

# 17th International HIV Drug Resistance Workshop



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## **IN VITRO CROSS-RESISTANCE PROFILE, ANTIVIRAL ACTIVITY, SAFETY AND PHARMACOKINETICS IN HIV-1-INFECTED PATIENTS OF IDX899, A NOVEL HIV-1 NNRTI WITH HIGH BARRIER TO RESISTANCE**

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**BACKGROUND:** IDX899, a second generation non- nucleoside reverse transcriptase inhibitor (NNRTI), was studied *in vitro* to determine its cross-resistance potential versus other NNRTIs (etravirine, efavirenz and rilpivirine) and in a clinical study to assess its antiviral activity, safety and pharmacokinetics in HIV-1-infected patients naïve to antiretroviral therapy.

**METHODS:** Wild-type HIV-1 was passaged under increasing drug pressure to generate drug-resistant mutant viruses. Resistance and cross-resistance profiles were determined (as EC<sub>50</sub> fold-shifts versus wild type) for each viral supernatant. Thirty treatment-naïve patients with HIV-1 RNA viral load  $\geq 5,000$  copies/ml and CD4+ T-cell count  $\geq 200$  cells/mm<sup>3</sup> were enrolled and randomized (8:2) to receive IDX899 or placebo once a day for 7 days. IDX899 doses of 800, 400 and 200 mg by mouth daily were assessed. HIV-1 RNA levels were measured using Roche Cobas TaqMan® HIV-1 assay and IDX899 plasma levels were quantitated using a validated LC/MS-MS methodology.

**RESULTS:** *In vitro* selection experiments IDX899 resistance required more passages and mutations than efavirenz; IDX899 selected mutations at codons V90I, E138K, Y181C/I, S134I, I135R, G190E and M230L and exhibited less *in vitro* cross-resistance than efavirenz and TMC125. In the clinical study, the median changes in HIV-1 plasma RNA from baseline to day 8 were  $-1.95 \log_{10}$  copies and median CD4 + T-cell count increased by 52.0 cells/ $\mu$ l in the 800 mg cohort. The median changes in HIV-1 plasma RNA from baseline to day 8 were  $+0.08 \log_{10}$  copies and median CD4+ T-cell count decreased by 14 cells/ $\mu$ l in the placebo cohort. There were no treatment discontinuations, treatment emergent serious adverse events or dose-limiting toxicities. No discernable patterns in adverse events, laboratory

abnormalities or ECG abnormalities were observed within or between treatment groups. Results from the 400 mg and 200 mg cohorts will be presented.

**CONCLUSIONS:** In a 7 day proof-of-concept study, IDX899 was well tolerated and demonstrated potent HIV-1 antiviral activity. These results, together with a favourable *in vitro* cross-resistance profile, support further evaluation of IDX899 in combination therapy to assess durability of antiviral response and long-term safety.

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