# 116

**Highly bioavailable prodrugs of the potent anti-Varicella Zoster Virus agent, 1-(β-D-arabinofuranosyl)-5-prop-1-ynyluracil (882C87).**

**S.G. Rahim*, N. Trivedi, M.J. Pether, D.J.M. Purifoy, P. Collins and K.L. Powell,**
**The Wellcome Research Laboratories, Beckenham, Kent, BR3 3BS, UK.**

Bioavailability studies in the rat have shown that 1-(β-D-arabinofuranosyl)-5-prop-1-ynyluracil, (882C87) a potent and selective anti-varicella-zoster virus agent, has modest oral availability as determined from plasma levels and urinary excretion. In an effort to improve the oral availability of 882C87, a series of 37 esters were synthesised and evaluated as prodrugs based on urinary excretion. These included 2',3' and 5'-monoesters and 2',3',5'-triesters using groups ranging from normal and branched alkyls to aromatic and amino acid groups. In general, the highest urinary recovery of 882C87 was achieved from 5'-alkyl esters with the 5'-pivaloate, butyrate, 2-ethylbutyrate and isobutyrate being the most effective. The percentage urinary recovery ranged from 40-65% compared with 10% for 882C87 itself after 50mg/kg doses. Also included in this range was the 3'-pivaloate ester. Modest improvement in oral availability was also seen with 3-N base acylated 882C87. On the other hand, 2'-alkyl and 5'-aromatic esters were less effective prodrugs, with some showing reduced availability compared with orally dosed 882C87. On the basis of physical properties such as solubility and stability, the 5'-pivaloate ester was selected for further study. Evaluation in the rat showed a four-fold increase in the plasma level (Cmax) of 882C87 when dosed at 25mg/kg compared with orally dosed 882C87. Significant increases in plasma levels were also observed in the monkey and the mouse. The pharmacokinetic properties of 882C87 can therefore be improved by prodrug synthesis. The 5'-pivaloate ester constitutes a promising prodrug candidate worthy of further investigation.

# 117

GR95168X (chiral carbocyclic BVdU) is highly effective against simian varicella virus infections of African green monkeys

RE Boehme[1], A Beresford[1], GJ Hart[1], SJ Angier[1], G Thompson[1], C Van Wely[1], J-L Huang[2], P Mack[2] and KF Soike[2]

[1]Glaxo Group Research Ltd, Greenford, Middlesex, UK; [2]Tulane Regional Primate Research Center, Covington, LA, USA

GR95168X (chiral carbocyclic BVdU; [1R-[1α(E),3β,4α]]-5-(2-bromovinyl)-1-[3-hydroxy-4-(hydroxymethyl)-1-cyclopentyl]-2,4(1H,3H)-pyrimidinedione) exhibits potent *in vitro* activity against lab strains and clinical isolates of varicella zoster virus (VZV). To help evaluate the clinical potential of this compound, the efficacy of GR95168X against simian varicella virus-induced disease in African green monkeys was determined. Dosing was initiated 48 hours after infection with a near-lethal inoculum of virus. Rash, viraemia, and serum antibody responses were monitored. Initially, a dose-ranging study determined that the minimum effective dose of GR95168X is <0.2 mg/kg/day with t.i.d. dosing by oral gavage. Secondly, in a comparison of the efficacy and pharmacokinetics achieved with different dosing frequencies, a dose of 1.0 mg/kg/day was shown to be highly effective when split among either one, two or three daily doses. Related biochemical studies showed that GR95168X is selectively phosphorylated in VZV-infected cells by the virus-encoded thymidine/thymidylate kinase and cellular kinases to yield GR95168X triphosphate. This triphosphate is a potent inhibitor of the VZV-encoded DNA polymerase, and is a very weak inhibitor of cellular DNA polymerases alpha, beta and gamma.