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ANTIVIRAL ACTIVITY AND RESISTANCE PROFILE OF AG-001859, A NOVEL HIV-1 PROTEASE INHIBITOR WITH POTENT ACTIVITY AGAINST PROTEASE INHIBITOR-RESISTANT STRAINS OF HIV

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BACKGROUND: The availability of highly active antiretroviral therapy for patients who have previously failed protease inhibitor (PI)-containing regimens is limited by the substantial amount of cross-resistance that exists among the currently approved PIs. A series of novel allophenylnorstatin-containing HIV-1 PIs, represented by AG-001859, has been identified, which demonstrate potent antiviral activity against strains of HIV resistant to the currently approved PIs.

METHODS: The *in vitro* antiviral activity of AG-001859 was characterized in biochemical and cellbased assays against wild-type and PI-resistant strains of HIV.

RESULTS: AG-001859 is a potent, tight binding inhibitor of both wild-type HIV protease and an I84V/L90M mutant HIV protease, exhibiting a K_i of <0.1 nM against both enzymes. In cell-based assays, AG-001859 demonstrated potent antiviral activity against several strains of wild-type HIV, including laboratory adapted and primary isolates, with EC_{50} values ranging from 14 to 60 nM. The antiviral activity of AG-001859 was only moderately attenuated in the presence of 50% human serum (3.7-fold change in EC_{50} , $P=0.013$). The antiviral activity of AG-001859 was also evaluated against a panel of 44 PI-resistant HIV-1 variants (PhenoSense™) containing a variety of primary and secondary amino acid substitutions that confer broad cross-resistance to the approved PIs (mean number of PI-resistance substitutions = 5; range 3–11). The median EC_{50} value against these PI-resistant variants was 34 nM (range 5.3–420 nM), and the median fold-change relative to wild-type HIV was 1.6 (range 0.3–19.8). In contrast, viruses in the panel demonstrated median fold-change values of 9.3, 9.6 and 17.0 to indinavir, lopinavir and nelfinavir, respectively. AG-001859 demonstrated potent activity against all primary

and secondary PI-resistance substitutions evaluated, and there was no correlation between the antiviral activity of AG-001859 and the number of PI-resistance substitutions present.

CONCLUSIONS: AG-001859 is one compound in a series of novel allophenylnorstatin-containing HIV-1 PIs which demonstrates potent antiviral activity against strains of HIV resistant to the currently approved PIs. The pharmacokinetics and safety of several compounds from this series are currently being evaluated in Phase I studies.

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