Model-Informed Drug Development

MIDD+

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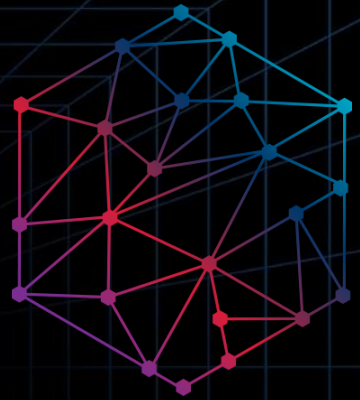

Pharmacometrics in Phase 2 – Proof-of-Concept and Dose Selection for Phase 3/Marketing

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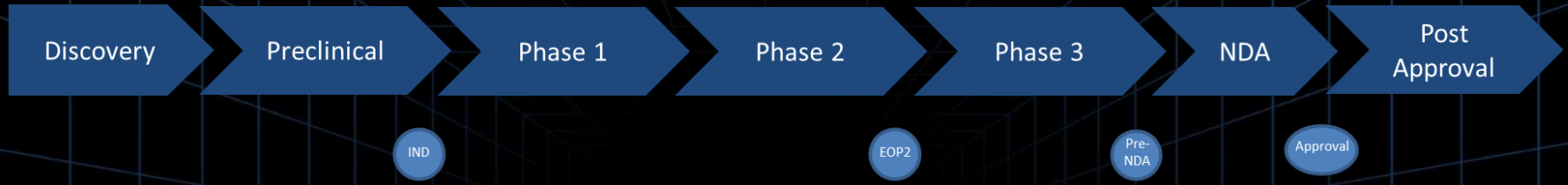
Phase 2 Studies

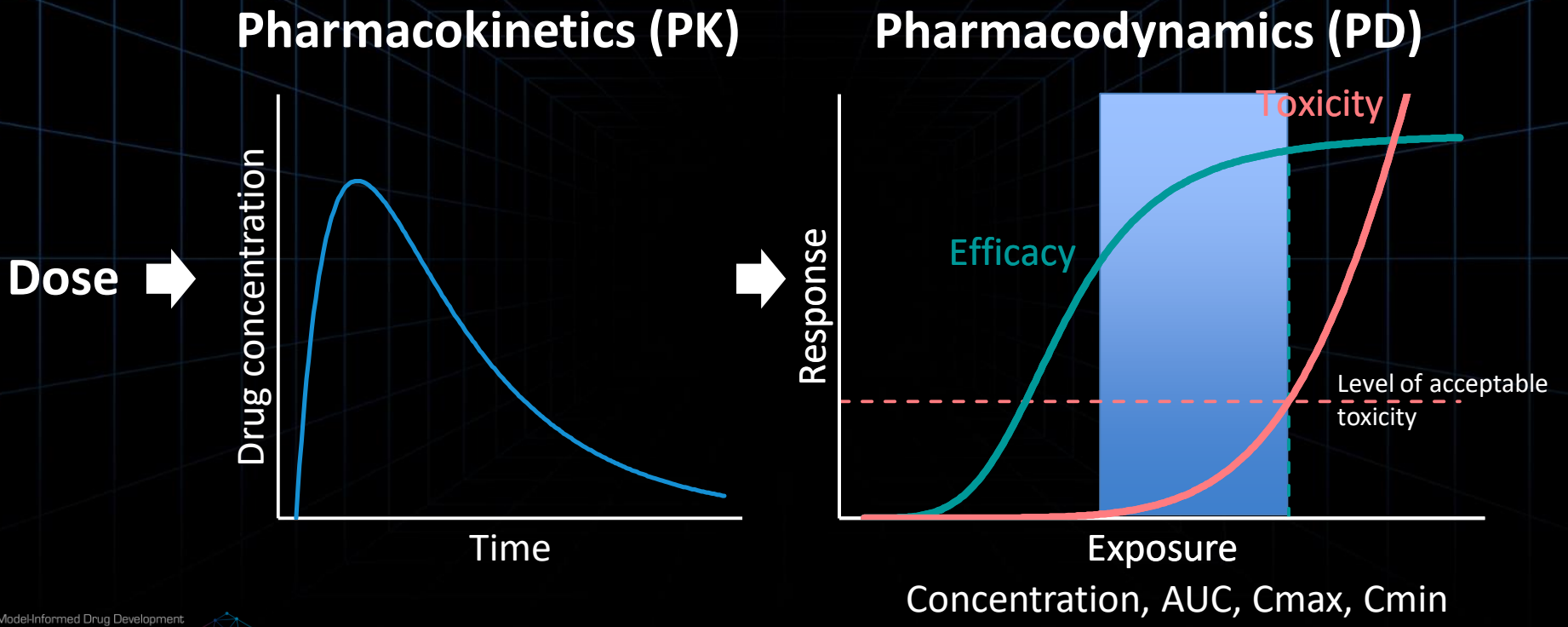


- Intent-to-treat (ITT) population
- Goals
  - Efficacy (proof-of-concept) 2a
  - Safety 2a, 2b
  - Dose selection for large-scale Phase 3 studies 2b

“Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs”

FDA’s Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

Exposure-Response

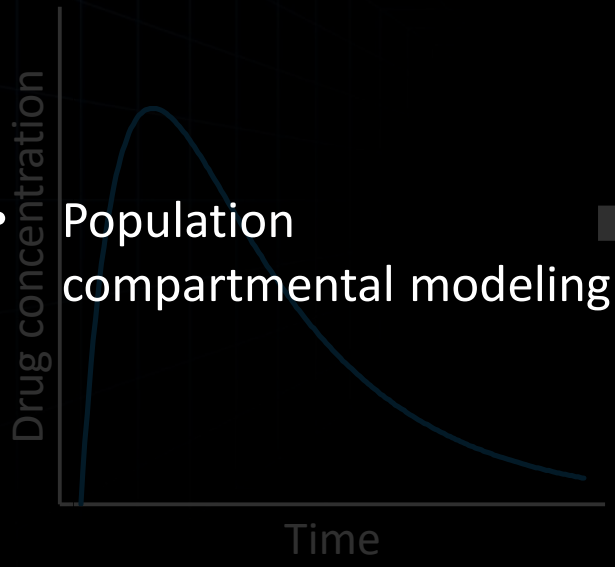


Exposure-Response

Pharmacokinetics (PK)

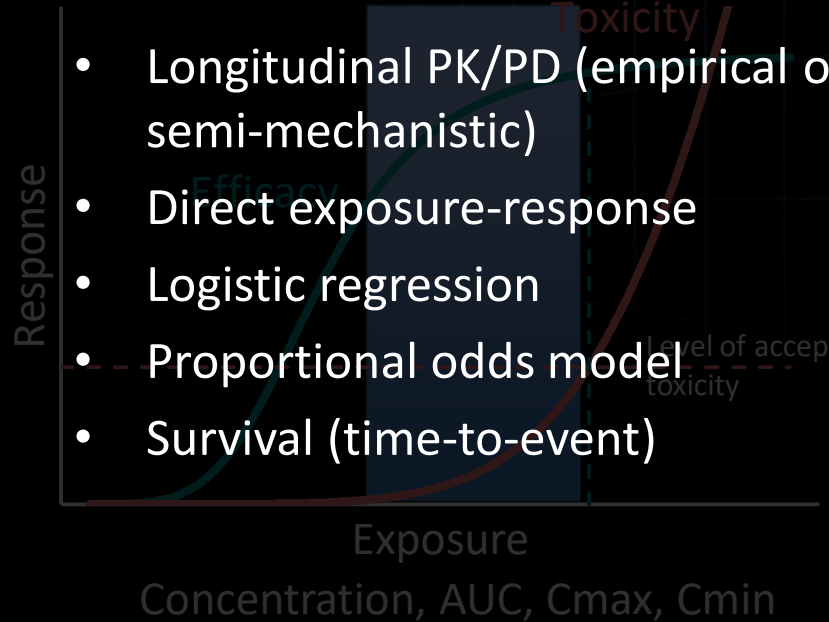
Dose

- Population compartmental modeling



Pharmacodynamics (PD)

- Longitudinal PK/PD (empirical or semi-mechanistic)
- Direct exposure-response
- Logistic regression
- Proproportional odds model
- Survival (time-to-event)



Pharmacometrics Analyses

- Determinants of drug PK
  - Dose, route of administration, formulation
  - Covariate effects (size, special populations, comedications, etc.)
- Determinants of response
  - Potential delay between drug exposure and response
  - Mechanism of action
  - Which exposures best relates to response
  - Disease progression, placebo response
  - Covariate effects (demographics, baseline, comedications, comorbidity etc.)

Where can pharmacometrics help?

- Design of Phase 2 studies
- Analysis of Phase 2 data
  - Support the understanding of efficacy and safety and their determinants
  - Support end-of-phase-2 meetings with regulatory agencies
- Design and dose selection of Phase 3 studies using model-based clinical trial simulation

PRIOR TO PHASE 2

Proof of Concept Studies

- Primary endpoint(s) typically defined as some measure(s) of efficacy at a given time point
- Traditional statistical methods
- Population size defined such as to achieve a given power to detect a target effect using this statistical approach

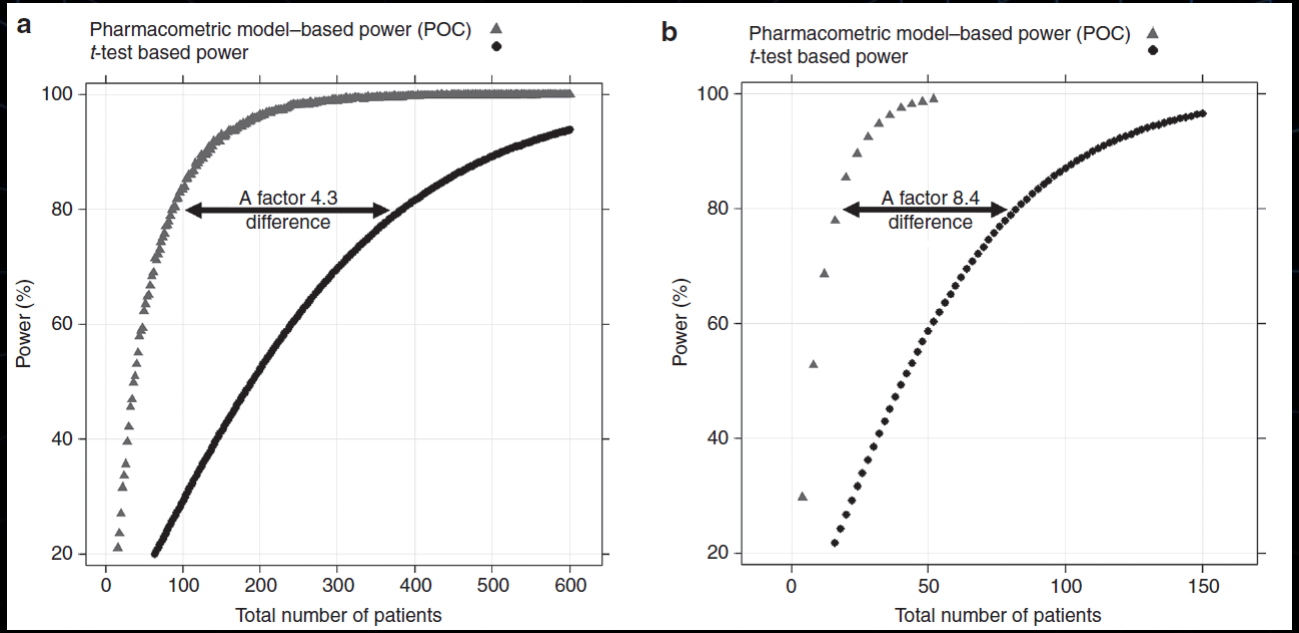
Model-based Power Approach

Phase 2a (PoC):

Active vs Placebo

Acute stroke (NIH Stroke Scale)

Type 2 diabetes (HbA1c)



Karlsson et al, doi:10.1038/psp.2012.24

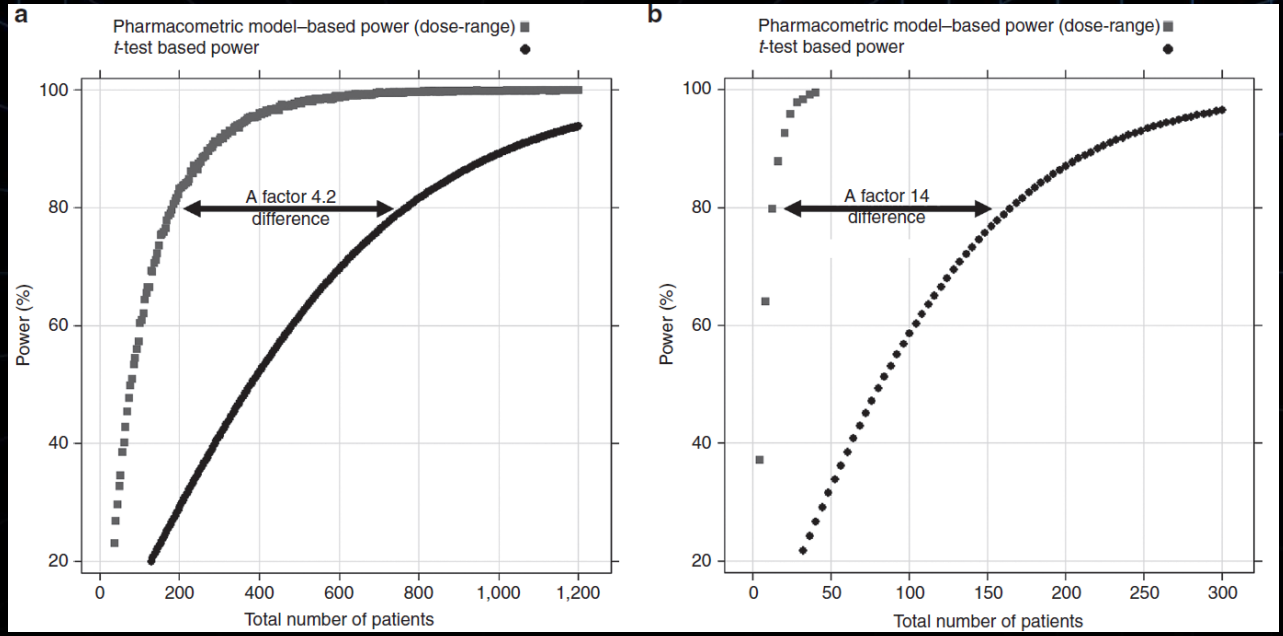
Model-based Power Approach

Phase 2b (dose ranging)

3 dose levels + placebo

Acute stroke (NIH Stroke Scale)

Type 2 diabetes (Hb_{A1c})



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Model-based Power Approach

- Pros:
  - Reduce the number of patients exposed to experimental treatment
  - Reduce trial cost and duration (especially if enrollment rate is slow)
- Cons:
  - Require prior knowledge of disease / biomarker models and “best guess” of pharmacokinetic and pharmacodynamic properties of the drug in the ITT population

DURING PHASE 2

Study Case: Dasotraline

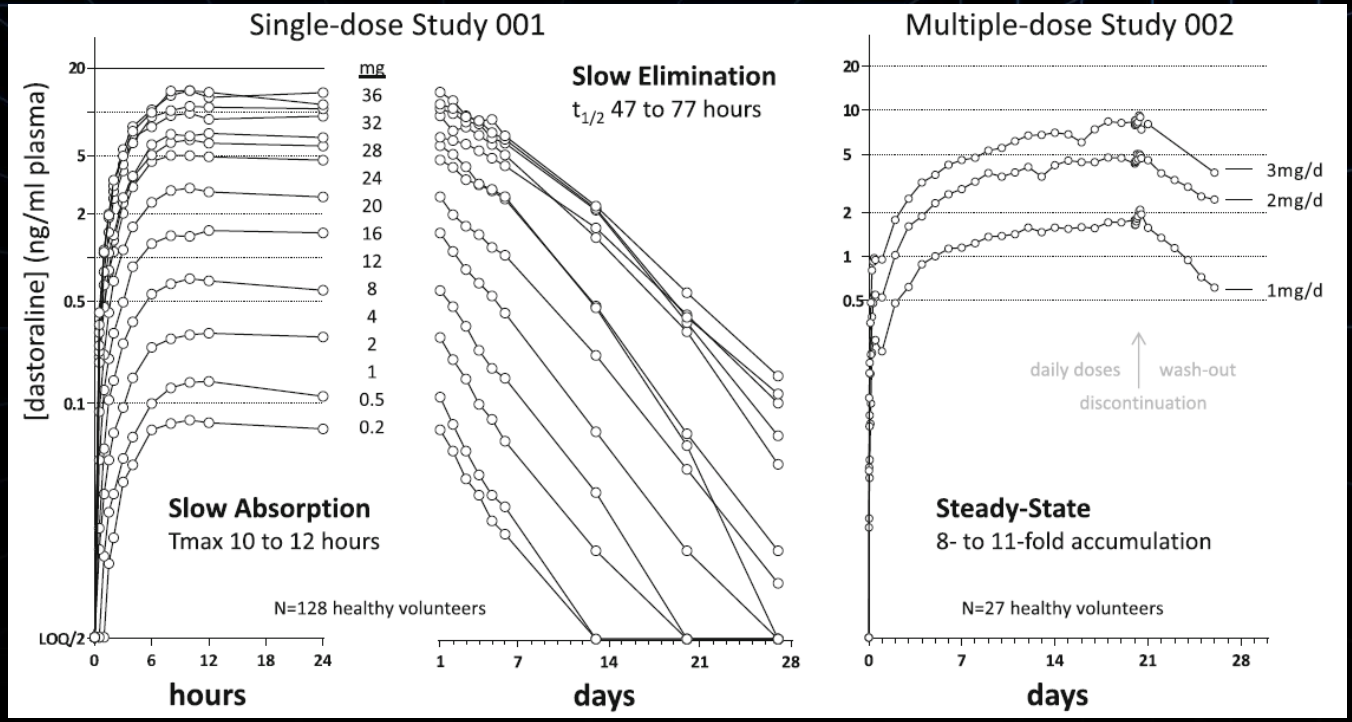
- Attention-deficit/hyperactivity disorder (ADHD)
- Inhibitor of dopamine (DAT), norepinephrine (NET), and serotonin (SERT) transporters
- 500+ participants in 3 phase 1 and 1 phase 2 studies
- Nonlinear mixed effect models:
  - PK model
  - E-R model of norepinephrine metabolite 3,4-dihydroxyphenylglycol (DHPG) dynamics (marker of NET inhibition)
  - E-R model of ADHD symptoms rating scale (ADHD RS-IV)
  - Dropout model

Hopkins et al, doi:10.1007/s40261-015-0358-7

Dosatraline PK

Data collected after single and multiple dose

Slow absorption and (nonlinear) elimination



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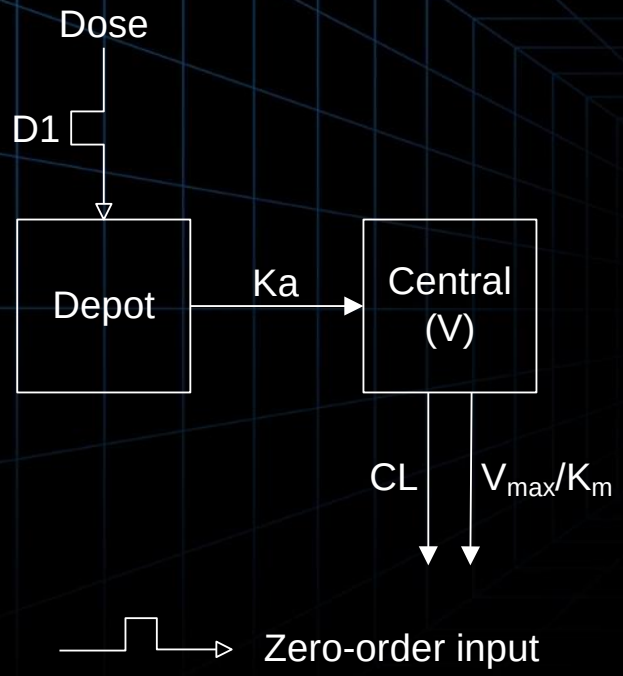
Population PK Model



- Complex time-dependent clearance with linear and saturable components

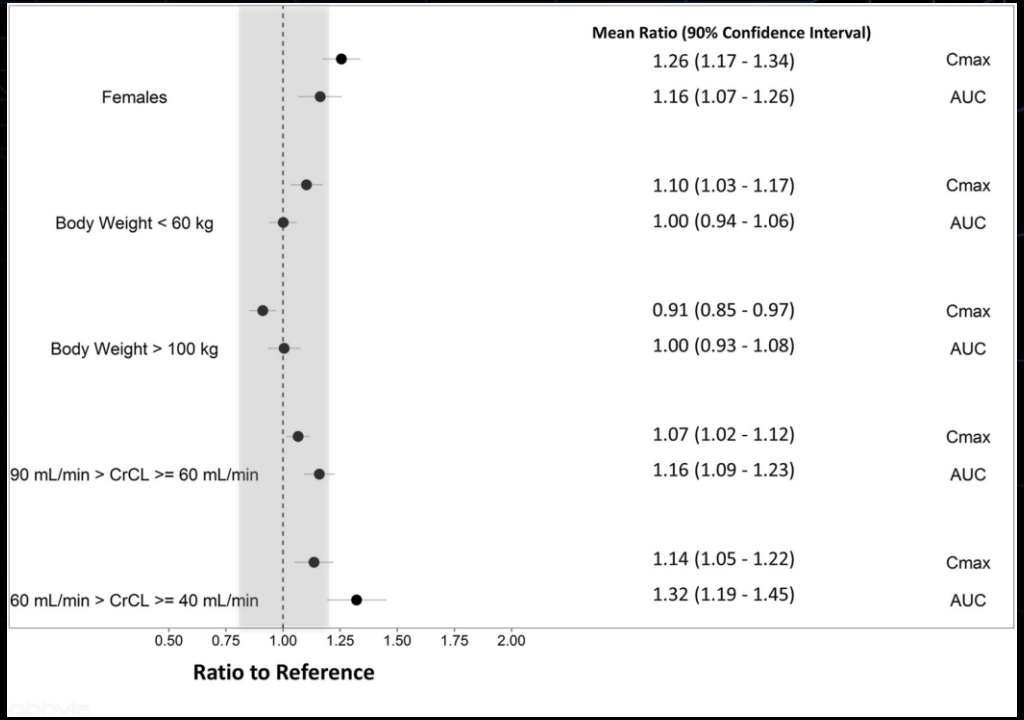
$$CL(t) = CL_{int} - CL_{ind} \times e^{-\alpha \times t}$$

- Covariate analysis tested effects of various demographic and lab variables
- Body weight significantly influenced clearance and volume of distribution

Hopkins et al, doi:10.1007/s40261-015-0358-7

Side-note about Forrest Plots

Plot generated based upon upadacitinib PK model using pooled phase 1 and phase 2 data



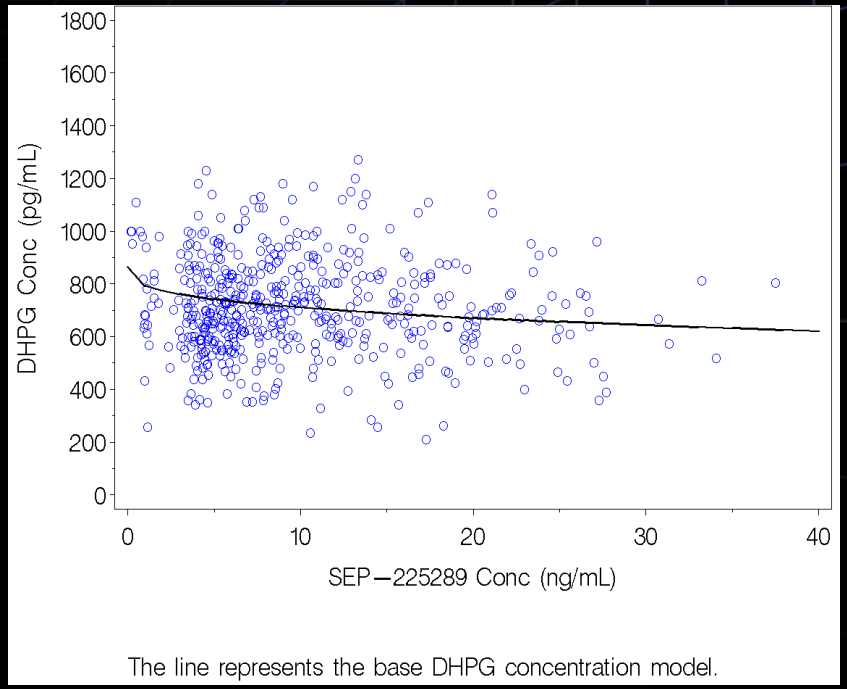
Klündler et al, doi:10.1007/s40262-017-0605-6

Modeling of DHPG

- ↘ DHPG concentration reflects ↘ norepinephrine uptake and metabolism by NET inhibitors
- DHPG relates to dosatraline PK following a power function

$$DHPG = DHPG_0 - \alpha \times \left(\frac{PK(t)}{\overline{PK}}\right)^{\gamma}$$

- Data and model estimates shows incomplete but still clinically relevant inhibition of NET
- None of the screened covariate was not be significant descriptor of DHPG response



The line represents the base DHPG concentration model.

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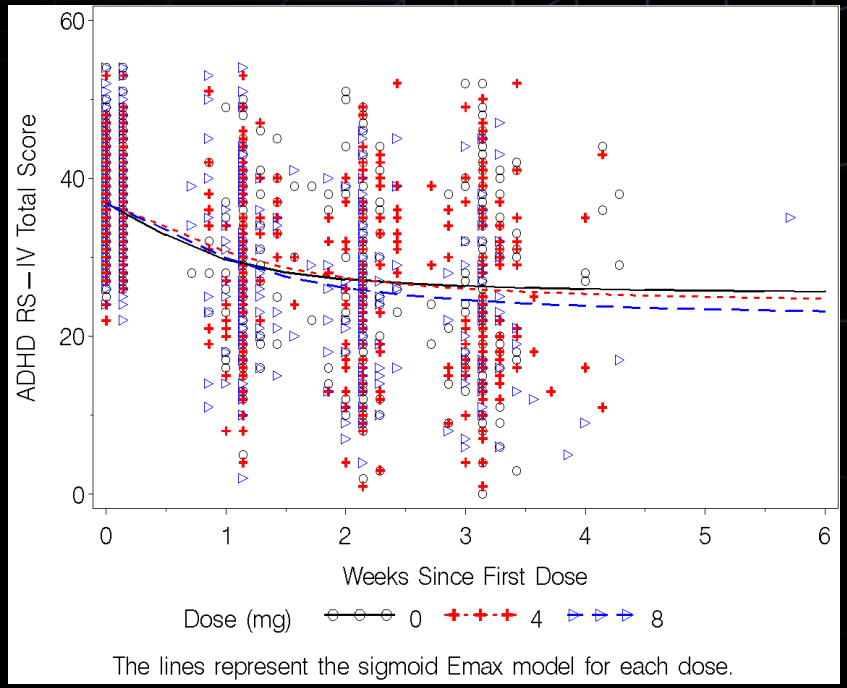
Modeling of ADHD Symptoms Scores

- Majority of ↘ ADHD RS-IV score occurred by week 1 during which dasotraline concentrations were low
- Additional reduction in ADHD RS-IV score achieved with dasotraline
- Placebo effect described by an inverse Michaelis-Menten model of time and dasotraline effect as a linear effect on the maximum effect of time.



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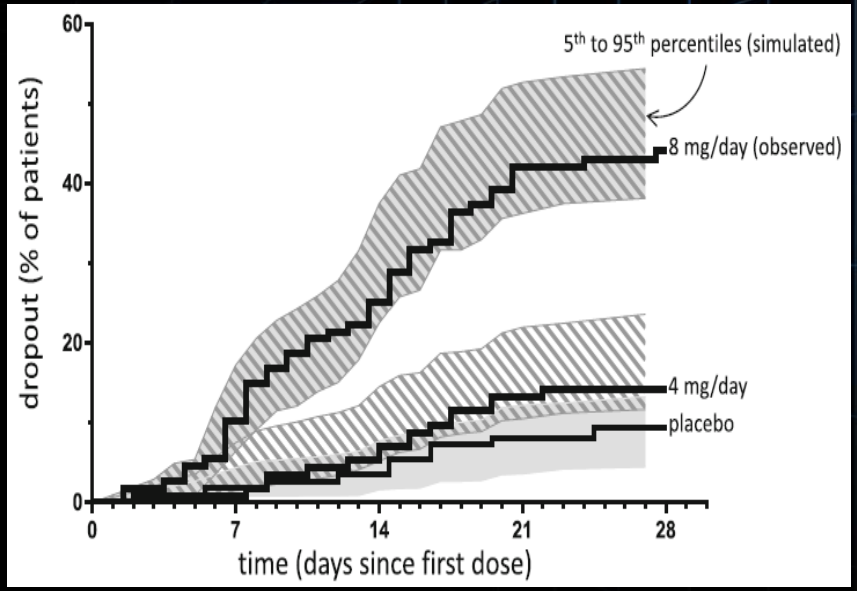
Modeling of Participant Dropout

- % dropouts ↗ with dose in phase 2 trial
- Dropouts were mostly due to AE
- Cox proportional hazard survival model linking dropout with ↗ in time and average dasotraline concentration: dropouts 4 times less likely at 4 mg than 8 mg QD



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Other Applications

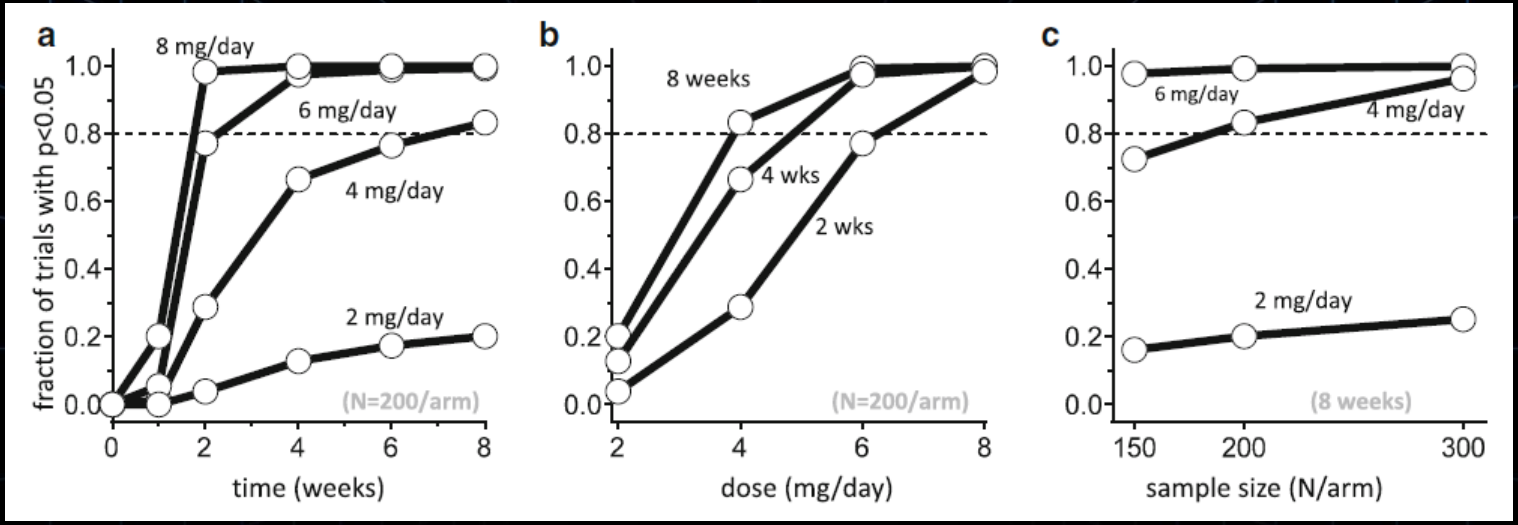
- Disease progression
- Adverse event incidence
- QT prolongation
- Meta-analysis and comparison to competitor products

STAGING PHASE 3

Clinical Trial Simulations

- PK models, disease-drug models of efficacy, safety, and dropout models from phase 2 data can be leveraged to simulate virtual phase 3 clinical trials to predict outcomes under various scenarios (dosing scheme, duration, population characteristics and size, etc)

Study Case: Dasotraline



- Minimal effective dose: 4 mg QD
- No effect dose at 2 mg QD
- Optimal duration of treatment: 8-week
- Sample size: ≥ 200

Hopkins et al, doi:10.1007/s40261-015-0358-7

Other Applications

- New target populations (eg, pediatrics) if similar pathophysiology
- Dose adjustment in subpopulation with specific intrinsic (eg, renal impairment) or extrinsic factors (eg, co-medications)
- New formulation, dose or route of administration

Conclusions

- Pharmacometrics can support design and analysis of phase 2 trials
- Evidence of efficacy and safety
- Integral part of documentation for end-of-phase 2 meetings
- Support design of phase 3 trials

Q&A

Questions & Answers

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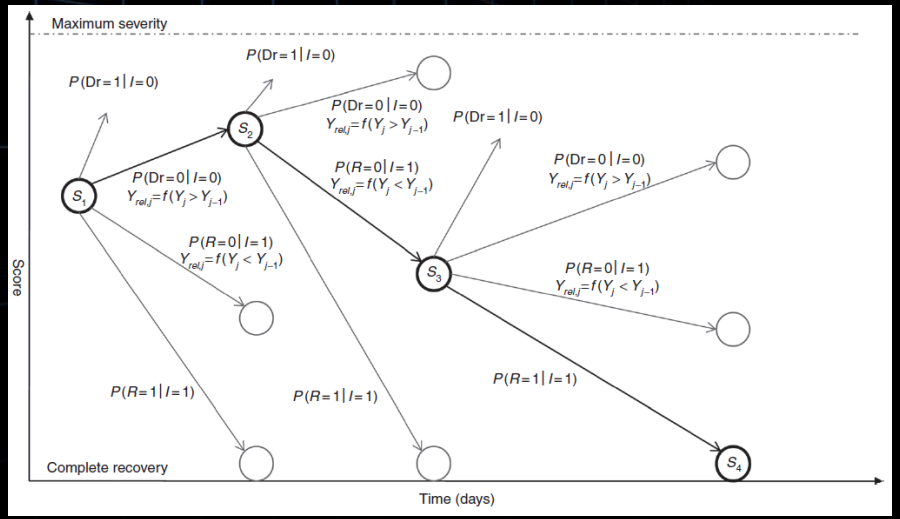
NIH Stroke Scale



FPG + HbA1c