CYP3A5*1 Allele Not Associated with Lower Maraviroc Exposures in the MERIT study

M Vourvahis,[1] L McFadyen,[2] SR Valluri,[3] B Weatherley,[2] LS Wood,[4] JC Marshall,[4] PLS Chan,[2] A Clark,[5] A Rinehart,[6] KY Smith,[6] J Heera[7]

[1]Pfizer, Clinical Pharmacology, New York, NY, USA; [2]Pfizer, Pharmacometrics, Sandwich, UK; [3]Pfizer, Biostatistics, New York, NY, USA; [4]Pfizer, Clinical Pharmacogenomics, Groton, CT, USA; [5]ViiV Healthcare, London, UK; [6]ViiV Healthcare, Research Triangle Park, NC, USA; [7]Pfizer, Clinical, Groton, CT, USA

16th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy; May 26-28, 2015; Washington, DC

Disclosures

- M Vourvahis, L McFadyen, SR Valluri, B Weatherley, LS Wood, JC Marshall, PLS Chan and J Heera are employees of Pfizer, Inc.
- A Clark, A Rinehart and KY Smith are employees of ViiV Healthcare

Background

- Maraviroc (MVC) is a substrate for CYP3A4, P-glycoprotein and OATP1B1.
- Recent in vitro data show that MVC is also a substrate for CYP3A5.[1,2]
- Recently published data (Lu et al, 2014) in healthy volunteers showed that those homozygous for the CYP3A5*1 allele (n=8) have 41% lower MVC exposures as compared to those with no CYP3A5*1 alleles (n=8) following a single 300 mg dose.[3]
- CYP3A5*1/*1 allele is highly prevalent in Blacks (39-70%).[4]

[1]Tseng E et al. *Drug Metab Dispos*. 2014;42(7):1163-73; [2]Lu Y et al. *Drug Metab Dispos*. 2012;40(12):2221-30;
[3]Lu Y et al. *Drug Metab Dispos*. 2014;42(11):1796-802; [4]http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=776746

Objectives (MERIT study - Post-hoc analysis)

- To describe the allelic frequencies for CYP3A5 variant alleles across the study population and racial subgroups.
- To assess the effect of CYP3A5 genotype on MVC exposure.

- *MERIT was a 5-year, multi-national, multi-center, double-blind, randomized (1:1:1), comparative, non-inferiority Phase 2b/3 hybrid study to compare the safety and antiviral activity of MVC at 300 mg QD and BID versus efavirenz (EFV) 600 mg QD, each in combination with zidovudine/lamivudine.*

Methods (MERIT study - Post-hoc analysis)

- DNA was extracted from 864 blood samples from subjects in the MERIT study and genotyped for CYP3A5.
- Allelic frequencies for CYP3A5 variant alleles across the study population and racial subgroups were described.
  - Deviation from Hardy-Weinberg equilibrium (HWE), by race was also assessed.
- Population pharmacokinetic (PK) estimates of C_{avg} for MVC 300 mg BID derived from BID and QD/open-label BID data from the original MERIT analysis were utilized.
- Graphical analysis and a univariate analysis (Mann-Whitney U-test) was conducted for PK (MVC C_{avg}) by CYP3A5 genotype.

MERIT Ad-hoc analysis: Sample Size

- **864 total subjects were genotyped from the MERIT study (maraviroc and efavirenz arms)**
  - 863 genotyped subjects were included in assessment of CYP3A5 genotype in MERIT study population.
    - 1 subject not included in analysis due to lack of result for CYP3A5 genotype
  - 494 subjects were included in assessment of the effect of CYP3A5 genotype on MVC exposure
    - MVC 300 mg BID and MVC 300 mg QD/OL BID

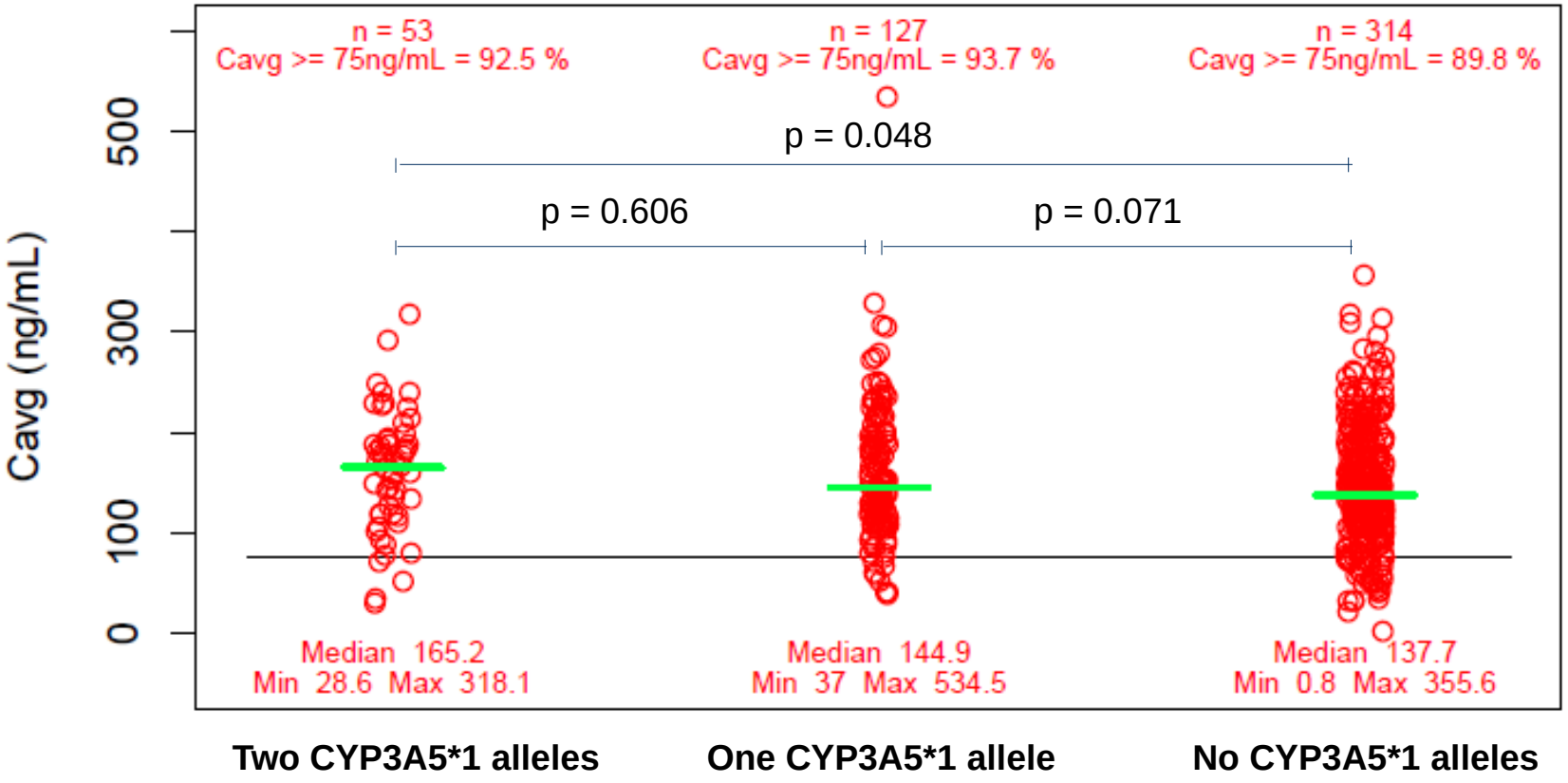
Allelic CYP3A5 genotype frequency by overall population and by race (N=863)

CYP3A5 Genotype	Racial subgroups				
	Total (n, %)	White (n, %)	Black (n, %)	Asian (n, %)	Other (n, %)
N	863 (100%)	501 (58.1%)	285 (33.0%)	16 (1.9%)	61 (7.1%)
2 CYP3A5*1 alleles (wild-type)	93 (10.8%)	5 (1.0%)	81 (28.4%)	2 (12.5%)	5 (8.2%)
1 CYP3A5*1 allele	246 (28.5%)	76 (15.2%)	141 (49.5%)	7 (43.8%)	22 (36.1%)
0 CYP3A5*1 alleles (mutant)	524 (60.7%)	420 (83.8%)	63 (22.1%)	7 (43.8%)	34 (55.7%)

- CYP3A5 genotype, by race/ethnicity are in Hardy Weinberg Equilibrium (HWE) (P>0.05).
  - Assessment not conducted for those of Asian race or other ethnicity due to small sample size.

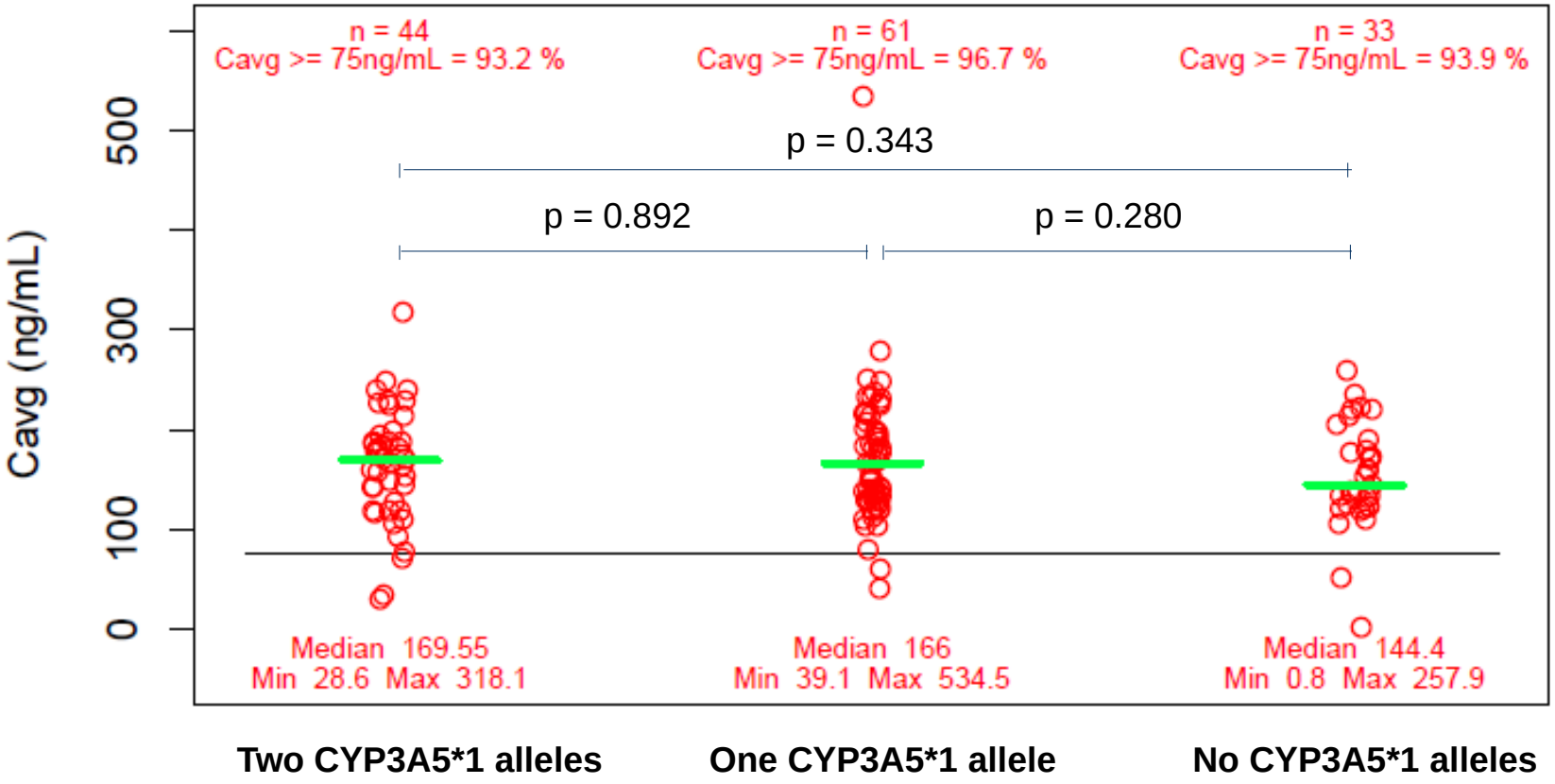
Vourvahis et al. 16th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy 2015; Washington, DC. Abstract #12

Effect of CYP3A5 genotype on MVC C_{avg} (n=494)



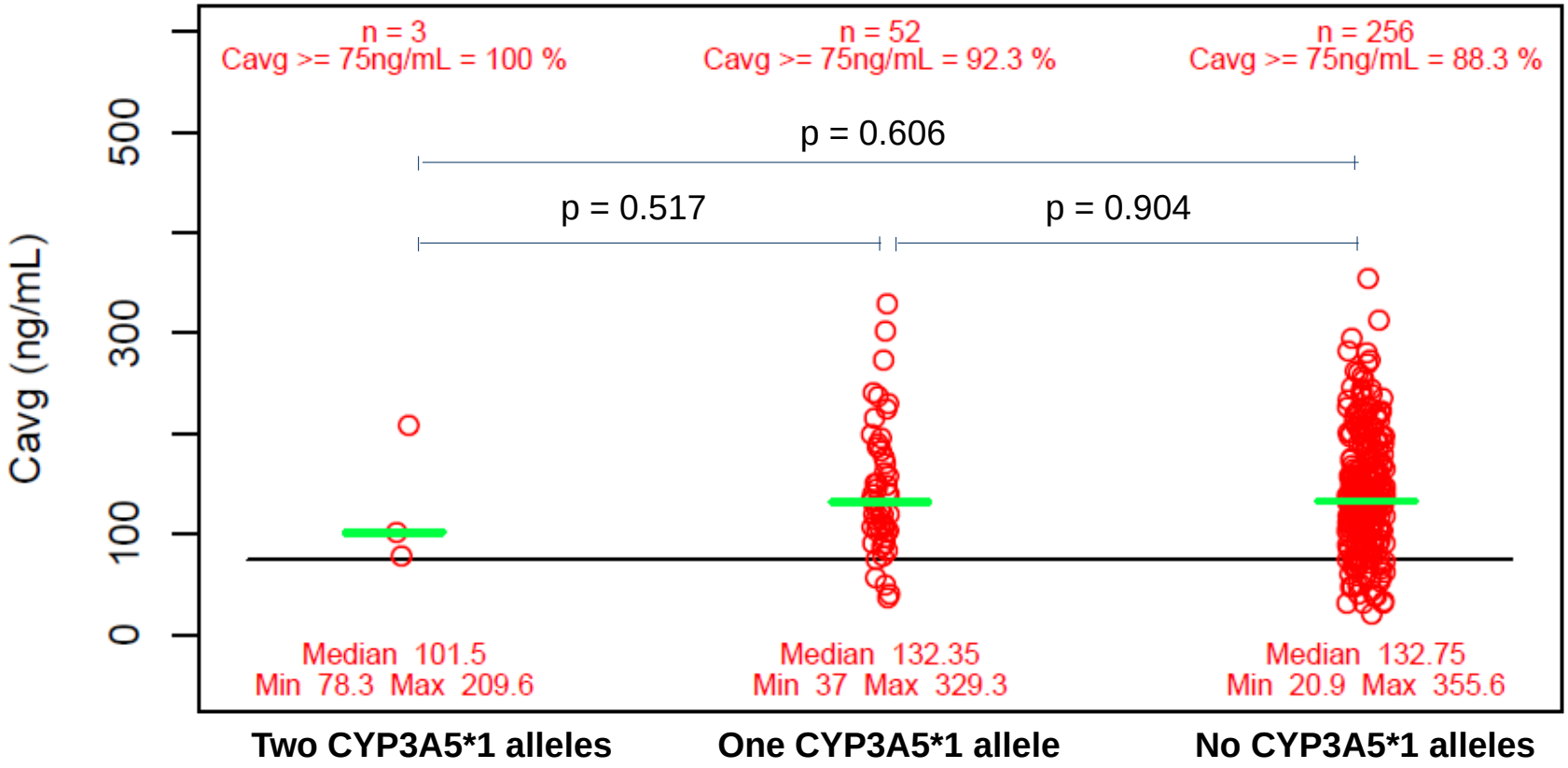
Green line represents median C_{avg} for distribution; Black reference line represents C_{avg} = 75 ng/mL, exposure associated with near-maximal virologic efficacy in the MERIT study (McFadyen LM et al. IAS 2008. Poster TUPE0053).

Effect of CYP3A5 genotype on MVC C_{avg} in Black patients (n=138)



Green line represents median C_{avg} for distribution; Black reference line represents C_{avg} = 75 ng/mL, exposure associated with near-maximal virologic efficacy in the MERIT study (McFadyen LM et al. IAS 2008. Poster TUPE0053).

Effect of CYP3A5 genotype on MVC C_{avg} in White patients (n=311)



Green line represents median C_{avg} for distribution; Black reference line represents C_{avg} = 75 ng/mL, exposure associated with near-maximal virologic efficacy in the MERIT study (McFadyen LM et al. IAS 2008. Poster TUPE0053).

MERIT MVC PopulationPK covariate analysis (Abstract 42 – PLS Chan et al)

- CYP3A5 genotype alone (or CYP3A4/CYP3A5 cluster) was never selected, in the univariate step or in later multivariate steps, as significantly explaining maraviroc's PK variability.
- As in the 2008 covariate analysis, food and race were the most significant covariates.
- The only significant genotype covariate was SLCO1B1 (OATP1B1).

Conclusions

- The prevalence of CYP3A5*1/*1 was higher in Blacks (28%) than in Whites (1%).
- CYP3A5*1/*1 was not associated with lower MVC exposures (but with higher concentrations) across the PK population as well as in Blacks.
- Maraviroc administered at recommended doses yielded a C_{avg}≥75 ng/mL in approximately 90% of patients, irrespective of CYP3A5 genotype or Black race.