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## ANTIVIRAL ACTIVITY OF TMC114, A POTENT NEXT-GENERATION PROTEASE INHIBITOR, AGAINST >4000 RECENT RECOMBINANT CLINICAL ISOLATES EXHIBITING A WIDE RANGE OF (PROTEASE INHIBITOR) RESISTANCE PROFILES

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**INTRODUCTION:** TMC114 is a potent, next-generation protease inhibitor (PI), active against wild-type as well as PI-resistant HIV. Recently, TMC114 showed *in vivo* antiviral efficacy in a 2-week Phase IIa trial in multiple PI-experienced patients. In order to assess the performance of TMC114 against currently circulating strains of HIV, the compound was tested against >4000 clinical isolates submitted for phenotypic resistance testing. The antiviral activity of TMC114 on these isolates was compared to the currently approved PIs: indinavir, ritonavir, nelfinavir, saquinavir, amprenavir and lopinavir.

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

**RESULTS:** From the 4024 tested recombinant clinical isolates, 1666 (41%) were resistant to at least one of the currently approved PIs, defined as a change in EC<sub>50</sub> >fourfold as compared to wild-type. The median fold change in EC<sub>50</sub> against these 1666 resistant isolates for TMC114 was 1.1, corresponding to an EC<sub>50</sub> of 3.5 nM. Eighty percent of these PI-resistant isolates were still susceptible (defined as fold change in EC<sub>50</sub> <4) to TMC114. For the remaining 20% isolates, the median fold change in EC<sub>50</sub> for TMC114 was 10, thus showing that the compound can inhibit 90% of the 1666 PI-resistant isolates with a fold change ≤10. A subgroup of 1501 isolates, for which data for all six approved PIs were available, was used to determine the influence of the number of PIs with a fold change >4 on the activity of TMC114. Among these PI-resistant isolates, 67% were resistant to 4 or more PIs, with 31% resistant to all 6 approved PIs, 23% to 5,

and 13% to 4. The median fold change in EC<sub>50</sub> for TMC114 was <4 for each of these subgroups, which illustrates the activity of TMC114 against PI-resistant isolates. A genotype was available for 498 of the 1666 PI-resistant isolates. The number of primary mutations (D30N, M46I/L, G48V, I50V/L, V82A/F/T/S, I84V or L90M) was determined for each of these isolates. One percent had no primary mutation, 23% had 1, 41% had 2, 31% had 3 and 4% had 4 primary mutations. The median fold change in EC<sub>50</sub> for TMC114 was <4 for each of these subgroups.

**CONCLUSIONS:** TMC114 is a potent, next-generation PI with activity against a wide range of PI-resistant recombinant clinical isolates. This activity, defined by a median fold change of <4, extended to isolates resistant to all currently-approved PIs and also to isolates carrying up to four primary PI mutations.

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