the trial, in light of the fact that most AEs occurred relatively early for all treatment arms. **Figure 9** provides the days to individual AEs experienced in the placebo group during Studies 1027 and 1028. Therefore, a treatment arm that has a shorter duration of follow-up may be enriched with AEs when analyzed by AEs per unit of time observed. There may have been multiple reasons for most AEs occurring early in these trials. Optimization of the background regimen prior to study entry may have led to an increase in early events. In addition, there are fewer subjects available with longer durations of monitoring. It is also possible that patients who are having medical problems are more likely to enroll in a clinical trial in the first place.

FDA Figure 9: Days to Individual AEs During the Active Period in the Placebo Group (Studies 1027 and 1028 Combined, As Treated Population)



Deaths

All deaths from the phase 2b/3 trials investigating the use of maraviroc were reviewed and are summarized in **Table 14**. In light of 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 is no evidence of an overall mortality imbalance with respect to MVC use. It should also 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 a particular cause of death within the MVC arms.

FDA Table 14: All Deaths by Treatment Group
(Studies 1026, 1027, 1028, and 1029, As Treated Population)

Subject #	Treatment	Cause of Death	Total Days on Therapy	Days Post-Therapy to Death
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
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 Tx
10210001	Placebo	Large cell lymphoma	298	84
1028				
10440002	MVC QD	Anorexia	198	26
10510032	MVC QD	Septic shock, lymphoma[3]	79	2
10820018	MVC QD	Myocardial infarction	206	On Tx
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	Liver failure[3]	18	1
12160009	MVC BID	Cause unknown[3]	35	On Tx
12050011	MVC BID	CNS lymphoma	62	48
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 Tx
11810004	Placebo	Multiple cerebral lesions	Unknown	Unknown
11260003	Placebo	Multifocal leukoencephalopathy	36	29

[1] Death occurred during open-label phase, subject originally randomized to MVC BID
[2] Death occurred during open-label phase, subject originally randomized to placebo
[3] Cause of death assessment by the FDA reviewer if it differs from the Applicant

There were several types of AEs of particular concern in light of the mechanism of action of maraviroc, pre-clinical data for maraviroc, or previous experience with other CCR5 co-receptor antagonists. These AEs are considered in the sections that follow.

Malignancy

All lymphomas reported during Studies 1027 and 1028 were assessed (**Table 15**). Given the 2:2:1 randomization, there was no increased frequency of lymphoma observed in association with MVC administration.

FDA Table 15: All Lymphomas by Treatment Group
(Studies 1027 and 1028 Combined, As Treated Analysis)

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

[1] Subject received placebo during the blinded phase, but subsequently received open-label maraviroc prior to the AE.

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

Hepatotoxicity

There were a total of 130 liver-related AEs reported during the double-blind phase of Protocols 1027 and 1028. Within the MVC QD arm, 32 subjects experienced 55 AEs. Of these AEs, 31 (56%) 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 duration of observation per subject in the MVC arms, there appears to be a modest increase in liver-related AEs in association with MVC.

The majority of liver-related AEs involved liver enzyme elevation (58%) and increased bilirubin (30%). Additional analyses are underway with respect to concomitant atazanavir use, the frequency with which Hy's rule was met, and whether the presence of viral hepatitis or alcohol use may potentiate a hepatotoxic effect of MVC.

Infection

There were a total of 897 infection-related AEs during the double-blind phase of Studies 1027 and 1028. Of these AEs, 43%, 41%, and 16% occurred in the MVC QD, MVC BID, and placebo arms, respectively. Based on the number of subjects per group, this reflects a modest increase in the MVC arms over placebo. However, there was a longer duration of follow-up per subject within the double-blind phase 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 between the MVC arms and placebo. When this is taken into account, there is no difference between the MVC and placebo arms with respect to infection-related AEs overall.

An additional analysis of all Grade 3/4 infection-related AEs during the double-blind phase 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. Therefore, in light of the number of subjects in each arm, 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 16**. After adjusting for the total time of observation by treatment group, there was an excess of influenza and influenza-like illnesses in the MVC arms, and a modest excess of herpes simplex infections. An excess of Candida infections was observed in the MVC QD arm only.

FDA Table 16: Most Common Infection-Related AEs During the Double-Blind Period by Treatment Group (Studies 1027 and 1028 Combined, As Treated Population)

Infection-related AE	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
Upper respiratory tract infection[1]	142	131	50
Candida infection[2]	41	18	11
Herpes simplex infection[3]	25	32	8
Influenza[4]	19	7	1

[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

Pneumonia, sepsis, and abscess formation occurred during the phase 3 trials and were analyzed due to their clinical significance. There was 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 as "pneumonia" 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. Lastly, 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 administration.

Category C Events

There were a total of 80 Category C events in 66 subjects following administration of study agent during Studies 1027 and 1028. Of these, 66 occurred during the double-blind phase and 14 occurred during the open-label phase. During the double-blind phase, there were 31, 19, and 16 events in the MVC QD, MVC BID, and placebo arms (**Table 17**).

FDA Table 17: Category C AEs During the Double-Blind Period by Treatment Group (Studies 1027 and 1028 Combined, As Treated Population)

Category C Event	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
Lymphoma[1]	2	1	2
Candidiasis[2]	14	3	2
Cryptosporidial gastroenteritis	0	0	1
Cytomegalovirus infection	2	2	0
Herpes virus infection[3]	11	6	2
Kaposi's sarcoma	1	2	3
Progressive multifocal leukoencephalopathy	0	1	0
Pneumonia[4]	1	0	3
Pneumocystis jiroveci pneumonia	0	2	0
Mycobacterium avium complex infection	0	1	3
Mycobacterial infection	0	1	0

[1] Also includes the terms Diffuse large B-cell lymphoma, Lymphoma
[2] Also includes the terms Oesophageal candidiasis and Worsening of candidiasis
[3] Also includes the term Herpes simplex
[4] Also includes the terms Lobar pneumonia, Pneumonia bacterial

There appeared to be an increase in candidiasis and herpes virus infections associated with MVC use based on the results in **Table 17**. Therefore, additional analyses were performed for these types of events. With respect to candidiasis, a total of 15 MVC subjects (13 MVC QD, 2 MVC BID) had 17 candidiasis events. A total of 4 of the 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/μL. The median time from beginning MVC to a candidiasis Category C event was 56 days. Of the 2 placebo subjects who had a candidiasis Category C event, they both had previous Category C events prior to enrollment, and their CD4 counts were 4 and 103. One of the events was considered Grade 3 as well as an SAE.

Category C candidiasis events during the open-label phase were also considered. The analysis of events occurring in the open-label phase is more complicated as such subjects are in this phase 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 phase, of whom two had previously received MVC at any time before the event. 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 arm, and no adjustment was made for multiple comparisons.

With respect to herpes virus infections, a total of 16 MVC subjects (10 MVC QD, 6 MVC BID) had 17 herpes virus events. 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/μL, and 1 had experienced a Category C event at baseline. 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 may be associated with an increase in herpes virus infections.

The most common AEs that occurred during the double-blind period are provided in **Table 18**. Additional analyses are underway to explore the events that appear to be in excess with the MVC arms. Due to concerns raised by the pre-clinical data, additional analyses are also being performed with respect to hypotension, arrhythmia (secondary to QT prolongation), and thyroid disease.

FDA Table 18: AEs Occurring ≥10 Times in Any Treatment Group
(Studies 1027 and 1028 Combined, As Treated Analysis, "Active Period")

Adverse Event Preferred MedDRA Term	MVC QD (n=414)	MVC BID (n=426)	Placebo (n=209)
Abdominal distension	14	11	6
Abdominal pain	19	22	7
Abdominal pain upper	22	17	7
ALT increased	10	10	1
Anaemia	11	14	6
Anorexia	21	16	8
Anxiety	8	12	5
Arthralgia	18	24	6
AST increased	7	17	1
Asthenia	18	12	5
Back pain	22	21	6
Blood CPK increased	5	13	1
Bronchitis	23	27	10
Constipation	21	24	6
Cough	38	51	11
Decreased appetite	10	15	5
Depression	14	14	6
Diarrhoea	113	104	52
Dizziness	40	34	14
Dysgeusia	3	12	2
Dyspepsia	10	11	5
Dyspnoea	13	11	2
Dysuria	7	11	1
Fatigue	50	55	33
Flatulence	16	16	9
Folliculitis	7	14	4
Headache	77	59	33
Herpes simplex	21	29	6
Hypertension	9	13	4
Hypoaesthesia	10	12	2
Influenza	15	6	0
Injection site reaction	29	31	18
Insomnia	23	29	9
Muscle spasms	13	10	9
Myalgia	19	14	2
Nasal congestion	10	13	5
Nasopharyngitis	36	31	9
Nausea	84	80	44
Night sweats	15	16	7
Oedema peripheral	15	11	6
Oesophageal candidiasis	13	2	2
Oral candidiasis	17	10	7
Pain in extremity	12	11	5

Paresthesia	12	11	5
Pharyngolaryngeal pain	17	10	6
Pneumonia	12	6	7
Pruritus	11	15	3
Pyrexia	33	60	20
Rash	28	40	11
Rhinitis	10	4	2
Sinusitis	16	30	9
Skin papilloma	11	9	3
Sleep disorder	10	6	3
Upper respiratory tract infection	42	51	13
Vomiting	48	33	25
Weight decreased	17	13	4

Additional analyses are ongoing with respect to laboratory results, particularly liver transaminases, bilirubin, and creatine phosphokinase and results of these analyses will be presented by the Division at the Antiviral Products' Advisory Committee meeting on April 24, 2007.