Model Based Drug Development at Lilly

CTSI Symposium on Disease and Therapeutic Response Modeling

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Answers That Matter.

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- External Collaborations: Academia, Consortiums and Consultants

Frame

1. Translational Science (PK/PD)

Identifying drug targets and drug candidates with the aim of improving clinical success

2. Drug-Disease (Trial) Models

Vehicle to enable translational efforts

Outline

1. Discuss tools and approaches that allows for decision–making over the research & development life cycle

2. Briefly, Translational Research versus Clinical Trial Simulation (CTS)

3. Two case studies: Oncology and Diabetes

4. Sustaining capabilities through collaborations

What Tools are used?

- Drug-Disease Models
  - Physiologic and metabolism representation of the disease
  - Models of disease progression
  - Exposure-Response Models
- Literature-Based Meta-analysis
- Trial Simulations
- Clinical Utility Index and Assessment of Development Strategies
- Population PK-PD that informs the label, i.e., special populations

In the Preclinical Phase…..

Current state:

Integrate CL, potency and bioavailability estimates for dose projection by incorporating uncertainty and expected variability

Limited use of physiological/mechanistic models that inform candidate selection

Future:

Availability of meta-analysis and mechanistic (systems) models that enables an integrated decision making criteria around the target (and candidate)

- ***integrate knowledge from basic and preclinical research***
- ***requires collaboration between basic and clinical researchers***

One Approach

- A single metric that integrates several estimated parameters, and usually has a high level of uncertainty in the preclinical stage

Potency

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Target Concn

- Exposure rather than dose based
- Possible to leverage comparator for preclinical-clinical potency scaling
- Set to some clinical relevance
- Usually has highest level of uncertainty

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Clearance

- Allometry and other scaling approaches

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Bioavailability

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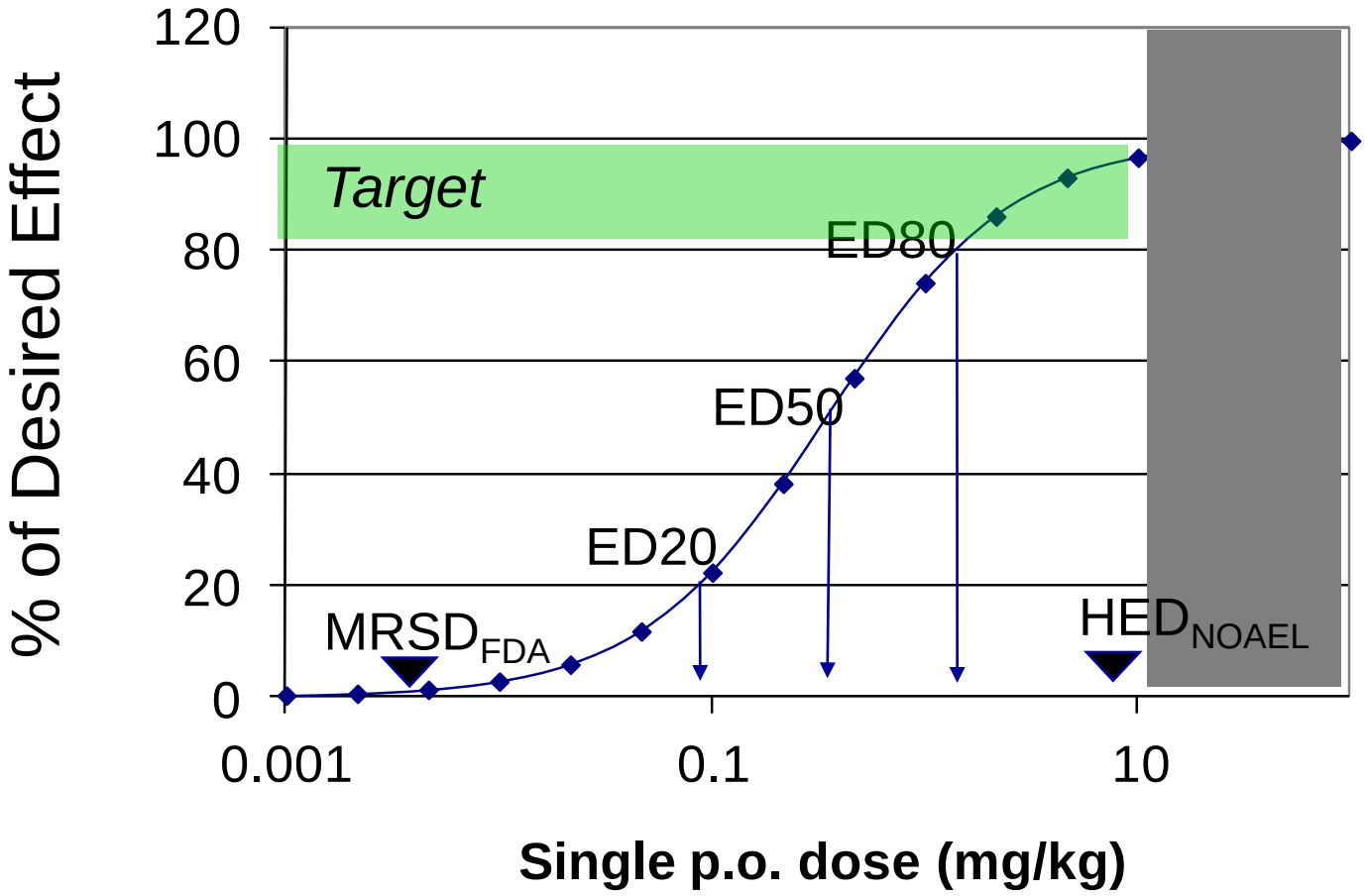
Efficacy Dose

And Then Exploring a Dose Range in Early Clinical Studies



Modelling & Simulation: How?

1. PK model
2. PD and efficacy data: Biomarker in tumor and tumor growth data
3. PD and efficacy model
   - Indirect response model for biomarker
   - Modified Gompertz Tumour growth model

Case Study: Oncology

With the advent of targeted therapies,

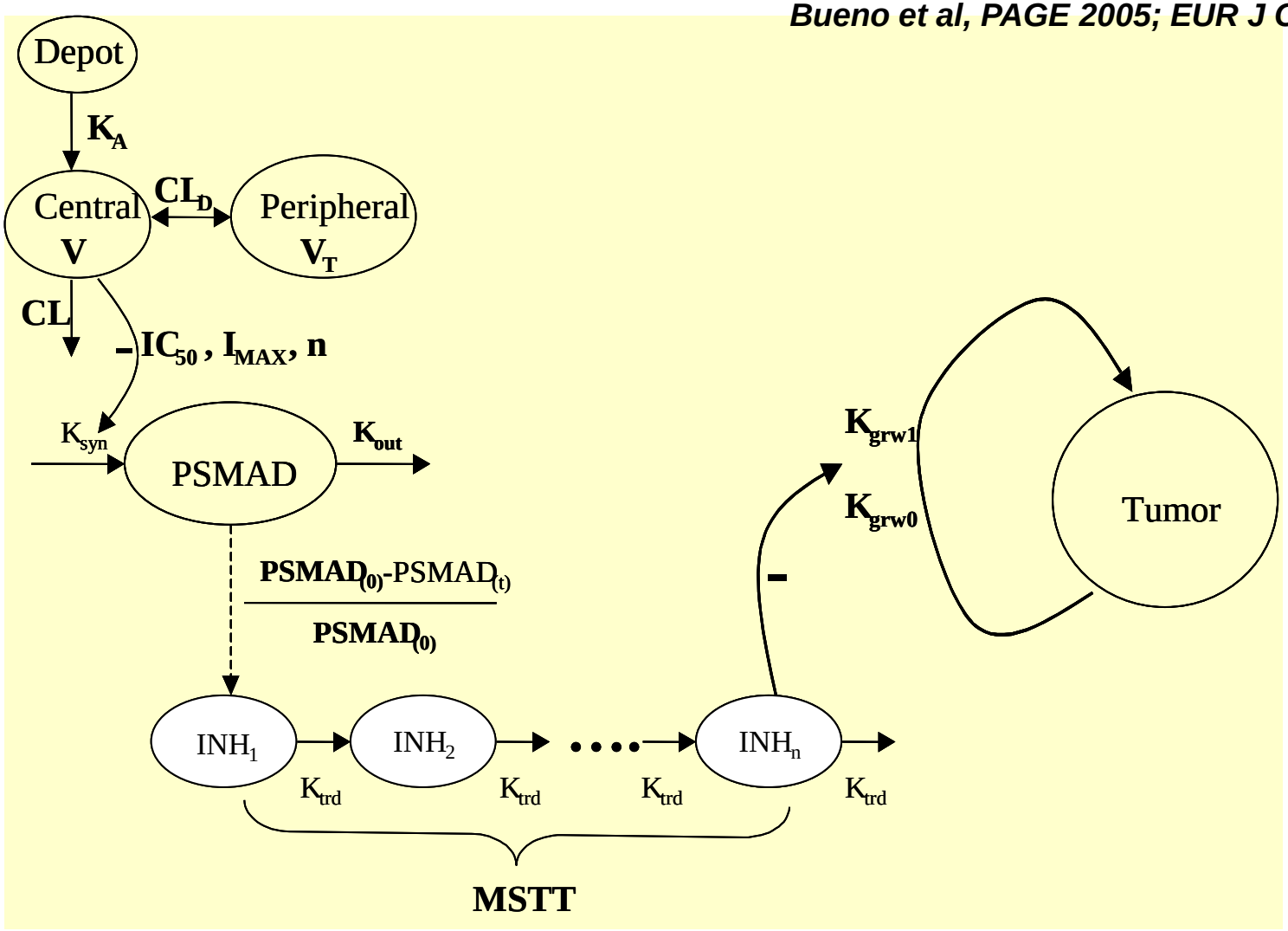
- We need to assess the impact on the target i.e., inhibition
- Key questions of degree and duration of target inhibition need to be addressed i.e., how much inhibition ?
- Issues with chronic oral dosing both pharmacokinetic and pharmacodynamic (e.g. time dependent kinetics or dynamics) come into play
- Translation to clinical efficacy is uncertain

An example of low prior information…

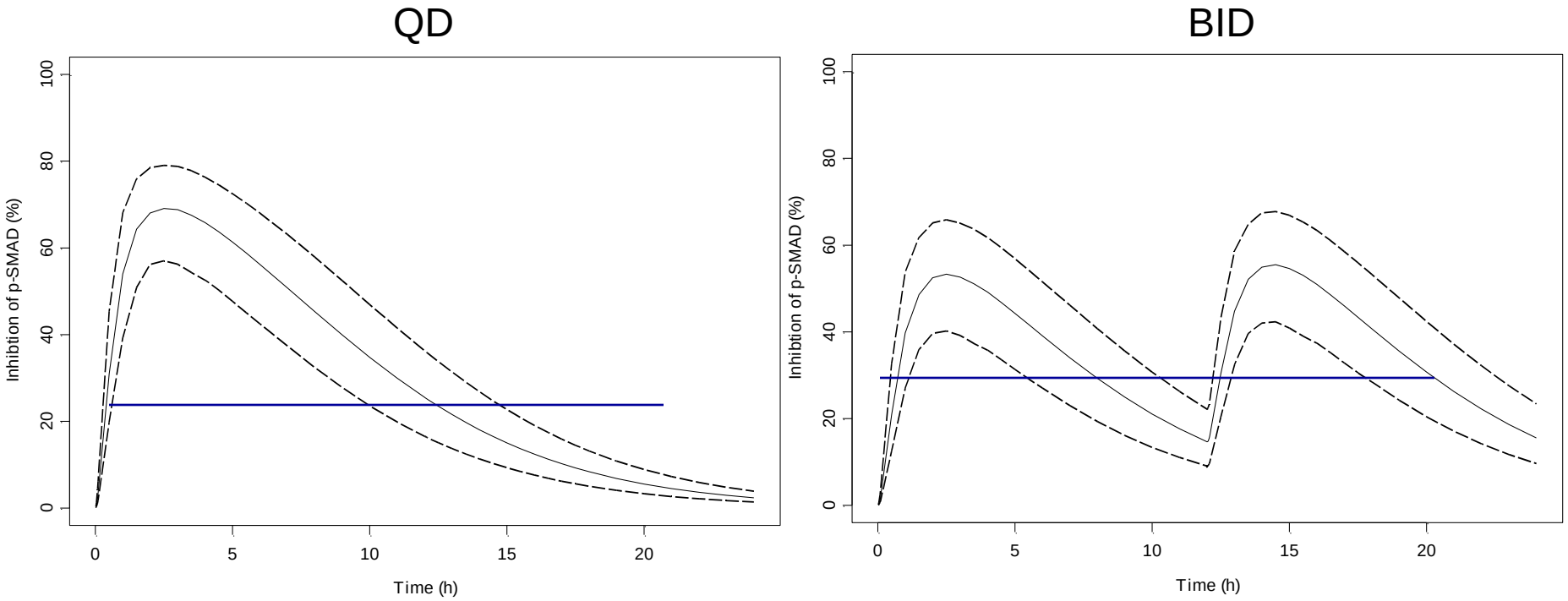
Case Study: Oncology

A PK/PD Model for Inhibition of Signal Transduction

Bueno et al, PAGE 2005; EUR J CAN, 2007



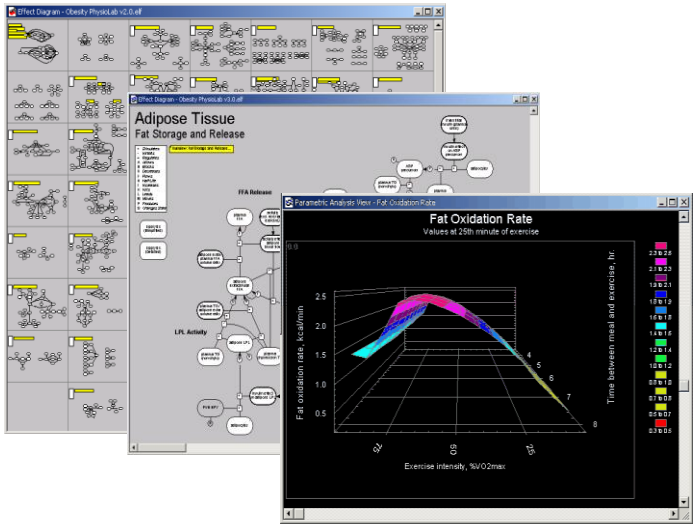
Predicting human biomarker response to assist the design and the dose range selection of FHD



Preclinical data suggested that at least 30% inhibition of biomarker over 24 hours and at least 50% inhibition at Tmax; simulations were performed in order to achieve this level of inhibition.

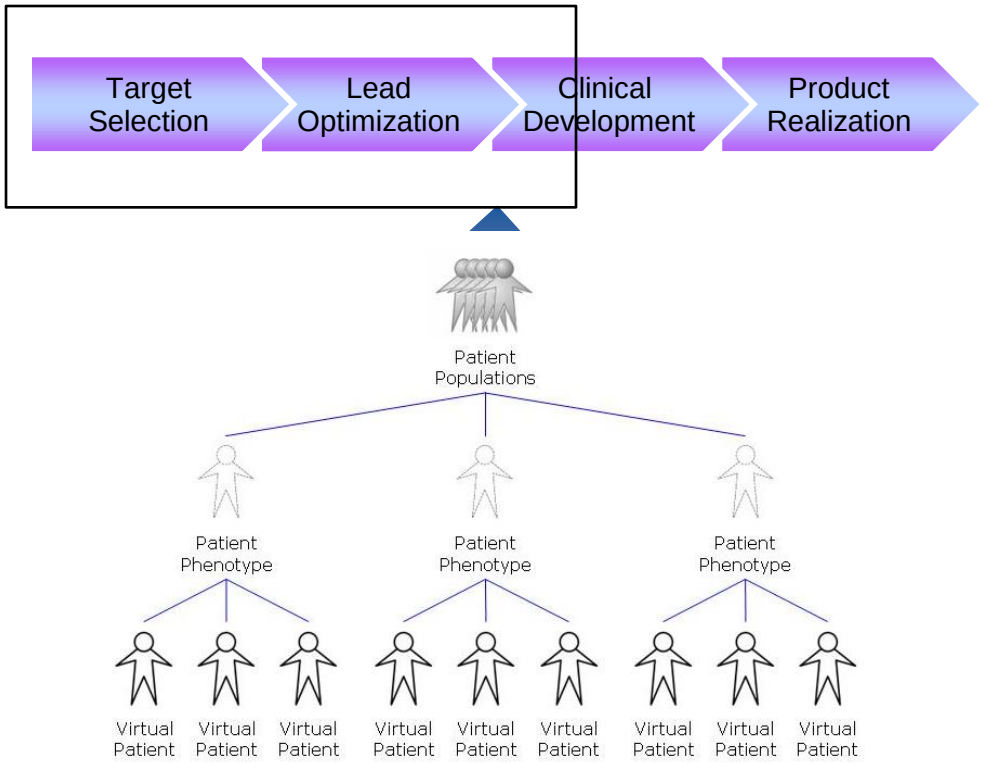
Value of developing disease platforms

Develop large-scale models that detail physiology and explicitly/implicitly represent targets



to simulate human physiology and create virtual patients….

…to predict human response and trigger experiments that test hypotheses



Literature Based Meta-Analysis

- Placebo has been studied extensively in a very heterogeneous patient population

– A meta analysis allows us to study the effect of disease progression

• Go from qualitative approaches of how your drug compares to the competition to quantifying the differences

• Provide comparative data without testing in a clinical program

• The required information may be accessible by quantifying public domain data

.

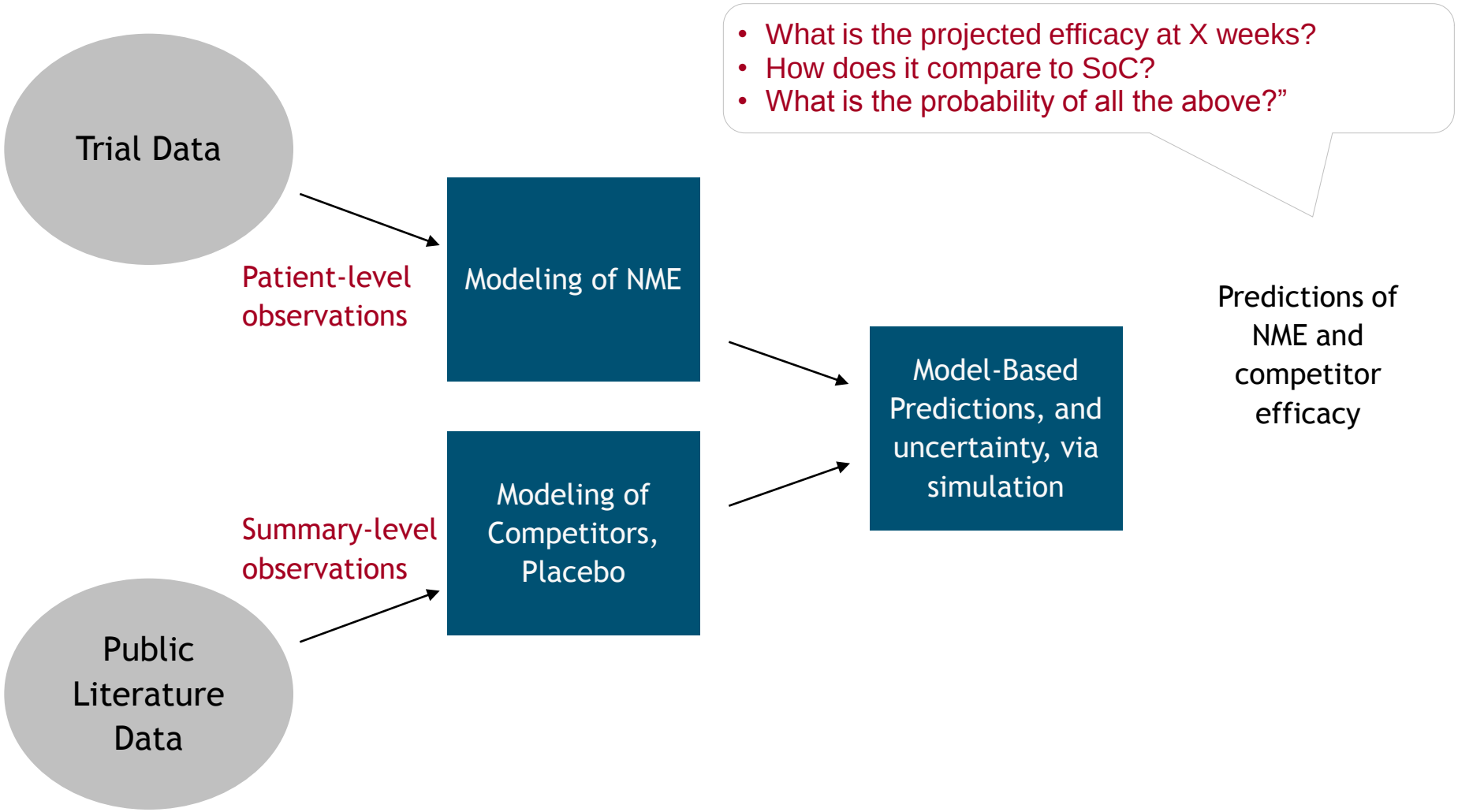
• Pool model predictions based on public domain with model predictions based on in-house data

– qualitative sense: more drugs & more factors of impact

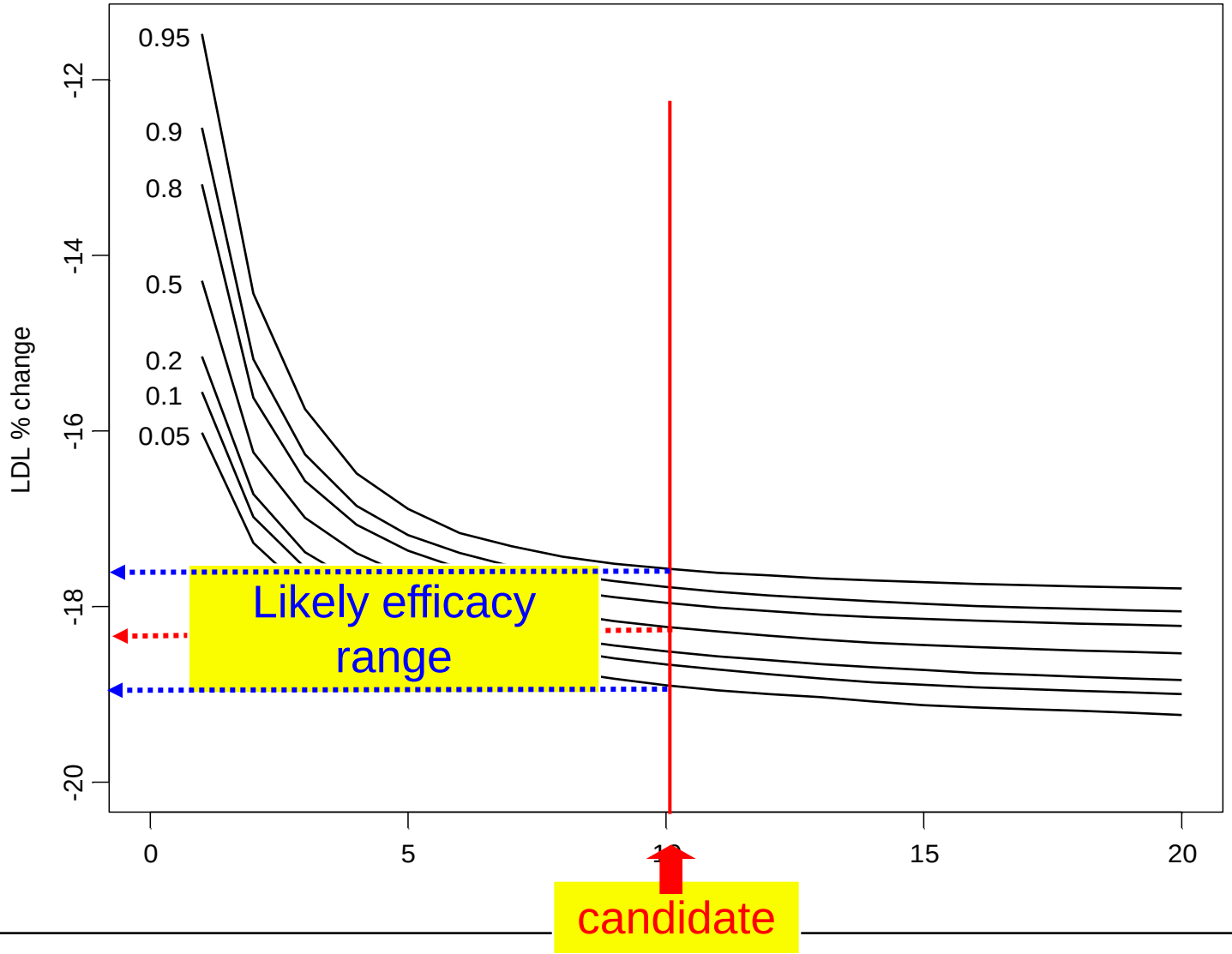
– quantitative sense: distributions rather than point estimates

•Last but not least: Everybody else is doing some form of meta-analysis with data !

Meta-analysis to inform development decisions



Understanding the Likely Efficacy Profile and Dose Response



In POC and Phase 2…..

Current state:

Use of PK and PD models to justify selection of dosing regimens

use of trial simulations (dose, patient population, type of study) in designing trials

Future:

Routine assessment of outcomes given a trial design (s) with focus on informativeness –

Removing uncertainty

Tailoring opportunities

Meta analysis at the EOP2 to supplement Phase 3 Go decisions

Case Study: Diabetes

Drug X:

- Clinical pharmacokinetics from Phase I
- Preclinical data: In vitro potency and response in an animal model with comparators
- Well-characterized biomarker - fasting plasma glucose (FPG)
  - Pre-clinical response thought to be predictive of clinical efficacy related to mechanism of action

An example of high prior information…

Case Study: Diabetes

Key Question (s):

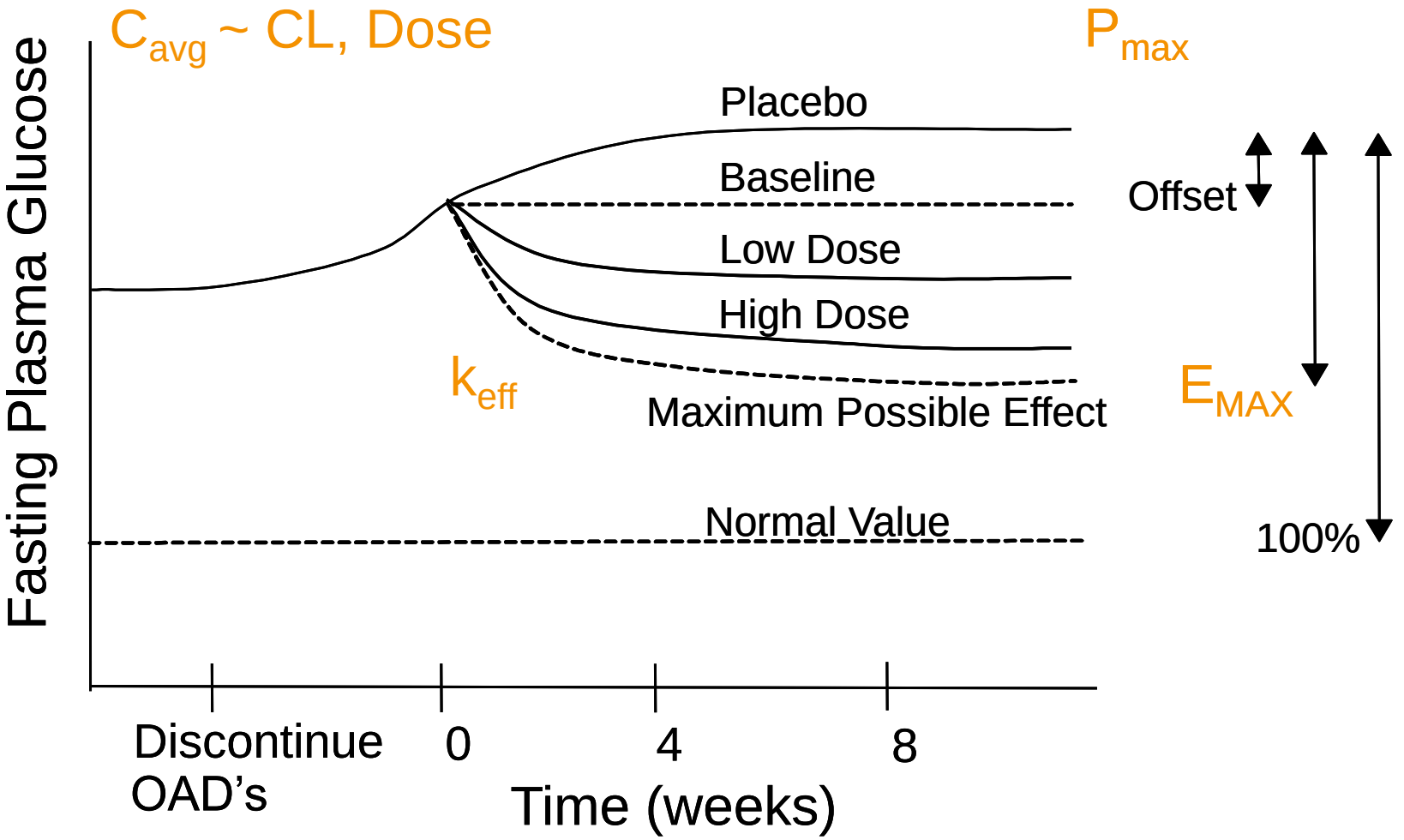
What, if anything, can we do to make quantitative inferences about the efficacy of Drug X given the available information ?

Need and design for a proof of concept study? Phase 2 design considerations?

One approach:

- Use model-based meta-analysis of published clinical efficacy data to construct dose-response models for the marketed drugs
- Combine that with a model to describe the relationship between preclinical and clinical exposure-response for the marketed drugs, i.e., preclinical-to-clinical scaling.
- Apply the resulting model to preclinical Drug X data to predict Drug X clinical efficacy.
- Conduct a trial simulation

Time Course of FPG



Change in FPG = Placebo + Drug

Case Study: Diabetes

An Useful Experiment is Estimating the Relative Potency

- Establish Dose -Concentration-Response relationship for Drug X vs. Comparator 1 and Comparator 2

$$EC_{50,X}^{human} = \frac{EC_{50,C}^{human} \bullet EC_{50,C}^{ZDF}}{EC_{50,C}^{ZDF}} = X \text{ ng/mL}$$

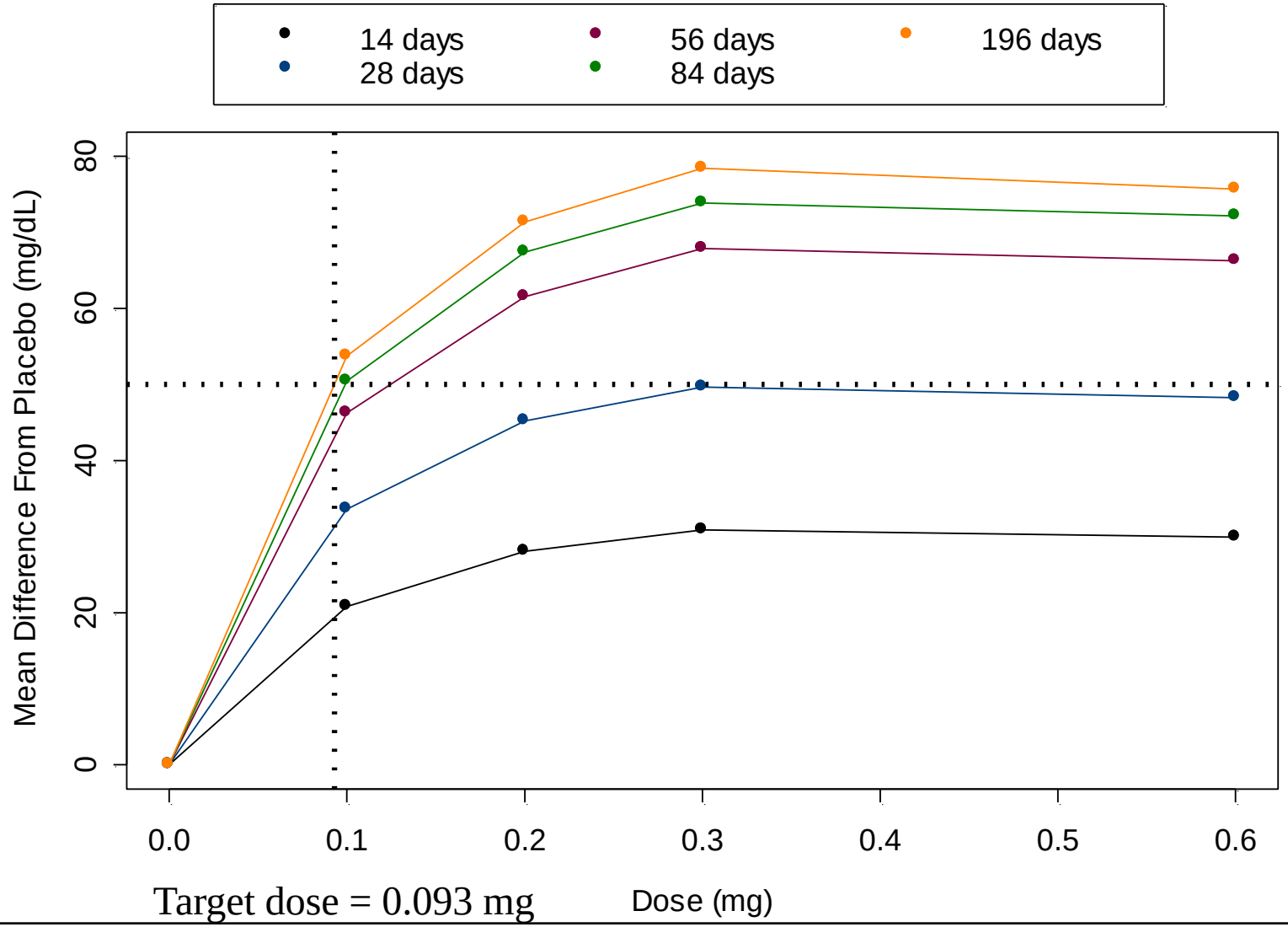
Thus, data from the pharmacology study reduces uncertainty in EC_{50} and allowed refinement to a plausible range for this distribution.

For Phase II simulations:

- Draw EC_{50} from an uncertainty distribution for each trial
- Incorporate inter-individual variability in EC_{50} (e.g. 30% as CV)

Case Study: Diabetes

Population Simulation: Identify a “target” Dose



Drug Disease Model(s)

Pharmacokinetics + Pharmacodynamics + Disease Models

Drug

Goal: Characterize the distribution of treatment outcomes as a

f (Dose, Disease, Patient)

+

Trial Models

Goal: Predict outcomes and reductions in uncertainty as a

f (Dose, Sample size, # Arms, Control, Patient,Duration)

⇩

Trial Outcome

Case Study: Diabetes

Phase II: Simulation Objectives

1. Ensure that all Drug X dose arms show a significant glucose reduction versus placebo.

2. Ensure that the highest Drug X dose arm will result in a glucose reduction that will be at least non-inferior to Comparator (or 50 mg/dL).

3. Ensure the trial will identify a statistically significant dose response relationship, i.e., at least two of the LY treatment arms are different.

In Addition,

- Determine the ability of the optimized trial to support an analysis predicting doses that will achieve a targeted glucose reduction.

Trial Simulation

PK/PD Model + Parameters

E_{max} , EC_{50}, BLGF, γ ,k_{eff} ,P_{max}, CL, BSV, ERR

Mega-Trial (CL, EC_{50})

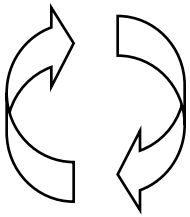
# of Arms: PCB + 3, 4, 5 Active

N = 24, 48, 72, 96
Duration (wks): 2, 4, 8, 12, 28

A Trial

0, 0.2, 0.6, 2, 6, 15 mg LY

N = 48; 4 weeks



- Simulate 200 replicates
- Analyses, Fit

Trial Outcome(s)/Metrics

Estimate a dose based on effect size

Case Study: Diabetes

Phase II Simulation Results

	Percentage of Successful Trials		
Doses (mg)	Placebo**	Dose Response	Non-inferior (X mg/50 mg/dL)
0.02, 0.1, 0.4, 1.0	3	100	100
0.04, 0.1, 0.5, 1.0	6.5	100	100
0.06, 0.2, 0.6, 1.0	22	99	100
0.08, 0.2, 0.8, 2	37	94	100
0.1, 0.5, 1, 2	**50**	**92**	**100**
0.2, 0.8, 2	90	90	100
0.06, 0.5, 2	29	92	100

Case Study: Diabetes

Key Takeaways

Integration of pre-clinical & public-source clinical data permits construction of a model for predicting effects on a biomarker/surrogate.

Leveraging prior information permits choice of trials and more informed design with the information on the probability of selecting a dose for Phase III

Summary

- In the preclinical – clinical phase, using drug disease models is best suited to selecting: target, indication, molecule
- The mechanistic depth of the model largely depends on prior knowledge
- Using disease platforms is a useful approach to understanding phenotypic behavior and variability in response
- Clinical trial simulation is one of program optimization: Combine a drug disease model with a trial model (sample size, dropouts, compliance)