7

Highly Polar, Water-Soluble Prodrugs Of The HIV Protease Inhibitor Amprenavir: A New Approach Toward A More Compact Dosing Regimen A. SPALTENSTEIN[1], C. BAKER[2], Y. GRAY-NUNEZ[1], I. KALDOR[1], W. KAZMIERSKI[1], D. REYNOLDS[1], R. TUNG[2], P. WHEELAN[1], E. FURFINE[1] [1]Glaxo Wellcome Inc., Res. Triangle Park, NC, USA and [2]Vertex Pharmaceuticals, Cambridge, MA, USA

Background: With twice a day dosing without regard to food and water intake (high-fat meals are not recommended) amprenavir, our recently approved HIV protease inhibitor, features a very convenient dosing regimen. Due to its low aqueous solubility, amprenavir requires a considerable amount of excipients to achieve satisfactory oral bioavailability. In our search for a more compact method for dosing amprenavir, we considered the use of a novel prodrug approach. Prodrugs are often designed to increase absorption by 1.) taking advantage of active transport mechanisms (e.g. valcyclovir), or 2.) "capping" polar/charged functional groups that prevent a molecule from penetrating lipophilic membranes (e.g. adefovir dipivoxil). Typically, these prodrugs are activated by plasma or hepatic enzymes. In the case of amprenavir, we reasoned that the low bioavailability of the solid, crystalline state (i.e. without excipients) might be related to inferior wetting and dissolution properties rather than intrinsically low membrane permeability. For this reason, we prepared a series of highly polar, water-soluble prodrugs of amprenavir that were designed to be minimally absorbed as the prodrug and instead be hydrolized by intestinal enzymes at or near the point of absorption in the gut wall. **Methods:** Starting from amprenavir or its penultimate precursor, we prepared a series of approximately 70 highly polar, and/or charged prodrugs. Wistar rats were dosed orally with an aqueous solution/suspension (without excipients) and exposure to amprenavir was determined. Lead candidates that gave amprenavir exposure similar to or better than amprenavir dosed in the clinical formulation were further evaluated in beagle dogs. **Results:** Of the 70 prodrugs prepared, five resulted in significant exposure to amprenavir when dosed in rats. The 2-aminoethylcarbamate and the 4-aminobutyl carbamate prodrugs were slightly inferior to the amprenavir clinical formulation, while the diethyleneglycolester, the bis-ethyleneglycol ester/amide and the phosphate ester showed equal or superior bioavailability. Dog pharmacokinetic studies with the top three molecules led to the selection of the phosphate ester (GW433908/VX175) as a candidate for pre-clinical and clinical evaluation.

8

HIV-1 RT Mutations in Patients After 24 Weeks of Tenofovir Disoproxil Fumarate (formerly PMPA Prodrug) Therapy

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Study GS-98-902 is a placebo-controlled, phase II study in 189 patients evaluating 3 doses of tenofovir disoproxil fumarate (DF) when added to stable background ART. Grouped HIV RNA results at week 24 showed statistically significant mean HIV RNA $\log_{10}$ reductions of -0.75, -0.40 and -0.45 for patients in the 300 mg, 150 mg and 75 mg dose groups, respectively. Blinded genotypic analyses of RT and protease genes in plasma HIV were performed at baseline and at week 24. Consistent with extensive treatment experience, 74% of patients had AZT resistance mutations at baseline, 66% had the lamivudine resistance mutation (M184V), 48% had both AZT and M184V mutations, 59% had primary PI resistance and 34% had primary NNRTI resistance mutations. At week 24, genotypic data is available for 121 patients; 51 patients were below evaluation limits and 17 patients are pending results. 42 of 121 evaluated patients developed additional NRTI-associated mutations, 35 of whom developed typical AZT/thymidine analog-associated RT mutations while taking AZT (n=13), d4T (n=20) or abacavir (n=2). Four patients developed L74V, all of whom were taking ddI or abacavir concomitantly. Three patients developed K65R, an RT mutation associated with ddI and abacavir in vivo, and also selected by tenofovir in vitro. Although these 3 patients may have been on active tenofovir DF therapy (blinded analysis), all three patients were also taking ddI or abacavir and none of these patients showed evidence of viral load rebound at week 24. Finally, there was no evidence for the development of novel RT mutations associated with tenofovir DF therapy. In conclusion, patients adding tenofovir DF to their existing antiretroviral regimen showed significant HIV RNA reductions at week 24. RT mutations developing appeared due to the patient's background regimen and were not associated with HIV RNA rebound.

9

Prevention of Mucosal HIV Transmission by Topical Anticellular Substances that Target the HIV-Infected Lymphocytes in Seminal Fluid. S. Baron, D. Nguyen, J. Poast, and M.W. Cloyd, Dept. of Microbiology & Immunology, University of Texas Medical Branch, Galveston, TX, USA

To prevent HIV transmission vaginally and rectally, substances that target the transmitting HIV-infected leukocytes are needed (Arch Intern Med. 159:303-310; JID, in press). Previously used preventives containing the surfactant nonoxynol-9 are ineffective in humans, probably because of mucosal inflammation. Therefore, less irritating anticellular substances are needed to prevent transmission by the HIV-infected leukocytes in seminal fluid. Experimentally, HIV-infected human leukocytes or cell-free HIV in seminal fluid were treated with candidate preparations including FDA-approved, over-the counter vaginal lubricants, bile salts, and disinfectants for blood products. Some of these substances inhibit lymphocyte production of HIV by >1,000-fold in 15-30 minutes, as well as inhibiting cell-free HIV. Medical application of such FDA-approved products or their individual components may interdict sexual transmission of HIV. Also, these products may be cost effective in underdeveloped countries.