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Oral presentation

Update on Aplaviroc: An HIV Entry Inhibitor Targeting CCR5

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Aplaviroc (873140) is a novel spirodiketopiperazine CCR5 antagonist that binds specifically to human CCR5 and allosterically inhibits HIV entry. Aplaviroc has exhibited potent in vivo antiviral activity (1.66 log decrease in viral load at nadir) following 10 days of monotherapy. In vitro studies of antiviral activity demonstrate that aplaviroc is active against HIV isolates from a variety of clades as well as those resistant to current HIV therapies targeting RT, PR, and gp41. In vitro studies suggest prolonged CCR5 receptor occupancy (RO) by aplaviroc with an offset half-life of >100 hours. In vivo studies following short term aplaviroc administration using CCR5-specific mAb demonstrate substantial and prolonged CCR5 RO (>50%) by aplaviroc, when plasma drug levels were undetectable, observed for approximately 5 days.

In the 10 day monotherapy study of aplaviroc in HIV+ subjects, one subject whose virus was R5-tropic at baseline and day 5 showed that R5X4-tropic (dual/mixed) virus was present at Day 10. Subsequent analysis revealed reversion to an R5-tropic only phenotype by day 24, with no decrease in sensitivity to aplaviroc (Fold IC50). The change in tropism at the population level observed on day 10 was the result of the emergence of pre-existing dual-tropic virus(-es) that were below the limits of detection on day 1. Viruses present in a subject's quasispecies that are below the limits of detection with currently available tropism assays may become detectable following monotherapy with a CCR5 antagonist; however, whether similar changes may occur on combination therapy with a CCR5 antagonist remains to be determined.

Aplaviroc has demonstrated potent anti-HIV activity in vitro and in vivo. Furthermore, aplaviroc exhibits a unique allosteric interaction with CCR5 and demonstrates prolonged receptor occupancy. CCR5 antagonists show promise for inhibiting entry of CCR5-using viruses in the clinical setting.