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CHARACTERIZATION OF RESISTANCE BEFORE AND AFTER SHORT-TERM THERAPY WITH TMC125 IN PATIENTS WITH DOCUMENTED NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR RESISTANCE

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BACKGROUND: TMC125-C207 was an open-label Phase IIa study to evaluate the antiviral activity, safety and tolerability of TMC125 in patients with documented non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance. Sixteen HIV-1-positive subjects on a failing antiretroviral regimen (viral loads above 2000 HIV RNA copies/ml), consisting of two NRTIs and an NNRTI, and with phenotypically confirmed resistance to efavirenz, were enrolled. They received TMC125 (900 mg twice daily) for 7 days as a substitution for the failing NNRTI; NRTI therapy remained unchanged. TMC125 was highly active in patients infected with NNRTI-resistant HIV-1, as demonstrated by a median viral load drop of 0.89 log RNA copies/ml from baseline to day 8, and was well tolerated. In the present study, comparative phenotypic and genotypic resistance data from screening, baseline and end of therapy have been analysed.

METHODS: Drug susceptibility profiles were determined using the Antivirogram® assay and mutational patterns were determined using VirtualPhenotype™. Both resistance determinations were performed on plasma samples taken at screening (within 49 days prior to treatment start), baseline (day 1) and end of therapy (day 8) time-points.

RESULTS: The population in this study had a wide range of mutations associated with resistance to NNRTIs, including changes at positions 98, 100, 101, 103, 108, 179, 181, 188, 190, 225 and 238. The median number of NNRTI mutations was two (range 1–4), at both screening and baseline. One patient acquired a partial NNRTI mutation (Y181C/Y) between screening and baseline (in the absence of TMC125). Between baseline and end of therapy, three patients acquired additional changes in the RT gene: these were all mutant/wild-type mixtures (K101Q/K, K103N/K and V189V/I). The appearance of these partial mutations was not associated with an increase in fold resistance for TMC125 or

any of the current NNRTIs. At baseline, there was no correlation between the fold resistance values of nevirapine or efavirenz with TMC125. The median (range) fold resistance values at baseline for nevirapine, efavirenz and TMC125 were 128 (58–136), 116 (5–820) and 2.2 (0.5–8.5), respectively. At the end of therapy, the median (range) fold resistance values for nevirapine, efavirenz and TMC125 were 120 (46–146), 103 (4–974) and 2.6 (0.8–11.6), respectively. Neither NNRTI fold resistance values at baseline nor the presence of mutations associated with NNRTI resistance at baseline were predictive for response in this group of patients.

CONCLUSIONS: TMC125 is effective in suppressing resistant HIV strains from patients failing on an NNRTI-containing regimen and with phenotypic evidence of resistance. No evidence has been found that TMC125 selected for increased resistance during 7 days of treatment. By overcoming class-associated NNRTI resistance, TMC125 is considered to be a next-generation NNRTI.

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