PI-110

THE SAFETY, TOLERABILITY AND PHARMACODYNAMIC RESPONSES OF INTERFERON BETA-1A (REBIF®) VERSUS INTERFERON BETA-1B (BETASERON®) IN HEALTHY MALE VOLUNTEERS. S. Gariepy, MSc, J. Marier, PhD, D. Potvin, MSc, M. Di Marco, PhD, W. Byrnes, A. Abdul-Ahad, PhD, MDS Pharma Services, St-Laurent (Montreal), Canada.

Interferon beta-1a (IFNβ-1a) and beta-1b (IFNβ-1b) are immunomodulators used for the treatment of relapsing-remitting multiple sclerosis (RRMS). The primary objective of this study was to compare the biological effects induced by subcutaneous administrations of IFNβ-1a (Rebif®, 44 μg, three times weekly) and IFNβ-1b (Betaseron®, 250 μg, given every other day) in healthy male volunteers (n=64). The secondary objectives were to assess the local injection site tolerability and safety of both treatments. IFNβ-1a and IFNβ-1b were administered over a 4-week period and biological response markers were measured (neopterin in serum, β2-microglobulin in serum, and MxA protein in blood). Pharmacokinetic parameters of the biological markers were calculated and injection site pain and reactions were determined using numerical rating scale (NRS) and visual analogue scale (VAS). Following treatments with IFNβ-1b and IFNβ-1a, baseline-adjusted area under the concentration-time curve of neopterin (149.2 and 153.0 nmol·day/L, respectively), β2-microglobulin (12.9 and 16.2 mg·day/L, respectively), and MxA protein (9091 and 9535 ng.day/mL, respectively) were similar. Betaseron® treatment was associated with less pain and reactions at the injection site. These results support the hypothesis that the administration of Betaseron® over 4 weeks resulted in similar pharmacodynamic responses to that of Rebif®, and with an improved safety and tolerability profile.

PI-111

NELFINAVIR (NFV) POPULATION PHARMACOKINETICS (PK) IN LONG-TERM SUPPRESSORS COMPARED WITH THE PK OF THE NEW 625 MG FORMULATION IN HEALTHY VOLUNTEERS. E. Capparelli, PharmD, F. D. Goebel, MD, I. Williams, MD, M. Opravil, MD, M. Nelson, MD, E. Daniels, MD, E. Pun, PhD, P. Hsyu, PhD, Ludwig-Maximilians Universität, Royal Free and University College of London, Universitätsspital Zürich, Chelsea & Westminster Hospital, Agouron Pharmaceuticals Inc., A Pfizer Company, Pfizer Global R&D, La Jolla, CA.

Background: We determined the NFV (250 mg tablet) AUC in patients who maintained undetectable HIV RNA for >72 weeks to understand the exposure of NFV in long-term responders. In addition, the exposure was compared to that from a new NFV formulation (625 mg tablet) to determine how well the new formulation achieves concentrations associated with maximal long-term HIV suppression.

Methods: Patients receiving NFV in combination with 2 NRTI's with HIV suppression (<50 copies/mL) for > 72 weeks were enrolled. PK samples were collected after observed doses of NFV (5 X 250mg tablets) BID. 46 subjects with PK samples contributed 225 levels to this analysis. NONMEM was used to construct a population pharmacokinetic model for NFV. Individual $AUC_{0\text{-}12}$ was estimated and compared to NFV AUC observed in a separate phase PK study of 14 healthy subjects taking 2 X 625mg NFV tablet BID.

Results: The median CL/F and $AUC_{0\text{-}12}$ were 53.7 L/hr and AUC was 23.3 mcg*hr/mL (range = 7.8-49), respectively. This NFV exposure is consistent with prior studies. NFV AUC following administration of the 625mg formulation was approximately double (median [range] = 48 [18.6-74.2] mcg*hr/mL) the exposure seen in long-term suppressors (250mg tablets).

Conclusions: Long term HIV suppression with NFV was achieved with typical NFV exposures. Initial PK of the new 625 mg tablet in healthy volunteers resulted in NFV exposures greater than that observed in long-term suppression.

PI-112

NONLINEAR MIXED EFFECTS MODEL ANALYSIS OF THE PHARMACOKINETICS OF METOPROLOL IN MIDDLE-AGED AND ELDERLY JAPANESE PATIENTS. M. Taguchi, MS, T. Nozawa, MD, PhD, K. Mizumaki, MD, PhD, H. Inoue, MD, PhD, K. Tahara, BS, C. Takesono, BS, Y. Hashimoto, PhD, Toyama Medical and Pharmaceutical University, Toyama, Japan.

Purpose. This study was performed to characterize the factors involved in the pharmacokinetic variability of routinely administered metoprolol in middle-aged and elderly Japanese patients.

Methods. The 65 whole blood concentration data after repetitive administration to 34 patients were analyzed using the nonlinear mixed effects model (NONMEM) program. A one-compartment model with rapid absorption was parameterized in terms of oral clearance (CL/F) and apparent volume of distribution. We investigated the effect of polymorphic alleles of cytochrome P450 (*CYP2D6*2*, *CYP2D6*10*, *CYP2C19*2* and *CYP2C19*3*), age, gender, and heart failure on the pharmacokinetic parameters of metoprolol.

Results. The CL/F was 64% decreased in the patients homozygous for the *CYP2D6*10/*10*, as compared with the patients with the *CYP2D6*1/*1* or **1/*2* genotype. In addition, the CL/F value in the older (> 70-year-old) patients was 26% lower than that in the younger (≤70-year-old) patients. On the other hand, the genotype of CYP2C19, gender, and heart failure showed no significant effect on the pharmacokinetic parameters of metoprolol.

Conclusion. These findings suggested that a lower dose of metoprolol may be used in the elderly Japanese patients with the *CYP2D6*10* allele.

PI-113

PHARMACOKINETICS OF SINGLE AND MULTIPLE ESCALATING DOSES OF DAPOXETINE IN HEALTHY VOLUNTEERS. M. Dresser, PhD, K. Lindert, MD, D. Lin, MS, S. Gidwani, MS, S. K. Gupta, PhD, N. B. Modi, PhD, ALZA Corp, Mountain View, CA.

Objective: To characterize the pharmacokinetics and safety of single and multiple doses of dapoxetine, a novel agent under development for the treatment of premature ejaculation, a urogenital disorder. **Methods:** This was a randomized, double-blind, placebo-controlled, single and multiple dose study in 77 healthy male volunteers. Dapoxetine was administered orally as a single dose of 60, 100, 140, or 160 mg or once-daily for 6 days at 80, 100, or 120 mg. Pharmacokinetic parameters were determined by non-compartmental methods. Safety was evaluated by physical exam; laboratory, vital signs and ECG measurements; and monitoring of adverse events. **Results:** Dapoxetine was quickly absorbed with peak plasma concentrations occurring at ~1.5 h after dosing followed by a rapid decline in plasma concentrations. C_{max} and AUC increased proportionally up to 100 mg. Dapoxetine had a terminal half-life of ~18 h. Single- and multiple-dose pharmacokinetics were comparable. No serious adverse events were reported, and there were no clinically relevant changes in any clinical laboratory tests, vital signs, or ECG. Nausea, the most common adverse event, was mild or moderate. **Conclusions:** Following oral administration, dapoxetine was rapidly absorbed; a fast decline in plasma concentrations followed. Dapoxetine was well tolerated following single and multiple doses to healthy volunteers.