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BASELINE AND ON-TREATMENT GP41 GENOTYPE AND SUSCEPTIBILITY TO ENFUVIRTIDE (ENF) AND T-1249 IN A 10-DAY STUDY OF T-1249 IN PATIENTS FAILING AN ENF-CONTAINING REGIMEN (T1249-102)

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BACKGROUND: T-1249 is a second-generation fusion inhibitor that has shown potent *in vitro* antiviral activity against most HIV isolates resistant to enfuvirtide (ENF). Study T1249-102 evaluated the short-term antiretroviral activity of T-1249 in patients failing a regimen containing ENF. Here we present the baseline and day 11 results of genotypic and phenotypic testing, and their correlation to treatment responses, for the first 25 patients included in the study's planned interim analysis.

METHODS: Patients with two viral loads >5000 copies/ml while dosing on an ENF-containing regimen discontinued ENF and added 192 mg/day of T-1249 subcutaneously to the unchanged background regimen for 10 days. The intent-to-treat population included patients with amplifiable plasma virus at baseline (BL) that demonstrated ENF-resistance mutations and/or decreased phenotypic susceptibility to ENF. Resistance data were generated on Env amplified from patient plasma samples using the novel GeneSeq™ and PhenoSense™ Entry Assays. Fold changes in ENF and T-1249 IC₅₀ were calculated in relation to reference strains tested in parallel with the patient samples (FCIC₅₀).

RESULTS: Plasma virus from 24 of 25 patients (98%) who entered T1249-102 exhibited ENF resistance-associated substitutions in gp41 amino acids 36–45 at BL. ENF IC₅₀ were available for viral envelopes from 23 (96%) patients at BL. Geometric mean (GM) BL ENF FCIC₅₀ was 150.1 (range 1.7–2041.6) and T-1249 FCIC₅₀ was 1.8 (range 0.14–12.6). For those patients with paired samples at BL in their ENF parent study and at BL for the T1249-102 study (*n*=13), there was a GM increase of 70.6- and 1.8-fold in FCIC₅₀ for ENF and T-1249, respectively. On day 11, 22 (92%) patients had both genotype and phenotype available for paired analysis. In four patients, there was a >fourfold increase in

T-1249 FCIC₅₀; plasma virus from these patients demonstrated genotypic substitutions in amino acid 36–45. Virological response was not associated with viral tropism, baseline HIV RNA or baseline FCIC₅₀ to ENF or T-1249, but was associated with length of time receiving a failing ENF-containing regimen and with day 11 fold change from BL in T-1249 FCIC₅₀.

CONCLUSIONS: T-1249 retains antiviral activity in most patients experiencing viral replication in the presence of isolates with reduced susceptibility to ENF and/or changes in the target region of ENF. Treatment emergent amino acid substitutions in gp41 and reduced susceptibility to T-1249 were identified in some patients.

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