PII-29

SINGLE DOSE PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD) OF BR-A-657, AN ANGIOTENSIN II (AII) ANTAGONIST. A. Lane, PhD, E. Engmann, MB ChB, S. Bryson, PhD, J. Lee, H. Tan, PhD, Y. Chi, Covance CRU, Boryung Pharm. Co. Ltd., Leeds, United Kingdom.

BACKGROUND/AIMS: BR-A-657 is a nonpeptide AII receptor antagonist being developed for hypertension. This Phase I study investigated the safety, PK and PD of single doses of BR-A-657.

METHODS: Fasted single oral tablet doses of 20–480 mg BR-A-657/placebo were administered to 40 healthy male subjects in a double-blind, sequential group design.

RESULTS/CONCLUSIONS: BR-A-657 was safe, well tolerated, and induced increases in plasma renin activity, angotensin I and AII that were not dose-dependent. Maximal increases occurred between 6–8 h post-dose, lasting up to 48 h. There were no drug-related changes in ACE or aldosterone. BR-A-657 was absorbed rapidly for all dose levels and demonstrated multiphasic disposition. For most subjects there were two peaks in the plasma concentration-time profile, suggesting enterohepatic cycling. Half-life could only be estimated for the higher dose levels (approx 9–16 h). Systemic exposure to BR-A-657 was broadly dose-proportional. There were no marked differences in systemic exposure or disposition of BR-A-657 following adminstration of 240 mg in the fed state. Urinary excretion of BR-A-657 was low, suggesting non-renal elimination.

PII-30

POPULATION PHARMACOKINETICS OF ABACAVIR IN CHILDREN. V. Jullien, PharmD, S. Urien, PhD, H. Chappuy, MD, J. Dimet, PharmD, E. Rey, PharmD, G. Pons, PhD, S. Blanche, PhD, J. Treluyer, PhD, Hopital Saint Vincent de Paul, Hôpital Necker Enfants Malades, Paris, France.

AIMS(s): To develop a population model of abacavir pharmacokinetics in children.

METHODS: Concentration-time data obtained from 105 children, ranging in age from 1 month to 16 years, were analyzed by the use of a non-linear mixed effects modeling method performed with NONMEM.

RESULTS: Abacavir pharmacokinetics was well described by a one compartment open model with linear absorption and elimination. Typical population estimates (% interindividual variability) of absorption rate constant (Ka), apparent distribution volume (V/F) and apparent plasma clearance (CL/F) were 1.79 h-1 (58 %), 42.9 L (53 %) and 24.3 L/h (30 %) respectively. Apparent plasma clearance was positively related to bodyweight. Individual Bayesian estimates of CL/F were used to calculate individual abacavir area under the concentration curve (AUC). For the current 8 mg/kg dosage regimen, abacavir exposure was found to be constant throughout the age range of the study, with an overall mean AUC value of 7.9 $\pm$ 3.0 mg.h/L, which is slightly greater than the mean AUC value reported in adults.

CONCLUSIONS: This study confirms the relevance of the current weight-based abacavir dosage regimen in pediatric patients.

PII-31

PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD) OF ENFUVIRTIDE IN HIV-1-INFECTED CHILDREN OVER 24 WEEKS OF TREATMENT. X. Zhang, PhD, T. Lin, PharmD, A. Dorr, PhD, A. Bertasso, MS, C. Evans, RGN, L. Rowell, MS, S. Kolis, MS, W. Veloso, BS, Roche, XIQ Coordination Inc., Nutley, NJ.

BACKGROUND/AIMS: Enfuvirtide (ENF, Fuzeon®) is the first of a new class of HIV drugs (fusion inhibitors) that block gp41-mediated viral fusion to host cells. The objective of this study was to measure sparse C_{trough} levels of ENF and its major metabolite and to explore its pharmacodynamics (PD) in a group of HIV-1-infected children over 24 weeks of treatment.

METHODS: 24 HIV-1-infected children (aged 5–11 years) who completed 24 weeks of a 48-week multi-center, open-label, non-randomized, non-comparative treatment study were included in the analysis. Patients were dosed at 2 mg/kg (to a max dose of 90 mg) bid subcutaneously plus an optimized antiretroviral regimen. Plasma samples for determination of the C_{trough} of ENF and its metabolite were collected at 12 ± 2 hr post-dose at various weeks. Blood samples for determination of HIV-1 RNA viral load and CD4 and CD8 cell counts were collected up to 24 weeks.

RESULTS: Mean ENF C_{trough} was 2.6 μg/mL at week 1 and 3.4 μg/mL at week 24. Mean ENF metabolite C_{trough} was 0.17 μg/mL at week 1 and 0.41 μg/mL at week 24. Mean decline in plasma HIV-1 RNA from baseline was -1.059 $\log_{10}$ copies/mL at week 24. Mean increase in CD4 cell count from baseline was 190 cells/mm^3 at week 24. Mean CD8 cell count decreased from BL by 115 cells/mm^3 at week 24.

CONCLUSIONS: A dose of ENF at 2 mg/kg bid in a group of HIV-1-infected children achieved PK exposure which is stable over 24 weeks of treatment and comparable to that achieved in HIV-1-infected adolescents at the same dose and in adults at a dose of 90 mg bid.

PII-32

EFFICACY OF METHYLENE BLUE AND ARTESUNATE AS COMBINATION ANTIMALARIAL THERAPY IN A RHESUS MONKEY MODEL OF UNCOMPLICATED BLOOD-STAGE MALARIA. T. L. Barker, MD, MPH, M. Gettayacamin, DVM, P. Hansukjariya, Y. Van Gessel, DVM, V. Melendez, PhD, P. Teja-Isavadharm, PhD, J. Vennerstrom, PhD, R. S. Miller, MD, C. K. Ohrt, MD, MPH, Walter Reed Army Institute of Research, Armed Forces Research Institute of Medical Sciences, University of Nebraska Medical Center, Silver Spring, MD.

BACKGROUND/AIMS: Methylene blue (MB), an FDA approved drug for methemoglobinemia, also demonstrates *in vitro* and *in vivo* antimalarial activity. Artesunate (AS) is widely used to treat malaria in malaria-endemic countries. The purpose of this study was to evaluate the anti-malarial efficacy and safety of intravenous MB when given alone and in combination with intravenous AS in rhesus monkeys.

METHODS: A Rhesus/*P. cynomolgi* model of uncomplicated blood stage malaria was used to evaluate different combinations of MB and AS. The study was conducted under an approved protocol in an AAALAC accredited animal facility. The study design used a 3 by 3-factorial design to compare 3 doses of MB (0, 2 and 8 mg/kg) in combination with 3 doses of AS (0, 1 and 8 mg/kg). Thirty-four healthy rhesus monkeys were randomly assigned to one of 8 different treatment groups or to an infection control group. Study drugs were administered as three once-daily intravenous injections after threshold parasitemia levels were attained.

RESULTS: Parasitemia clearance and cure rates demonstrated dose-dependency. Combinations were much more likely to result in cure. Four monkeys died with clinical and necropsy findings consistent with severe malaria that were not considered to be related to study drugs. All remaining study animals recovered with no adverse sequelae.

CONCLUSIONS: Intravenous methylene blue was well tolerated and demonstrated dose-dependent anti-malarial efficacy, as well as apparent synergy with intravenous artesunate.

Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the authors, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense.