

POSTER 38**EXPANDED IN VITRO RESISTANCE PROFILE OF THE NOVEL NUCLEOTIDE RT INHIBITOR GS-9131 AND ITS PARENT GS-9148**

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Background: Nucleoside(tide) reverse transcriptase inhibitors (NRTIs) are currently used as a backbone therapy in the vast majority of antiretroviral regimens. However, long-term clinical benefit of NRTIs can be limited by development of resistance, adverse effects, drug-drug interactions, and sub-optimal efficacy in treatment-experienced patients. We have previously shown that the novel NRTI GS-9148 has a favorable resistance profile in vitro against most NRTI-resistant viruses. A prodrug of GS-9148, GS-9131, is currently in early clinical development for the treatment of HIV-1. In this study, we have expanded our panel of NRTI-resistant HIV-1 to more fully describe the phenotypic profile of GS-9148 and the prodrug GS-9131.

Methods: Using the Monogram PhenoSense HIV-1 assay, twenty-four viruses consisting of patient-derived viruses containing multiple NRTI resistance mutations and site-directed mutants containing specific patterns of RT mutations were evaluated for susceptibility to both GS-9131 and GS-9148.

Results: As expected, the lipophilic prodrug GS-9131 showed higher potency as compared to its parent GS-9148 against wild-type NL4-3 (0.018 μ M vs. 3.39 μ M), but showed nearly identical resistance profiles. Fold change values were highly correlated for GS-9131 and GS-9148 ($r^2=0.98$) over a broad range of susceptibilities (fold change values of 0.22 to 6.4). Antiviral activity was retained (\leq 2-fold change compared to wild-type) against patient-derived viruses containing 4-6 thymidine analog associated mutations (TAMs), TAMs+T69ins, K65R, L74V, M184V, and combinations of these mutations. These observations were further confirmed using a panel of site-directed mutants containing these mutations. Only viruses containing the Q151M complex of mutations (A62V+V75I+F77L+F116Y+Q151M) showed $>$ 2-fold reduced susceptibility to GS-9131 and GS-9148, however, Q151M on its own did not cause decreased susceptibility. The potencies of GS-9131 and GS-9148 were both increased for viruses that contained the M184V mutation either alone or when present with other NRTI mutations.

Conclusions: The prodrug GS-9131 and its parent drug GS-9148 showed identical resistance patterns, with near wild-type activity against most NRTI drug-resistant viruses, increased susceptibility to M184V, but reduced susceptibility to viruses containing the Q151M complex of multi-NRTI resistance that is present in \sim 3% of treatment-experienced patients. GS-9131 is in early clinical trials for the treatment of HIV-1 infection.