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1592U89 Succinate - Preclinical Toxicological and Disposition Studies and Preliminary Clinical Pharmacokinetics. S.S. GOOD, S.M. DALUGE, S.V. CHING, K.M. AYERS, W.B. MAHONY, M.B. FALETTO, B.A. DOMIN, B.S. OWENS, R.E. DORNSIFE, J.A. McDOWELL, S.W. LaFON, and W.T. SYMONDS. Wellcome Research Laboratories, Research Triangle Park, NC 27709, USA.

Preclinical toxicity and disposition studies demonstrated the novel anti-HIV agent (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (1592U89) to be an attractive candidate for clinical evaluation in HIV-infected patients. High concentrations of 1592U89 (≥100 μM) were required to inhibit *in vitro* growth of human bone marrow progenitors and HBV-producing human liver tumor cells (2.2.15, HB611). 1592U89 did not inhibit mitochondrial DNA synthesis in Molt-4 cells (100 μM, 8 days). In cynomolgus monkeys given oral 1592U89 succinate (50, 140 or 420 mg/kg/day) for 90 days, drug-related findings (sporadic emesis, transient body weight loss, and slight, reversible increases in female liver weights) were limited to the highest dose. Neurophysiological parameters were unaffected. In CD-1 mice given 1592U89 succinate (110, 330 or 1000 mg/kg/day) orally for 90 days, the only findings were liver effects (reversibly elevated serum ALT, total protein and triglycerides at the highest dose; reversibly elevated cholesterol, hepatocellular hypertrophy, biliary stasis and individual hepatocellular necrosis at 330 and 1000 mg/kg/day). The i.v. pharmacokinetics of 1592U89 succinate in monkeys were dose-independent up to 35 mg/kg ($t_{1/2}$≈1.3 hr, CL≈0.8 L/hr/kg, Vd_{SS}≈1.1 L/kg). The pharmacokinetics in mice were dose-dependent ($t_{1/2}$=0.8 hr, CL=2.0 L/hr/kg, Vd_{SS}=1.3 L/kg at the highest dose, 77 mg/kg). Oral bioavailabilities in both species were excellent (76-92%). Orally administered radioactive doses were completely recovered in urine (≥90%) and feces (≥7%). Metabolism was the primary route of elimination of 1592U89 in both species, with only 11-13% of the dose recovered unchanged in urine. Major metabolites were the 5'-carboxylate and the 5'-glucuronide; less than 2% of the doses were recovered as carbovir. In a Phase I single-dose escalation trial in HIV-infected subjects, dose-dependent kinetics were observed for doses ranging from 100 to 1200 mg 1592U89 succinate. Mean $t_{1/2}$ values increased (from 0.87 to 1.5 hr) and CL/F decreased (from 1.8 to 0.6 L/hr/kg) with increasing dose. As in animals, carbovir levels were negligible (mean C_{max} and AUC_{0-t} <1% those of 1592U89). With encouraging kinetics and tolerance of single doses, trials with 1592U89 succinate are progressing to multiple-dose regimens, including combinations with Retrovir®.

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A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE I/II EVALUATION OF 9-[-2-(BISPIVALOYLOXY-METHYL) PHOSPHONYL-METHOXY]ADENINE (bis-POM PMEA), AN ORALLY BIOAVAILABLE PRODRUG OF THE ANTI-HIV NUCLEOTIDE, PMEA. PA BARDITCH-CROVO, J TOOLE, H BURGEE, M WACHSMAN, D EBELING, KC CUNDY, HS JAFFE, PS LIETMAN. The Johns Hopkins University, Baltimore MD and Gilead Sciences Inc., Foster City, CA.

PMEA, a nucleotide analog with *in vitro* and *in vivo* activity against a broad spectrum of retro- and herpesviruses was shown to decrease p24 levels in HIV-infected individuals following multiple dose parenteral administration in two previous clinical trials. Because of PMEA's poor oral bioavailability, an oral prodrug, bis-POM PMEA, was developed, and shown to be orally bioavailable when administered as either a granule or tablet formulation. A randomized, double-blind, placebo-controlled Phase I/II study of three dose levels of bis-POM PMEA in p24 antigenemic HIV-infected subjects is currently underway. Nine subjects receive active drug and three subjects receive placebo at each dose level. This study is designed to evaluate the safety, tolerance, pharmacokinetics, and anti-HIV activity of bis-POM PMEA after 14 days of once daily administration. Twenty-four subjects (twelve at a dose level of 125 mg and twelve at a dose level of 250 mg) have completed 14 days of dosing to date. Based on safety and tolerance data, neither dose studied was considered to be a maximum tolerated dose. Therefore, a dose of 500 mg daily will be studied in 12 additional subjects. Pharmacokinetic and safety data and the results of bis-POM PMEA's effect on p24 antigen levels will be presented.