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Clinical Trials of (S)-1-[3-Hydroxy-2-(phosphonylmethoxy)propyl]cytosine (HPMPC). H.S. JAFFE, Gilead Sciences, Inc., Foster City, CA.

HPMPC is a nucleotide analog with potent *in vitro* and *in vivo* activity against a broad spectrum of herpesviruses. Phosphorylation of HPMPC to its active intracellular metabolite is independent of virus infection and associated with prolonged antiviral effect. Initial clinical investigation was performed in three complementary Phase I/II studies (n=80 patients) at Mt. Zion-UCSF, NIH-NIAID, and Johns Hopkins with objectives of determining the safety, tolerance, and pharmacokinetics of HPMPC administered according to a variety of treatment regimens in HIV-infected patients with asymptomatic CMV infection. Additionally, serial cultures of urine, semen, and/or blood were performed to assess anti-CMV activity. The patient population enrolled in the Phase I/II studies was representative of patients with advanced HIV infection, i.e., AIDS patients with CD4 counts $\leq$ 100 cells/mm^3 on multiple concomitant medications. The results of these studies indicate that administration of HPMPC is associated with dose-dependent nephrotoxicity and anti-CMV effect in urine and semen consistent with preclinical animal studies. Early identification of the sequence of urinalysis and serum chemistry abnormalities associated with HPMPC-related nephrotoxicity (proximal tubular cell dysfunction), as well as demonstration of prolonged anti-CMV effect, led to modifications in the methods of HPMPC administration. Utilization of longer dosing intervals (one, two, or three weeks), as well as concomitant administration of probenecid (to compete with HPMPC for uptake at the proximal tubular cell) and saline hydration has permitted the chronic intermittent administration (e.g. > 52 weeks) of HPMPC without significant drug-related nephrotoxicity, while preserving the potent anti-CMV effect of HPMPC. Pharmacokinetic analysis is consistent with dose-proportional C_{max} and AUC without evidence of accumulation. Urinary recovery of HPMPC was essentially complete without evidence of metabolites. Concomitant administration of probenecid appeared to increase C_{max} and AUC at HPMPC doses $\geq$ 5 mg/kg. Further study is required to define the effect of HPMPC administration on end-organ disease (e.g., CMV retinitis) and potential for cumulative toxicity.

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In Vivo Anti-Herpesvirus Activity of the N7-Isomeric Acyclic Nucleoside Analogue 2242 and its Prodrug HOE 961

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We evaluated the activity of 2-amino-7-[1,3-dihydroxy-2-propoxy)me-thyl)purine (2242) and its oral prodrug (HOE 961) in several animal models for herpesvirus infections. When administered subcutaneously (s.c.) [9 doses of 7 mg/kg], the compound efficiently prevented HSV-1 induced mortality in immunocompetent mice. When applied topically to hairless (hr/hr) mice that had been infected intracutaneously with HSV-2, compound 2242 was about 5-fold more effective than acyclovir in preventing mortality and appearance of HSV-2-induced lesions. In SCID mice that had been infected with a thymidine kinase (TK)-deficient strain of HSV-1, compound 2242, when administered s.c. at doses ranging from 2 to 50 mg/kg/day proved markedly superior over acyclovir and foscarnet in delaying virus-induced mortality. Compound 2242 was at least 5-fold more effective than ganciclovir in preventing murine cytomegalovirus (MCMV)-induced mortality, both in NMRI and SCID mice. The compound proved more effective when a total dose of 100 mg/kg was administered as 5 doses of 20 mg/kg/day for 5 subsequent days then when this dose was given as one single injection. A five-day treatment course with compound 2242 (10 and 50 mg/kg/day) of MCMV-infected newborn NMRI mice efficiently prevented virus-induced mortality. Moreover, these doses appeared to be non-toxic as based on body weight determinations. Finally, the efficacy of oral therapy with HOE 961 (the diacetyl ester of 2242) against MCMV-induced mortality in SCID mice was studied. The compound proved highly effective in this model when given as one single gavage a day (2.5 to 50 mg/kg/day) for 15 days.