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COST-EFFICIENT HIGHER-ORDER CROSSOVER DESIGNS IN COMPARATIVE BIOAVAILABILITY STUDIES. J. Zhou, MD, PhD, Y. Yuan, MS, R. Reynolds, BS, S. Raber, PharmD, Pfizer Inc., San Diego, CA.

OBJECTIVE: To compare cost efficiency of five commonly used, statistically optimal or near-optimal higher-order crossover designs for comparative bioavailability studies.

METHODS: Monte Carlo simulations were carried out to obtain empirical sample sizes of the five higher-order crossover designs using Schuirmann's Two One-Sided Tests Procedure, under a 90% power and a 5% significance level, based on the equivalence criteria (80%, 125%). The five designs were the 2-period 4-sequence (2x4), the 3-period 2-sequence (3x2), the 3-period 4-sequence (3x4), the 4-period 2-sequence (4x2), and the 4-period 4-sequence (4x4). Costs were then determined by a cost function, which takes into account recruiting and screening cost, cost associated with period, and the overhead incurred for multiple sequences. The costs of the designs were compared under different scenarios.

RESULTS: No single design uniformly dominates others. The 3x2 design and the 4x4 design, especially the latter, have the best overall performance in terms of cost efficiency. The 4x4 design is often better than the 3x2 design, but the 3x2 design can outperform the 4x4 design under high sequence cost or high period cost increment. The 2x4 design had the worst performance.

CONCLUSIONS: The 3-period 2-sequence design and the 4-period 4-sequence design are recommended for higher-order crossover designs in comparative bioavailability studies. The 2-period 4-sequence design is least favorable in terms of cost efficiency.

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OPTIMAL SPARSE PHARMACOKINETIC (PK) SAMPLING STRATEGIES (OSS) FOR MULTI-DRUG ANTIRETROVIRAL (ARV) REGIMENS. J. Z. Zack, A. Forrest, Q. Ma, S. Rosenkranz, M. F. Para, E. Adams, R. C. Reichman, K. Yaresheski, G. D. Morse, SUNY-Buffalo, Harvard University, Ohio State University, NIAID, University of Rochester, Washington University, Buffalo, NY.

AIMS: ARV therapy is a rapidly evolving area that requires an excellent understanding of drug interactions & metabolism as well as adaptive feedback control (PK/PD individualization). Clinicians & patients are confronted with increasingly complex regimens in order to optimize treatment & to prevent emergence of resistance, failure or toxicity. ARV regimens often include 3 or 4 drugs, making population PK/PD analysis based on traditional sampling strategies difficult. Our goal was to develop a sparse efficient multi-drug OSS for the evaluation of PK in patients receiving ARV regimens.

METHODS: Saquinavir (SQV) & efavirenz (EFV) data from 10 healthy subjects also on amprenavir, in AACTG A5043, were fit to compartmental models (maximum likelihood, ADAPT II). Optimal Sampling Theory (ADAPT II, D-optimality) was used to determine sparse, efficient study designs (best 6-, 4-, 3- & 2- sample OSS) constrained to 8h post-dose, at steady state. Bias & precision of clearance (CL) estimates were evaluated.

RESULTS: OSS3 included samples at 0, 4 & 8h post-dose; OSS4 added a 6h & OSS6 added 1 & 2h samples. CL estimates for all OSSs were unbiased & even OSS3 provided acceptable precision; mean absolute errors, with OSS6, for SQV & EFV were 14.9 & 4.1% respectively & with OSS3, for SQV & EFV were 16.9 & 5.4%. No OSS with <3 samples was adequate for SQV.

CONCLUSIONS: CL for both SQV & EFV were reasonably estimated using ≥ 3 sample strategy. This approach will facilitate population PK/PD analyses of combined ARV regimens.

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POPULATION PHARMACODYNAMIC MODELING OF ZOLMITRIPTAN FOLLOWING ADMINISTRATION OF CONVENTIONAL TABLETS. J. Li, PhD, H. Kimko, PhD, R. Bies, PharmD, PhD, C. Peck, MD, H. Su, PhD, K. McKenna, PhD, AstraZeneca LP, Center for Drug Development Science, Wilmington, DE.

PURPOSE: To build a population pharmacodynamic (PD) model of zolmitriptan (ZOL) following administration of ZOL conventional tablets.

METHODS: ZOL concentration and headache scores (HS) were obtained in 235 migraine patients from AstraZeneca studies 8311CIL/006, 311CIL/007 and 311CIL/017. NONMEM likelihood estimation method was used to build a population PD model. The individual probabilities of headache scores (HS) ≤ 1 (no pain), 2 (mild pain), 3 (moderate pain), or 4 (severe pain) at various times following administration of the drug were modeled using a logistic model. The placebo (time) effect was modeled as a first-order increase with an upper bound. A sigmoidal Emax-type equation with a high sigmoidicity factor was chosen to mimic the step function of pain relief.

RESULTS: The built population PD model yielded 78% perfect match, 10% under prediction and 12% over prediction of the observed HS, respectively. Baseline HS is a significant covariate for pain relief.

CONCLUSIONS: A logistic model adequately described the time courses of HS following the administration of ZOL conventional tablets. Patients with moderate baseline HS had a higher probability of improvement of pain. Demographic factors do not impact the PD relationship between HS and ZOL concentration.

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A NON-LINEAR MIXED EFFECT DYNAMIC MODEL USING ADHERENCE TO TREATMENT TO DESCRIBE LONG-TERM THERAPY OUTCOME IN HIV-PATIENTS. L. Labbé, PhD, D. Verotta, PhD, University of Montreal, University of California San Francisco, Montréal, PQ, Canada.

AIM: Poor drug-adherence is an important factor explaining the resurgence of HIV-1 virus. Complex non-linear models have been developed to describe the population dynamics of HIV virus, but they are not used in clinical trials due to their complexity. Linearized models have been applied to real data. However, they can only explain the decay of the virus following antiviral treatment. The objective of our project is to develop a population non-linear mixed effect model characterizing the long-term dynamics of viral load in clinical data, and to quantify the effect of adherence in the dynamic of HIV virus.

METHODS: The basic model incorporates physiologically meaningful variables (free virus, total T-cells, and latent T-cells), uses standard rescaling techniques to guarantee identifiability of its parameters given measurements of the free virus (viral load), and takes into account intra-subject variability. Drug-adherence is incorporated on the basic reproductive ratio of the virus (RR) as follows: $RR = \lambda + \gamma * A_j(t)$, where λ is the RR for non compliers ($A_j(t)=0$) and $\lambda + \gamma$, $\gamma \leq 0$, is the RR for perfect compliers ($A_j(t)=1$). The model is applied on real AIDS clinical data.

RESULTS: We show that adherence affects the RR. Perfect adherence decreases RR by 3% resulting in an important reduction of RNA levels.

CONCLUSIONS: The model may be used to draw biologically relevant interpretations from repeated HIV-1 RNA measurements and quantify the relative effect of drug-adherence on viral response in HIV-infected patients.