Effective application of modelling, simulation and knowledge sharing in drug development
JSM 2019, Denver, Colorado

Integration of Pharmacometrics and Statistics to Support Study Design Optimization

Michael Heathman, MS
Metrum Research Group & Eli Lilly and Company (retired)

August 1, 2019

METRUM RESEARCH GROUP

Pharmacometrics is Inherently Multi-Disciplinary

*"Pharmacometrics (PMX) is a quantitative discipline integrating pharmacokinetics (PK), pharmacodynamics (PD), pharmacology, physiology, and statistics to describe and predict drug disposition and effect in individuals and populations." **

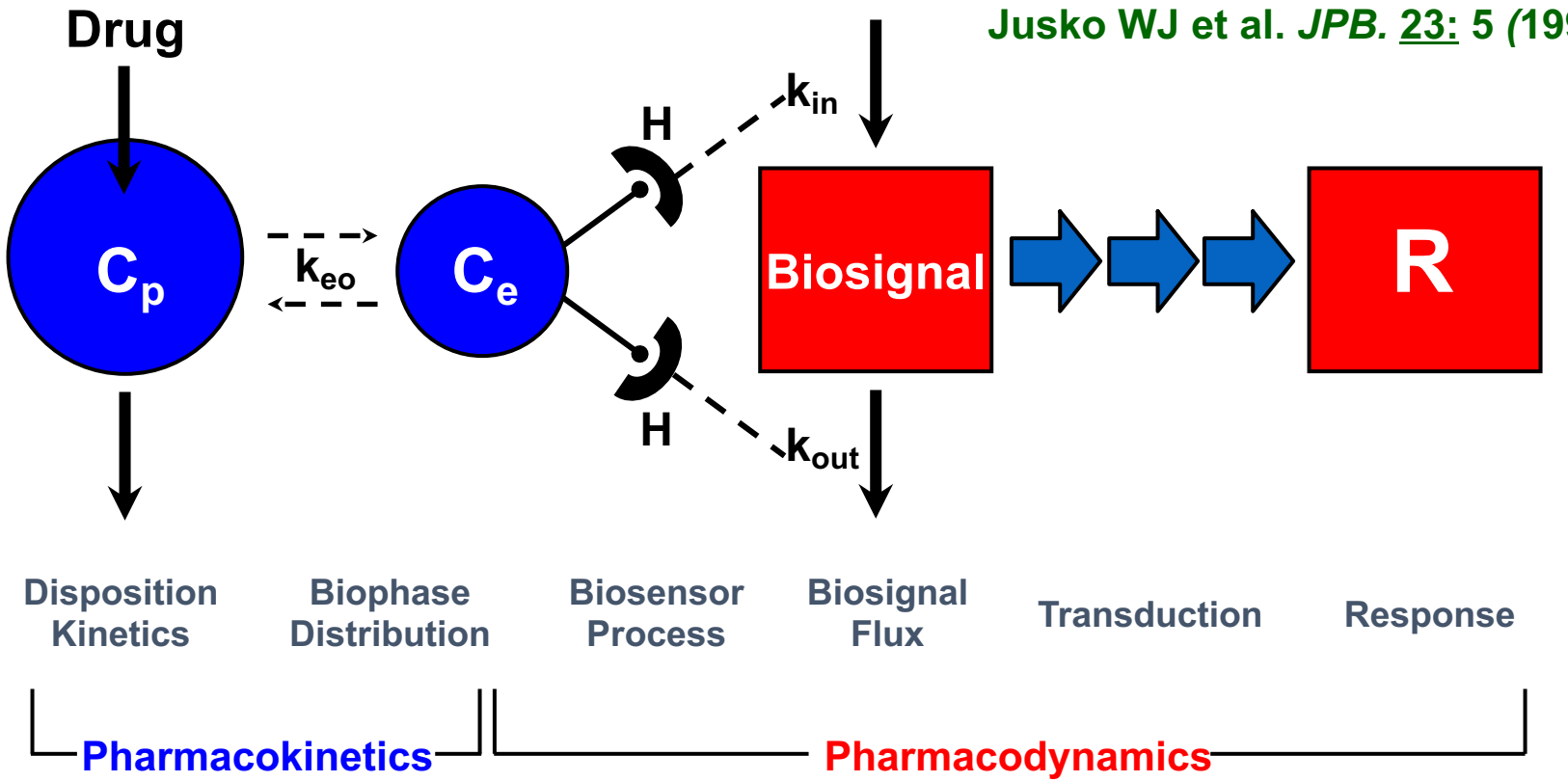
We have no impact on drug development if we work in isolation.

- Must collaborate with Biology, ADME, etc, to ensure that our models adequately represent the biology and pharmacology of interest.
- Must collaborate with Clinical Pharmacology, Medical, and Regulatory, to understand where we can have the most impact on development.
- Must collaborate with Statistics to:
  - Coordinate modeling strategies.
  - **Optimize future study designs.**

*Thoughtflow: Standards and Tools for Provenance Capture and Workflow Definition to Support Model-Informed Drug Discovery and Development. CPT 2017. Wilkins et al

What is a PK/PD Model?

A PK/PD model is a mixed effects model built on a mathematical structure informed by our understanding of the underlying biology and pharmacology.



The goal of a PK/PD model is usually **quantitative prediction** of a pharmacological effect or safety/efficacy outcome measure – central tendency and distribution in the patient population.

METRUM RESEARCH GROUP

PK/PD Models are Knowledge Management Tools

PK/PD models allows us to integrate our knowledge of biological systems with emerging data, as compounds move through development.

- Prior knowledge and assumptions about the underlying physiology, pathology, and pharmacology.
- In vitro data (potency, binding affinity)
- Data from preclinical studies (PK, PD, ADME, Tox)
- Clinical data (PK, AEs, biomarkers, clinical endpoints, variability)

The model becomes a mathematical representation of our accumulated knowledge, which can be used to answer drug development questions.

The structural and statistical components of the model determine what questions it can be used to answer.

Simulations allow us to Extract Information from Models

A model is a mathematical representation of our accumulated knowledge about the relevant physiology and pharmacology.

Through simulation, the model can be used to answer questions in a **quantitative** fashion, throughout drug development.

- What clinical effect might be observed if this target is inhibited?
- What will be the likely effect of this combination therapy?
- What is a safe starting dose in humans?
- What dosing regimen will optimize benefit/risk?
- What dose has a high probability to differentiate current standard of care?
- Are dose adjustments needed for this population?

This enables informed decision-making and improves the probability of success in every phase of development.

Opportunity Knocks

Pharmacometrics and Statistics simulations can be complementary:

Pharmacometrics

- Run simulations to understand potential responses to treatment.
  - Optimize dosing regimens.
  - Optimize treatment for specific populations.

Statistics

- Run simulations to understand experimental designs.
  - Optimize the operating characteristics of upcoming studies.
  - Maximize probability of correct decision-making.

Collaboration

- Can we use PMX models to inform statistical simulations
  - Maximize probability of technical success given all available information.
- How do we integrate PMX models with statistical simulations?

Potential Inputs to Statistical Simulations

Simulation output from PK/PD models:

- Mean/stdev at specified timepoints
  - Allows statistics to sample from empirical distributions
  - May include longitudinal correlations
- Virtual patients
  - Simulated responses at specified timepoints (typically 10,000+ replicates)
  - May be sampled with replacement for large simulations
- **Direct access to PK/PD simulation models**
  - Allows Statistics to simulate responses as needed
  - Challenging to implement

Simulation output from QSP models:

- Good prediction of mean responses.
- Realistic patient-level variability is not generally possible
  - May be derived from existing patient-level data*

*An Approach to Incorporating Variability into a Quantitative Systems Pharmacology Model for Diabetes. ACoP8 abstract. Waterhouse et al

R as a Framework for Shared Tools

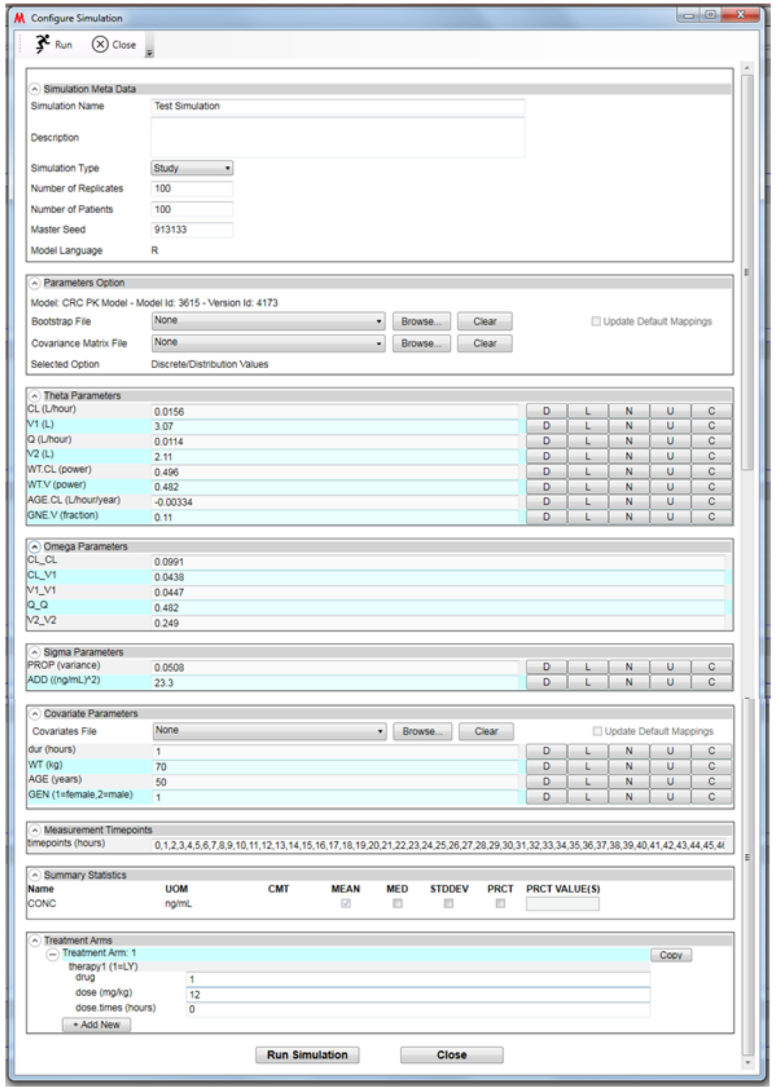
- Commonly used in both PMX and Stats communities.
- Open-source and easily extensible.
- Multiple simulation tools available for PK/PD models
  - mrgsolve, Metrum Research Group
  - RxODE, Wang et al
  - PKPDsim, Ron Keizer
  - Mlxr, Lavielle et al
  - Create your own with deSolve, etc.
- A PK/PD model can be packaged as a function, which can be called by a trial simulation process.

Patient characteristics/Dosing Regimen → PK/PD Model → Patient Responses

Simulation Infrastructure at Eli Lilly and Company

MuSE: PK/PD Simulation Platform

- Models specified in either R or NONMEM
- Both GUI and R command line interfaces
- Massively parallel simulation execution
- Allows models to be handed off to colleagues who are not proficient in PK/PD modeling:
  - Simulation can be run through GUI without any technical knowledge.
  - R command line interface allows PK/PD simulation to be integrated into Statistics trial simulation workflows.



FACTS

Fixed and Adaptive Clinical Trial Simulator

- Virtual patient responses can be accessed through function calls to MuSE from R when using FACTS command line interface.
- Can also be imported using CSV files.

METRUM RESEARCH GROUP

Case Study

Dulaglutide is a once-weekly glucagon-like peptide-1 receptor agonist (GLP-1) for the treatment of type 2 diabetes

AWARD-5: A two-stage, adaptive dose-finding, inferentially seamless Phase 2/3 study, designed to streamline dulaglutide development.

Objectives of study

- Identify up to two doses (low and high) that have a high probability of meeting criteria for safety and efficacy.
- Demonstrate that these doses show robust glycemic control compared to an active comparator and placebo in patients with Type 2 Diabetes Mellitus at 12 months.
- Primary objective is to demonstrate non-inferiority to the active comparator for the high dose.
- Five other secondary objectives are included in the primary analysis.

Adaptive Phase 2/3 Study

Stage 1 (N≤400)

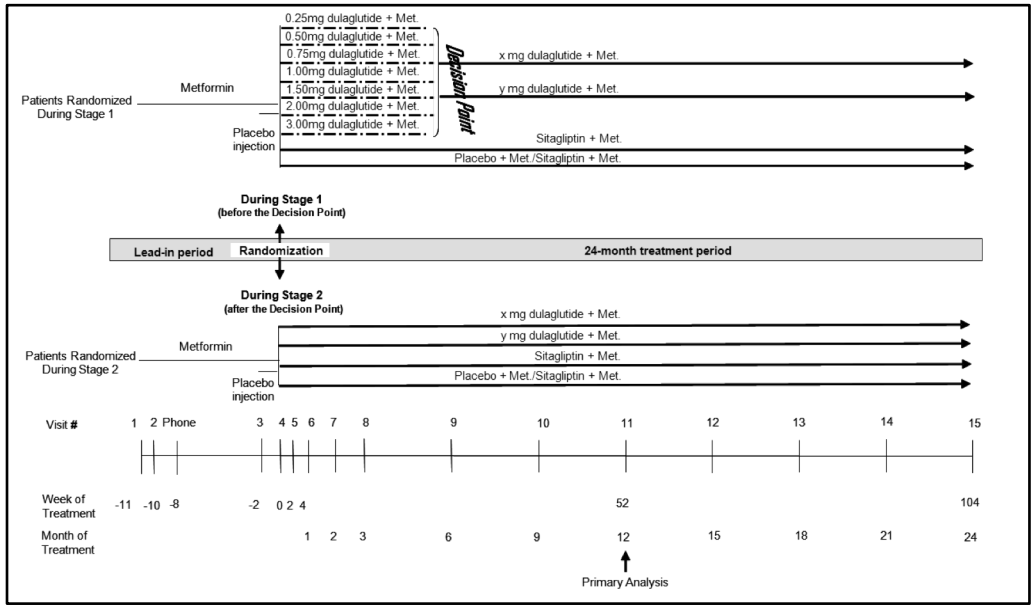
- 7 LY doses, active comparator, and placebo
- Burn-in period of 5 patients per arm
- Adaptive dose randomization after burn-in, on 2 safety and 2 efficacy endpoints.
- Bi-weekly updating of safety and efficacy data, and randomization probabilities.
- After 200 patients enrolled, bi-weekly assessment of decision alternatives
  - Continue in Stage 1
  - Stop for ”futility” (efficacy and safety)
  - Start Stage 2

Stage 2 (N ~ 800)

- Up to two LY doses, active comparator, and placebo
- ≥70% of patients in each arm added in Stage 2
- Fixed allocation to all arms/fixed sample size

Final Analysis

- Includes data from both stages for all of the arms continuing into Stage 2.



METRUM RESEARCH GROUP

Study Design Challenges

Data Available:

- Single dose safety study (SAD) in healthy volunteers, dose range 0.1 to 12 mg.
- Multiple dose safety study (MAD) in Type 2 diabetics, dose range 0.05 to 8 mg, QW for 5 weeks.

Endpoints:

- Primary clinical endpoint is reduction in HbA1c
- Weight loss is important from a marketing perspective
- Increases in vitals signs (blood pressure and heart rate) seen at higher doses.

Challenges:

- Selection of dose range for Stage 1
- Optimize adaptive design
  - Duration of Stage 1
  - Dose allocation algorithm
  - Adaptive decision rules
- Optimize overall study design
  - Probability of selecting the correct dose(s) for Stage 2
  - Minimize Type 1 error rate

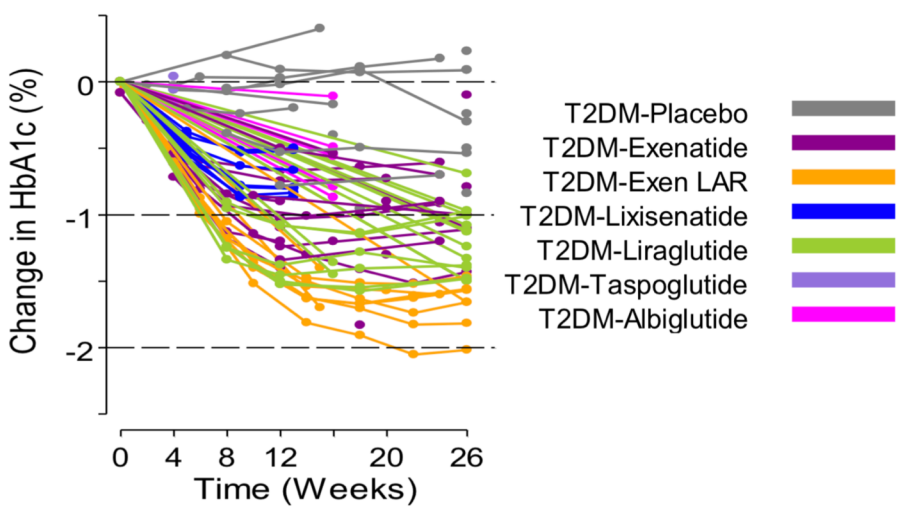
Information from Literature

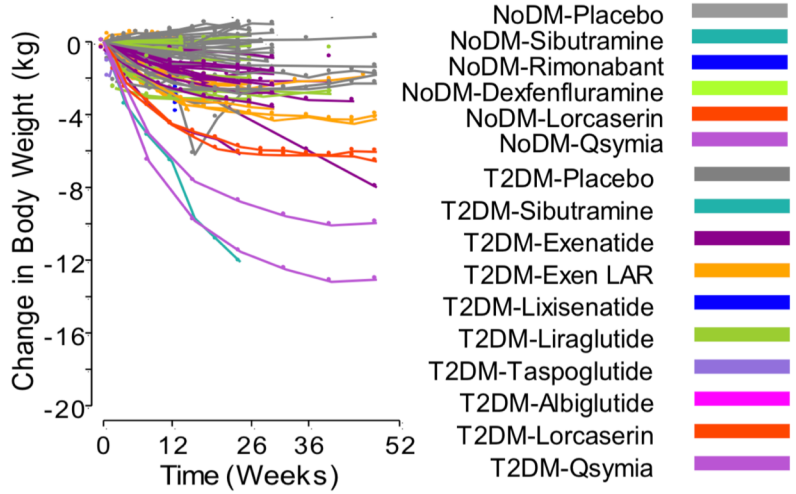
Mechanistic understanding of HbA1c response

- Relationship between short-term fasting glucose response and long-term HbA1c response
- Correlation between individual glucose/HbA1c responses
- Physiologic limit for HbA1c response
- Turnover rate of glucose/HbA1c response for other GLP-1 molecules

Literature weight loss data

- Time course of weight loss response for other GLP-1 molecules.

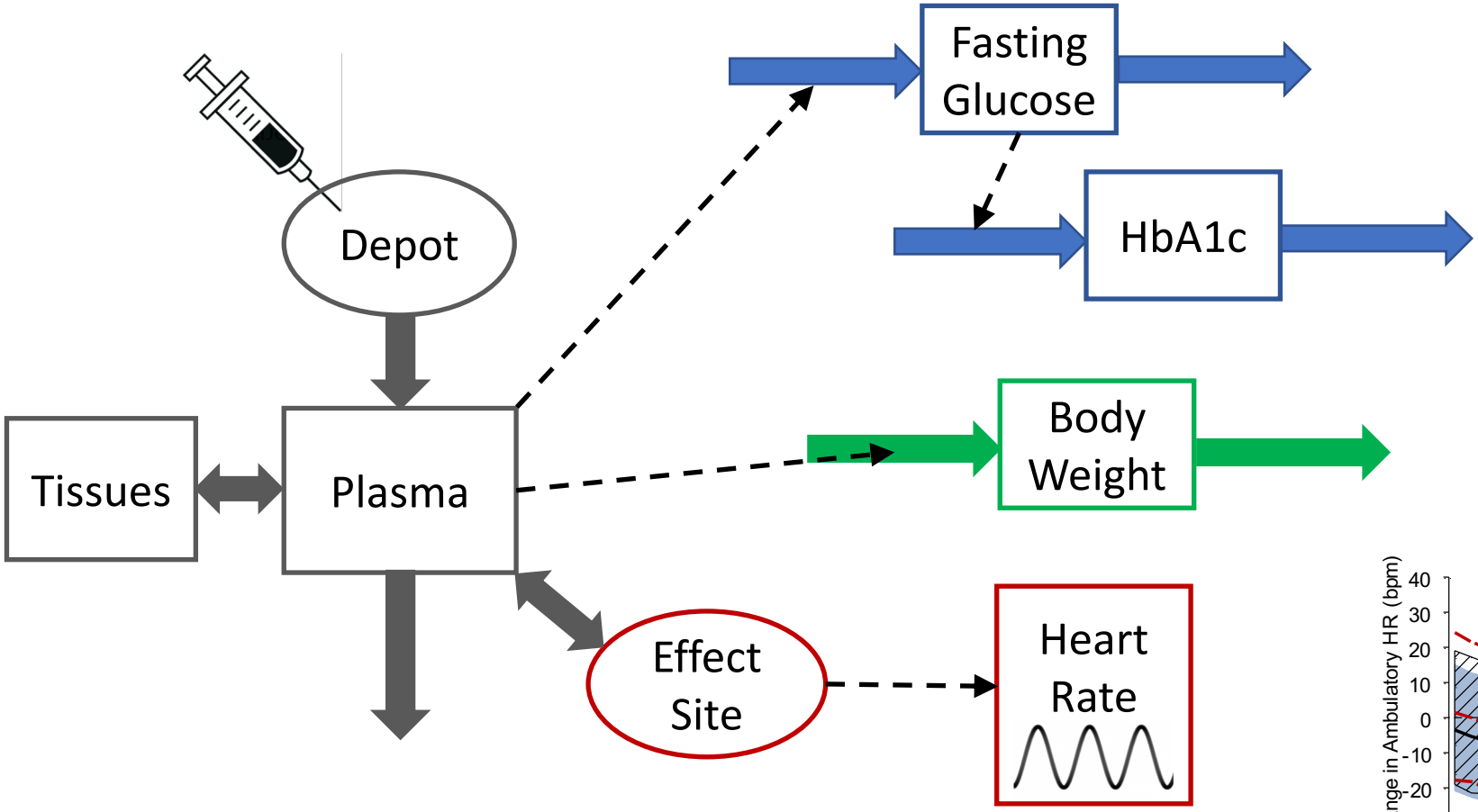


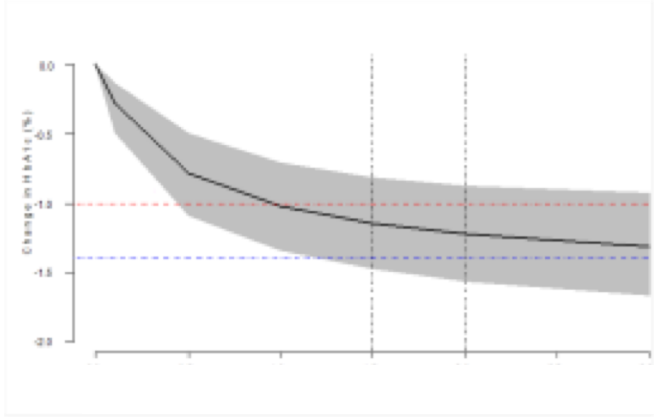


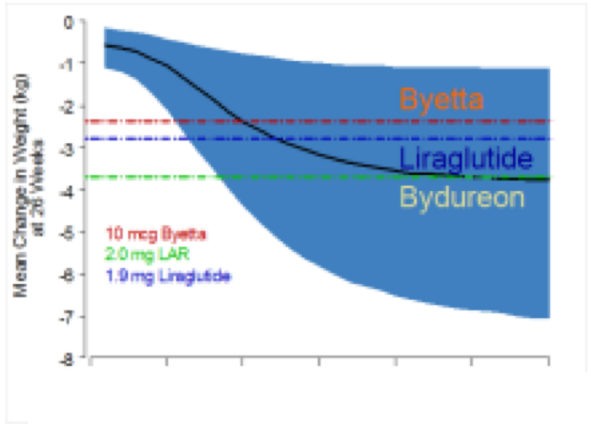
METRUM RESEARCH GROUP

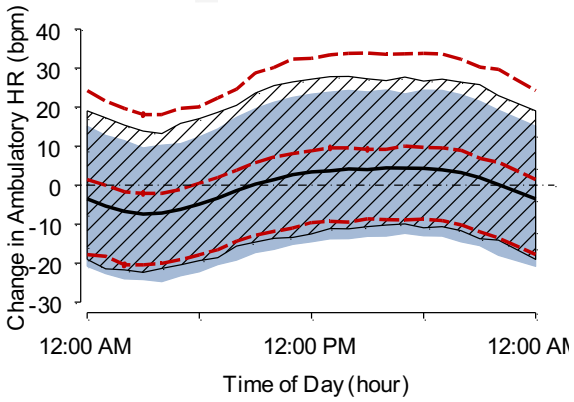
Trulicity PK/PD Models

Informed by literature, and SAD/MAD study data.



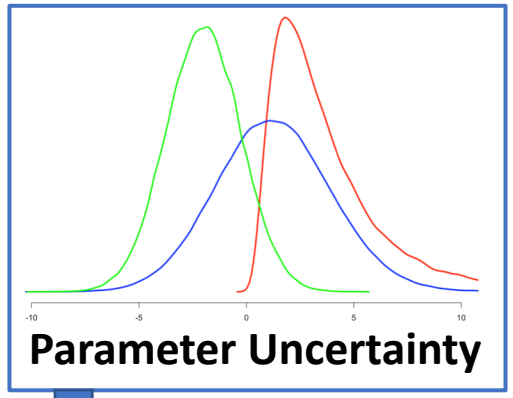






METRUM RESEARCH GROUP

Simulation Process



Simulation Design

Treatment regimen
Study duration
Sampling schedule

Population Parameters

$\theta \quad \omega^2 \quad \sigma^2$

Patient Characteristics

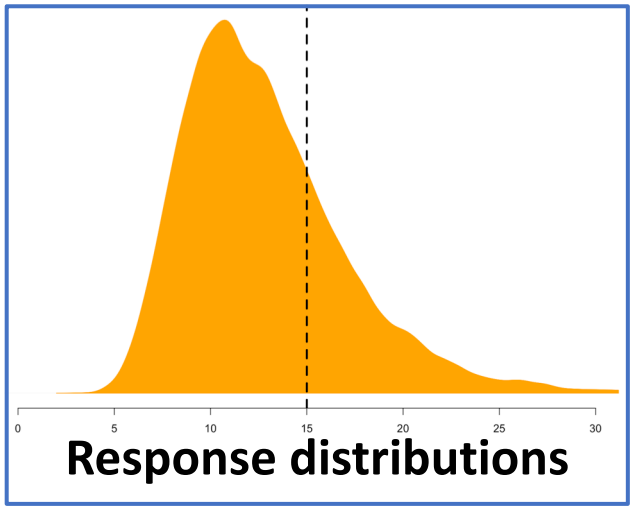
AGE	WT	BMI
27	68	23
48	85	34
33	78	29

Individual Parameters

KA, CL, V, E_0, E_{MAX}, EC_{50}, …

PK/PD Model

$$\frac{dA}{dt} = K_{IN} \cdot \left(1 + \frac{C_p * E_{max}}{C_p + EC_{50}}\right) - K_{OUT} \cdot A$$



METRUM RESEARCH GROUP

Simulation Process

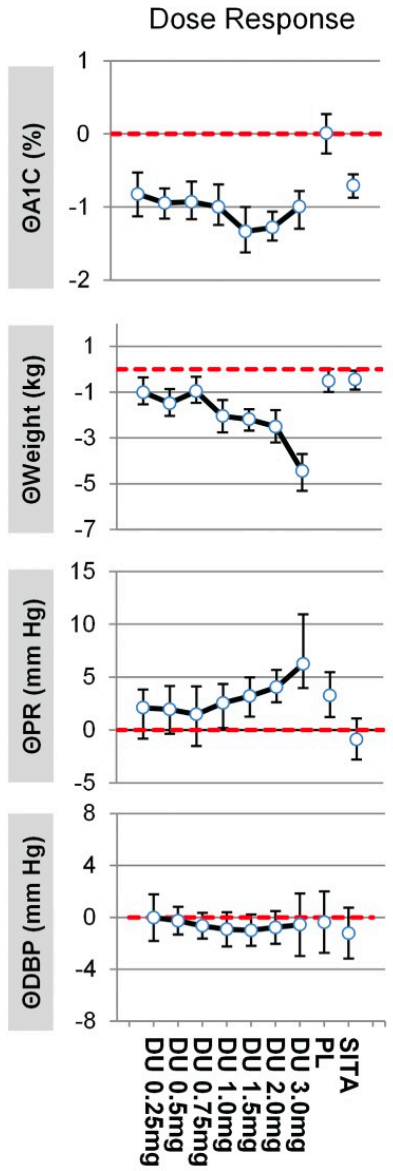
HbA1c, weight loss, and safety models used to simulate virtual patients for optimization of adaptive study design:

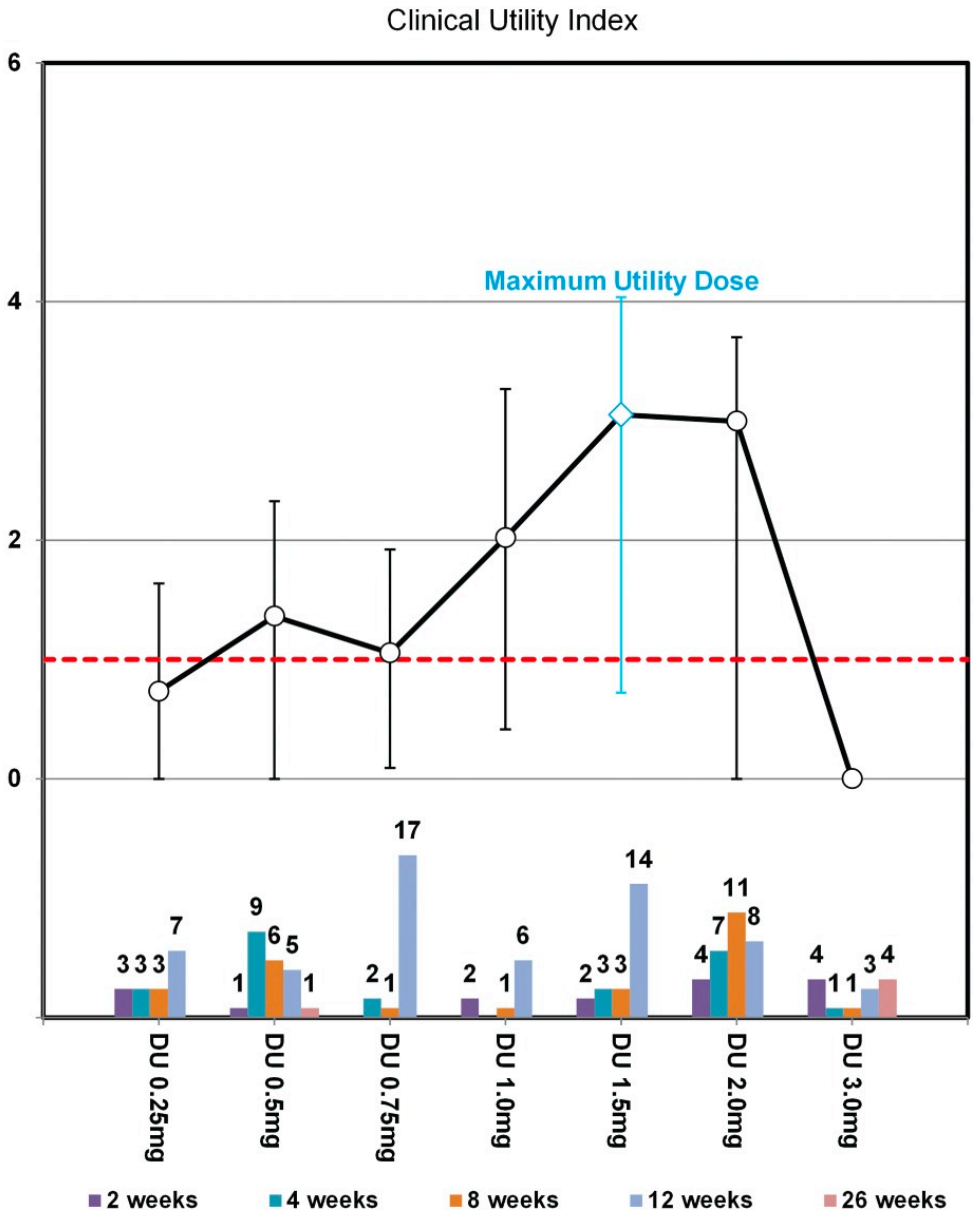
- Patient characteristics drawn from clinical database of T2DM patients.
- Three virtual study populations created based upon parameter uncertainty.
  - **Most likely response**
    Maximum likelihood parameter values
  - **Most pessimistic response**
    5^{th} percentile efficacy, 95^{th} percentile safety
  - **Most optimistic response**
    95^{th} percentile efficacy, 5^{th} percentile safety
- Virtual study populations used:
  - To select dose range for Stage 1.
  - To inform statistical trial simulations for study optimization.

Clinical Utility Index (CUI)

Clinical Utility Index allows assessment across multiple endpoints.

Dose optimized across glycemic control, weight loss and safety

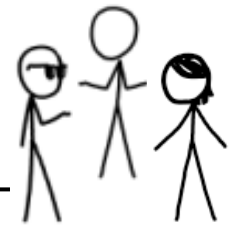




Skrivanek et al. 2013. "The Application of Drug-Disease and Clinical Utility Models in the Design of an Adaptive Seamless Phase 2/3 Study." *Clinical Pharmacology & Therapeutics* 93 (S45).

Trial Simulation Workflow

Virtual patients used to inform statistical trial simulation
- Sampled with replacement from CSV file
- Simulated interactively using R command line interface



Response Models
- **PK/PD**
- Empirical statistical models (null or alternative)

Data Analysis Model
- ANCOVA
- LOCF
- Gatekeeping

Trial Performance Metrics
- Type I error (Scenario in null)
- Probability of correct dose selection
- Probability of stopping for safety
- Probability of stopping for lack of efficacy

Virtual Patients → **Trial Simulator** → Virtual Results → Operating Characteristics

Trial Design
- Inclusion/exclusion criteria
- Visit schedule

Trial Execution Models
- Drop out models
- Accrual models
- Adaptive decision rules:
  - Loss function
  - Futility threshold
- Predictive models:
  - Longitudinal model to predict patient outcomes for ongoing patients
  - Dose-response model to assess population effect

Decision Rules

- Decision rules are informed by Bayesian longitudinal dose-response models, which are used to project efficacy responses at 12 months.
- Objective is to select a high dose for Stage 2.
  - A low dose may also be selected if p(CUI ≥ 0.6) > 60%.

IF(N < 200)

- Dose randomization probabilities updated

IF((N ≥ 200) & (N < 400))

- Stop for futility if: P(non-inferiority) < 5% | P(CUI ≥ 0.6) < 5%
- Go to Stage 2 if: P(non-inferiority) > 85% & P(CUI ≥ 0.6) > 60%
- Otherwise continue with Stage 1

IF(N == 400)

- Go to Stage 2 if: P(non-inferiority) > 70% & P(CUI ≥ 0.6) > 60%
- Otherwise stop the study

Study Design Optimization

The simulation exercise ensured that the study design would operate as intended for a wide range of possible responses.

Allowed the optimization of:

- Dose allocation algorithm for Stage 1
- The duration of Stage 1 (dose-finding)
- Adaptive decision rules
  - When to stop for futility
  - When to proceed to Stage 2
- Type 1 Error Rate (minimize false positives)
- **Probability of Selecting the Correct Dose(s)**

The adaptive study design identified the correct dose 90% of the time, compared to 12% for a traditional fixed design (4 LY arms + placebo for 26 weeks)

Conclusions

The adaptive dose finding aspect of the design:

- Patients allocated more often to optimal doses rather than doses that do not demonstrate a good safety/efficacy profile
- More doses studied (7 vs the typical 3 to 4 doses studied in a fixed design)
- Better decisions (dose selection, futility)

The seamless aspect of the design:

- Is a more efficient use of patient data.
- Eliminates “white space” in development.
- Provides long term safety data sooner in development.

The dose-finding algorithm correctly identified the optimal (marketed) dose.

The cross-functional trial simulation exercise ensured that the study was conducted as efficiently as possible.

Acknowledgments

Eli Lilly and Company

PK/PD & Pharmacometrics

- Jenny Chien
- Jeanne Geiser

Global Statistical Sciences

- Zak Skrivanek
- Bill Prucka

Metrum Research Group

- Marc Gastonguay
- Bill Knebel

the end