OPTIMAL STUDY DESIGN TO EVALUATE THE CLINICAL RESPONSE OF EXTENDED RELEASE FORMULATIONS OF METHYLPHENIDATE (MPH) IN A PEDIATRIC POPULATION

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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 disorders (ADHD).

Objective

The aim of this work was to determine the optimal trial design for characterizing the PK profile and the clinical response (SKAMP scores) using extended-release formulations of MPH.

Methods

- Use the MPH PK model previously developed associated with Concerta® at the dose of 54 mg.
- Use the PK/PD model previously developed and accounting for multi-phase MPH release, placebo response and acute tolerance as prior information for determining the optimal design in a pediatric study.
- Determine the minimal number of PK samples and the minimal number of clinical measurements (SKAMP scores) appropriate for characterizing the response by limiting the observational time to 12 hours post-dose in a clinical trial including up to 20 subjects.
- Estimate the sample size appropriate for estimating the model parameters with a good precision estimated by the Relative Standard Error of the estimated parameters (RSE≤20%)

The design features were estimated using the PopED software [1]

The PK model

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

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

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

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

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

$$Cp = A2/V$$

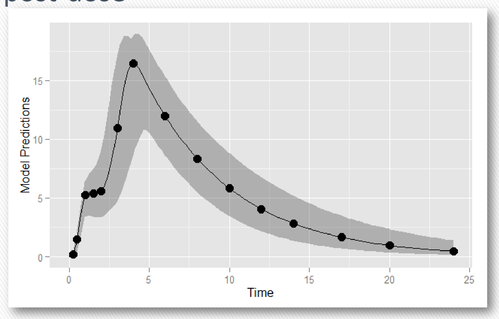
ff = fraction of the dose released in the 1st process
td = time to absorb 63.2% of the dose released in the 1st process
td1= time to absorb 63.2% of the dose released in the 2nd process
ss= sigmoidicy factor for the 1st process
ss1= sigmoidicity factor for the 2nd process

Optimizing the PK sampling times

Parameters	Values	RSE
Kel (hr-1)	0.18	1.70%
V (L)	1520	4.00%
ss	3.18	2.90%
ss1	6.33	1.50%
td (hr)	0.759	5.60%
td1 (hr)	3.4	2.80%
ff (%)	0.189	5.00%

Estimated PK parameter values for Concerta ®

The reference study design [2] was based on 20 subjects with 15 PK sampling times to characterize the Concerta® at 0.25, 0.5, 1, 1.5 , 2, 3, 4, 6, 8, 10, 12, 14, 17, 20, 24 hours post-dose

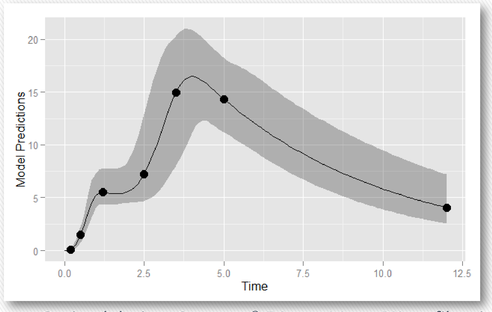


*Precision of the parameter estimates in the optimal design with **15** samples*

Parameters	RSE
Kel (hr-1)	3.97%
V (L)	4.74%
ss	4.31%
ss1	15.78%
td (hr)	4.40%
td1 (hr)	4.39%
ff (%)	7.22%

Reference design. Concerta® 54 mg: Mean PK profile with the 90% prediction interval. The dots represent the PK samples used.

The optimized design was based on 20 subjects with 7 sampling times collected at 0.2, 0.5, 1.2, 2.5, 3.5, 5 , 12 hours post-dose



*Precision of the parameter estimates in the optimal design with **7** samples*

Parameters	RSE
Kel (hr-1)	6.11%
V (L)	5.96%
ss	4.12%
ss1	10.97%
td (hr)	4.71%
td1 (hr)	4.42%
ff (%)	7.92%

Optimal design. Concerta® 54 mg: Mean PK profile with the 90% prediction interval. The dots represent the PK samples used.

The PK/PD model

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

R(t) is the placebo response defined by:

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

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

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

Optimize the SKAMP scores measurements

Estimated parameters of the PK/PD model

Placebo

Parameters	Values	RSE
Bas	11.1	1.70%
Kout	0.168	1.70%
P1	0.211	9.20%
P2	6.47	173.10%
AA	2.12	3.00%

SKAMP scores: estimated parameter values for placebo response

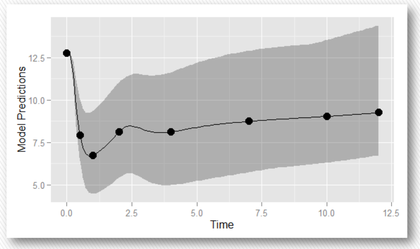
MPH

Parameters	Values	RSE
Emax	0.643	1.70%
EC50	0.725	32.60%
t50	2.05	33.80%
ga	8.59	20.40%
Delta	1.64	38.50%

SKAMP scores: estimated parameter values for the Concerta® 54 mg response

For the purpose of the present evaluation, the SKAMP scores resulting from the Concerta® 54 mg were considered only function of the Emax and EC_{50} (maximal model-predicted concentration of the time-varying EC_{50} value).

The reference study design was based on 20 subjects with 8 sampling times to characterize the SKAMP scores at 0, 0.5, 1, 2, 4, 7, 10, and 12 hours post-dose

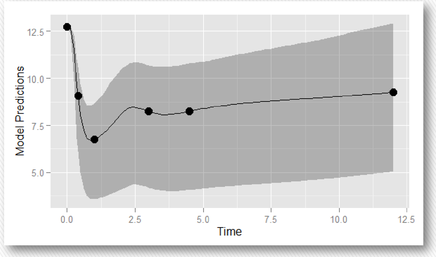


*SKAMP scores: precision of the parameter estimates in the reference design with **8** samples*

Parameters	RSE
Emax	4.71%
EC50	20.94%

Reference design. SKAMP scores expected for Concerta® 54 mg: Mean SKAMP profile with the 90% prediction interval. The dots represent the SKAMP samples.

The optimized design was based on 20 subjects with 6 sampling times collected at 0, 0.4, 1, 3 , 4.5, and 12 hours post-dose



*SKAMP scores: precision of the parameter estimates in the optimal design with **6** samples*

Parameters	RSE
Emax	4.55%
EC50	19.79%

Optimal design. SKAMP scores expected for Concerta® 54 mg: Mean SKAMP profile with the 90% prediction interval. The dots represent the SKAMP samples.

Conclusions: The optimal design approach provides a quantitative criteria for implementing clinical trials in a pediatric population by minimizing the number of samples required to properly characterize either the complex PK profiles of the extended release formulations of MPH or the clinical response evaluated by the SKAMP clinical scores.

References:

1. *Nyberg et al. Comput Methods Programs Biomed. 2012 Nov;108(2):789-805*
2. *Modi et al. J Clin Pharmacol. 2000 Apr;40(4):379-88*