Informing study designs at decision points through data and modeling driven approaches

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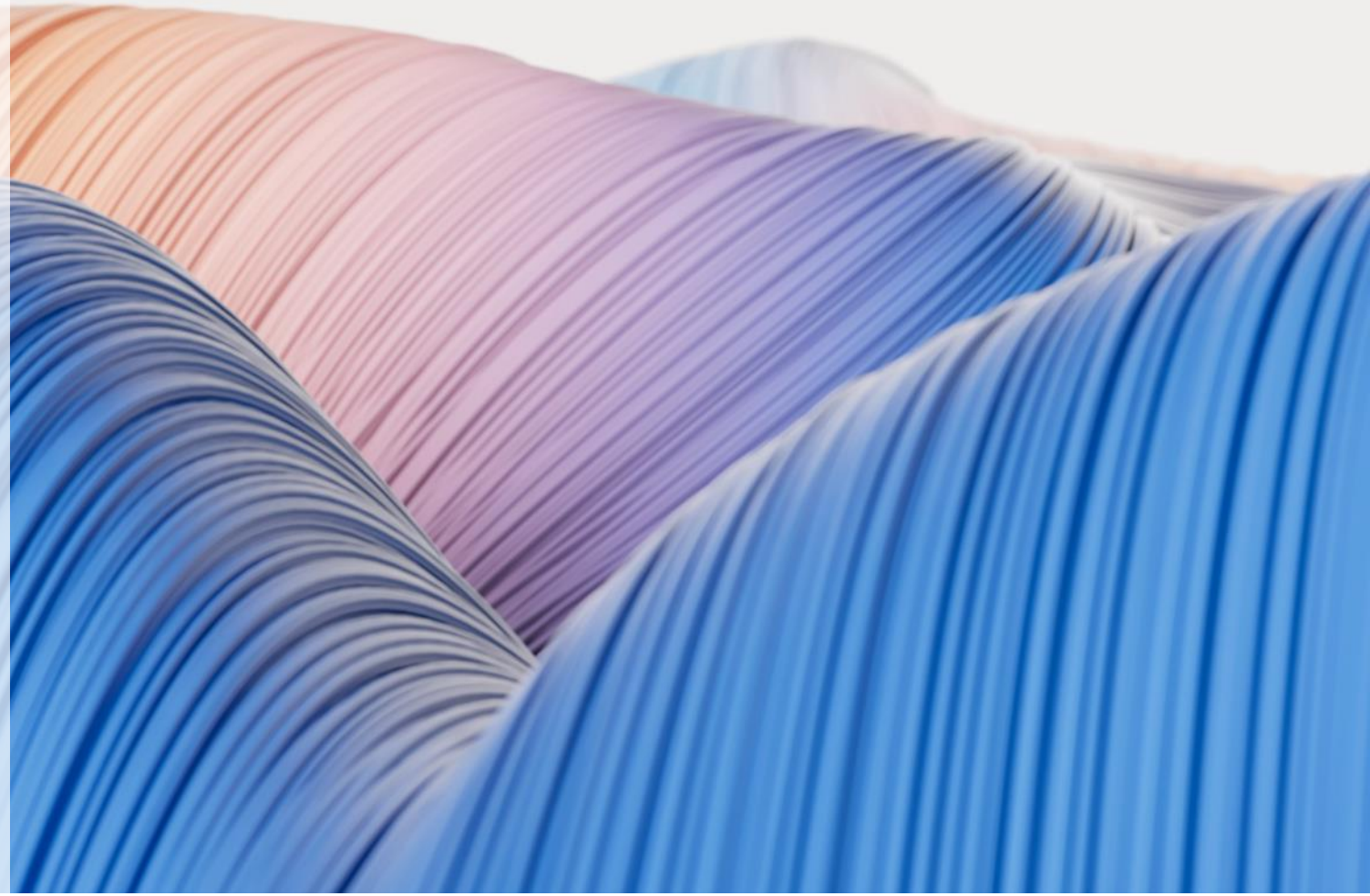


2024 ASA Biopharmaceutical Regulatory-Industry Statistics Workshop
Rockville, MD

Two papers I recommend:

If you want to go fast, go alone. If you want to go far, go together.
– most commonly referenced as an African proverb

1. **My Career as a Pharmacometrician and Commentary on the Overlap Between Statistics and Pharmacometrics in Drug Development**
   Kenneth G. Kowalski (2015) Statistics in Biopharmaceutical Research, 7:2, 148-159,
   DOI: 10.1080/19466315.2015.1008645

2. **Integration of Pharmacometric and Statistical Analyses Using Clinical Trial Simulations to Enhance Quantitative Decision Making in Clinical Drug Development.**
   Kenneth G. Kowalski (2019) Statistics in Biopharmaceutical Research, 11:1, 85-103,
   DOI: 10.1080/19466315.2018.1560361

Outline

Probability Calculations at Decision Points:

1. Probability of Achieving the Target Value – Abrocitinib in Atopic Dermatitis
2. Probability Technical Success – Dazukibart in Dermatomyositis

Clinical Trial Simulation with Virtual Study Cohort:

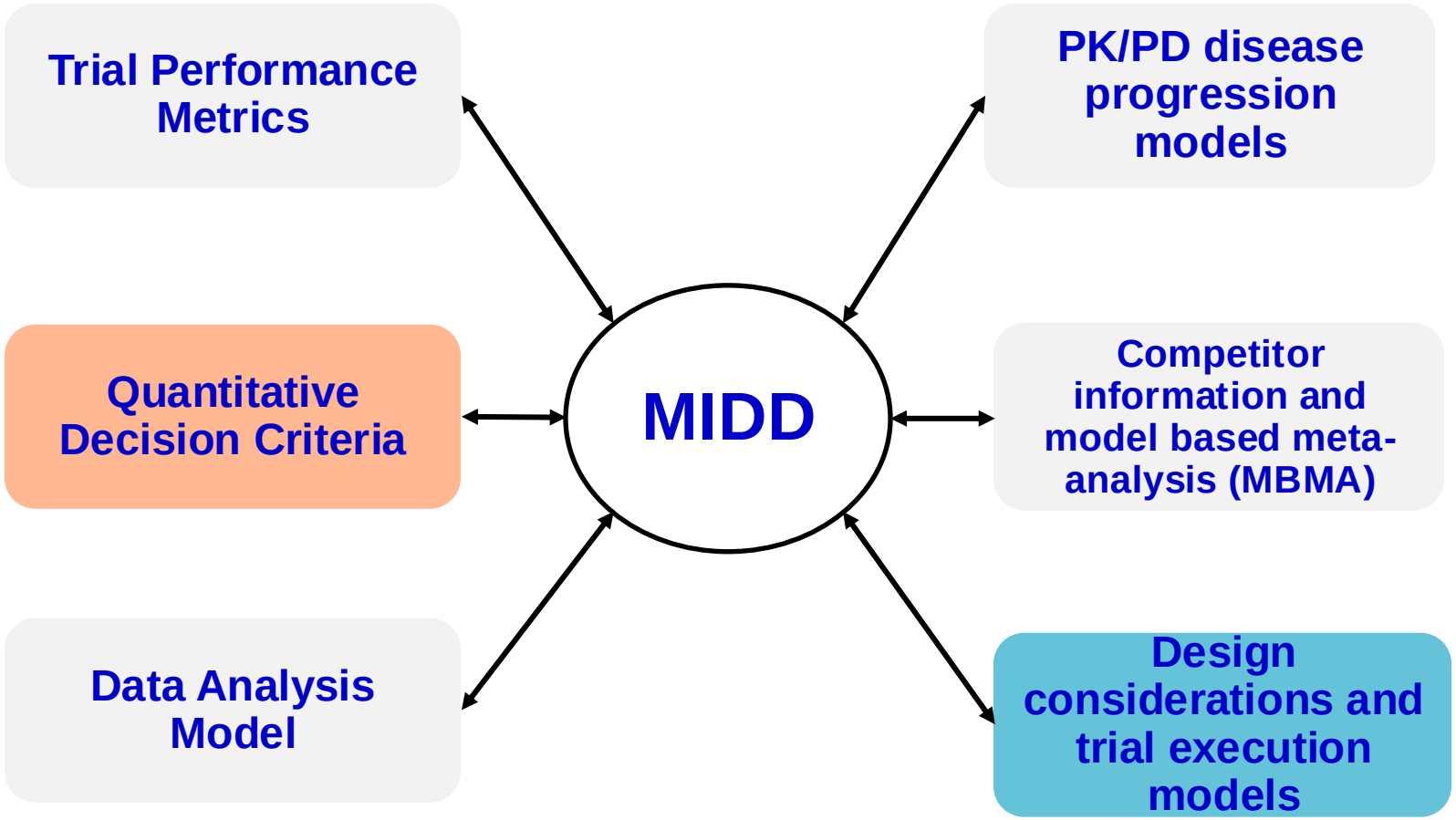
3. Collaboration on an *in silico* Healthy Participant Arm for Organ Impairment Studies: Ritlecitinib Renal Impairment Study Interrupted by COVID-19

Learn, then confirm!

Lalonde et al (2007) proposed six key components for model-informed drug development (MIDD).

Statistics and Pharmacometrics can work together in all these areas.

I will discuss an examples of clinical trial simulation to support decision points and modeling to support a clinical trial outcome



Model-based Drug Development, Lalonde et all (2007)
Clinical Pharmacology & Therapeutics, 82, 21–32. doi:10.1038/sj.clpt.6100235;

Pharmacometric models are **statistical** models

PK/PD: pharmacokinetics/pharmacodynamics

Population Models – these are usually nonlinear mixed effects models with population fixed effects parameters with variance components to describe the interindividual variability in the subject's specific PK and PD parameters.

$$y_{ij} = f\left(\boldsymbol{x}_{ij}, \boldsymbol{\theta}_i\right) + h\left(\boldsymbol{x}_{ij}, \boldsymbol{\theta}_i, \boldsymbol{\lambda}\right)\epsilon_{ij}$$

- y_{ij} is the response for subject *i* at time *j*
- f() is a nonlinear "structural" model (commonly defined using a system of differential equations)
- h() is a variance function describing heteroscedasticity in the errors

Case Study 1: Abrocitinib

Clinical Trial Simulation for Probability of Achieving the Target Effect (PTE)

Work completed by:
Elena Soto
Chenhui Deng
Mark Peterson

Abrocitinib Phase 3 Decision Point

- Abrocitinib (CIBINQO) is a JAK1 inhibitor that is approved for the treatment of moderate to severe atopic dermatitis (AD). Both 100 mg and 200 mg strength are approved in 56 countries.
- A Phase 2b dose ranging study was conducted in 266 patients with moderate to severe AD:
  - Doses: placebo, 10 mg, 30 mg, 100 mg, and 200 mg (~50 subjects/dose group)

- <u>Desired Target Profile:</u>
  1. >30% placebo-corrected response rate in Investigators Global Assessment (IGA)
  2. >30% placebo-corrected response rate in Patients achieving a 75% reduction from baseline in their Eczema Area and Severity Index score (EASI75).
  3. <2.5% incidence rate of patients where platelets drop below 100 x 10^9 counts/L

- Regulatory success required demonstrated efficacy in <u>both</u> IGA and EASI75.

Efficacy and Safety of Oral Janus Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis - PMC (nih.gov)
JAMA Dermatol. 2019 Dec; 155(12): 1371–1379.
Published online 2019 Oct 2. doi: 10.1001/jamadermatol.2019.2855

Efficacy Outcomes in Phase 2b Trial

Week 12		Placebo N=52	10 mg N=46	30 mg N=45	100 mg N=54	200 mg N=48
IGA	Estimate (90% CI)	5.8 (-0.2; 12.9)	10.9 (2.2; 14.1)	8.9 (4.9; 19.7)	29.6 (14.8; 40.9)	43.8 (26.7; 62.3)
	Δ-Placebo (90% CI)		1.8 (-0.7; 4.4)	6.0 (-1.8; 13.8)	**21.5[a] (5.5; 37.6)**	**38.2[b] (19.7; 56.6)**
EASI	Change from Baseline (%) (90% CI)	-35.2 (-46.1 to -24.4)	-31.1 (-42.8 to -19.4)	-40.7 (-52.0 to -29.5)	-59.0 (-69.3 to -48.8)	-82.6 (-92.8 to -72.4)
	EASI75%	15.4	17.4	13.3	**40.7**	**64.6**
Platelets	Number of incidences of Platelet Counts < 100 $x10^9$ U/L	1	0	0	**0**	**1**

Targets:

- IGA: >30% placebo-corrected response
- EASI75: >30% placebo-corrected response rate
- Platelets: <5% incidence rate at any time during treatment

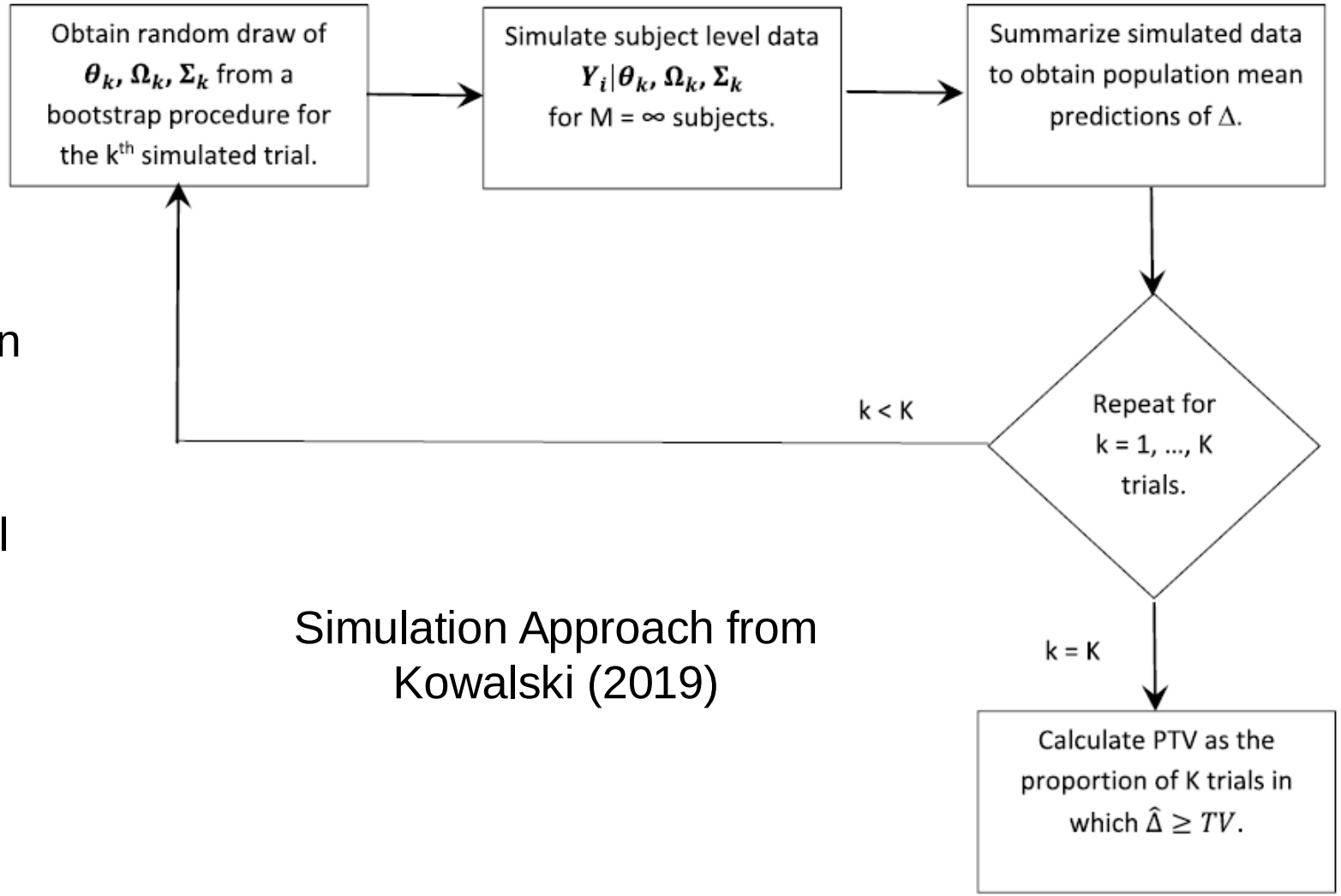
The team needed to decide on what two doses to evaluate in Phase 3.

- The team was open to selecting doses that had not been formally studied in a clinical trial.

Stochastic Approach to estimating Probability of Achieving the Target Effect using Pharmacometric Models

Mechanistic response models were developed for:

- Longitudinal myelosuppression model for platelet counts (based on exposure)
- Longitudinal continuous model for absolute EASI scores (based on dose)



Simulation Approach from Kowalski (2019)

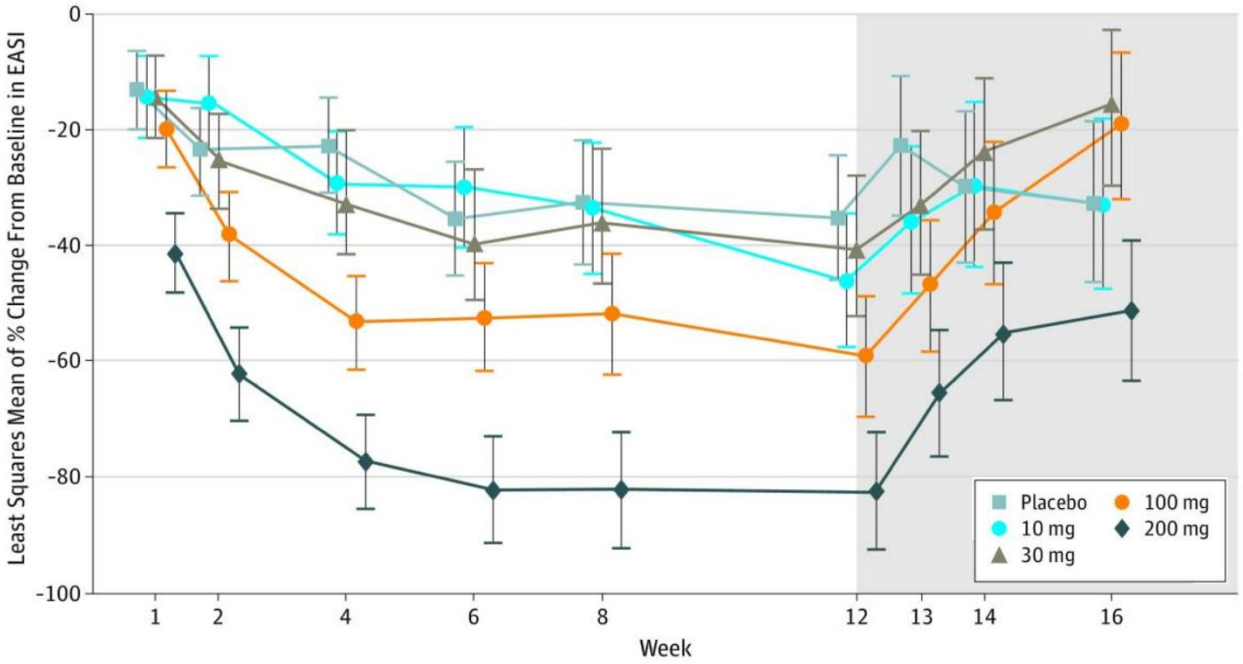
EASI Efficacy Model

An empirical model was developed with the structural components characterized using an indirect response model – the stimulation on kout parameterization – to characterize the longitudinal relationship.

$$\frac{dR}{dt} = k_{in} - k_{out} \cdot (1 + \beta_{dose} + \beta_{pbo}) \cdot R$$

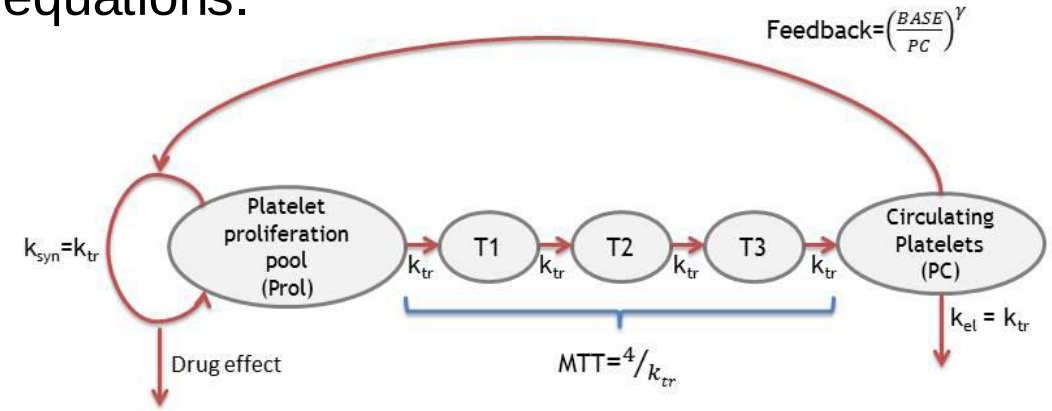
- The total effect of treatment is a placebo effect plus a treatment effect.
- Dose was parameterized as a linear effect.
- The variance was parameterized as a combination of both an additive and proportional variance parameter.

Percentage Change in EASI



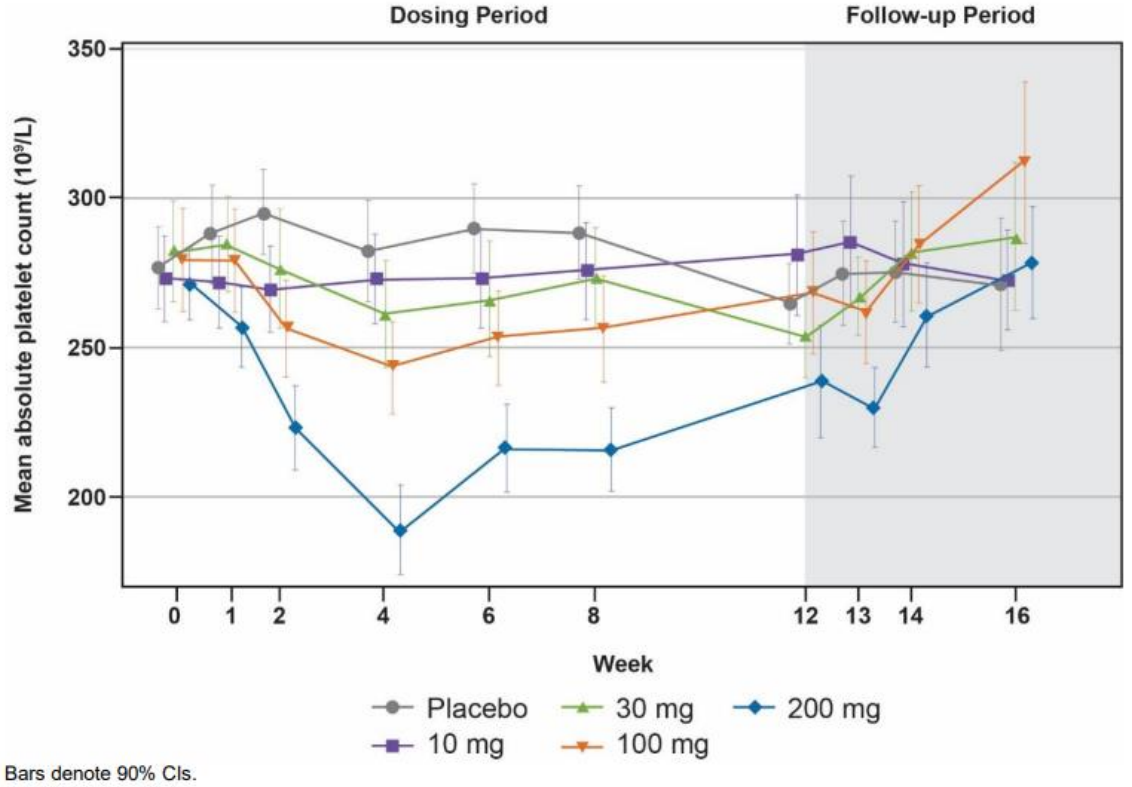
Platelet Myelosuppression Model

An empirical model was developed with the structural components characterized using a transit compartment model which is commonly a system of 6 differential equations.



The amount of drug in circulation inhibits the proliferation rate of the progenitor cells.

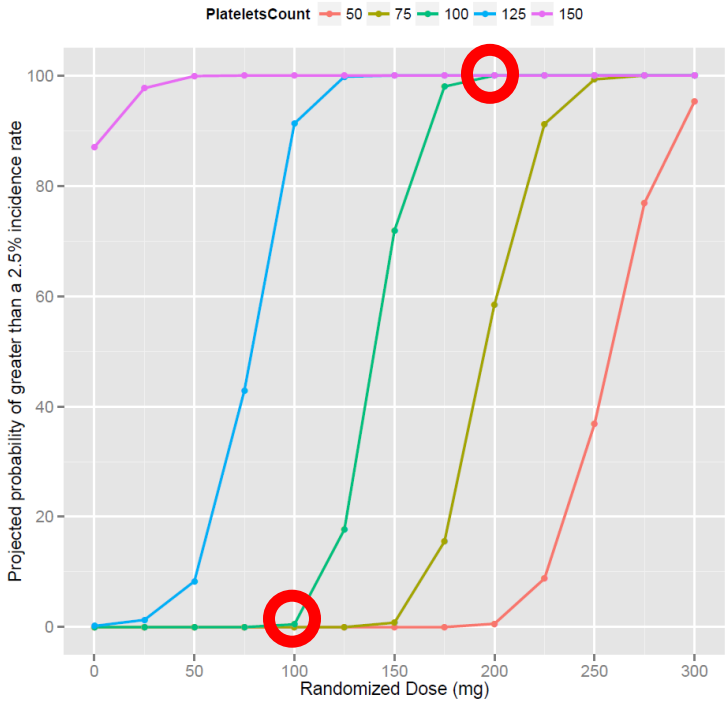
Variability was a combination of an additive and a proportional residual error



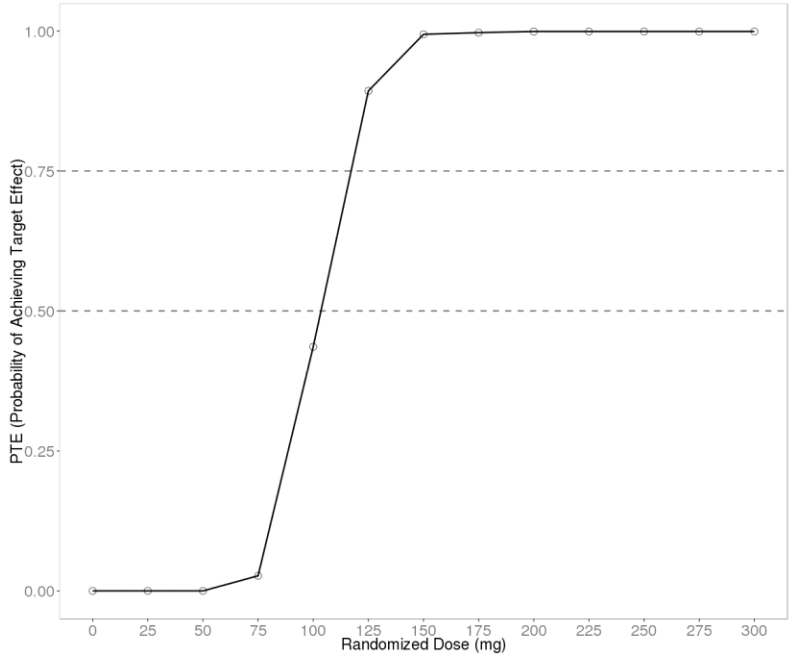
PTE at Week 12 – following Kowalski 2019 approach

- **IGA:** There was determined to be a 0% chance of achieving the target effect with 100 mg.
- **Platelets**: The probability of observing platelet counts under $100*10^9$ count/L in over 2.5% of patients increases from 0% at a dose of 100 mg to 100% for a dose of 200 mg.
- **EASI75:** 100 mg and 125 mg QD would have about 44% and 89% probability to achieve >30% placebo-corrected EASI75.

Platelets: Probability of incidence rates at trial level of Platelet counts exceeding $100*10^9$ count/L in 2.5% of population



EASI75 Efficacy with >30% Target Effect



Pharmacometric Models can Support Effect Size Predictions

Opportunity for Collaboration

- Pharmacometric models can support the assessment of the predicted effect sizes for each of the different outcomes for a given dose.
- Particularly for Go/No-Go development decisions that are multi-faceted, we can work together and should try to avoid just “staying in our own lanes” to answer the same questions.

For Abrocitinib:

- A solid understanding of IGA, EASI75, and Platelet reduction was needed to select the best dose to achieve the targets.
- Predictions based on a mechanistic structure can be easier to defend.

Case Study 2: Dazukibart

Clinical Trial Simulation for Probability of Technical Success (PTS)

Work completed by:
John Prybylski
Min Zhang

Probability of Technical Success - Dermatomyositis

- Dermatomyositis (DM) is a rare skin/muscle disease, associated with elevated IFNβ
  - Relevant clinical scores:
  - CDASI (Cutaneous Dermatomyositis Disease Area and Severity Index): Validated for skin manifestations
  - TIS (Total Improvement Score): Holistic

Mean TIS by Arm before crossover

Arm	Week 4	Week 8	Week 12
Placebo (N=9)	25.83	36.67	36.94
600 mg (N=9)	36.67	49.17	56.39
LSM Delta	10.83	12.50	19.44

Improvement level: Minimal (≥20), Moderate (≥40)

CDASI-A Mean CFB @ Wk12 in skin-predominant (Stage 1 - 2), and muscle-predominant (Stage 3)

Arm	Stage 1	Stage 3
Placebo	-3.44	-5.89
600 mg	-19.6	-8.56

Stage 2 results complicated by various dosing approaches, so not shown

EoP2 and P3 Planning problems

With only N=9 subject per arm there were observed:

- strong CDASI response (in Stages 1-2)
- modest (but uncertain) TIS response in Stage 3:

Questions:

- What is the most likely TIS effect size?
- What is the expected response in Phase 3?
- What is the **Probability of Technical Success** for a Phase 3 Study?

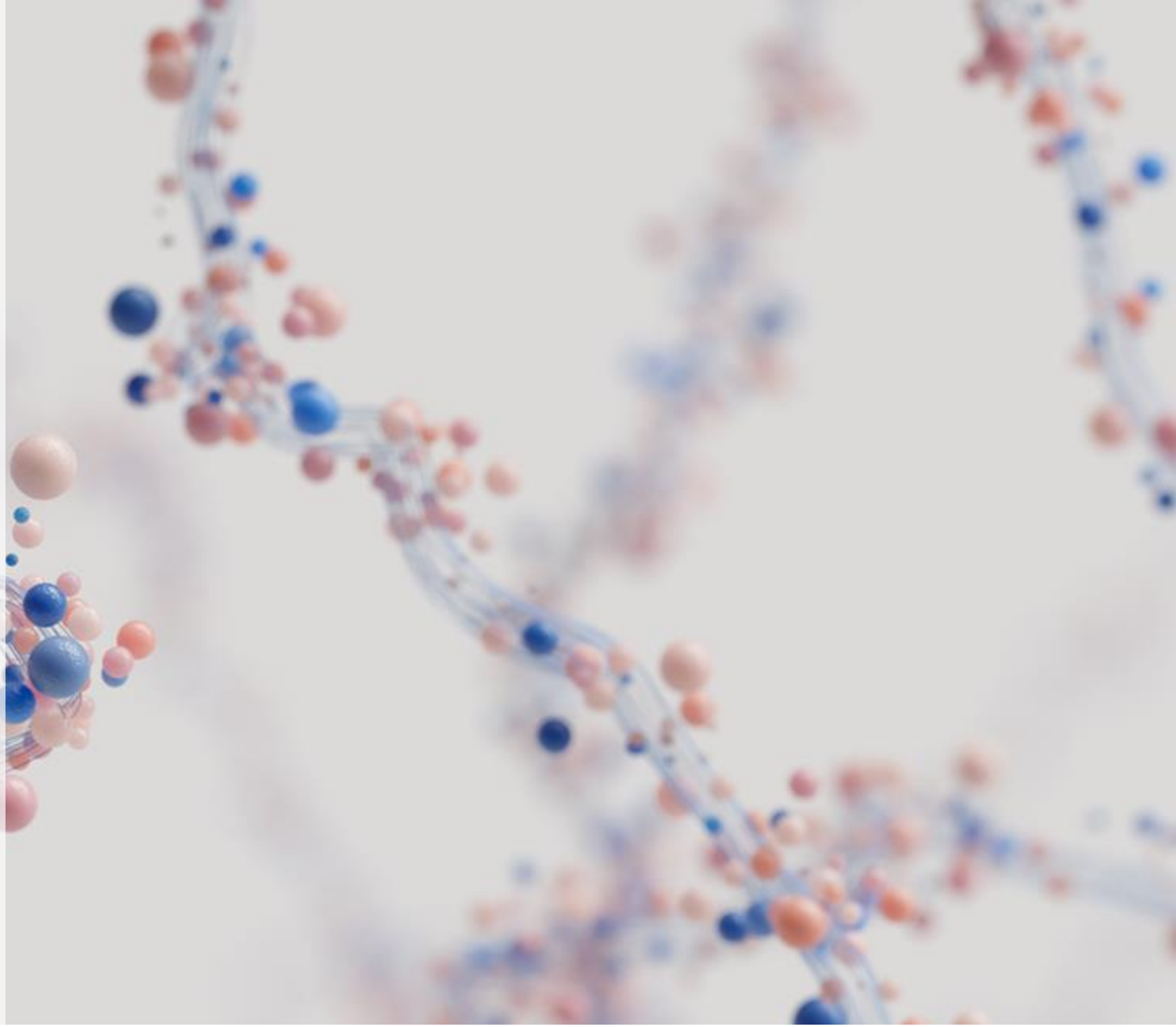
Statistics and Pharmacometrics worked together to determine the best estimate of PTS including the sensitivity assessment

- An Exposure-Response model was developed to jointly model 11 different response metrics including TIS sub-scores.
  - Response was driven by the Percent unbound IFNβ.
- The model-based effect size, jointly incorporating all the efficacy measures with a longitudinal and pharmacological structure, predicted a larger effect size than was observed from the N=18 subjects.
- PTS was calculated for the observed effect size and model-predicted effect size (with and without a penalty) using clinical trial simulation which resulted in a higher calculated PTS.
- A higher PTS was calculated based on the collaborative work in which the modeling was incorporated and was an important consideration for the funding decision for Phase 3.

Case Study 3: Ritlecitinib

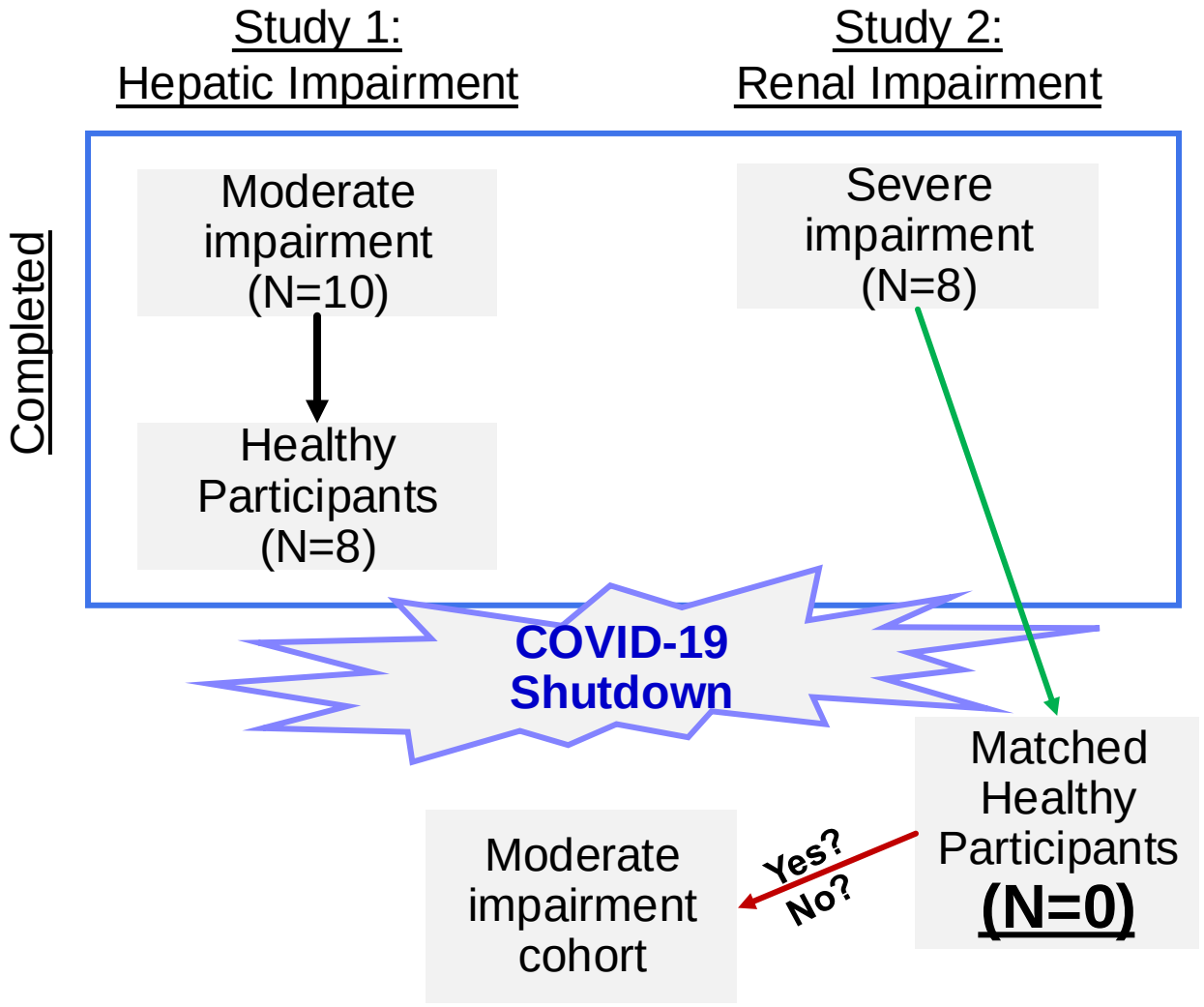
Clinical Trial Simulation with an *in silico* healthy participant arm

Work performed by:
Vivek Purohit



In Silico Healthy Participant Arm for impairment trials

- Standard Renal and Hepatic impairment studies were in progress when the COVID-19 shutdown began indefinitely pausing the trials with no anticipated continuation.
- Statistics and Pharmacometrics worked together to determine how the study could be completed without the matched healthy participant arm.



Question:

1. The renal impairment trial required a moderate impairment cohort if the severe impairment geometric mean ratio of AUC is >2.
   Is this cohort needed for the study?

The AAPS Journal (2023) 25:32
https://doi.org/10.1208/s12248-023-00792-8

Collaboration was key to completing the study

- After discussions between Statistics and Pharmacometrics, two approaches were agreed to be assessed. The demographic characteristics of the Healthy Participant cohort in Study 1 closely matched the Study 2 cohort.

Statistics:

Use the “shared” Healthy Participant cohort from the hepatic impairment study as the control.

6 participants from the matched healthy participant cohort from study 1 met all the matching criteria from Study 2

- (two subjects had eGFR<90 and were excluded)

Pharmacometrics:

Use an existing population PK model to simulate exposures for a healthy participant cohort.

Simulate 1000 healthy cohorts that meet the HP matching criteria.

Validate approach using the hepatic impairment study.

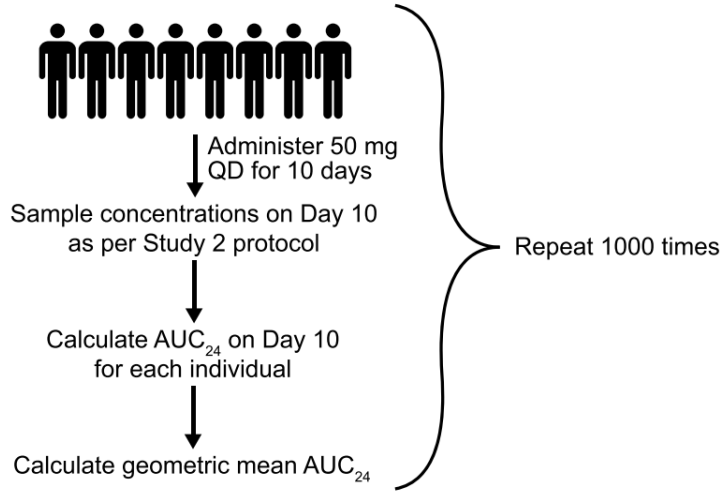


Fig. 1 Simulation and analysis of an *in silico* cohort. AUC_{24}, area under the plasma concentration–time curve for 24-h dosing interval; QD, once daily

Clinical Trial Simulation with simulated exposures was able to replace the Healthy Participant arm

Statistics:

Shared HP cohort approach:

The estimated AUC_{0-24} geometric mean ratio:

- 155.15% (90% CI, 122.83–195.98%)

Pharmacometrics:

Population PK simulation approach:

The estimated AUC_{0-24} geometric mean ratio:

- 171% (90% CI, 152–192%)

Based on the concordance of the two approaches, the team was able to determine that the additional cohort was not needed.

Additionally, the threshold for a dose adjustment was previously determined to be a 2-fold increase. Neither estimate suggested a clinically meaningful effect on exposure.

Final Thoughts on Opportunities for Collaboration

- Pharmacometric models are able to provide predictions of the effect sizes for a given dose. This can be integrated into trial design and go/no-go decision points in development.
- Pharmacometric models can be used to extrapolate to different doses and dose regimens, including dose titration and loading doses.
- Pharmacometric models can be used to incorporate virtual cohorts which could reduce sample sizes and limit the number of subjects who would be exposed to an investigational treatment.

<u>Scientific journals:</u>

- Collaboration can also include publishing in both pharmacometrics journals and statistics journals.
- Clinical Pharmacology and Therapeutics: Pharmacometrics and Systems Pharmacology (CPT:PSP) is the highest impact pharmacometrics journal and is entirely open-access
- Pharmacometricians should submit manuscripts to stats journals like SBR.

Thank You