

## AN UPDATE OF THE LIST OF NNRTI MUTATIONS ASSOCIATED WITH DECREASED VIROLOGICAL RESPONSE TO ETRAVIRINE: MULTIVARIATE ANALYSES ON THE POOLED DUET-1 AND DUET-2 CLINICAL TRIAL DATA

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J Vingerhoets<sup>1</sup>, M Peeters<sup>1</sup>, H Azijn<sup>1</sup>, L Tambuyzer<sup>1</sup>, A Hoogstoel<sup>1</sup>, S Nijs<sup>1</sup>, MP de Béthune<sup>1</sup> and G Picchio<sup>2</sup>

<sup>1</sup>Tibotec BVBA, Mechelen, Belgium; <sup>2</sup>Tibotec Inc., Yardley, PA, USA

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**BACKGROUND:** Etravirine (TMC125) is a next generation non-nucleoside reverse transcriptase inhibitor (NNRTI), with activity against NNRTI-resistant HIV-1 and a high genetic barrier to development of resistance. Analyses of the pooled DUET-1 and DUET-2 Phase III clinical trials identified 13 etravirine resistance-associated mutations (RAMs; V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V and G190A/S). The presence of three or more of these RAMs was associated with decreased virological response to etravirine. In this study, additional statistical approaches were used to refine this list and improve the genotype/phenotype correlation.

**METHODS:** The effect of baseline resistance on virological response (<50 copies/ml) to etravirine at week 24 was studied in patients not using enfuvirtide *de novo* and excluding those who discontinued for reasons other than virological failure ( $n=406$ ). Multivariate analyses included logistic regression controlling for baseline viral load, darunavir fold change (FC) in EC<sub>50</sub> and nucleoside reverse transcriptase inhibitor sensitivity. Mutations were identified based on the association with decreased virological response and/or increased etravirine FC. Mutations in the reverse transcriptase (amino acids 1–400) were included in the final analysis if present in  $\geq 5$  patients.

**RESULTS:** The analyses confirmed the effect on response of the 13 etravirine RAMs identified previously and also identified K101H, E138A and V179T as associated with a decreased virological response and/or increased etravirine FC. The V179F/T, Y181V and G190S mutations were associated with the lowest virological response but were present in <5% of patients at baseline. Virological response decreased in subgroups with increasing numbers of baseline etravirine RAMs (77%, 61%, 56% and 38% for 0, 1, 2 and  $\geq 3$  RAMs, respectively). Relative weighting of the 16 etravirine RAMs improved the correlation between baseline etravirine FC and the number of etravirine RAMs.

**CONCLUSIONS:** A comprehensive analysis of baseline resistance data from DUET-1 and DUET-2 identified three additional mutations resulting in a list of 16 etravirine RAMs (V90I, A98G, L100I, K101E/H/P, V106I, E138A, V179D/F/T, Y181C/I/V and G190A/S). Weighting these mutations improved the correlation between genotypic and phenotypic resistance interpretations. Decreased virological response was a function of the number of baseline etravirine RAMs with the largest effect observed in the subgroup of patients with three or more RAMs.

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