Can application of quantitative clinical pharmacology improve early clinical development success in neurodegenerative diseases?

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Early Clinical Development Clinical Pharmacology,
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Model-based Drug Development

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Model-Based Drug Development: A Rational Approach to Efficiently Accelerate Drug Development


Understanding Placebo Responses in Alzheimer’s Disease Clinical Trials from the Literature Meta-Data and CAMD Database

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Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

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This document was developed to enable greater consistency in the practice, application, and documentation of Model-Informed Drug Discovery and Development (MIDD) across the pharmaceutical industry. A collection of “good practice” recommendations are assembled here in order to minimize the heterogeneity in both the quality and content of MIDD implementation and documentation. The three major objectives of this white paper are to: i) inform company decision makers how the strategic integration of MIDD can benefit R&D efficiency; ii) provide MIDD analysts with sufficient material to enhance the planning, rigor, and consistency of the application of MIDD; and iii) provide regulatory authorities with substrate to develop MIDD related and/or MIDD enabled guidelines.
Can application of quantitative clinical pharmacology improve early clinical development success in neurodegenerative diseases?

Depends on the meaning of the word “success”
What is early clinical development success?

- Better Dose Selection?
- Better Designs?
- Better Decisions?
- More Efficient Development?
- Higher Proportion of Positive PoC?
• **Proof of Mechanism**: Exposure-response for CSF biomarkers after single and steady state dosing?

• **Dose selection**: What is the dose to achieve $A\beta_{42}$ inhibition and optimize shorter $A\beta$ peptides?

• **Combination**: What would be the biomarker response if GSM and BACEi were combined? What would be the optimal combo dose?

**Efficient**  **Design**  **Dose**

**Courtesy**
JE Ahn, R Qiu, D Chen
GSM Clinical PK/PD Data

- Frugal CDP (all CP studies)
- Dedicated Single Dose PK/CSF
  - Variable, placebo drift, delayed, serial samples
- Multi Dose PK/CSF (part of MAD)
  - Less variable, no placebo drift, dose response, sparse samples
GSM PK/PD Modeling: results & simulations

**Plasma PK**
- Absorption
- Elimination
- PF-06648671 Concentration

**CSF PD**
- $A\beta_{42}$
- $A\beta_{40}$
- $A\beta_{38}$
- $A\beta_{37}$

\[
1 - \frac{Imax \cdot Conc}{IC50 + Conc}
\]
\[
1 + \frac{Emax \cdot Conc^\gamma}{EC50^\gamma + Conc^\gamma}
\]

$\frac{(A\beta_{42}+40+38+37)}{A\beta_{tot}} = \text{constant}$

**Graphs**
- Steady-state average CSF $A\beta_{42}$
- Average CSF $A\beta_{42-38}$ ratio

**Additional Notes**
- Absorption
- Elimination
- PK/PD models
- Simulation results
BACEi/GSM combo: Aβ model based dose selection

- BACE and GSM while in same pathway, affect amyloid differently
  - Model combines Aβ PKPD for GSM and BACEi
  - Goal: dose select both agents to maximize Aβ42 lowering maintaining differentiation from BACEi in overall Aβ37-38 and Aβ42/40 ratio
BACEi/GSM combo: M&S to optimize dose selection

<table>
<thead>
<tr>
<th>GSM dose (mg)</th>
<th>BACE dose (mg)</th>
<th>Aβ42 average reduction (%)</th>
<th>Aβ40 average reduction (%)</th>
<th>Ratio (42/40) at trough</th>
<th>Aβ37 average reduction (%)</th>
<th>Aβ38 average reduction (%)</th>
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</tbody>
</table>
Parkinson’s Disease designs: Quantitative Questions

• Do we understand symptomatic motor symptoms scores over time?
• What are appropriate target values for Go/No-Go decisions and study duration?
• Can we answer the same questions for disease modifying treatments in early and late stage PD?

Efficient Design Decision

Courtesy
S Duvvuri, T Nicholas, JE Ahn, D Gorman
Symptomatic effect on motor effects with DA: Off Time

Longitudinal Model based meta-analysis of Off Time

- Mean placebo effect at steady state (~ -0.7 hr).
- Mean DA class effect: (~1.6 hr reduction)
- Steady state achieved by 10 weeks

- Target values for Go/No-Go (at least 1.5 hr reduction in off-time)
- Optimize the study duration (15 weeks – including titration)
- Informed Bayesian prior reducing sample size and quicker decisions
Symptomatic effect on motor scores: UPDRS Part III

Longitudinal model based meta-analyses of UPDRS part III with L-DOPA background

- Quantify time course of placebo effect (max ~ 2.1)
- Quantify competitor time course
- DA effects max (~5.3) with half-life of 2.7 weeks to reach the full effects

- Competitive positioning: max therapeutic effect, study duration
- Interpretation of placebo effects in motor fluctuator studies
• MBMA to quantify the rate of disease progression in moderate to severe PD (based on DBS)
• Simulate magnitude of effect and trial duration to detect a meaningful clinical change
• Slowing or even halting disease progression is not sufficient to detect a clinically important signal within a reasonable trial duration in moderate/severe PD (will take >3 years halting progression)
• Early PD: Disease progression combining randomized studies and natural disease progression database

• Early disease progression slope makes for more reasonable design for a treatment offering 50% reduction in disease progression (9 months and 270 patients randomized 2:1 with Bayesian prior)

• Enrich populations, set appropriate inclusion criteria
• Identification of sub/composite scores for better signal detection
Therapeutic Hypothesis:
- AD patients have sleep fragmentation, circadian phase delay, may develop sundowning.
- CK1 is critical for the circadian clock. Circadian correction will normalize behavior in AD

Can we bridge circadian rhythm changes from nonclinical (nocturnal) to human (diurnal)?
Can we inform design of Phase 1 and Proof of mechanism study?

Design  Dose

Courtesy Cheng Chang & Francois Gaudreault
Enabling Translation with QSP model of CK1 Inhibition

**Challenge:** Translate from rodent to human pharmacology. Accounting for the effect of light and time of CK1i dosing on the magnitude and time course of circadian rhythm modulation.

**Approach:** Development of a systems model to account for the pharmacological effect of CK1 inhibition in the context of circadian biology.

**Highly nonlinear and time dependent system**
Model informed Proof of Mechanism Design

- Efficient study design (POM as part of MAD, also inclusion of active comparator)
- Dosing regimen and time of dosing (AM vs PM) PM dose escalation scheme (slower than typical study due to predicted super-pharmacology)
- Time of PD sampling (day 7 and 14 PD observations based on simulated time course)
- Study cohort design (parallel instead of cross-over due to simulated PD washout)

Model-based translation (Preclinical to clinical Simulation)

Clinical study results

- 1 hr
- > 12 hrs

Observed biomarker modulation
Can MID3 improve ECD success in neuro diseases?

<table>
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<th>Answer</th>
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<td>Higher Proportion of Positive PoC?</td>
<td>✗</td>
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</table>
Confidence in Target & Compound → Confidence in PoC

Confidence in Proof of Concept

Confidence in Compound

Confidence in Target

Pharmacokinetics-Pharmacodynamics

Systems Pharmacology

Target Exposure

Target Engagement

Target Modulation

Pathway Modulation

(Patho)-Physiological Regulation

Disease Modification

Paolo Vicini and Piet van der Graaf
Clinical Pharmacology & Therapeutics (2013); 93 5, 379–381;
What is the story at Pfizer (in Neuro)?

- Few QSP examples in neuro

However were too late to impact target selection, and efforts were too isolated.
Conclusions

• Quantitative pharmacology integrates all available data to improve the probability of making the right decision in an efficient manner in early clinical development in neurodegenerative diseases

• However to improve probability of successful PoC it requires for us to be able to inform better target selection & validation through earlier and broader use of QSP to help
  – Prioritize targets
  – Select more appropriate patient populations
  – Link nonclinical observations to clinical predictions
  – With combination drug strategies
Many Pfizer colleagues and collaborators that influenced the NPRU discovery and development

Particular THANKS to the authors of the examples presented:

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