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No Clinical Impact of CYP3A5 Gene Polymorphisms on the Pharmacokinetics and/or Efficacy of Maraviroc in Healthy Volunteers and HIV-1–Infected Subjects

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Abstract

Maraviroc is a C-C chemokine receptor type-5 antagonist approved for the treatment of HIV-1. Previous studies show that cytochrome P450 3A5 (CYP3A5) plays a role in maraviroc metabolism. CYP3A5 is subject to a genetic polymorphism. The presence of 2 functional alleles (CYP3A5*1/*1) confers the extensive metabolism phenotype, which is rare in whites but common in blacks. The effect of CYP3A5 genotype on maraviroc and/or metabolite pharmacokinetics was evaluated in 2 clinical studies: a post hoc analysis from a phase 2b/3 study (NCT00098293) conducted in 494 HIV-1–infected subjects (study 1) in which the impact on maraviroc efficacy in 303 subjects was also assessed, and a study conducted in 47 healthy volunteers (study 2). In study 2 (NCT02625207), extensive metabolizers had 26% to 37% lower mean area under the concentration-time curve compared with poor metabolizers (no CYP3A5*1 alleles). This effect diminished to 17% in the presence of potent CYP3A inhibition. The effect of CYP3A5 genotype was greatest in the formation of the metabolite (1S,2S)-2-hydroxymaraviroc. In study 1, the CYP3A5*1/*1 genotype unexpectedly had higher maraviroc area under the curve predictions (20%) compared with those with no CYP3A5*1 alleles. The reason for this disparity remains unclear. The proportions of subjects with viral loads <50 and <400 copies/mL for maraviroc were comparable among all 3 CYP3A5 genotypes. In both studies maraviroc exposures were in the range of near-maximal viral inhibition in the majority of subjects. These results demonstrate that although CYP3A5 contributes to the metabolism of maraviroc, CYP3A5 genotype does not affect the clinical response to maraviroc in combination treatment of HIV-1 infection at approved doses.

Keywords

maraviroc, MERIT study, C-C chemokine receptor type-5 antagonist, cytochrome P450, CYP3A inhibition, CYP3A5 genotype

Maraviroc is a first-in-class potent selective C-C chemokine receptor type-5 antagonist indicated for the treatment of C-C chemokine receptor type-5–tropic HIV-1 infection. Absorption of maraviroc is predicted to be approximately 84%, but it undergoes 60% first-pass extraction, resulting in about 33% relative bioavailability at a 300-mg dose.[1,2] Maraviroc undergoes extensive metabolism via N-dealkylation and hydroxylation primarily by hepatic cytochrome P450 (CYP) 3A enzymes, with negligible metabolic activity from other CYP enzymes.[3–5] Maraviroc also exhibits nonlinear pharmacokinetics.[2,6] Maraviroc is a substrate for efflux transporter P-glycoprotein, also known as ATP-binding cassette subfamily B member 1, as well as for organic anion-transporting polypeptide 1B1, an uptake transporter.[1,7] In vitro studies with human liver microsomes and recombinant human enzyme systems showed that CYP3A5 contributes to the metabolism of maraviroc.[5,8,9]

CYP3A5 is subject to a genetic polymorphism, with CYP3A5*1 being the only functional allele. In vitro, human liver microsomes from extensive

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metabolizers (EMs; 2 CYP3A5*1 alleles) and poor metabolizers (PMs; no CYP3A5*1 alleles) in the presence and absence of ketoconazole and CYP3cide (a selective CYP3A4 inactivator) were used to calculate the contribution of CYP3A5 to metabolism. CYP3A5 metabolism accounted for approximately 32% and 2% of in vitro maraviroc metabolism in CYP3A5 EM donors and PM donors, respectively.[9] A 2014 publication by Lu et al described the effect of CYP3A5 genotype on maraviroc plasma concentrations in healthy volunteers.[10] In this study EMs and intermediate metabolizers (IMs; those who only possess 1 CYP3A5*1 allele) had a 41% and 16% lower median maraviroc area under the plasma concentration-time profile (AUC), respectively, compared with PMs following a single dose of maraviroc 300 mg, suggesting that the CYP3A5 genotype may have clinical implications in the treatment of HIV with maraviroc.

The CYP3A5 allele frequency varies among racial and ethnic groups.[11] In whites and Asians, the nonfunctional CYP3A5 alleles (*3, *6, *7) are predominant, mainly as CYP3A5*3, whereas the prevalence of the CYP3A5*1/*1 genotype (conferring extensive metabolism via CYP3A5) is approximately 1% for whites and 5% to 15% for Asians, respectively. However, the prevalence of the CYP3A5*1/*1 genotype in blacks is significantly higher and ranges from approximately 25% to 70%, implying that if CYP3A5 were to play an important role in maraviroc clearance, then blacks are more likely than whites and Asians to have lower maraviroc exposures. Understanding the role of CYP3A5-mediated metabolism of maraviroc is especially important for the treatment of HIV given that blacks, who have the highest prevalence of the CYP3A5*1 allele, are also disproportionately infected with HIV. In 2015, blacks accounted for 45% of US HIV diagnoses although they comprise only 12% of the US population. Globally, in 2016, 69% of those living with HIV/AIDS and 64% of those newly infected were in Africa (excluding North Africa and the Middle East).[12,13]

In a multivariate analysis of the MOTIVATE phase 3 studies, whites had a better response to maraviroc at 48 weeks than blacks (odds ratio 3.27).[14] These differences were not attributed to pharmacokinetics, given that the difference in response in blacks between the once- and twice-daily maraviroc groups (2-fold daily dose difference) was minimal (28% and 26% with viral load <50 copies/mL at 48 weeks, respectively), with little difference in maraviroc exposure distributions between blacks and whites (data on file). This was confirmed in a post hoc analysis of the MOTIVATE studies, where maraviroc exposure was not a significant factor once adherence and disease-state factors were taken into account.[15] However, race remained a prognostic factor. This is consistent with maraviroc phase 2a monotherapy viral dynamics modeling, which predicts near-maximal viral inhibition with maraviroc 300 mg once and twice daily, delivering concentrations well above the in vivo concentration for 50% inhibition of ~8 ng/mL for the dose intervals.[16]

In this article we describe our findings from an analysis of 2 studies: a phase 1 pharmacokinetic study conducted in healthy volunteers (denoted study 2) and a post hoc analysis from a large global phase 2b/3 study conducted in HIV-1–infected subjects (denoted study 1). The primary aim of this analysis was to investigate the effect of CYP3A5 genotype, specifically the CYP3A5*1 allele, on the pharmacokinetics of maraviroc in addition to its impact on maraviroc efficacy. The effect of CYP3A5 genotype on the pharmacokinetics of 4 CYP3A-derived maraviroc metabolites was also assessed. In addition to being administered alone, maraviroc was also coadministered with darunavir/cobicistat, a potent CYP3A inhibitor combination, in the phase 1 study.[17] The hypothesis was to test whether the impact on maraviroc exposures by CYP3A5 genotype, if present, would be diminished in the presence of potent CYP3A inhibition. In the treatment of HIV-1 infection, maraviroc is commonly coadministered as part of an antiretroviral regimen containing protease inhibitors, most being potent inhibitors of CYP3A.

Methods

Both studies were approved by the institutional review boards or independent ethics committees of each participating center and were conducted in compliance with the principles derived from the Declaration of Helsinki and with all International Conference on Harmonisation Good Clinical Practice guidelines and local regulatory requirements. The complete list of study sites can be found in Supplemental Table S1. All participants gave written informed consent. Some subjects from study 1 were excluded from the analysis because some countries and/or clinical sites did not allow stored samples to be utilized for retrospective genotyping of drug-metabolizing enzymes/drug transporters.

Study Design

Study 1. Study A4001026 (Clinicaltrials.gov identifier NCT00098293), also known as MERIT (Maraviroc versus Efavirenz in Treatment-Naive Patients), was a 96-week, multicenter, double-blind, randomized (1:1:1), comparative, noninferiority phase 2b/3 hybrid (run-in) study conducted in North and South America, Europe, Africa, and Australia to compare the safety and antiviral activity of maraviroc at 2 different doses (300 mg once daily and 300 mg twice daily) versus

efavirenz (600 mg once daily), each in combination with zidovudine/lamivudine (300/150 mg twice daily).[18] There were no food restrictions for maraviroc in this study. The maraviroc 300-mg once-daily group was discontinued at week 16 on recommendation of the Data Safety Monitoring Board because the prespecified noninferiority criteria were not met for this treatment group. In total, 917 subjects were randomized, with 895 subjects receiving study drug (174 subjects on maraviroc 300 mg once daily, 360 subjects on maraviroc 300 mg twice daily, and 361 subjects on efavirenz 600 mg once daily). Responders in the maraviroc 300-mg once-daily group were given the option to switch to open-label maraviroc 300 mg twice daily; 130 subjects went on to receive open-label maraviroc 300 mg twice daily.

The enhanced-sensitivity Trofile HIV coreceptor tropism assay (ESTA; Monogram Biosciences, South San Francisco, California) analysis was used to gain treatment-naive approval in the United States and is the only phenotypic tropism assay that is commercially available; therefore, post hoc comparisons of the ESTA efficacy results (excluding subjects from the maraviroc 300-mg once-daily group) were assessed in the CYP3A5 genotype-efficacy analysis. Maraviroc pharmacokinetic comparisons (predictions for 300 mg twice daily) were assessed on available genotype and pharmacokinetic data from all subjects irrespective of maraviroc treatment group.

Study 2. Study A4001110 (Clinicaltrials.gov identifier NCT02625207) was an open-label, parallel-group, multiple-dose study conducted in a group of 47 healthy male and female subjects of black or white self-reported race at the Pfizer Clinical Research Unit (New Haven, Connecticut). Eligible subjects were aged 18 to 55 years with a body mass index of 17.5 to 30.5 kg/m^2 and a total body weight >50 kg (110 lb). Key exclusion criteria included positive result for HIV-1 or HIV-2, hepatitis B virus serology, or anti–hepatitis C virus serology; evidence or history of clinically significant hematological, renal, endocrinological, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease; history of febrile illness within 5 days before the first study dose; and any condition possibly affecting drug absorption. To limit confounding variables, subjects who had a CYP3A4*22 allele and/or had a solute carrier organic anion transporter 1B1 (SLCO1B1; encodes for organic anion-transporting polypeptide 1B1) *5 or *15 allele were excluded. Subjects were also excluded if their DNA sample provided an unknown CYP3A4, CYP3A5, or SLCO1B1 genotyping result. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever was longer) before the first dose of study medication was not permitted except for limited use of acetaminophen and nonprescription medications that were not believed to affect subject safety or the overall results of the study. Consumption of alcohol and caffeine-containing products was not permitted within 24 hours before the first dose of study medication and was prohibited until collection of the final pharmacokinetic blood sample of each period. Use of tobacco- or nicotine-containing products was not permitted while subjects were confined in the clinical research unit. Subjects were confined to the clinical research unit the day before dosing on day 1 (day 0) and discharged on part 1, day 6 (cohorts 2 and 4 only) and on part 2, day 11 (cohorts 1 and 3 only).

Subjects were placed into 1 of 4 study cohorts on the basis of CYP3A5 genotype and race: cohort 1 (black), no CYP3A5*1 alleles (PM); cohort 2 (black), 1 CYP3A5*1 allele (IM); cohort 3 (black), 2 CYP3A5*1 alleles (EM); and cohort 4 (white), no CYP3A5*1 alleles (PM). The study comprised a prescreen genotype visit, a screening visit up to 28 days before the start of dosing, and 2 treatment periods: part 1 (days 1–5) and part 2 (days 1–10, cohorts 1 and 3 only). A washout period was not required between parts 1 and 2. Tablet formulations of maraviroc and darunavir/cobicistat were administered during the study. In part 1, all subjects received maraviroc 300 mg twice daily on days 1 to 5 (day 5, morning dose only); in part 2, subjects from cohorts 1 and 3 received maraviroc 150 mg once daily with darunavir/cobicistat 800/150 mg once daily for 10 days on days 1 to 10. For part 1, maraviroc could be administered with food except for the morning dose on day 5 (pharmacokinetics day). For part 2, maraviroc and darunavir/cobicistat were to be coadministered with food because darunavir exposures are significantly reduced when given in a fasted state.[19] Investigator site personnel administered the study medication during each study period with 240 mL ambient-temperature water. Subjects were to swallow the study medication whole and not chew the medication before swallowing.

Studies 1 and 2. Blood samples of 4 mL were taken to provide a minimum volume of 1.5 mL of plasma for pharmacokinetic analysis and were transferred into tubes containing sodium heparin. All samples were centrifuged at approximately 1700*g* for approximately 10 minutes at 4°C. Plasma was extracted and stored in screw-capped polypropylene tubes at approximately −20°C within 1 hour of collection.

Pharmacokinetic Sampling

For study 1, single pharmacokinetic samples for determination of maraviroc exposures were collected at

weeks 4, 8, 12, 16, 20, 24, 32, and 40. At weeks 2 and 48, 2 blood samples were collected from each subject as far apart as possible but separated by at least 30 minutes. For study 2, pharmacokinetic samples for determination of maraviroc and the 4 hydroxylated metabolites were collected at 0 (predose), 0.5, 1, 2, 3, 4, 6, 9, and 12 hours following maraviroc administration on day 5 of part 1 and at 0 (predose), 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 hours postdose during part 2, days 10 to 11.

Blood samples of 4 mL were taken to provide a minimum volume of 1.5 mL of plasma for pharmacokinetic analysis and were transferred into tubes containing sodium heparin. All samples were centrifuged at approximately 1700*g* for approximately 10 minutes at 4°C. Plasma was extracted and stored in screw-capped polypropylene tubes at approximately −20°C within 1 hour of collection and assayed within the 1203 days and 206 days of established stability for maraviroc and maraviroc metabolites, respectively.

Genotyping

For study 1, a 9-mL blood sample was collected at the baseline visit. However, in some instances, this sample was collected at later visits. Only 1 sample per patient was analyzed for genotyping. If more than 1 sample existed for any given subject, the earliest sample available was analyzed. For study 2, 4-mL samples were collected at the prescreen genotype visit. Whole-blood host-genotyping samples were collected into tubes containing dipotassium ethylenediaminetetraacetic acid and stored frozen at −20°C or colder at the investigative site until shipment on dry ice to the Pfizer Clinical Pharmacogenomics Laboratory (Groton, Connecticut), where samples were stored at −70°C until analysis.

DNA was extracted from whole-blood samples using the QIAsymphony automated sample preparation platform, the QIAsymphony DSP DNA Mini Kit, and the Blood_200_V7_DSP protocol (Qiagen Inc, Valencia, California). Three single-nucleotide polymorphisms (SNPs) for CYP3A5 (*3, *6, and *7); 1 for CYP3A4 (*22); and 2 for SLCO1B1, 521T>C (rs4149056), and 388A>G (rs2306283) were determined using commercially available TaqMan® assays and analyzed on a QuantStudio 12K Flex Real-Time PCR System (Thermo Fisher Scientific, Waltham, Massachusetts). DNA extraction and genotype assays were performed in the Clinical Laboratory Improvement Amendments–compliant Pfizer Pharmacogenomics Laboratory. The performance characteristics (eg, accuracy, precision, dynamic range) of these clinical assays were established and within expected parameters.

Analytical Methods for Maraviroc and Metabolite Concentrations

The chemical structures of maraviroc and its CYP3A-generated hydroxymaraviroc metabolites are reported by Tseng et al.[5]

Plasma samples were analyzed for maraviroc concentrations at Tandem Laboratories/Covance (West Trenton, New Jersey) using a validated, sensitive, and specific liquid chromatography tandem mass spectrometric (LC-MS/MS) method.[20] Calibration standard responses were linear over the range of 0.500 to 500 ng/mL using a weighted ($1/concentration^2$) linear least-squares regression. Those samples with concentrations above the upper limits of quantification were appropriately diluted into the calibration range. Clinical specimens with plasma maraviroc concentrations below the lower limit of quantification were reported as <0.500 ng/mL.

The between-day assay accuracy, expressed as percentage relative error, for quality control concentrations ranged from 1.6% to 12.0% for the low, low-medium, medium, high, and diluted quality-control samples. Assay precision, expressed as the between-day percentage coefficient of variation of the mean estimated concentrations of quality-control samples was ≤4.3% for low (1.50 ng/mL), low-medium (50.0 ng/mL), medium (150 ng/mL), high (375 ng/mL), and diluted (2500 ng/mL) concentrations.

Plasma samples were analyzed for concentrations of (1S,2S)-2-hydroxymaraviroc (previously reported as PF-06857639), (1R,2R)-2-hydroxymaraviroc (previously reported as PF-06857640), (1S,3S)-3-hydroxymaraviroc (previously reported as PF-06883686/PF-06927572), and (1S,3R)-3-hydroxymaraviroc (previously reported as PF-06883683/PF-06927573) at York Bioanalytical Solutions (Sandwich, Kent, UK) using a qualified, sensitive, and specific LC-MS/MS method.

For internal standard preparation, maraviroc-D5 (0.429 mg) was dissolved in 0.1 mol/L KH_2PO_4 (pH 7.5; 16.5 mL) to generate a 50 μmol/L solution, which was incubated (10 mL) at 37°C for 2 hours with recombinant human CYP3A4 enzyme (1 mL; 5.7 nmol/mL P450 concentration) in 0.1 mol/L KH_2PO_4 buffer (pH 7.5; 6334 μL) with $MgCl_2$ (500 mmol/L; 66 μL) and nicotinamide adenine dinucleotide phosphate (NADPH; 10 mmol/L ; 2.6 mL). At the end of the incubation, Na_2CO_3 (1 mol/L ; 20 mL) was added, and the resulting sample was extracted twice with ethyl acetate (40 mL). The extract was evaporated to dryness under nitrogen and reconstituted in acetonitrile (4 mL), after which the solution was sonicated, and water (4 mL) was added to give a final volume of 8 mL. The resulting solution was diluted 1:10 with 75:25 water:acetonitrile (v/v) and quantified against a calibration line of the

4 individual (nondeuterated) metabolite standards to determine the concentrations before use as an internal standard solution.

Plasma samples, calibration standards, and quality controls were aliquoted (100 μL) into a 96-well plate. Internal standard (10 μL) and borate buffer solution (pH 10; 50 μL) were added, and the samples were mixed. The samples were extracted by mixing thoroughly with ethyl acetate (800 μL) followed by centrifugation (8 minutes at 5°C in a centrifuge set at 2000*g*), after which an aliquot of the supernatant (600 μL) was transferred to a clean plate. A second extraction was performed by mixing with ethyl acetate (600 μL) followed by centrifugation, after which an aliquot of the supernatant (600 μL) was transferred and added to the first aliquot. The transferred supernatant was evaporated to dryness under nitrogen at 40°C. Samples were reconstituted (300 μL) with 90:10 water:acetonitrile (v/v) before injection (40 μL) onto an LC-MS/MS system. The LC-MS/MS system consisted of an API5000 mass spectrometer (AB Sciex, Framingham, Massachusetts), a 1290 pump (Agilent, Santa Clara, California), and an HTS PAL autosampler (CTC Analytics, Zwingen, Switzerland). Mass spectrometric data were acquired in positive-ion mode with a source temperature of 700°C, an IonSpray voltage of 4.5 kV, and a declustering potential of 80 V. Multiple reaction-monitoring transitions from m/z 530 to 405 were used for all the metabolites and from m/z 535 to 410 for all the internal standards with a collision energy of 20 V and a collision gas setting (collisionally activated dissociation) of 7 in all cases. The LC-MS/MS system used an Acquity UPLC HSS T3 column (1.8 μm 2.1 × 100 mm; Waters, Milford, Massachusetts) with gradient elution using 0.1% formic acid in water (solvent A) and methanol (solvent B) as mobile phases. Chromatographic separation was achieved with a linear gradient from 15% B to 25% B over 15 minutes, followed by a linear gradient to 90% B over 4 minutes, after which solvent composition was kept at 90% B for 3 minutes. The flow rate was 400 μL/min, and the column temperature was set at 60°C. All quantitative data were acquired and processed using Analyst 1.6.2 (AB Sciex, Framingham, Massachusetts).

The bioanalytical assay was prequalified using calibration standards (n = 10) and quality-control samples (n = 6) at 4 different concentration levels (lower limit of quantification, low, mid, and high). Additional quality-control low samples (n = 6) were overspiked with darunavir (6900 ng/mL) and cobicistat (1200 ng/mL) to assess any comedication effects; freeze/thaw and long-term stability were additionally assessed to cover the duration of sample storage before assay. On each day of sample analysis, plasma hydroxymaraviroc metabolite concentrations were determined using a 10-point calibration curve (prepared fresh daily) and quality-control samples at 3 different concentration levels (low, mid, and high), prepared separately, and stored frozen before sample analyses. Calibration standard responses were linear over the range of 0.100 to 50.0 ng/mL for each of the analytes using a weighted ($1/concentration^2$) linear least-squares regression. Those samples with concentrations above the upper limit of quantification were then diluted into the calibration range. Clinical specimens with plasma hydroxymaraviroc metabolite concentrations below the lower limit of quantification are reported as <0.100 ng/mL.

The within-day assay accuracy of the prequalification run, expressed as percentage relative error, for lower limit of quantification and low, mid, and high quality-control concentrations, was from 1.0% to 4.4% for (1S,2S)-2-hydroxymaraviroc, from 4.1% to 7.0% for (1R,2R)-2-hydroxymaraviroc, from −3.5% to 4.5% for (1S,3S)-3-hydroxymaraviroc, and from 3.0% to 4.0% for (1S,3R)-3-hydroxymaraviroc, respectively. Assay precision, expressed as the cumulative coefficient of variation of the mean estimated concentrations of low, mid, and high quality-control samples across all sample analytical runs was between 7.2% and 8.2% for (1S,2S)-2-hydroxymaraviroc, between 5.4% and 5.6% for (1R,2R)-2-hydroxymaraviroc, between 4.8% and 8.4% for (1S,3S)-3-hydroxymaraviroc, and between 6.4% and 14.1% for (1S,3R)-3-hydroxymaraviroc, respectively.

Pharmacokinetic Analysis

Study 1. Empirical Bayes estimates of pharmacokinetic parameters, specifically average plasma concentration (C_{avg}), were determined by population pharmacokinetic modeling derived from sparse pharmacokinetic sampling. A 2-compartment partition model, developed with phase 1/2a maraviroc data (without interacting drugs), was adapted and applied to the concentration-time data from study 1 using NONMEM® (ICON Development Solutions, Ellicott City, Maryland).[21,22] This semiphysiological model was used to partition bioavailability into extent of absorption and first-pass elimination effect with estimation of extraction ratio. The model also included a maximum-effect function to describe the nonlinearity in maraviroc absorption/dose. NONMEM analysis involved an estimation step in which some parameters and their random effects were estimated together with residual variability while other parameters were fixed (both fixed and random effects), either to phase 1/2a population modeling estimates or to 0 for some random effects. For the current post hoc analysis, individual estimated maraviroc C_{avg} data from the population

pharmacokinetic analysis for study 1 were utilized only for subjects for whom CYP3A5 genotype results were available.

Study 2. Pharmacokinetic parameters were calculated by noncompartmental analyses for each subject and each treatment using standard methods with internally validated electronic noncompartmental analysis software (eNCA version 2.2.4; Pfizer, Inc, New York, New York). Areas under the plasma concentration-time curve from predose (0 hours) to 12 hours (AUC_{12}; part 1) and 24 hours (AUC_{24}; part 2) were determined by the linear/log trapezoidal method. C_{avg} was calculated by dividing AUC_{12} or AUC_{24} by the dosing interval (12 hours and 24 hours for parts 1 and 2, respectively). The metabolite/parent ratio based on AUC (MRAUC) was calculated by $(AUC_{metabolite}/AUC_{parent}) \times (MW_{parent}/MW_{metabolite})$. Molecular weight (MW) for maraviroc and each of the 4 maraviroc metabolites are 513.68 g/mol and 529.68 g/mol, respectively. Plasma concentration observed at 12 hours (C_{12}) and 24 hours (C_{24}), maximum plasma concentration (C_{max}), and time to C_{max} (T_{max}) were determined by direct observation. Samples below the lower limit of quantification were set to 0 ng/mL for analysis. Actual sample collection times were used for pharmacokinetic analysis.

Statistical Methods

Study 1. Allele CYP3A5 genotype frequencies were assessed for deviation from Hardy-Weinberg equilibrium, by race/ethnicity, using the chi-squared test. Differences of maraviroc pharmacokinetics between CYP3A5 genotypes were assessed by a Wilcoxon rank-sum test (also known as Mann-Whitney U) test for comparison between 2 groups and by a Kruskal-Wallis test for comparison between ≥ 3 groups. *P* values were provided to test differences in maraviroc pharmacokinetics between CYP3A5 genotypes for all methodologies. All statistical methods for these post hoc assessments were conducted with R software (version 3.0.2 or later; The R Project for Statistical Computing, Vienna, Austria). Efficacy/responder status, by CYP3A5 genotype, for maraviroc 300 mg twice daily and efavirenz was compared at week 48 and week 96 based on the ESTA population (ESTA R5 tropism result at screening).

Study 2. A minimum sample size of 11 evaluable subjects per cohort was to provide 90% confidence intervals (CIs) for the difference between cohorts of ± 0.1837 on the natural log scale for maraviroc AUC with 80% coverage probability.

Natural log–transformed AUC, MRAUC, C_{avg}, C_{max}, C_{12} (part 1), and C_{24} (part 2) were analyzed for maraviroc and/or hydroxymaraviroc metabolites using a mixed-effect model with cohort as a fixed effect and subjects as a random effect, separately for parts 1 and 2. The mixed-effect model was implemented using SAS Proc Mixed, SAS version 9.2 (SAS Institute Inc, Cary, NC), with a restricted maximum-likelihood estimation method and Kenward-Roger degrees-of-freedom algorithm. Estimates of the adjusted mean differences between cohorts and corresponding 90% CIs were obtained from the model. Comparisons were made between cohorts 1 and 2 (part 1), cohorts 1 and 3 (parts 1 and 2), cohorts 2 and 3 (part 1), cohorts 1 and 4 (part 1), and cohorts 3 and 4 (part 1). The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means and 90% CIs for the ratios. Additionally, unadjusted *P* values were provided to assess differences between cohorts.

Results

Subject Demographics

CYP3A5 genotype data were available for 872 subjects and 170 subjects (screening population) from studies 1 and 2, respectively. In study 1, there were 494 subjects with both CYP3A5 genotype and maraviroc pharmacokinetic data available (including the maraviroc once-daily group) and 593 subjects with both CYP3A5 genotype and efficacy data available from the ESTA population (excluding the maraviroc once-daily group but including the efavirenz group; Supplemental Table S2). Although the majority of subjects from study 1 were white males, approximately 28% to 40% of subjects were black. For study 2, 47 healthy subjects were enrolled into the study, with the majority being male (Supplemental Table S3). The mean age for cohorts 1 to 3 ranged from 35 to 38 years of age, whereas subjects from cohort 4 were approximately 10 years older.

CYP3A5 Genotyping

For study 1, CYP3A5 genotype data were available for a total of 872 subjects included in the genotype/pharmacokinetic and genotype/efficacy analyses. Race was reported for 863 of the 872 subjects that had CYP3A5 genotype results (Table 1). Of these, 501 subjects (58%) were white, and 285 (33%) were black. All the SNPs for CYP3A5 were in Hardy-Weinberg equilibrium, indicating that the frequency of each allele observed in this study for each SNP had the expected value. Subjects of other races/ethnicities ($n = 77$) were not assessed for the Hardy-Weinberg equilibrium given the limited sample size. For study 2, CYP3A5 genotype data were available for 179 subjects who participated in prescreening/screening. The majority of white subjects were PMs (84% and 95% for studies 1 and 2,

Table 1. Summary of CYP3A5 Genotype by Study and Race

Phenotype, n (%)	CYP3A5 Genotype	Study 1 Total (N = 863)	White (n = 501)	Black (n = 285)	Asian (n = 16)	Other (n = 61)	Study 2 Total (N = 179)	White (n = 41)	Black (n = 135)	Other (n = 3)
Poor metabolizer	*3/*3, *3/*6, *3/*7, *6/*6, *6/*7, *7/*7	524 (60.7)	420 (83.8)	63 (22.1)	7 (43.8)	34 (55.7)	71 (39.7)	39 (95.1)	31 (23.0)	1 (33.3)
Intermediate metabolizer	*1/*3, *1/*6, *1/*7	246 (28.5)	76 (15.2)	141 (49.5)	7 (43.8)	22 (36.1)	73 (40.8)	2 (4.9)	69 (51.1)	2 (66.7)
Extensive metabolizer	*1/*1	93 (10.8)	5 (1.0)	81 (28.4)	2 (12.5)	5 (8.2)	35 (19.6)	0 (0)	35 (25.9)	0 (0)

respectively). Most blacks were either IMs (~50%) or EMs (28% and 26% in studies 1 and 2, respectively).

Effect of CYP3A5 Genotype on Maraviroc and Metabolite Pharmacokinetics

In study 1 the median estimated maraviroc C_{avg} was 20% higher in subjects with CYP3A5*1/*1 genotype compared with subjects with no CYP3A5*1 alleles for the overall pharmacokinetic population (Figure 1; Table 2). The subpopulation of blacks had similarly higher C_{avg} results (17%). Despite the higher C_{avg}, the CYP3A5*1/*1 genotype did not confer the EM phenotype to subjects. In whites, the median estimated maraviroc C_{avg} was 24% lower for EMs than for PMs, consistent with expectations, although it is important to note that only 3 of the 311 whites included in this analysis were EMs. The direct comparison between genotypic EMs and PMs for the overall population was the only assessment that was statistically significant ($P < .05$), but with the difference in the opposite direction from that expected.

In study 2, part 1, following multiple oral doses of maraviroc 300 mg twice daily administered alone, maraviroc absorption was variable with multiple peaks observed across all cohorts (Figure 2). Mean C_{max} values were observed within a median (range) T_{max} of 2 to 3 (0.5-4.0) hours postdose. Maraviroc plasma exposure based on adjusted geometric mean AUC_{12} for black EM subjects (cohort 3) was approximately 37% and 26% lower compared with black (cohort 1) and white (cohort 4) subjects, respectively, with a CYP3A5 genotype that conferred PM (Table 3). The adjusted geometric mean C_{max} for black EM subjects (cohort 3) was approximately 39% and 28% lower in comparison with black (cohort 1) and white (cohort 4) subjects, respectively. Additionally, adjusted geometric mean C_{12} for black EM (cohort 3) subjects was 45 ng/mL, the lowest C_{12} across all cohorts and 24% to 28% lower than black (cohort 1) and white (cohort 4) PMs, respectively. Maraviroc exposures (C_{avg}) in black IMs (cohort 2) were comparable to those in white PMs (cohort 4) and 14% lower compared with black PMs (cohort 1; Figure 3). In subjects with a PM genotype, blacks were shown to have 17% higher maraviroc exposures (C_{avg}) compared with whites.

Mean C_{max} values for all 4 metabolites were observed within a median (range) T_{max} of 1.52 to 3.0 (0.5–4.0) hours postdose across all cohorts (Supplemental Table S4). Mean $MRAUC_{12}$ values for the hydroxymaraviroc metabolites were low, ranging from 0.016 to 0.043 across all cohorts.

Adjusted geometric mean (1S,2S)-2-hydroxymaraviroc plasma $MRAUC_{12}$ for black EM subjects (cohort 3) was 98% and 172% higher than those in black PM (cohort 1) and white PM (cohort 4) subjects, respectively (Supplemental Table S5). Black IMs (cohort 2) had 64% greater (1S,2S)-2-hydroxymaraviroc $MRAUC_{12}$ than black PMs (cohort 1). For PMs, blacks had a 37% higher (1S,2S)-2-hydroxymaraviroc $MRAUC_{12}$ than did whites. $MRAUC_{12}$ values for (1S,2S)-2-hydroxymaraviroc $MRAUC_{12}$ were approximately similar between black EMs and IMs.

For (1R,2R)-2-hydroxymaraviroc, black EMs had a 20% higher $MRAUC_{12}$ than white PMs with comparable mean $MRAUC_{12}$ values for black IMs and PMs and white PMs. Mean (1S,3S)-3-hydroxymaraviroc and (1S,3R)-3-hydroxymaraviroc $MRAUC_{12}$ were comparable across all cohorts.

Intersubject variability for maraviroc exposure, as measured by adjusted geometric mean coefficient of variation for AUC_{12} and C_{max}, was similar across all cohorts and ranged between 23% and 34%. Intersubject variability for metabolite exposures ranged from 18% to 66%. Higher variability was observed for IMs across all metabolites.

For part 2, following coadministration of multiple oral doses of maraviroc 150 mg once daily with darunavir/cobicistat 800/150 mg once daily, mean maraviroc C_{max} values were observed approximately within a median (range) T_{max} of 3.0 (1.0 to 6.0) hours postdose (Supplemental Table S4). In blacks, maraviroc exposure for EMs (cohort 3) was approximately 17% and 32% lower based on adjusted geometric mean AUC_{24}

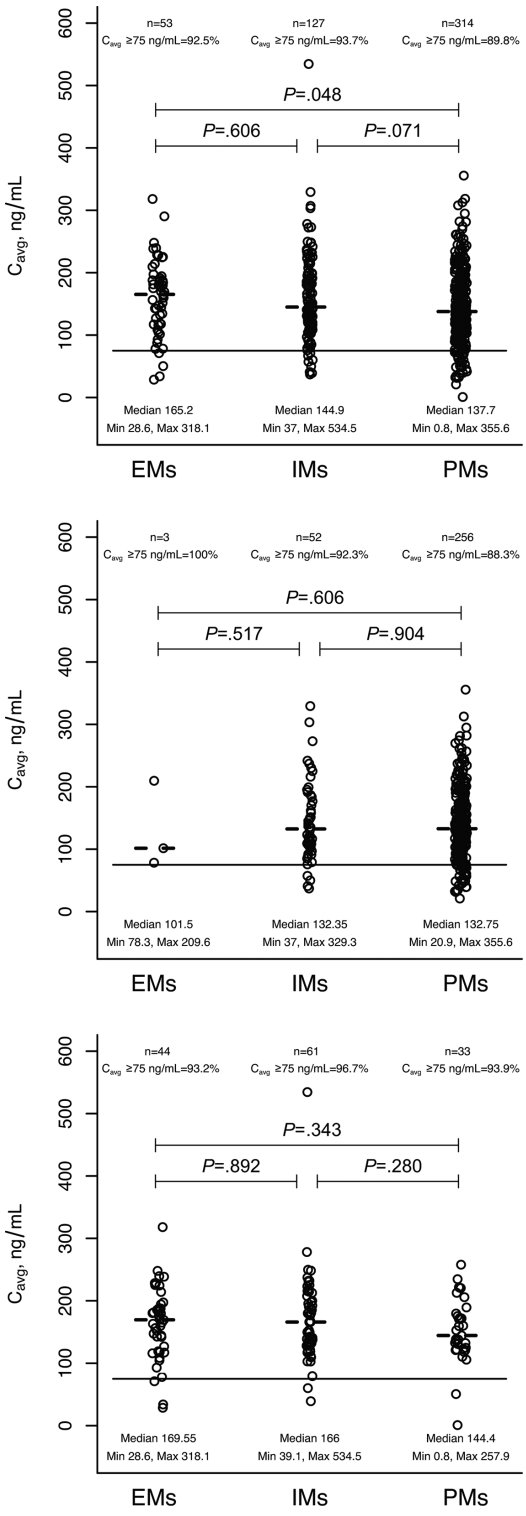

Figure 1. Effect of CYP3A5 genotype on estimated maraviroc C_{avg} in HIV-infected subjects (study 1). Upper plot, all maraviroc subjects (n = 494); middle plot, whites (n = 311); lower plot, blacks (n = 138). Dashed line represents median C_{avg} for distribution; solid reference line represents C_{avg} = 75 ng/mL, exposure associated with near-maximal virologic efficacy.[28] C_{avg} indicates average plasma concentration; EM, extensive metabolizer (2 CYP3A5*1 alleles); IM, intermediate metabolizer (1 CYP3A5*1 allele); PM, poor metabolizer (no CYP3A5*1 alleles).

and C_{max} values, respectively, compared with PMs (cohort 1; Table 3). Adjusted geometric mean maraviroc C_{24} values observed between EMs and PMs were similar. Intersubject variability for maraviroc exposure for AUC_{24} and C_{max} was slightly higher for EMs (25% to 53%) compared with that observed for PMs (20% to 37%).

Maraviroc metabolite pharmacokinetic comparisons were not assessed for part 2 because a substantial number of the pharmacokinetic samples were below the lower limit of quantification. Therefore, metabolite pharmacokinetic parameters could not be calculated reliably.

Effect of CYP3A5 Genotype on Maraviroc Efficacy. In study 1, where maraviroc 300 mg twice daily or efavirenz 600 mg once daily was dosed with zidovudine/lamivudine in HIV-1 treatment-naive patients, the proportions of subjects with HIV-1 RNA <50 and <400 copies/mL for maraviroc and efavirenz at weeks 48 and 96 were comparable among all 3 CYP3A5 genotypes in subjects in whom CYP3A5 genotyping data were available (Table 4; Supplemental Figure S1). Additionally, through week 96, the percentage of subjects receiving maraviroc who discontinued the study because of lack of efficacy was numerically lower among EMs (4/43; 9.3%) than among PMs (25/175; 14.3%) and similar compared with IMs (8/85; 9.4%).

Discussion

Maraviroc is principally metabolized by CYP3A4 to hydroxylated metabolites with partial contribution from CYP3A5 to the generation of (1S,2S)-2-hydroxymaraviroc.[3–5] CYP3A5 is subject to genetic polymorphism in which the CYP3A5*1/*1 genotype, which confers extensive metabolism, is common among individuals of African descent but rare in whites.[23] This implies that blacks, in general, may have lower maraviroc exposures than whites.

Results from study 2 demonstrated that black EMs had 26% to 37% lower mean maraviroc exposures than white and black PMs following administration of maraviroc 300 mg twice daily. This is consistent with results from Lu et al, who found that CYP3A5 EMs (n = 8) had 41% lower exposures than PMs (n = 8) following a single dose of maraviroc 300 mg.[10] These results also are consistent with in vitro data that estimated that the CYP3A5 contribution to overall maraviroc metabolism was 32% based on the depletion of maraviroc in human liver microsomes from a CYP3A5*1/*1 donor (EM).[9] In contrast, a post hoc pharmacokinetic/genotype analysis of study 1 showed that black EM genotype subjects had higher rather than lower maraviroc exposures compared with black

Table 2. Statistical Summary of Estimated Maraviroc C_{avg} Based on CYP3A5 Genotype for Maraviroc 300 mg Twice-Daily Dosing (Study 1)

	C_{avg}, Median (Range), ng/mL			*P* Value			
	CYP3A5 EM	CYP3A5 IM	CYP3A5 PM	CYP3A5 EM vs IM vs PM	CYP3A5 EM vs PM	CYP3A5 EM vs IM	CYP3A5 IM vs PM
All subjects	165.2 (28.6–318.1) n = 53	144.9 (37.0–534.5) n = 127	137.7 (0.8–355.6) n = 314	.0517	.0476	.6057	.0710
Whites	101.5 (78.3–209.6) n = 3	132.4 (37.0–329.3) n = 52	132.8 (20.9–355.6) n = 256	.8548	.6062	.5166	.9042
Blacks	169.6 (28.6–318.1) n = 44	166.0 (39.1–534.5) n = 61	144.4 (0.8–257.9) n = 33	.5135	.3431	.8915	.2796

C_{avg} indicates average plasma concentration; EM, extensive metabolizer (2 CYP3A5*1 alleles); IM, intermediate metabolizer (1 CYP3A5*1 allele); PM, poor metabolizer (no CYP3A5*1 alleles).

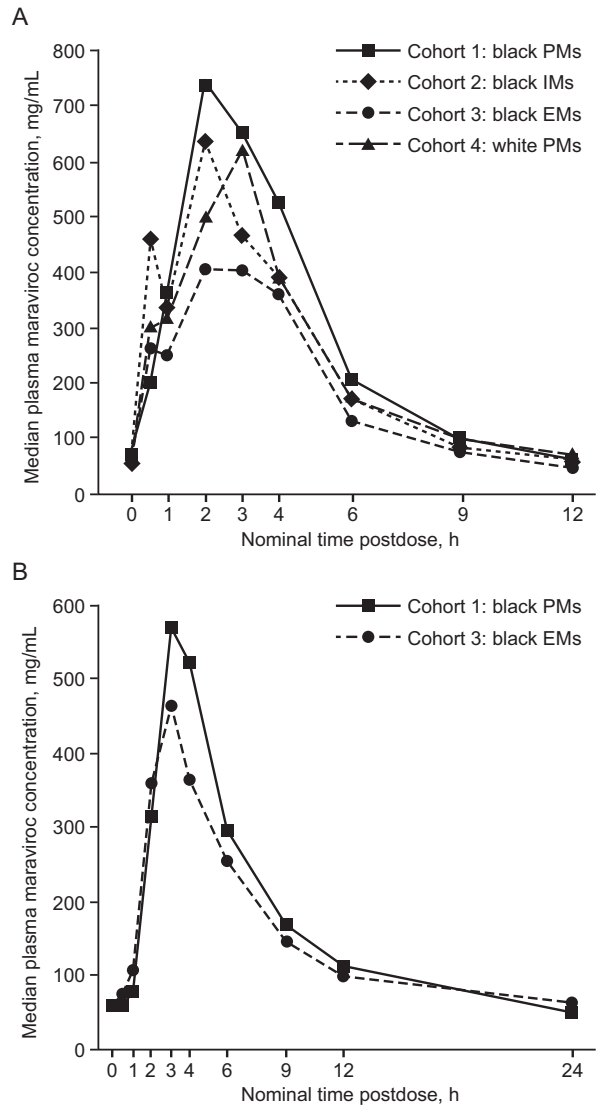

Figure 2. Maraviroc plasma concentration-time profiles by CYP3A5 genotype (study 2). A, Maraviroc plasma concentrations following maraviroc 300 mg twice-daily dosing in part 1. B, Maraviroc plasma concentrations following maraviroc 150 mg + darunavir/cobicistat 800/150 mg once-daily dosing in part 2. EM indicates extensive metabolizer (2 CYP3A5*1 alleles); IM, intermediate metabolizer (1 CYP3A5*1 allele); PM, poor metabolizer (no CYP3A5*1 alleles).

PMs, whereas in the few white EM subjects (n = 3), the median predicted C_{avg} was 24% lower than that in PMs. The reason for this disparity remains unclear; however, there are distinct differences between the studies that could be responsible for confounding the CYP3A5 genotype effect. Both study 2 and the study conducted by Lu et al were carefully controlled for pharmacokinetic sampling and intake of food in relation to administration.[10] In study 1, maraviroc C_{avg} was estimated by population pharmacokinetic modeling derived from sparse pharmacokinetic sampling (1 or 2 samples per dose interval) with patient-reported dosing and involved an HIV-1–infected patient population receiving maraviroc + zidovudine/lamivudine with or without food and with or without other concomitant nonantiretroviral drug(s). Maraviroc, when administered without CYP3A inhibitors, shows a dose- and time-dependent food effect.[21] In a phase 1 study conducted in Singapore (Study A4001043), a geometric mean reduction of 33% (range from 62% decrease to 25% increase [unpublished data]) in relative bioavailability has been shown for single-dose maraviroc 300 mg given with a high-fat meal.[1] The real-world dosing of maraviroc with or without food and variability associated with patient-reported dosing in study 1 may have confounded the results of the CYP3A5 genotype/pharmacokinetic analysis. Also, CYP3A activity was significantly reduced in HIV-infected subjects compared with healthy volunteers, likely driven by inflammatory processes (higher plasma tumor necrosis factor α concentrations) that downregulate CYP3A transcription.[24–26] Therefore, before the completion of this post hoc analysis, it was theorized that maraviroc exposures would be lower in EMs compared with PMs in study 1 but likely not be as pronounced as observed in healthy volunteers.[10]

In study 2, the CYP3A5 genotype was shown to have limited relevance when maraviroc was given in combination with the potent CYP3A inhibitors darunavir and cobicistat in black EMs compared with PMs (17% versus 37% lower maraviroc AUC without

Table 3. Statistical Summary of Cohort Comparison for Maraviroc Plasma Pharmacokinetic Parameters: Part 1 and Part 2 (Study 2)

Parameter (Unit)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means (90% CI)	*P* Value
	Test	Reference		
Part 1: Maraviroc 300 mg twice daily				
Cohort 1 (black PMs; test) vs cohort 4 (white PMs; reference)				
AUC_{12} (ng•h/mL)	3441	2947	1.17 (0.99, 1.38)	.1318
C_{avg} (ng/mL)	286.8	245.8	1.17 (0.98, 1.38)	.1338
C_{max} (ng/mL)	863.9	731.0	1.18 (0.95, 1.47)	.1997
C_{12} (ng/mL)	59.84	63.10	0.95 (0.77, 1.17)	.6761
Cohort 2 (black IMs; test) vs cohort 1 (black PMs; reference)				
AUC_{12} (ng•h/mL)	2954	3441	0.86 (0.72, 1.02)	.1369
C_{avg} (ng/mL)	246.2	286.8	0.86 (0.72, 1.02)	.1370
C_{max} (ng/mL)	754.0	863.9	0.87 (0.70, 1.08)	.2947
C_{12} (ng/mL)	63.09	59.84	1.05 (0.85, 1.30)	.6771
Cohort 3 (black EMs; test) vs cohort 1 (black PMs; reference)				
AUC_{12} (ng•h/mL)	2181	3441	0.63 (0.54, 0.75)	<.0001
C_{avg} (ng/mL)	181.6	286.8	0.63 (0.53, 0.75)	<.0001
C_{max} (ng/mL)	529.0	863.9	0.61 (0.49, 0.76)	.0004
C_{12} (ng/mL)	45.32	59.84	0.76 (0.61, 0.94)	.0331
Cohort 3 (black EMs; test) vs cohort 2 (black IMs; reference)				
AUC_{12} (ng•h/mL)	2181	2954	0.74 (0.63, 0.87)	.0036
C_{avg} (ng/mL)	181.6	246.2	0.74 (0.63, 0.87)	.0036
C_{max} (ng/mL)	529.0	754.0	0.70 (0.57, 0.87)	.0071
C_{12} (ng/mL)	45.32	63.09	0.72 (0.58, 0.88)	.0104
Cohort 3 (black EMs; test) vs cohort 4 (white PMs; reference)				
AUC_{12} (ng•h/mL)	2181	2947	0.74 (0.63, 0.87)	.0038
C_{avg} (ng/mL)	181.6	245.8	0.74 (0.63, 0.87)	.0037
C_{max} (ng/mL)	529.0	731.0	0.72 (0.59, 0.89)	.0135
C_{12} (ng/mL)	45.32	63.10	0.72 (0.58, 0.88)	.0104
Part 2: Maraviroc 150 mg + darunavir/cobicistat 800/150 mg once daily				
Cohort 3 (black EMs; test) vs cohort 1 (black PMs; reference)				
AUC_{24} (ng•h/mL)	3645	4413	0.83 (0.70, 0.97)	.0531
C_{avg} (ng/mL)	151.7	184.1	0.82 (0.70, 0.97)	.0507
C_{max} (ng/mL)	432.9	633.6	0.68 (0.50, 0.94)	.0505
C_{24} (ng/mL)	56.34	56.56	1.00 (0.83, 1.19)	.9713

AUC_{12} indicates area under the plasma concentration-time profile from time 0 to 12 hours postdose; AUC_{24}, area under the plasma concentration-time profile from time 0 to 24 hours postdose; C_{12}, plasma concentration at 12 hours postdose; C_{24}, plasma concentration at 24 hours postdose; C_{avg}, average plasma concentration; C_{max}, maximum plasma concentration; CI, confidence interval; EM, extensive metabolizer (2 CYP3A5*1 alleles); IM, intermediate metabolizer (1 CYP3A5*1 allele); PM, poor metabolizer (no CYP3A5*1 alleles).

CYP3A inhibitors). This is important to note because coadministration of CYP3A-inhibiting cobicistat or ritonavir-boosted protease inhibitors with maraviroc is common in clinical practice for the treatment of HIV.

In study 2, blacks were shown to have 17% higher maraviroc exposures compared with whites following administration of maraviroc 300 mg twice daily in subjects phenotyped as PMs. This is aligned with the post hoc analysis from study 1, in which the estimated median maraviroc C_{avg} in PMs was approximately 9% higher in black subjects compared with whites. Furthermore, in the original population pharmacokinetic modeling analysis from the MERIT study that evaluated demographic covariate effects on relative maraviroc exposure, it was estimated that blacks have 17.5% higher maraviroc exposures than whites when the data are adjusted for sex, weight, and age.[22]

Tseng et al identified 5-hydroxymaraviroc metabolites that are products of CYP3A-mediated maraviroc metabolism.[5] It was determined that CYP3A5 contributes approximately 25% to the formation of these hydroxymaraviroc metabolites in EMs. In study 2, the pharmacokinetics of 4 of the 5 metabolites was assessed. A synthetic standard for instrument calibration was not available to suitably measure exposures of the fifth metabolite, hydroxymethylmaraviroc; however, the estimated CYP3A5 contribution to the formation of this metabolite in human liver microsomes of CYP3A5*1/*1 (EM) donors was minimal at 1%. The largest impact on metabolite exposures by CYP3A5 genotype was observed with

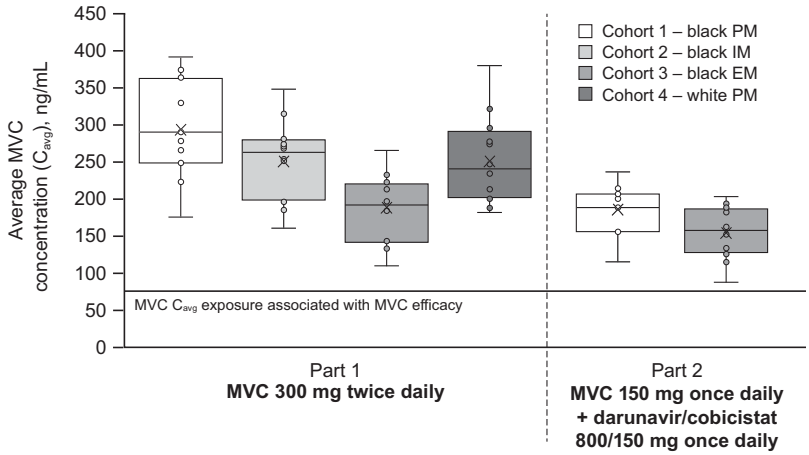

Figure 3. Maraviroc C_{avg} exposure by CYP3A5 genotype with and without CYP3A inhibition (study 2). Solid reference line represents $C_{avg} = 75$ ng/mL, exposure associated with near-maximal virologic efficacy in study 1.[28] Each boxplot shows the interquartile range with the median (horizontal line) and mean (×) C_{avg} values indicated. Whiskers show the minimum and maximum values. The circles represent individual scores. C_{avg} indicates average plasma concentration; EM, extensive metabolizer (2 CYP3A5*1 alleles); IM, intermediate metabolizer (1 CYP3A5*1 allele); MVC, maraviroc; PM, poor metabolizer (no CYP3A5*1 alleles).

Table 4. Proportion of HIV-1–Infected Subjects HIV-1 RNA <50 Copies/mL and <400 Copies/mL by CYP3A5 Genotype/Phenotype at Week 48 and Week 96 in Study 1

	HIV-1 RNA <50 Copies/mL		HIV-1 RNA <400 Copies/mL	
	Maraviroc 300 mg Twice Daily (n/N, %)	Efavirenz 600 mg Once Daily (n/N, %)	Maraviroc 300 mg Twice Daily (n/N, %)	Efavirenz 600 mg Once Daily (n/N, %)
CYP3A5 Phenotype				
Week 48				
Overall	209/303 (69.0)	200/290 (69.0)	225/303 (74.3)	210/290 (72.4)
EMs (2 CYP3A5*1 alleles)	30/43 (69.8)	19/30 (63.3)	32/43 (74.4)	20/30 (66.7)
IMs (1 CYP3A5*1 allele)	53/85 (62.4)	68/96 (70.8)	61/85 (71.8)	71/96 (74.0)
PMs (no CYP3A5*1 alleles)	126/175 (72.0)	113/164 (68.9)	132/175 (75.4)	119/164 (72.6)
Week 96				
Overall	179/303 (59.1)	183/290 (63.1)	195/303 (64.4)	187/290 (64.5)
EMs (2 CYP3A5*1 alleles)	23/43 (53.5)	17/30 (56.7)	26/43 (60.5)	17/30 (56.7)
IMs (1 CYP3A5*1 allele)	47/85 (55.3)	62/96 (64.6)	52/85 (61.2)	63/96 (65.6)
PMs (no CYP3A5*1 alleles)	109/175 (62.3)	104/164 (63.4)	117/175 (66.9)	107/164 (65.2)

EM indicates extensive metabolizer; IM, intermediate metabolizer; N, sample size for the overall population or subpopulation; PM, poor metabolizer.

(1S,2S)-2-hydroxymaraviroc when maraviroc was given as monotherapy. The $MRAUC_{12}$ for black EMs was approximately 2- to 3-fold higher compared with black and white PMs, which is consistent with the impact of CYP3A5 genotype on maraviroc parent exposures. These data, along with CYP3A5*1/*1 human liver microsome data showing that CYP3A5 contributes 42% to the formation of (1S,2S)-2-hydroxymaraviroc, clearly demonstrate that CYP3A5 has a role in the generation of this metabolite.[5] (1S,2S)-2-Hydroxymaraviroc is also likely the "M1" metabolite that was described by Lu and colleagues in 2012.[8] The comparison of M1 metabolite/maraviroc parent AUC ratios between EMs and PMs by Lu et al were comparable to what was observed with (1S,2S)-2-hydroxymaraviroc in study 2, part 1.[10] The impact of CYP3A5 genotype on the $MRAUC_{12}$ of the other 3 maraviroc metabolites assessed in study 2 [(1R,2R)-2-hydroxymaraviroc, (1S,3S)-3-hydroxymaraviroc, and (1S,3R)-3-hydroxymaraviroc] was not statistically significant ($P = .0590$, .9536, and .7913, respectively), as predicted based on minimal CYP3A5 contribution to the formation of these metabolites in human liver microsomes.[5] In study 2, part 2, exposures of hydroxymaraviroc metabolites were low and undetectable in a substantial number of plasma samples, demonstrating that coadministration with darunavir/cobicistat significantly inhibited CYP3A-mediated metabolite formation. The antiviral activities of the hydroxymaraviroc metabolites have not been evaluated. However, their contribution to the overall antiviral activity of maraviroc would likely be minimal, regardless of their activities, given that the metabolite-to-parent ratios do not exceed 5% for any 1 metabolite in this study.

Lu and colleagues stated that maraviroc may be underdosed in EMs given that the lower exposure (41%) observed in EMs compared with PMs is similar to the 45% lower maraviroc exposure observed with the concomitant use of efavirenz, a potent CYP3A inducer that warrants a doubling of the maraviroc dose when coadministered.[10] In general, this statement could be misleading because both inter- and intraindividual maraviroc pharmacokinetic variabilities were taken into account in decisions concerning maraviroc twice-daily dose recommendations. EMs were also well represented in study 1 (~9% of maraviroc treatment population) and likely the MOTIVATE studies, a phase 3 global study in treatment-experienced HIV-1–infected patients where blacks accounted for approximately 14% of all patients randomized to the maraviroc treatment group.[14,27] In the case of efavirenz, a doubling of the maraviroc dose is the approved dose, given the magnitude of the drug interaction, the observed pharmacokinetic variability, and the maraviroc exposures that correlate with clinical efficacy.

Exposure-response analyses from study 1 demonstrate a near-maximal virologic response of maraviroc C_{avg}.[28] Maraviroc 300 mg administered twice daily yielded a predicted $C_{avg} \geq 75$ ng/mL in approximately 90% of subjects, irrespective of CYP3A5 genotype or race. Moreover, CYP3A5 genotype did not impact the efficacy of maraviroc. In study 2, despite lower exposures observed with EMs, individual C_{avg} values ranged between 110 and 392 ng/mL (part 1) and between 88.1 and 238 ng/mL (part 2) across all CYP3A5 genotype/race cohorts dosed with maraviroc 300 mg twice daily (part 1) and maraviroc 150 mg + darunavir/cobicistat 800/150 mg once daily (part 2), demonstrating that all subjects enrolled into the study achieved the C_{avg} associated with near-maximal virologic response with maraviroc. In the 2014 study by Lu et al, target exposures were also achieved in the EM group given that the median (interquartile range) maraviroc C_{avg} was 103 (90-117) ng/mL.[10] Furthermore, maraviroc exposures when it was coadministered with a potent CYP3A inhibitor such as darunavir/cobicistat would be significantly higher if maraviroc were dosed at the approved dose of 150 mg twice daily (with potent CYP3A inhibitors) rather than 150 mg once daily. The once-daily dose of maraviroc 150 mg in combination with boosted protease inhibitor regimens has been previously investigated for the treatment of HIV.[29–34] As a result, maraviroc 150 mg once daily with darunavir/cobicistat was examined in this study to assess the worst-case scenario for low maraviroc exposure where maraviroc C_{avg} achieved exposures associated with near-maximal maraviroc virologic response, with C_{avg} ranging from 88 to 204 ng/mL in black EMs. The magnitude of the effect of CYP3A5 genotype on maraviroc exposures is expected to be comparable with exposures for maraviroc administered at the approved dose of 150 mg twice daily in combination with darunavir/cobicistat. In addition, maraviroc is being assessed at lower daily doses (300 mg once daily) for HIV preexposure prophylaxis, commonly referred to as PrEP, in healthy men and women at high risk for HIV infection.[35,36] The impact of CYP3A5 genotype for HIV PrEP cannot be determined until maraviroc has been shown to be effective for use in PrEP and exposure-response analyses determine what target maraviroc exposure is needed for HIV prevention.

Conclusions

Overall, these results demonstrate that although CYP3A5 plays a role in the metabolism of maraviroc to 1 of its metabolites, the CYP3A5 genotype does not have a clinically relevant impact on maraviroc efficacy as part of combination therapy for the treatment of HIV-1 infection at recommended maraviroc doses. Maraviroc efficacy and the exposures required for HIV prevention have not been established; therefore, the clinical relevance of these findings for maraviroc use in PrEP is unknown.

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Data Sharing

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Declaration of Conflicting Interests

M.V., L.M., S.R.V., A.F., L.S.W., J.-C.M., P.L.S.C., and J. Heera are employees of Pfizer and own stock and stock options in Pfizer. A.N., J. Haynes, and M.E.S. are employees of York Bioanalytical Solutions. A.C. and K.Y.S. are employees of ViiV Healthcare and own stock in GlaxoSmithKline. S.N. and G.F. have nothing to disclose.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.