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CHARACTERIZATION OF SUSCEPTIBILITY PROFILES FOR THE CCR5 ANTAGONIST VICRIVIROC IN TREATMENT-NAÏVE HIV-INFECTED SUBJECTS

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BACKGROUND: A phase 2 trial of vicriviroc at 3 doses (25 mg daily, 50 mg daily, and 75 mg daily) in combination with Combivir versus. efavirenz + Combivir was conducted in treatment-naïve subjects. A total of 92 subjects received vicriviroc or placebo as monotherapy for 14 days, after which Combivir was added to the vicriviroc arms and placebo subjects were provided open-label efavirenz + Combivir. The trial was stopped prematurely due to an unexpectedly high rate of virological breakthrough in the vicriviroc-containing arms. Safety, efficacy, and RT resistance profiles have been presented previously (Greaves, et al. *Conf Retrovir Opportunistic Infect* 2006 Feb 5-8;13:[abstract no. 161LB](#)).

METHODS: Phenotypic susceptibility to vicriviroc and genotyping of RT, PR, and gp120 genes were performed on viral isolates from subjects at baseline, Day 14, Week 24, and at Week 48 or time of virological breakthrough. IC₅₀ values for individual isolates, fold-change values (FC) to reference virus, percent maximal suppression (PMS), and relative PMS (RPMS) values were calculated. Mean values and 95% confidence intervals were calculated for IC₅₀, fold-change, and RPMS parameters at baseline for change over the first 14 days for each parameter. RPMS value outliers were further characterized.

RESULTS: The mean baseline parameter values in breakthrough (B) and non-breakthrough (NB) subjects and 95% CIs were: IC₅₀ B: 7.0 nM (5.3–8.6) NB: 6.7 nM (4.9–8.5); FC B 0.7 (0.5–0.8) NB 0.6 (0.5–0.8); PMS B: 96.0% (94.9–97.2); NB 95.9% (94.7–97.0); RPMS B -3.8 (-5.0 – -2.6) NB -3.9 (-5.2 – -2.7). At the time of breakthrough,

4/26 (15%) subjects with evaluable dose-response curves had reduction in RPMS to below +6.

CONCLUSIONS: Baseline susceptibility assessed by multiple parameters did not appear to be associated with long-term virological breakthrough, nor was change in these parameters during the period of monotherapy of this study. It is unlikely that resistance was generated during the initial 14 days of this trial by the administration of monotherapy. The breakthrough parameters suggest that either susceptibility to vicriviroc was unaltered or not detected by these assays in the majority of isolates. The significance of the reduced RPMS values seen in 15% of breakthrough subjects requires further investigation.

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18

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