Population PK/PD Modeling of Efficacy and Safety of CB1R Inverse Agonist Taranabant in Obese Patients

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MERCK

Introduction and Objectives

- Taranabant is a cannabinoid-1 receptor (CB1R) inverse agonist, that was being developed by Merck and Co., Inc. as a potential treatment of obesity[1].
- Endocannabinoids have been implicated in the regulation of appetite and food intake. Exogenous cannabinoids, such as tetrahydrocannabinol, are agonists of brain cannabinoid-1 receptors (CB1R) and are associated with increases in food intake[2].
- Taranabant has exhibited dose-dependent increases in both weight-loss and adverse experiences (AE) in clinical studies.
- The objective of the present work was to develop exposure-response models for both efficacy and safety (16 pre-specified AEs) to better characterize the therapeutic window of taranabant in overweight or obese patients.

Patients

- Population PK/PD modeling was conducted by pooling data from four Phase II/III clinical studies in which 0.5-6 mg taranabant or placebo was administered once daily for up to 2 years in 3985 obese patients.
- Up to 6 predose trough PK samples were collected in each patient. In addition, one 2 hour postdose sample was obtained in 385 patients from one Phase IIa study.
- The body weight of obese patients were recorded at least monthly for up to 52 weeks.

Table 1: Baseline Median Demographic Characteristics

	Taranabant Patients	Placebo Patients	All Patients
N	3140	838	3978
Baseline Weight (kg)	99.3	99.2	99.3
Baseline BMI (kg/m^2)	35.0	34.9	35.0
Age (year)	48.7	47.6	48.6
Gender (n (%))			
Male	1044 (26.2%)	285 (7.2%)	1329 (33.4%)
Female	2096 (52.7%)	553 (13.9%)	2649 (66.6%)
Race (n (%))			
White	2601 (65.4%)	689 (17.3%)	3290 (82.7%)
Black	209 (5.3%)	59 (1.5%)	268 (6.7%)
Asian	90 (2.3%)	25 (0.6%)	115 (2.9%)
Hispanic	177 (4.5%)	50 (1.3%)	227 (5.7%)
Others	63 (1.6%)	15 (0.4%)	78 (2.0%)

Methods

- Based on a previously developed population PK model[3], individual C_{24hr} values were predicted based on sparse PK samples, and used as the PK measure for PK/PD analysis.
- Change in body weight over time was described by an indirect response model implemented in NONMEM VI. Covariates were evaluated using standard forward selection (α=0.05) and backward elimination (α=0.001) procedures.
- Covariates evaluated for the efficacy (weight loss) model were: baseline body weight (BWT), run-in weight loss (RIWL), age, gender, race, baseline BMI, baseline metabolic syndrome status, and compliance.
- Incidences of thirteen pre-specified AE categories were related to taranabant trough concentrations using logistic regression models. Each AE category was treated as a binary variable (occurrence or lack of occurrence). All safety analyses were performed using SAS version 9.1.

Conclusions

- Taranabant has a narrow therapeutic window across the dose range tested in the taranabant obesity clinical development program. The gain in efficacy at higher doses (or higher concentrations at a given dose) is coupled with an increased risk for adverse experiences over the 0.5-2.0 mg dose range. Taranabant was discontinued for further development for obesity.

References

1. Addy C, Li S, Agrawal N, Stone J, et al. *J Clin Pharmacol* 2008;48(4):418-427.
2. Addy C, et al. The acyclic CB1R inverse agonist taranabant mediates weight loss by increasing energy expenditure and decreasing caloric intake. *Cell Metab* 2008; 7(1): 68-78.
3. Nielsen J., et al. Development of a population pharmacokinetics model for taranabant. ACCP annual meeting, 2008.

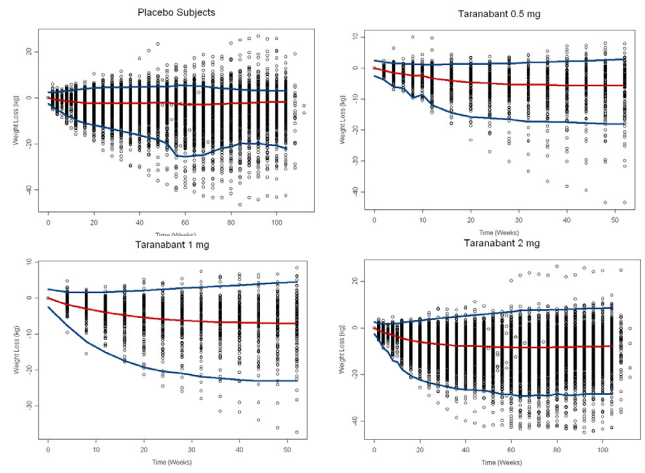
Results: Longitudinal PK/ Weight Loss Model

$$\frac{d(BW)}{dt} = Kin * (1 - \frac{\mathrm{Im}ax * C_{24hr}}{IC_{50} + C_{24hr}} - Plc * \exp(-Kplc * time)) - Kout * BW$$

Kin: body weight formation rate constant, kg/week
Imax: maximal inhibitory effect of taranabant, range 0-1
C_{24hr}: Steady-state taranabant trough concentration, nM
IC_{50}: taranabant concentration achieving half of maximal inhibitory effect, nM
Plc: Placebo effect magnitude, range 0-1
Kplc: Placebo effect declining rate constant, 1/week
Kout: Body weight elimination rate constant, 1/week

- Indirect response; Emax-type model for drug effect
- Inter-subject variability was estimated on Imax, *Plc*, *Kplc* and *Kout*.
- RIWL was the most significant covariate affecting *Imax* and *Kout*; compliance was also a significant covariate affecting *Imax*

Visual Predictive Check



Circles: observations; Lines: median (red), 5th and 95th (blue) of of simulations;

Table 2: Parameter Estimate from the Final Weight Model

Parameter Estimate		Inter - Individual Variability	
Kout (1/week)	0.0418	73.55% CV	Exponential
Plc$	0.0604 FIX	147.98% CV	Proportional
Kplc$ (1/week)	0.0233 FIX	0.029 SD	Additive
Imax	0.112	135.65 CV	Proportional
IC50 (nM)	1.96	0 FIX	
Covariate Effect			
Slope of RIWL on Imax @ (/kg)		- 0.143	
Slope of RIWL on Kout @ (/kg)		- 0.101	
Slope of Comp on Imax		0.00319	
Residual Error			
Additive residual error (kg)		1.53 SD	

$ The inter-individual variability in Plc and Kplc were only estimated for placebo subjects and fixed to 0 for taranabant subjects.

@ The value of RIWL was reported as negative, thus negative slope indicating larger absolute RIWL, larger Imax and Kout which is consistent with clinical observation.

Results: PK/AE Model

The probability (p) of an AE was related to taranabant trough concentration through one of the following three types of base structural models:

Linear logistic model: $\log it(p) = \log \frac{p}{1-p} = b_0 + b_1 C_{24h}$

E_{max} logistic model: $\log it(p) = \log \frac{p}{1-p} = E_0 + \frac{E_{max} C_{24h}}{EC_{50} + C_{24h}}$

Biphasic logistic model:

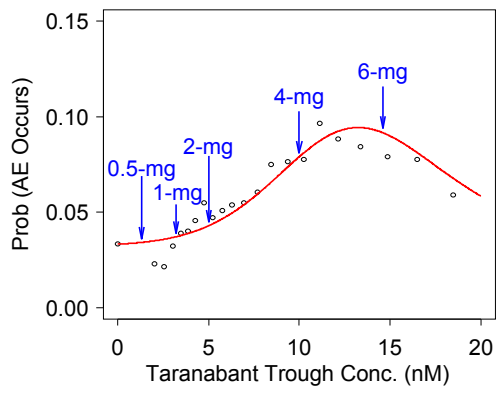
$$p = p_0 + p_e - p_i$$

$$\log it(p_e) = \log \frac{p_e}{1-p_e} = b_0 + b_1 C_{24h}$$

$$\log it(p_i) = \log \frac{p_i}{1-p_i} = b_0 + t * b_1 * C_{24h}$$

- p_0 is the probability of an AE without administration of taranabant; p_e and p_i represent excitatory and inhibitory probability, respectively.
- Emax-type or biphasic logistic models were used to capture the phenomenon that incidences of certain psychiatric AEs appear to reach plateau, or initially increase, reach a maximum, then decrease with taranabant concentration over the studied dose range.
- These three types of models were fit to the data for each of the AE categories and Akaike's Information Criterion (AIC) was used for model selection.

Anxiety grouping



Legend:

- Moving average of observed AE rate
- Model fit
- Median C_{24hr} value at each dose

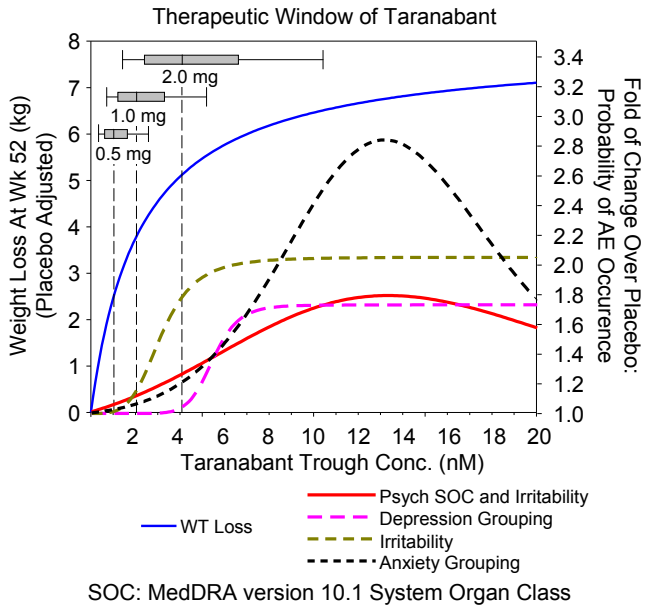
Observed Data:

Group patients into 20 bins based on taranabant trough concentration with ~ 250 patients per bin; then observed AE rate was calculated for each bin

Model:

†: Biphasic logistic model for anxiety grouping:
p_0 = 0.03; b_{0v}= -3.62; b_1 = 0.32; t = 0.94

Therapeutic Window of Taranabant



SOC: MedDRA version 10.1 System Organ Class

- The predicted PK/weight loss at Week 52 and probability for 4 prespecified AEs were overlaid in the same figure to visualize the therapeutic window for taranabant.
- The trough concentration distributions (10th, 25th, median, 75th, and 90th percentile) for each dose are displayed using horizontal box-plots.
- The predicted probability of irritability increases more sharply along with weight loss while the other three safety signals rise more slowly at first with increased concentration.
- Overall, both efficacy and risk for AE increase over the trough concentration ranges obtained with doses of 0.5 mg to 2.0 mg. That is, the gain in efficacy at a higher dose (or higher concentration within a dose) is coupled with increased risk for adverse experiences over 0.5-2.0 mg dose range.