Population Pharmacokinetic/Pharmacodynamic (PKPD) Modeling for Long Acting Injectable(LAI) Products and Statistical Analysis for Bioequivalence(BE) Assessment

Prokash Paul[a], Seongkyu Yoon[a], Namjoon Kim[a], Nicholas Trunfio[a], Garry Handelman[b], Jaeyeon Kim[c]
[a]Department of Chemical Engineering; [b]Pharmacology, Clinical Bioanalytical Chemistry, University of Massachusetts, Lowell, MA 01854, USA
[c]Merrimack Pharmaceuticals, Cambridge, MA 02139, USA

Motivation

- Current BE guidance of generic formulations requires the same degree of PK metrics as much as the reference in statistical analysis on both qualitative and quantitative approaches
- The parallel BE study of LAI products is very challenging due to
  - high inter-subject variability
  - complex PKPD profiles
  - study strength and expenditure
- Office of Generic Drug (OGD) of Food and Drug Administration (FDA) is looking for innovative paradigm to reduce residual variability and to identify appropriate PK metrics
- A population PKPD modeling and subsequent statistical analysis will help to establish scientific and regulatory standards for assuring therapeutic equivalence of generic LAI products

Data Set

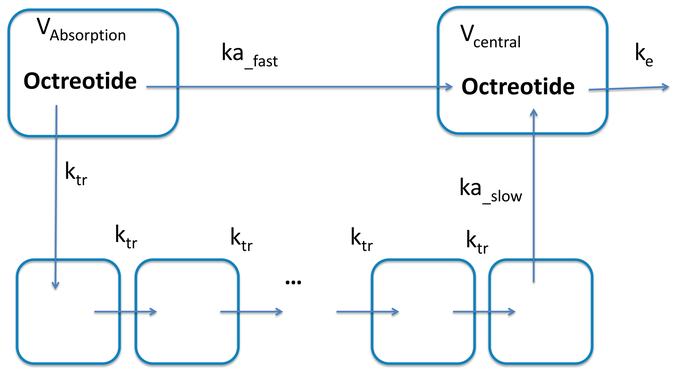
- Study title: A single dose, sequentially assigned, open-label, one-period, two-treatment, parallel, comparative bioavailability study
- Sample size: 32 subjects ; healthy non-smoking male volunteers
- Analytical method: LC/MS/MS assay with an analytical range of 0.025 to 25 ng/mL

Baseline Demographic and Clinical Characteristics of Study Population

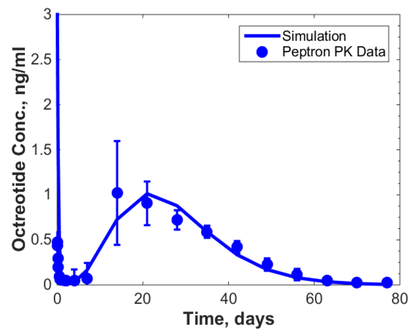
Characteristic	Value
Age (years)	
Mean[SD]	42.9[10.6]
Range	23-60
Weight(lb)	
Mean[SD]	78.6 [11.9]
Range	58.4-100.4
Height(in)	
Mean[SD]	174.0 [2.1]
Range	158.4-186.4
Body mass index(kg/m^2)	
Mean[SD]	25.9[2.7]
Range	21.2-29.9

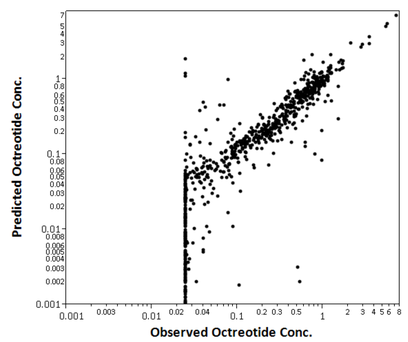
Suggested PK Model for LAI

Transit compartmental model was used to describe time delay from slow absorption process. (Savic et al., 2007 J PK PD)



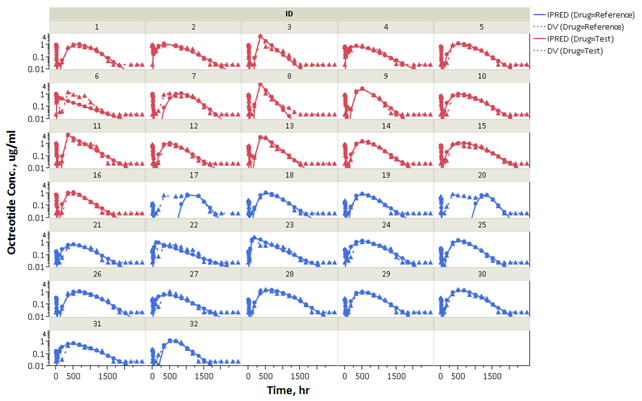
- Two phase behavior could be captured with the suggested model structure
- Due to the numerical instability, non-linear mixed effect modeling is still underway





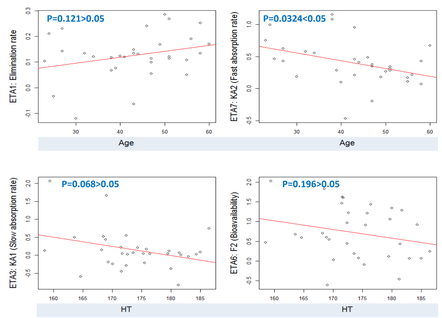
Naïve-Pooling was Used to Confirm the Adequacy of the Proposed Model Structure

Comparison of simulation results with observed PK data



Covariates Identification

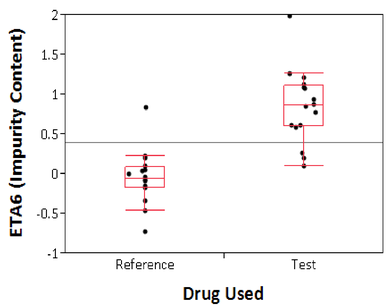
- Selecting covariates based on statistical significance test
  H_0: Co-efficient of covariate = 0
  H_1: Co-efficient of covariate ≠ 0
  If P< 0.05 ; rejects null hypothesis.
  Thus, the covariate is statistically significant



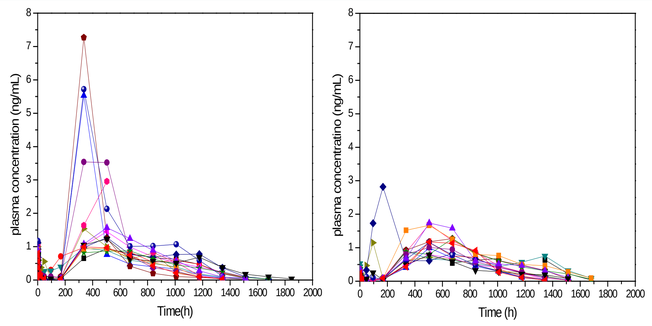
List of Covariates:
- Age
- Height(HT)
- Weight (WT)
- Body Mass Index (BMI)
- Drug Type (Reference vs. Test)

Test drug has higher impurity content than reference drug

- Among all model parameters, only one parameter showed significant difference between reference and test drug molecules
  - F: Fraction of drug for immediate release resulted from free drug impurity in the formulation



Parametric Test



Pharmacokinetic Parameter	Test/Reference Ratio of Geometric Means (90% Confidence Interval)	Inter-Subject CV (%)
AUC_t	128.68 % (105.66% - 156.73%)	31.81
AUC_{inf}	129.21% (105.93% - 157.61%)	31.53
C_{max}	149.28% (104.34% - 213.58%)	57.79

- There were 4 subjects (03, 08, 11 and 13) with a much higher Cmax in the test group than the rest of the study population.
- Further study with those subjects may be useful in order to assess the test product performance.

Acknowledgement

Funded by U.S. Food and Drug Administration (FDA). This technical effort was performed under the RFA-FD-15-008 of Center for Drug Evaluation and Research.

Future Work

- Detail NONMEM modeling
- Covariate structure identification
- Criteria development for BE assessment for LAI
- BE assessment for Generic LAI drugs
- Develop detail statistical assessment methods