Population Pharmacodynamic Modeling and Simulation of Clinical Trials to Explore Longitudinal Weight Loss in Obesity

Combes FP[1], Vakilynejad M[2], Lahu G[3], Lesko LJ[1], Trame MN[1]

[1]Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, College of Pharmacy, University of Florida, Orlando, FL, USA; [2]Takeda Pharmaceuticals Research Division, Pharmacometrics, Deerfield, IL, USA; [3]Takeda Pharmaceuticals Research Divsion, Pharmacometrics, Zurich, Switzerland; Corresponding author: mtrame@cop.ufl.edu

Introduction

- Metabolic diseases, such as Type 2 *Diabetes Mellitus* (T2DM) and Obesity may be treated by a combination of LifeStyle Intervention (LSI), and drug treatment. Oftentimes no more than 5% body weight (BW) loss is achieved at the end of a 56 week anti-obesity trial
- High observed dropout rates during anti-obesity trials can be due to non-compliance, weight regain, environmental factors (e.g. low education, costs for healthy food, too little exercise), medical and/or genetic factors, and inadequate systemic drug exposure due to variation in the PK[1]
- Models have been developed to describe disease progression, as well as placebo and drug effects on anti-obesity biomarkers such as BW
- Nevertheless, inter-individual differences in drug responses have been observed but not modeled. Populations can usually be separated in two groups: responders (R) and non-responders (NR). In addition, a dropout (D) is sometimes observed, leading to missing data. This dropout seems to be linked to drug response

Objectives

1. To develop a Population Pharmacodynamic (PopPD) model to describe the BW time-courses for the placebo effect[2] of naltrexone-bupropion (NB) trials
2. To examine and predict the time-course of the transition probabilities between responders, non-responders and dropout states using a Markov Model[3]

Methods

Subjects

- 1102 patients from 5 NB studies were included with a total of 5122 BW measurements (sparse data: 3 to 4 samples per subject)
- Similar population across the 5 studies: obese patients with BMI > 27
- Study follow-up: from 20 to 60 weeks
- All subjects were administered placebo and LSI:
  - Hypocaloric diet (-500 to -1000 kcal/day)
  - Increase of physical activity (at least 30 minutes walk 3 times per week)
  - Follow-up program: written instructions and closed group sessions

Population PD Model

- PopPD model used to describe the BW time-course for each patient and at each time point:
  1. Disease progression model ($BW_{DP}(t)$) to describe the usual BW gain of an obese population using k_{pro} = 0.7kg/year which is based on NHANES long-term surveillance data

$$BW_{DP}(t) = BW_{baseline} + k_{pro} \times t$$

  2. Indirect -Response Model to describe placebo and LSI effect

$$\frac{dBW}{dt} = k_{in} - k_{out} \times BW(t) \times \left(1 + \frac{DSTIM \times k_{de}}{k_{de} - k_{rel}} \times \left(e^{-k_{rel} \times t} - e^{-k_{de} \times t}\right)\right)$$

k_{in}, k_{out}: Bateman-like (zero-order) rate constants for IDR with

$$k_{in} = k_{out} \times BW_{DP}(t)$$

k_{de}, k_{rel}: Onset and loss of the LSI effect

$DSTIM$: Maximum fractional increase in k_{out}

- Population parameters estimated using Monolix 4.3.2

Markov Model

- Three-states Markov Model including a Dropout Model:

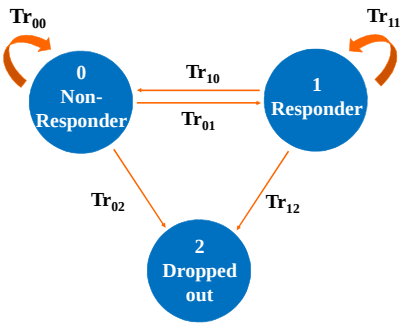

Figure 1: Markov Model showing the transition rates between the three possible states of NR, R and D

- States defined by BW change from baseline (1kg threshold for placebo)
- Transition rates between states modeled using MLXTRAN library models implemented in Monolix[4]
- At each time point, the rate of transition is influenced by the previous state
- BW effect (predicted using PopPD model) added on the transition rates:

$$E_{BW_i,10}(t) = slope_{10} \times BW_i(t)$$

- Estimation of Tr_{xx} performed using Monolix 4.3.2
- Simulation of clinical trials were performed using Monolix 4.3.2

- Data analyzed following a sequential methodology:
  1. Development of PopPD model
  2. Development of Markov model
  3. Simulation of 1000 clinical trials using the Markov Model
  4. Estimation of a longitudinal BW effect on Markov transition rates

Results

1. Population PD Model

- Model described the data adequately for all NB studies:

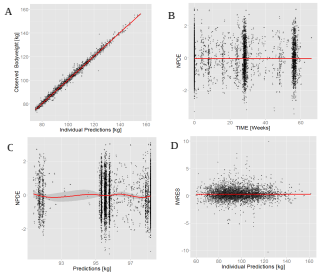

Figure 2: GOF plots for final PopPD Model: Observed BW *vs* individual predictions (A); Normalized prediction distribution errors (NPDE) *vs* Time (B) and *vs* population predictions (C); Absolute Individual Weighted Residuals (IWRES) *vs* Individual predictions (D)

Parameters	Estimate		RSE (%)
	Population Parameters		
k_{out} (week^{-1})	0.0207		6
k_{rel} (week^{-1})	0.0315		8
k_{de} (week^{-1})	0.441		25
$DSTIM$ (%) Study 1-2	1.43		113
$DSTIM$ (%) Study 3	8.71		21
$DSTIM$ (%) Study 4	24		11
$DSTIM$ (%) Study 5	9.71		19
$Baseline\ BW$ (kg)	98.2		0
k_{pro} (kg/year)	0.7		(FIXED)
	Between Subject Variability		
$IIV_{k_{out}}$ (%)	Additive	1.73	7
$IIV_{k_{pro}}$ (%)	Additive	21.6	3
IIV_{DSTIM} (%)	Additive	14.7	3
$IIV_{baseline}$ (%)	Exponential	14.7	2
	Residual Unexplained Variability		
Additive part (%)	1.21		2

Table 1: Final Parameter Estimates for NB studies

Compared to literature values[2]:

- Slight change in parameter value (k_{out})
- Higher LSI effect for study 3, 4 and 5

	Fixed effects (RSE)	Random effects (%) (RSE)
Tr_{10} (Responder to Non-responder)	0.908 (1)	8.75 (10)
Tr_{01} (Non-responder to Responder)	1.11 (2)	7.85 (11)
Tr_{12} (Responder to dropout)	0.0717 (1)	10.13 (12)
Tr_{02} (Non-responder to dropout)	0.0802 (2)	12.24 (11)

Table 2: Estimated transition rates for Markov Model

2. Markov Model

- Markov Model allowed to describe the transition rates between states with adequate precision
- Higher transition rate to dropout when the subject is Non-Responder than Responder

3. Simulations of Clinical Trials using the Markov Model

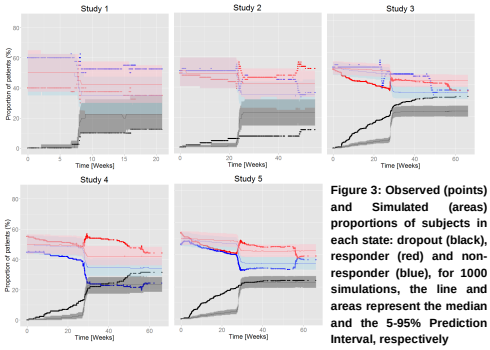

Figure 3: Observed (points) and Simulated (areas) proportions of subjects in each state: dropout (black), responder (red) and non-responder (blue), for 1000 simulations, the line and areas represent the median and the 5-95% Prediction Interval, respectively

- Estimated transition rates allowed for clinical trial simulations with similar responder and non-responder proportions compared to observed data
- However, observed dropout proportions were outside the simulated dropout prediction intervals in some studies as a result of the sparse dropout data in this analysis given that placebo data were used only

4. Estimation of BW effect

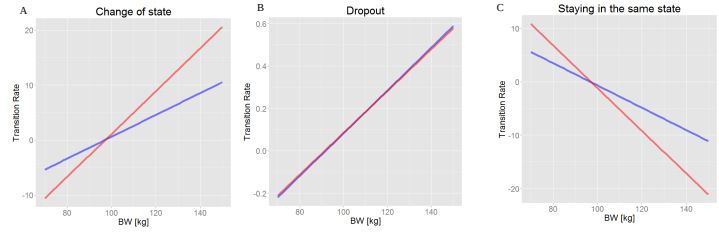

Figure 4: BW effect on transition rates to change state (A), to dropout (B), or to stay in the same state (C), from the responder state (red line) or from the non-responder state (blue line)

- Significant effect of BW on transition rates
- Increase in BW influences the transition rates
  - Increase in rate: Change of state and Dropout
  - Decrease in rate: Staying in the same state

Conclusion

Population PD Model

- PopPD Model describes the BW time-course of each subject included in the naltrexone-bupropion clinical trials adequately well

Markov Model

- Markov Model describes adequately well the transition rates between Responder, Non-Responder and Dropout states
- Predicted BW from the PopPD Model was found to be an important covariate on the Markov Model probabilities
- Models will be used as a simulation tool for clinical studies to inform go/no-go decisions in drug development

Further developments

- Evaluate other relationships between BW and transition rates, such as E_{max} models
- Extend the analysis to other diseases such as Type 2 *Diabetes Mellitus*
- Include treatment effect on BW time courses and transition probabilities

REFERENCES

1. Guidance for industry: Developing products for weight management Revision 1, Draft Guidance, Food and Drug Admnistration, February 2007.
2. Van Wart S, Tsai M, Chan J, Cirincione BB, *American Conference on Pharmacometrics (*2011).
3. Lacroix BD, Lovern MR, Stockis A, Sargentini-Maier ML, Karlsson MO, Friberg LE. *Clin Pharmacol Ther* (2009).
4. Monolix 4.3 MLXTRAN user guides, Lixoft, Orsay

Presented during the Population Approach Group Europe (PAGE) annual meeting, Hersonissos, Crete, Greece, June 2-5, 2015.

ACKNOWLEDGMENTS

This study was supported by Takeda Pharmaceuticals Research Division, Pharmacometrics, Deerfield, IL, USA

CLINICAL TRIAL REG. NO. NCT00364871, NCT00532779, NCT00567255, NCT00456521