Background

• Methylphenidate (MPH) is a drug with a short duration of effect used in the treatment of ADHD in children, adolescents, and adults

• Extended-release (ER) products with different release profiles over the dose interval have been developed to eliminate the need for dosing during the school or working day

• Concerta® is controlled-release formulation
Objective

Extrapolation size, maturation
PK Adults MPH
PK Pediatrics MPH
PKPD Link
PK Pediatrics MPH
PK Adults Drug x
PK ?? Pediatric Drug X
PD ?? Pediatric Drug X
Comparison
Clinical Measures of ADHD

• SKAMP-Composite
  – A composite score from the Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale
  – SKAMP-deportment & SKAMP-attention components
  – A validated classroom assessment tool used to evaluate the behavioral symptoms of ADHD in children in repeated fashion over a specified period of time
  – Smaller SKAMP-Composite scores indicate behavioral improvement

• PERMP
  – PERManent Product measures
  – PERMP-Attempted: quantifies the rate of behavior within a defined period of time (accurate measure of productivity)
  – PERMP-Correct: measures the ability to learn how to do math problems (not a precise measure)
A Daily Schedule
During Laboratory Classroom Day

- A good well-controlled study setting
- 7 scores per study day
- Measurements at the same clock times per study day
  - Every 1.5 hours from 7:30 am
  - Sampling time error interval ± 15 minutes

<table>
<thead>
<tr>
<th>Study Hour*</th>
<th>Preparation</th>
<th>−0.75</th>
<th>0 (Dose)</th>
<th>1.5</th>
<th>3.0</th>
<th>4.5</th>
<th>6.0</th>
<th>7.5</th>
<th>9</th>
<th>12</th>
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<tbody>
<tr>
<td>Time</td>
<td>[6:45 AM]</td>
<td>[7:30 AM]</td>
<td>[9:00 AM]</td>
<td>[10:30 AM]</td>
<td>[12:00 PM]</td>
<td>[1:30 PM]</td>
<td>[3:00 PM]</td>
<td>[4:30 PM]</td>
<td>[7:30 PM]</td>
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</tr>
<tr>
<td>Vital sign†</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>SKAMP deportment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>SKAMP attention</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Complete Barkley Scale (parent/guardian)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Assess AEs</td>
<td>X</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Swanson *et al.* Pediatrics, 113:e206, 2004
Challenges in Model Building

• Combination of summary data from literature and individual data from J&J studies
  – Model-based meta-analysis

• Lack of trials with simultaneous PK and PD data collection
  – PK from adult
  – PD from pediatrics

• Lack of a disease progress model
  – To separate true drug effect from observed combined placebo & drug effects

• Various study designs
  – Titration to a desired effect in each subject, and administration of the individual optimal dose during the assessment days in some studies
  – Different treatments between assessment days
Individualized Dose I
An ADHD Study Design: Laboratory School (Study ABC)

Screening/Washout Phase (up to 28 days)

Open-Label Dose Adjustment Period (1 to 6 weeks)

Visit 1 (up to Day -28)
Visit 2 (Day -1)
Visit 3 (Day 3 to 7)
Visit 4 (Days 10 to 14)
Visit 5 (up to Day 42)
Lab School Practice

Dose increases until an optimal dose is achieved

Double-Blind Assessment Period (up to 6 weeks)

Lab Assessment Day 1
Lab Assessment Day 2
Final Visit

2 period cross-over placebo vs. optimal dose Concerta®
7 days between Day 1 and Day 2

Low dose: 16 subjects
Med. dose: 46 subjects
High dose: 77 subjects
Individualized Dose II
An ADHD Study Design: Laboratory School (COMACS Study)

- Subjects assigned to the dose closest to their previous dose & remained at the level for the study duration
- 3-way cross-over: placebo, Concerta®, Metadate CD®
- 7 days in each treatment: assessment on the 7th days
- No wash-out period
- 184 subjects

Swanson et al. Pediatrics, 113:e206, 2004
Baseline is Different Depending on Treatment History

COMACS: delta needed (7th day assessment)

ABC: delta not needed (optimal MPH given between study visits)
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Design</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-MPH 20 mg/ Placebo</td>
<td>Patients were stabilized on Concerta 36-54 or d-MPH (^a) 20-30. Then, 7 days of 20 mg d-MPH or placebo with assessment on the last of seven days. 2 period cross-over</td>
<td>SKAMP-Composite; PERMP-attempted and PERMP-correct \textbf{change from baseline} at 0, 0.5, 1, 2, 4, 6, 8 hrs</td>
</tr>
<tr>
<td>Concerta 36 mg/ Concerta 54 mg/ d-MPH 20 mg/ d-MPH 30 mg/ Placebo</td>
<td>Patients were stabilized on Concerta 36-54 or d-MPH (^a) 20-30 mg/day. Then, 5 treatment period cross-over with assessments on day 7 of each period.</td>
<td>SKAMP-Composite, PERMP-attempted and PERMP-correct \textbf{change from baseline} at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 11, 12 hrs</td>
</tr>
<tr>
<td>Ritalin LA 20 mg/ Concerta 18 mg/ Concerta 36 mg/ Placebo</td>
<td>Patients were stabilized on 10 mg BID MPH and remained on this medication during the study except for 4 assessment days when they were administered randomized treatments. There was a washout day without medication before each assessment. 4 period cross-over.</td>
<td>SKAMP–Composite, PERMP–attempted, and PERMP–correct \textbf{change from baseline} at 0, 0.5, 1, 2, 3, 4, 6, 8 hrs can be derived from the presented data</td>
</tr>
<tr>
<td>d-MPH 20 mg/ d-MPH 30 mg/ Concerta 36 mg/ Concerta 54 mg/ Placebo</td>
<td>Patients were stabilized on Concerta 36-54 or d-MPH (^a) 20-30 mg/day. Then, 5 treatments 7 days each, assessments on day 7 of each treatment. 4 period cross-over</td>
<td>SKAMP–Composite, PERMP–attempted, and PERMP–correct \textbf{change from baseline} at 0, 0.5, 1, 2, 3, 5, 7, 9, 10, 11, 12 hrs</td>
</tr>
<tr>
<td>d-MPH 20 mg/ Placebo</td>
<td>Patients were stabilized on MPH 20–40 mg/day. Then, 5 days of randomized treatment, then 1 day washout, then assigned treatment and assessments. 2 period cross-over</td>
<td>SKAMP–Composite, PERMP–attempted, and PERMP–correct \textbf{change from baseline} at 0, 1, 2, 4, 6, 8, 9, 10, 11, 12 hrs can be derived from the presented data</td>
</tr>
</tbody>
</table>
PK & PD Data Used

- Four different PK profile formulations
  - Concerta®, Metadate CD®, Focalin XR®(d-MPH), Ritalin LA®
- Nine PD study
  - 8 studies for model building
  - 1 study for external evaluation

<table>
<thead>
<tr>
<th>ID</th>
<th>PD type</th>
<th>Source of Data</th>
<th>Available Treatments / Dose Levels</th>
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<tr>
<td></td>
<td></td>
<td>PK</td>
<td>PD</td>
</tr>
<tr>
<td>1</td>
<td>raw score</td>
<td>PK1, PK6</td>
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<tr>
<td>4</td>
<td>change from baseline</td>
<td>PK4</td>
<td>PD4</td>
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<tr>
<td>5</td>
<td>change from baseline</td>
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<tr>
<td>11</td>
<td>raw score</td>
<td>PK6</td>
<td>ABC</td>
</tr>
</tbody>
</table>
No PK Model Building

- The PK model of each formulation was not built
- The published mean PK data were used as a driver in the PD model

Swanson, Pediatrics 2004

Focalin XR®

Ritalin LA®

Lopez, Pediatric Drugs 2003

Fig. 1. Ritalin® LA™ 20mg versus Concerta® 18mg concentration versus time profile (reproduced from Markowitz et al.,[11] with permission).
Some of the SKAMP Data Used

Silva Psych Bull, 2008

Lopez, Pediatric Drugs 2003

Swanson, Pediatrics 2004

Note placebo effect / disease progression!
Disease Progress (Placebo) Model

- Disease progress was described from the placebo data
- Inversed indirect response model with time varying coefficient

\[ \frac{dB}{dt} = k_{in} - \alpha(t) \cdot k_{out} \cdot B \]

at S.S, \( B_0 = \frac{k_{in}}{k_{out}} \)

\[ \frac{d\left(\frac{B}{B_0}\right)}{dt} = k_{out} - \alpha(t) \cdot k_{out} \cdot \frac{B}{B_0} \]

\[ \frac{dA}{dt} = k_{out} \cdot \{1 - \alpha(t) \cdot A\} \quad 0 < A \leq 1 \]

\[ \text{placebo score} = \text{constant} - B_0 \cdot A \]

Empirically, constant \( \rightarrow B_0 \)

\[ \text{placebo score} = B_0 \cdot (1 - A) \]
PK-PD Model

\[ \text{Effect} = \text{delta} + \frac{E_{\text{max}} \cdot C}{EC_{50} + C} \]

\[ EC_{50} = EC_{50,\text{start}} \cdot \left(1 + \frac{E_{c} \cdot \text{time}^\gamma}{T_{50}^\gamma + \text{time}^\gamma} \right) \]

- A simple Emax-type model
- \text{delta}: The score difference at baseline depending on the treatment between assessment days
- Tolerance on EC50:
  - as time passes, higher EC50 \( \rightarrow \) more drug is needed to achieve the same effect

\[ \text{Score}(t) = \text{Placebo}(t) - \text{Effect}(t) \]

\[ Y = \text{Score}(t) + \frac{1}{\sqrt{n_{ik}}} \varepsilon_{ik} \quad \text{or} \quad Y = \text{Score}(t) - \text{Score}_{\text{Baseline}} + \frac{\sqrt{2}}{\sqrt{n_{ik}}} \varepsilon_{ik} \]

- Available PD data: raw scores or change from the baseline
Weighting in Meta-Analysis

Individual score \( \blacklozenge \rightarrow Y_{ij}(t) = \text{score}(t) + \eta_i^{\text{study}} + \eta_{ij}^{\text{subject}} + \varepsilon_{ij}(t) \)

Each arm has a different number of subjects: \( n_{ik} \)

Mean score in an arm \( \bigcirc \rightarrow \bar{Y}_{ik}(t) = \frac{1}{n_{ik}} \sum_{\text{arm}_{ik}} Y_{ij}(t) \)

\( \approx \text{score}(t) + \eta_i^{\text{study}} + \frac{1}{\sqrt{n_{ik}}} \eta_{ik}^{\text{arm}} + \frac{1}{\sqrt{n_{ik}}} \delta_{ik} \)

\( n_{ik}^{\text{arm}} = \frac{1}{\sqrt{n_{ik}}} \sum_{(\omega)} \eta_{ij}^{\text{patient}} \) and \( \delta_{ik}(t) = \frac{1}{\sqrt{n_{ik}}} \sum_{(\omega)} \varepsilon_{ij}(t) \)

\( \eta_{ik}^{\text{arm}} \sim N(0, \omega_i^2) \quad \delta_{ik}(t) \sim N(0, \sigma^2) \)

Ahn & French, JPKPD 2010, 37:179-201
Monte Carlo simulations generated 1000 datasets with the same doses and sampling times of the original dataset

Symbol: Observed mean
Red: median
Blue: 90% interval of simulated scores
External Evaluation

B₀ missing

This study was not included in the model building

Placebo

Ascending

TID

TID-AM

TID-PM

Red: median

Blue: 90% prediction interval

Symbol: observed mean

SKAMP-Composite
Closing Remarks

• The DP-PK-PD model allowed prediction of response in pediatrics with various PK profiles from adults

• Model-based meta-analysis is a useful tool to do “competitive landscaping” of compounds of interest
  – Go/no-Go decision
  – Decision of a study design (power calculation with n, study period, doses, etc.)
Data Sources

PK

• PK1: Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology April 13, 2010, BRIEFING INFORMATION Page 32

• PK2: Ritalin® LA label (file 21-284_Ritalin LA_prntlbl.pdf)


PD

• PD1: Study ABC, J&J


