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Antiviral Efficacy of PMPA in Macaques Chronically Infected with SIV.

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(R)-9-(2-phosphonylmethoxypropyl)adenine (PMPA), an acyclic phosphonomethyl ether nucleoside analogue, acts as a reverse transcriptase inhibitor and has shown potent *in vivo* efficacy against acute SIV infection in adult and newborn macaques. The current study evaluated the effects of PMPA treatment in chronically SIV infected macaques. For this study, nine cynomolgus macaques (*Macaca fascicularis*) that had been chronically infected with SIVmne for at least 19 weeks were treated with PMPA (30 mg/kg); or with PMPA (75 mg/kg). The agent was administered subcutaneously in a single daily dose for four weeks. The clinical and virologic status of the macaques was evaluated weekly throughout treatment and periodically thereafter. The efficacy was evaluated by monitoring cell-free and cell-associated virus load, cell-associated viral DNA, plasma viral RNA levels and absolute numbers of lymphocyte subsets. Although SIV was undetectable by PBMC coculture from animals treated with PMPA, the animals continued to have SIV DNA as determined by PCR. In conclusion, PMPA showed significant inhibition of SIV during treatment, however, SIV reappeared after treatment was stopped.

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Efficacy of 6-chloro-2',3'-dideoxyguanosine in rhesus monkeys infected with simian immunodeficiency virus.

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6-Chloro-2',3'-dideoxyguanosine (6-Cl-ddG), which is a lipophilic prodrug of ddG, can exert potent antiretroviral activity against HIV-1 *in vitro*. The effect of 6-Cl-ddG on acute infection of rhesus monkeys with simian immunodeficiency virus (SIVmac239) were investigated. A dose of 25 mg of 6-Cl-ddG per kg was administered subcutaneously every 8 hr for 10 days. The administration was started 24 hr before challenging with $1x10^5$ $TCID_{50}$ of SIV. The antigenemia (p27 antigen) and the antibody were monitored for up to 29 days after virus inoculation. The peaks of p27 antigenemia significantly delayed in the 6-Cl-ddG treated group than in untreated group. Additionally significant difference was observed in the time for appearance of SIV antibody.

We examined the effect of 6-Cl-ddG on an AIDS/ARC rhesus monkey. The clinical features of the monkey infected with SIVmac251/32H were recurrent weight loss, severe diarrhea, neuropathy and the decline of the number of $CD4^+$ and $CD8^+$ cells. 6-Cl-ddG (50mg/kg) was administered subcutaneously every 8 hr for 14 days. The monkey began to show improvement of clinical signs, including weight gain, recovery from diarrhea and disappearance of neuropathy after the onset of drug administration. The ratio of $CD4^+$ $CD8^+$ and T cell count also increased and the levels were maintained during treatment. On the other hand, B cell count decreased during the treatment. We will also report the efficacy of 6-Cl-ddG (25mg/kg) on three macaques with chronic SIV infection.

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Pharmacokinetics of 141W94 After Multiple Dosing in Patients with HIV Infection: A Preliminary Report. BM Sadler[1], C Rawls[1], J Millard[1], C Hanson[1], P Dowd[2], 160-002 Clinical Investigators. Glaxo Wellcome Research and Development, [1]RTP, NC, USA and [2]Beckenham, Kent, UK

141W94 (VX-478) was synthesized by Vertex Pharmaceuticals, Inc. and has been licensed for development by Glaxo Wellcome, Inc. and Kissei Pharmaceuticals. It is a potent and specific inhibitor of HIV protease with *in vitro* IC_{50}s of 0.084 and 0.080 μM against $HIV\text{-}1_{IIIB}$ in MT-4 cells and PBLs, respectively, and mean IC_{50}s of 0.012 and 0.019 μM against six zidovudine-sensitive and three zidovudine-resistant clinical isolates, respectively, evaluated in PHA-stimulated PBLs. In a previous clinical study, 141W94 was well tolerated by HIV-infected volunteers at single, oral doses between 150 and 1200 mg. The present study is an open-label, Phase I/II trial designed to evaluate the pharmacokinetics of multiple doses of 141W94 administered alone for four weeks to patients with CD_4 lymphocyte counts between 150 and 400 cells/mm^3. Plasma samples were obtained 0 (per-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours after the first dose of 141W94. Subsequent doses were withheld until after the 24 hour plasma sample. After three weeks of multiple-dose treatment, plasma samples were obtained over a steady-state dosing interval at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours after dosing. The 10 and 12 hour samples are collected only from patients receiving 141W94 *b.i.d.* Samples are assayed for 141W94 using a validated HPLC method and pharmacokinetic parameters calculated by model-independent methods. Comparisons of $AUC_{0-\infty}$ after the first dose with AUC_{ss} at steady-state provide information that can be used to select dosing regimens for subsequent studies. Data will be presented from a full cohort of ten HIV-infected patients, all of whom have now completed four weeks of therapy with 141W94 at 300 mg *b.i.d.* These data constitute the first report of multiple dosing of 141W94 in HIV-infected patients.

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A Clinical Study of the HIV-1 Protease Inhibitor, 141W94 (VX-478) to Evaluate a New Soft Gelatin Capsule Formulation and to Determine the Effects of Food Upon Bioavailability. WT Symonds[1], BM Sadler[1], GE Chittick[1], J Moss[2]. Glaxo Wellcome Research and Development, [1]KTP, NC, USA and [2]Greenford, Middlesex, UK

Background: 141W94 (VX-478) is a new HIV-1 protease inhibitor synthesized by Vertex Pharmaceuticals, Inc. and licensed for development by Glaxo Wellcome, Inc. and Kissei Pharmaceuticals. 141W94 is a potent and effective inhibitor of HIV protease *in vitro* with mean IC_{50} values of 0.080 μM in infected PBL's. In a previous study, 141W94 was well tolerated by HIV-infected volunteers following single, oral doses between 150 and 1200 mg. **Objectives**: To assess the relative bioavailability of a soft gelatin capsule of 141W94 to the hard gelatin capsule formulation and to assess the effects of food upon the soft gelatin capsule formulation. **Methods**: This was a single-center, randomized, balanced three-period crossover design. Following a screening evaluation, subjects were randomized to receive the following treatments: 600mg of 141W94 as a soft gelatin capsule, 600mg of 141W94 as a hard gelatin capsule and 600mg of 141W94 as soft gelatin capsule following a high-fat meal. Subjects were monitored throughout the study period for adverse events and changes in clinical laboratory parameters. Blood samples for pharmacokinetic analysis were obtained prior to dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 24 hours post-dosing. Pharmacokinetic analysis will be performed utilizing model-independent methods. **Results**: 18 HIV-infected subjects (15 male, 3 female) were enrolled into the trial. The clinical phase is complete with all subjects receiving all treatments per protocol. Reported adverse experiences were generally mild in severity with headache being most common. The analysis of plasma samples for 141W94 is currently underway using a validated HPLC method. **Conclusions**: 141W94 was safe and well tolerated following single doses of both formulations. Pharmacokinetic data will be presented evaluating the relative bioavailability of the two formulations and its impact upon future dosing regimens.