An Enhanced Version of the Tropfile HIV Co-receptor Tropism Assay Predicts Emergence of CXCR4 Use in ACTG5211 Vicriviroc Trial Samples

BACKGROUND

• HIV entry inhibitors which block infection via CCR5 have shown efficacy in suppressing CCR5 (R5) but not CXCR4+ (X4) or dual/mixed-tropic (DM) HIV.

• The Tropfile™ assay (Monogram Biosciences) (Figure 1) is useful for selection and monitoring of patients receiving these inhibitors.

• In mixed envelope (env) populations, Tropfile detects minor variants at 10% and 5% of the population with 100 and 83% sensitivity, respectively (levels below 5% were not tested). Minor variants below the detection limit of Tropfile can sometimes be identified by clonal analysis and may be selected following therapy with entry inhibitors targeting CCR5.

• An enhanced sensitivity Tropfile assay has been developed that allows improved minor CXCR4-using variant detection in any env mixtures (0.1-0.3%) and earlier detection of minor CXCR4-using subpopulations in longitudinal samples from PI/RT inhibitor-experienced patients (2,3,4).

• We hypothesized that enhanced Tropfile might better identify CXCR4-using virus in the screen-baseline samples from subjects enrolled into ACTG 5211 (5,6).

• ACTG5211 was a placebo controlled dose ranging (5, 10, 15 mg) phase 2b study of the CCR5 antagonist vicriviroc (VCV) in 118 treatment-experienced subjects with R5 virus at study screen.

• Reduced virologic response was observed among 12 subjects with R5 virus at screen and DM at baseline, and in 18 subjects with CXCR4-using virus on study as determined by the standard Tropfile assay.

METHODS

• The co-receptor tropism of virus populations obtained at screen and baseline from 116 subjects enrolled into ACTG5211 was determined with the enhanced Tropfile assay and compared to original tropism results. The number of subjects reclassified with DM virus at screen and who would have been excluded from the study by the enhanced assay was determined and compared to the number of patients with CXCR4-using virus on-study by the standard Tropfile assay.

RESULTS

• Figure 2. Of 12 subjects with R5 virus at screen and DM at study baseline by the standard Tropfile assay, enhanced Tropfile reclassified 7 subjects (58%) with DM virus at screen.

• Figure 3. Of 18 additional subjects with CXCR4-using virus detected on study by standard Tropfile, enhanced Tropfile reclassified 9 subjects (50%) with DM virus at screen.

• Figure 4. Of 86/88 subjects tested with R5 virus only at all time points by standard Tropfile, enhanced Tropfile reclassified 9 subjects (10%) with DM virus at screen.

• Figure 5. 15 subjects with DM virus at screen by enhanced Tropfile received VCV on study. 12/15 subjects had early emergence of CXCR4-using variants detected by standard Tropfile.

SUMMARY & CONCLUSIONS

• In total, 25/116 ACTG5211 subjects previously defined as having R5 virus at study screen by standard Tropfile were reclassified with DM virus at screen by enhanced Tropfile. On-study, 15 of these 25 reclassified subjects received VCV and 12/15 had CXCR4-using virus detected at week 2-8 (by standard Tropfile).

• The enhanced Tropfile assay is a better predictor of subsequent CXCR4-use in 12 VCV recipients and would have excluded 3 VCV recipients with subsequent R5 virus only by standard Tropfile.

• On balance, the enhanced Tropfile assay appears to be an improved screening tool for determining eligibility for CCR5 antagonist therapy.

• Reanalysis of virologic response to VCV in light of enhanced Tropfile assay results is ongoing.

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REFERENCES