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ANTIVIRAL ACTIVITY OF TMC125, A POTENT NEXT-GENERATION NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NNRTI), AGAINST >5000 RECOMBINANT CLINICAL ISOLATES EXHIBITING A WIDE RANGE OF NNRTI RESISTANCE

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BACKGROUND: TMC125 is a potent next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), active against wild-type as well as NNRTI-resistant HIV-1. *In vitro* selection experiments have demonstrated an increased genetic barrier to the development of resistance to the compound. TMC125 also showed *in vivo* antiviral activity in patients with documented phenotypic NNRTI resistance in a 7-day Phase IIa trial. In the present study, we determined the antiviral activity of TMC125 in more than 5000 clinical isolates submitted for phenotypic resistance testing in 1999–2000 (panel A) and 2001–2003 (panel B). The antiviral activity of TMC125 on these isolates was compared to the currently approved NNRTIs.

METHODS: Recombinant clinical isolates were constructed according to the Antivirogram® method. Phenotypic and genotypic analyses were performed by the Antivirogram® and VirtualPhenotype™ assays, respectively. Data analysis was performed using SAS and Spotfire DecisionSite software.

RESULTS: The prevalence of mutations at 15 NNRTI resistance-associated positions (98, 100, 101, 103, 106, 108, 179, 181, 188, 190, 225, 230, 236, 238 and 318) was compared between panels A ($n=2065$) and B ($n=3545$). A relative increase in frequency of mutations K101P, K103S, V106A, V179I and Y188L was observed in panel B. No significant change was observed for V106M, a recently described NNRTI resistance mutation. TMC125 inhibited 91% of all samples ($n=5610$) with an $EC_{90} < 10$ nM, while efavirenz only inhibited 67% at 10 nM. The number of samples resistant to at least one of the three current NNRTIs (defined as a fold change in $EC_{90} > 10$) was 1050 (51%) and 1580 (45%) for panels A and B, respectively. Most (79%) of these 2630 samples were

resistant to efavirenz and 69% were resistant to all current NNRTIs. At 10 nM, TMC125 inhibited 80% of the samples resistant to at least one NNRTI and 76% of the samples resistant to all current NNRTIs. The corresponding percentages for efavirenz were 29% and 9%, respectively. In addition, TMC125 inhibited 78% of the EFV-resistant subset ($n=2066$), at 10 nM. The median EC_{90} of TMC125 for samples containing V106M, which was observed together with at least one other NNRTI resistance mutation, was 1.6 nM ($n=11$). Sixty-three percent of the samples harbouring four NNRTI resistance mutations still had an EC_{90} below 10 nM for TMC125, whereas 70% of the samples with only two mutations had an EC_{90} above 10 nM for efavirenz.

CONCLUSIONS: TMC125 is a potent next-generation NNRTI, with activity against most of recently circulating strains of HIV, including samples that are resistant to all marketed NNRTIs. The antiviral activity against class-associated NNRTI resistance together with the increased genetic barrier to development of resistance, are unique features of TMC125.

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