A recent publication by Lu et al. (2014) described the effects of the CYP3A5 genotype on Selzentry/Celsentri (maraviroc) concentrations. Maraviroc is a chemokine (C-C motif) receptor 5 inhibitor approved for the treatment of human immunodeficiency virus (HIV) infection (Dorr et al., 2005). Maraviroc pharmacokinetics in subjects who were heterozygous (n = 8; one CYP3A5*1 and one dysfunctional allele) and homozygous for the wild-type alleles (n = 8; two CYP3A5*1 alleles) were compared with those who were homozygous for the dysfunctional alleles (n = 8; two dysfunctional alleles: CYP3A5 *2, *3, *6, and *7). The median (interquartile range) maraviroc area under the plasma concentration-time curve from time 0 to infinity was 2099 (1422–2568), 1761 (931–2640), and 1238 (1065–1407) ng·h/ml, respectively, for the homozygous dysfunctional, heterozygous, and homozygous wild-type group following a single 300 mg dose of maraviroc. Thus, the heterozygous group and the homozygous wild-type group had a 16 and 41% lower median maraviroc area under the plasma concentration-time curve from time 0 to infinity, respectively, compared with the homozygous mutant group.

These results suggest that CYP3A5 may play a role in the metabolism of maraviroc, specifically for those with functional CYP3A5 alleles. This is consistent with recent data in human liver microsomes (HLMs) showing that the estimated CYP3A5 contribution to maraviroc metabolism in HLMs from wild-type CYP3A5 *1/*1 donors (homozygous functional allele) was 32% compared with only 2% in HLMs from CYP3A5 *3/*3 donors (homozygous dysfunctional allele) (Tseng et al., 2014).

Lu et al. (2014) also concluded that maraviroc may be underdosed in patients who are homozygous for the CYP3A5*1 allele, which includes nearly one-half of all black individuals (Xie et al., 2004; Abel et al., 2008; Lu et al., 2014). Lu and colleagues are the first to present results on the effect that the CYP3A5 genotype has on maraviroc pharmacokinetics (PK). Although there are no other in vivo data on the effect of the CYP3A5 genotype on maraviroc PK, comparisons of maraviroc PK and efficacy by race from the maraviroc phase 3 registrational studies may be able to provide some additional insight. It is known that the majority of white individuals carry the mutant alleles with approximately 90% being homozygous for the mutant alleles, whereas approximately 40% of African Americans and 70% of Sub-Saharan Africans are homozygous wild type for CYP3A5*1, suggesting that Blacks are more likely than Whites to have lower maraviroc exposures (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=776746).

We commend the authors for their contributions to the understanding of maraviroc’s PK variability; however, we believe their general conclusions of CYP3A5 genotype being the major factor in maraviroc’s variability may be misleading. Maraviroc’s inter- and intraindividual PK variability was recognized and taken into account when decisions concerning maraviroc dose were made, specifically for recommendations of twice daily (BID) dosing of maraviroc when used in combination with other active antiretrovirals. Moreover, the CYP3A5 genotype is likely to have very limited relevance when maraviroc is dosed with ritonavir-boosted protease inhibitors. In addition, maraviroc, dosed in the absence of interacting drugs, does not appear to result in lower exposures in black subjects in population PK modeling (Abel et al., 2009).

Maraviroc dose selection for the phase 2b/3 trials was based on in vitro virology (in vitro protein-adjusted IC50 = 2.1 ng/ml) (Dorr et al., 2005), PK-viral dynamics modeling utilizing a broad range of doses in monotherapy (in vivo IC50 of 8 ng/ml) (Rosario et al., 2008), and an extensive healthy volunteer drug interaction program (Abel et al., 2009). In a maraviroc monotherapy study, greater than 80% viral inhibition (range: 88–96%) was demonstrated with PK-viral dynamics modeling at exposures observed with 300 mg BID (Cavg [AUC divided by the dosing interval] range: 141–338 ng/ml) (Fatkenheuer et al., 2005; Rosario et al., 2006).

The phase 3 trials in highly treatment-experienced patients (MOTIVATE studies) compared placebo to maraviroc, with the majority of those receiving maraviroc at 150 mg daily (QD) or BID doses in the presence of CYP3A9-inhibiting protease inhibitors. Maraviroc exposures are not expected to be significantly different between expressors and nonexpressors of CYP3A5 when dosed in combination with CYP3A9-inhibiting ritonavir-boosted protease inhibitors, as ritonavir is a potent inhibitor of both CYP3A4 and CYP3A5 (Ernest et al., 2005; Granfors et al., 2006). Indeed, in these studies, there was little difference in the outcome between QD and BID (43% vs. 46% HIV-1 RNA <50 copies/ml at week 48), with both maraviroc groups performing significantly better than placebo (17% HIV-1 RNA <50 copies/ml) (Gulick et al., 2008).

The MERIT study in treatment-naïve subjects, which utilizes MVC with an NRTI backbone (zidovudine/lamivudine) that does not significantly affect the activity of cytochrome P450 enzymes, is the most informative source for assessing drug exposure achieved with 300 mg BID dosing and the effect of race on PK. Sparse PK samples were collected across 48 weeks and used in a population PK analysis. Concentration-time data (split by race and maraviroc dose frequency) from the MERIT study used in this analysis are presented in Fig. 1. Black subjects, about one-third of the study population, generally had higher exposures (from post-hoc Bayesian estimates) with predicted median Cavg exposures of 168 ng/ml (n = 110) versus 132 ng/ml (n = 202) for white subjects randomized into the maraviroc 300 mg BID arm (Abel et al., 2009). The PK model predicts the typical black subject to have 17.5% higher maraviroc exposure compared with the typical white subject after adjusting for age, weight, and gender. However, the proportion of blacks receiving 300 mg of maraviroc BID who met the primary endpoint in the MERIT study (HIV-1 RNA <50 copies/ml at week 48) was approximately 10% points lower than whites (Cooper et al., 2010). This result was driven by higher rates of discontinuation from the study due to withdrawal of consent or loss to follow-up in black subjects. This underscores the importance of several confounding variables in the interpretation of clinical responses, particularly in light of the fact that discontinuation from maraviroc treatment due to lack of
CYP3A5 homozygous dysfunctional, heterozygous, and homozygous determined and comparisons of PK and efficacy will be made between participated in the phase 3 MERIT study. CYP3A5 genotypes will be a retrospective study of DNA samples stored from subjects who efficacy in light of the results from Lu et al. We have undertaken additional work to better understand the effect that the genotype) on maraviroc pharmacokinetics may not be as pronounced top of any PK variability observed across the population. Furthermore, which have been shown to significantly alter maraviroc exposures on warranted in the presence of potent CYP3A inhibitors and inducers, of exposures when given in combination therapy. Dose adjustment is range) maraviroc Cavg was 103 ng/ml (90 – 117). The maraviroc dose of 300 mg BID should provide near-maximal efficacy across the range of quantitation.

clinical response was slightly higher in whites (10.8%) as compared with blacks (7.0%) (data on file).

Exposure-response analyses from the maraviroc phase 3 trials (MERIT and MOTIVATE studies) show a flat response with maraviroc Cavg above 75–100 ng/ml (McFadyen et al., 2008; Jacqmin et al., 2013). Therefore, the exposures achieved in the homozygous wild-type CYP3A5 group as reported in the Lu et al. (2014) study should be sufficient for virologic response given that the median (interquartile range) maraviroc Cavg was 103 ng/ml (90–117). The maraviroc dose of 300 mg BID should provide near-maximal efficacy across the range of exposures when given in combination therapy. Dose adjustment is warranted in the presence of potent CYP3A inhibitors and inducers, which have been shown to significantly alter maraviroc exposures on top of any PK variability observed across the population. Furthermore, racial comparisons of the PK data suggest that race (and/or CYP3A5 genotype) on maraviroc pharmacokinetics may not be as pronounced as suggested by Lu et al. (Abel et al., 2009).

ViIV Healthcare and Pfizer are committed to patient care and have undertaken additional work to better understand the effect that the CYP3A5 genotype may have on maraviroc pharmacokinetics and efficacy in light of the results from Lu et al. We have undertaken a retrospective study of DNA samples stored from subjects who participated in the phase 3 MERIT study. CYP3A5 genotypes will be determined and comparisons of PK and efficacy will be made between CYP3A5 homozygous dysfunctional, heterozygous, and homozygous wild-type groups, in the context of other factors known to affect maraviroc PK and efficacy.

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