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ELVUCITABINE: POTENT ANTIVIRAL ACTIVITY DEMONSTRATED IN MULTI-DRUGRESISTANT HIV INFECTION

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BACKGROUND: Elvucitabine (ELV) is an L-nucleoside analogue with potent *in vitro* anti-HIV activity, particularly against strains with resistance mutations to numerous other drugs, including nucleosides, all non-nucleosides (NNRTI) and HIV protease inhibitors (PI). ELV exhibits reduced potency against strains harbouring the M184V mutation [lamivudine (3TC)-resistant], but the inhibitory concentration (IC₅₀) remains within the range of achievable plasma concentrations. This multicentre study was designed to assess the anti-HIV activity of ELV in an otherwise unchanged combination of highly active antiretroviral therapy (HAART) in individuals with the M184V mutation.

METHODS: Adults receiving triple, 3TC-containing HAART therapy whose genotype included the M184V mutation were eligible; full genotypic profiles were available for each subject. Subjects had HIV RNA levels of 1000–30,000 copies/ml and CD4 counts >200 cells/μl. Minimum baseline safety parameters were required, together with stable clinical disease and no active AIDS-defining conditions. Subjects were randomized to receive blinded ELV 50 or 100 mg/day or continued 3TC 300 mg/day in a ratio of 25:25:10, while continuing the other two agents of their HAART regimen. Subjects were treated for 28 days; HIV RNA and safety determinations were measured weekly. Open-label ELV was available for subjects who wished to continue ELV after the 4 weeks.

RESULTS: Fifty-nine subjects were randomized, 56 initiated treatment and 46 completed 28 days of therapy. Mean age was 43.5 years (range 21–65), mean CD4 count was 471 cells/μl (range 120–960) and mean plasma HIV RNA level was 10300 copies/ml (range 120–75,000; Roche Amplicor 1.5® assay). Prior antiretroviral therapies included all commercially available agents. HIV genotypes (HIV Genosure™) revealed one primary nucleoside resistance mutation (in addition to the required M184V) and primary resistance mutations to either the entire class of NNRTIs or PIs in all subjects. Potent

anti-HIV activity was observed in both ELV groups: mean declines at 28 days of -0.67 and $-0.78 \log_{10}$ copies/ml in the 50 and 100 mg groups, respectively, as compared with an increase of $+0.01 \log_{10}$ copies/ml in the 3TC group ($P < 0.0001$ for both comparisons). Baseline genotypes were not clearly correlated with antiviral activity. Myelosuppression was the only study-related adverse event observed and was generally associated with the ELV 100 mg dose group.

CONCLUSIONS: ELV demonstrated potent anti-HIV activity in patients with multidrug-resistant HIV, comparable or superior to other potential 'salvage' therapies, with a convenient single daily oral dose. Doses of 50 and 100 mg/day were similarly potent; the safety profile of 50 mg daily was more desirable than 100 mg. Further study with doses up to 50 mg daily is warranted to identify the optimum dose for long-term clinical development of ELV in this population with limited treatment options.

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