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IMPACT OF BASELINE K103N OR Y181C ON THE VIROLOGICAL RESPONSE TO THE NNRTI TMC-125: ANALYSIS OF STUDY TMC-125-C223

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BACKGROUND: TMC-125 is a novel NNRTI with a high genetic barrier to the development of resistance and *in-vitro* and *in vivo* activity against NNRTI-resistant HIV. TMC-125-C223 is a randomized controlled phase IIb dose-finding study of TMC-125 in heavily pretreated patients with documented NNRTI resistance and ≥ 3 primary PI mutations at baseline. In this study, TMC-125 showed significant antiviral efficacy at 24 weeks with a mean change in viral load of $-1.18 \log_{10}$ copies/ml versus $-0.19 \log_{10}$ in control ($P < 0.05$). In a previous intent-to-treat analysis, an association between a higher number of NNRTI mutations, the baseline fold change (FC) for TMC-125 and virological response at 24 weeks was observed.

METHODS: The effect of the NNRTI mutations K103N and Y181C on the virological response at 24 weeks in patients receiving TMC-125 800 mg twice-daily ($n=79$) was determined on observed data.

RESULTS: Both K103N and Y181C were each present at baseline in 29 out of 79 patients, and always observed in combination with one to four other NNRTI mutations. Ten of these 48 patients carried both K103N and Y181C. The number of additional NNRTI mutations was similarly distributed for the samples with K103N or Y181C. The median TMC-125 FC for all patients was 1.95. The median TMC-125 FC for patients with and without K103N or with and without Y181C was 1.70 and 1.95 or 4.50 and 1.10, respectively. Patients with K103N at baseline achieved a mean reduction in viral load of $1.43 \log_{10}$ copies/ml, similar to the $1.40 \log_{10}$ reduction in patients without K103N, and similar to the overall response of $-1.41 \log_{10}$ in all patients. Patients with Y181C at baseline achieved a mean $0.86 \log_{10}$ reduction, which was lower than the $1.70 \log_{10}$ reduction in patients without Y181C.

CONCLUSIONS: These data showed that TMC-125 retained activity in the presence of multiple NNRTI mutations, including K103N and Y181C, where current NNRTIs were not expected to be active. The presence of Y181C, in combination with other NNRTI mutations, seemed to be associated with higher FC values for TMC-125 and decreased virological response. Additional data are required to confirm these findings.

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