USE OF A CLINICAL RESPONSE INDEX DERIVED FROM A PK/PD MODEL TO ESTIMATE THE OPTIMAL IN VIVO RELEASE RATE OF EXTENDED RELEASE FORMULATIONS OF MPH

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Background

Methylphenidate is a central nervous system stimulant used to treat children over 6 years old, adolescents, and adults with attention-deficit hyperactivity disorder (ADHD). Methylphenidate immediate release formulations should be given one to three times a day to provide symptom coverage throughout the day. Several extended-release formulations usually characterized by a dual release process have been developed for improving efficacy.

Objective

The aim of this work was to determine the *in-vivo* release properties of a MPH formulation associated with an optimal clinical response defined by the SKAMP total scores over 12 or 24 hours post-dose period.

Methods

The MPH PK data and SKAMP scores were extracted from the literature following administration of Concerta ® (16mg, 36mg, and 54mg) and used for model development [1].

An integrated PK/PD model accounting for multi-phase *in-vivo* release of MPH, placebo response and acute tolerance was developed by generalizing an initially proposed model [1].

A clinical response index was defined by the area under the change from baseline of the SKAMP scores between 0-12 hours or 0-24 hours post-dose. A surface-response analysis was used to connect the *in-vivo* release rate with the clinical response index. A non-linear optimizer was applied to estimate the *in-vivo* release rate parameters that maximize the clinical response index.

PKModel

The multi-phase release profile of MPH products in-vivo and in-vitro were modeled using a double Weibull function r(t):

$$r(t) = ff \cdot e^{-\left(\left(\frac{time}{td}\right)^{ss}\right)} + (1-ff) \cdot e^{-\left(\left(\frac{time}{td1}\right)^{ss1}\right)}$$

$$f(t) = \frac{dr}{dt}$$

$$\frac{dA1}{dt} = -A1 * f(t)$$

$$\frac{dA2}{dt} = A1 * f(t) - Kel \cdot A2$$

$$\mathbf{Cp} = A2/V$$

ff = fraction of the dose released in the 1st process
td = time to absorb 63.2% of the dose released in the 1st process
td1= time to absorb 63.2% of the dose released in the 2nd process
ss= sigmoidicy factor for the 1st process
ss1= sigmoidicity factor for the 2nd process

PK/PD Model

$$\boldsymbol{SKAMP(t) = R(t) + Delta - \frac{Emax \cdot C_p}{EC_{50}(t) + C_p}}$$

R(t) is the placebo response defined by:

$$\frac{dR}{dt} = k_{in} \cdot \left(1 + p(t)\right) - k_{out} R$$

$$p(t) = AA \cdot (e^{-t \cdot P1} - e^{-t \cdot P2})$$

$$p(t) = 0 \; for \; t = 0$$

$$0 \; for \; t \to \infty$$

$$R(t=0) = Bas = \frac{K_{in}}{K_{out}}$$

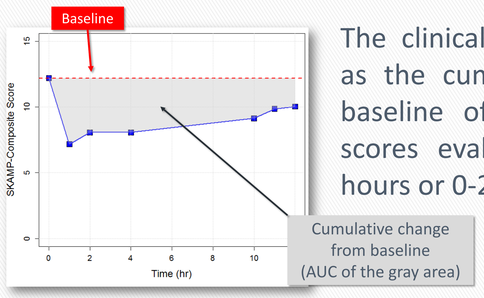
EC50(t) is the time varying EC50 defined by:

$$EC_{50}(t) = EC_{50b}\left(1 + \frac{t^{ga}}{t50^{ga} + t^{ga}}\right)$$

Delta is the score difference at baseline depending on the treatment between assessment days

Emax is the maximal MPH related effect

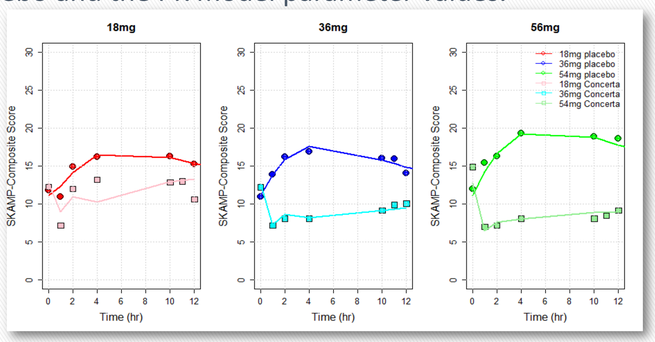
Clinical Benefit



The clinical Benefit was defined as the cumulative change from baseline of the SKAMP clinical scores evaluated between 0-12 hours or 0-24 hours post-dose.

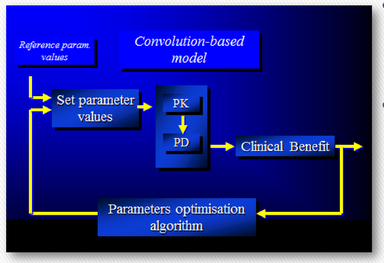
PK/PD Modeling results

The modeling approach was based on a sequential strategy. First, the PK data and the placebo data were independently analyzed then the SKAMP scores were modeled by fixing the placebo and the PK model parameter values.



Concerta® PK/PD modeling results: Observed (dots) and model predicted (solid line) SKAMP scores in the placebo and in the treated arms by dose

Optimize the *in-vivo* MPH release



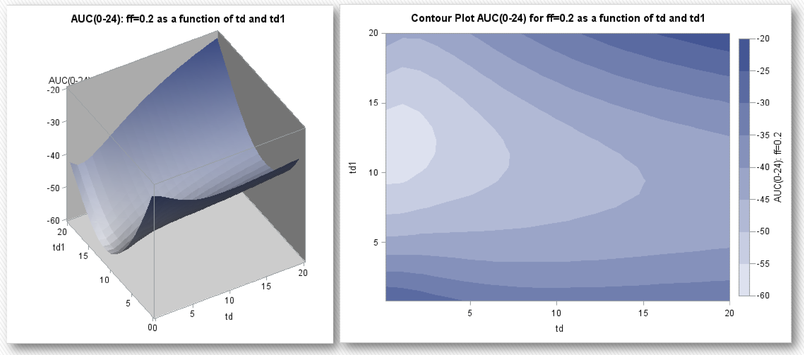
- The optimal values of the target parameters (td, ss, ss1, td1, and ff) are the ones that maximize the Clinical Benefit
- The estimate of these parameter values is a classical optimization problem that is solved using the derivative-free non-linear optimization algorithm implemented in the R library NLOPTR

The optimization is conducted using an iterative approach: at each iteration the Clinical Benefit is computed given the values for the target parameters selected by the optimization algorithm. At the end of the iterative process the values of the parameters associated with the largest Clinical Benefit are retained as the optimal parameter values.

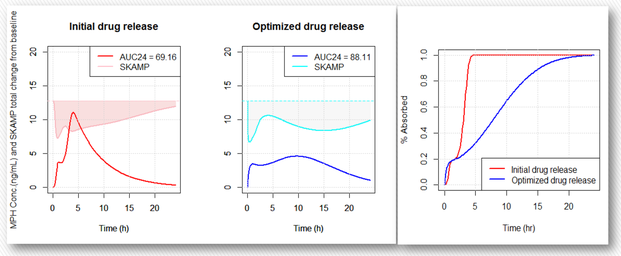
Results of the optimization

The optimized in-vivo release parameter values a shorter time for delivering the first fraction of the dose (td) and a prolonged time for delivering the second fraction of the dose (td1). The fraction of the dose released in the first and in second release step (ff and 1-ff) remains the same in the initial and in the optimal scenario. Finally the rate of release (ss and ss1) was lower in the optimized scenario with respect to the initial scenario.

	td	ss	ss1	td1	ff
Intial	0.76	3.18	6.33	3.40	0.19
Optimized	0.31	1.00	2.15	10.84	0.18



Surface response – Clinical benefit as a function of td and td1. AUC(0-24) for a fixed value of ff, ss and ss1



Initial and optimized PK and SKAMP profiles with the comparison of the n-vivo release rate of the initial and optimized MPH formulations

Conclusions: The proposed modeling approach provides a quantitative criteria for predicting the clinical performances of extended-release formulations of MPH, and for comparing the expected clinical benefit of alternative MPH products.

References: 1.*Kimko et al. J Pharmacokinet Pharmacodyn (2012) 39:161–176*