ASCPT 2018

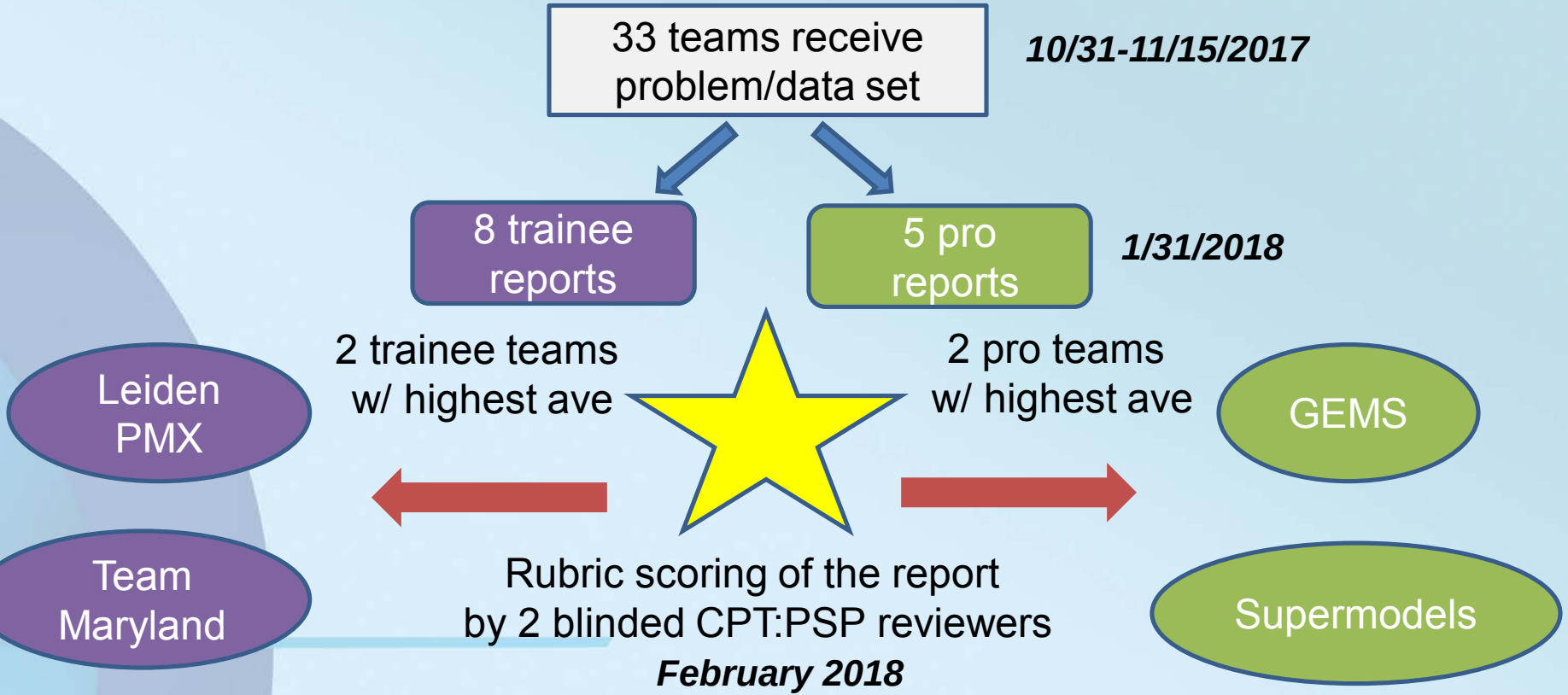
ANNUAL MEETING

MARCH 21 - 24, 2018 · HILTON ORLANDO · ORLANDO, FL

Welcome & Introduction

- WHY: Communication skills!
- WHAT: a challenging drug development problem to be solved by pharmacometricians and presented to clinical decision makers
- WHO:
  - UNC: Alan Forrest, Julie Dumond
  - Certara: Mark Lovern, Nathan Teuscher, Shuhua Hu
    - Organizers/Expert Panel were not involved in the team evaluation process

MIDD Gran Prix Workflow



MIDD Gran Prix Workflow

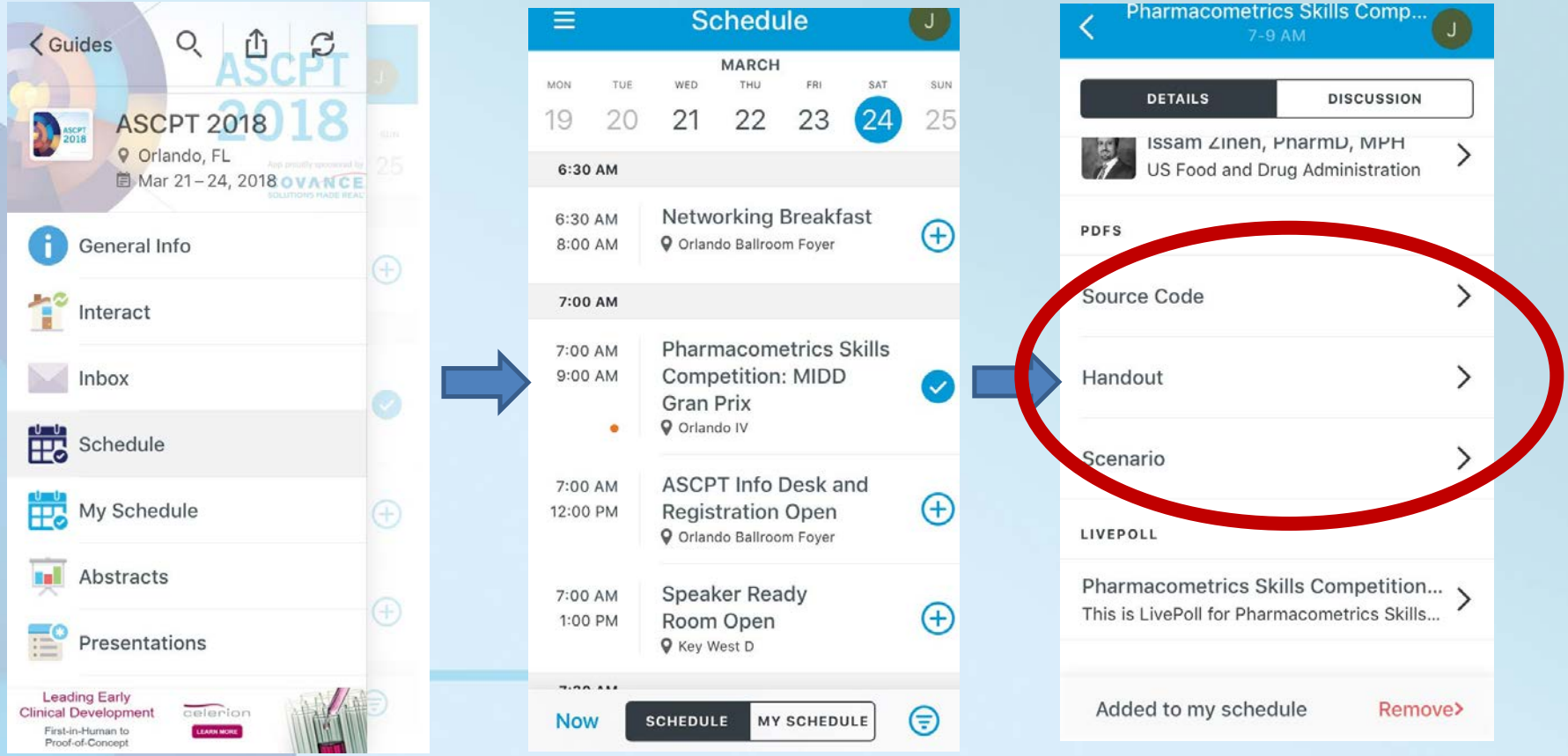
Expert Panel Judging and Awards

Audience Winners and Audience Q&A

MIDD Gran Prix Expert Panel

- Jill Fiedler-Kelly, Cognigen Corporation
- Richard L. Lalonde, Bradenton, FL
- France Mentré, University of Paris Diderot
- Carl Peck, UCSF Center for Drug Development Science
- Issam Zineh, US Food and Drug Administration

The Case of Drug D



The Challenge to the Contestants

- Develop dosing guidelines for Drug D
  - Restrictive protein binding, active metabolite
  - Increases concentrations of R
  - Consider precision dosing
- Quantify the % of patient days that are below, within, and above the R target range with your dosing regimen

The Challenge to the Contestants

- Should we proceed directly to a Phase 3 study?
- Identify and propose solutions to the critical gaps in knowledge that might affect the success of Drug D
- Compared to D0, the current standard of care, what is the commercial viability of Drug D?
  - D0 is dosed twice daily
  - ~70% of patients receiving D0 achieve R concentrations in the target range
  - Graded and defined adverse event profile

Student/Trainee Team Presentations

Trainee Team 1: Leiden PMX

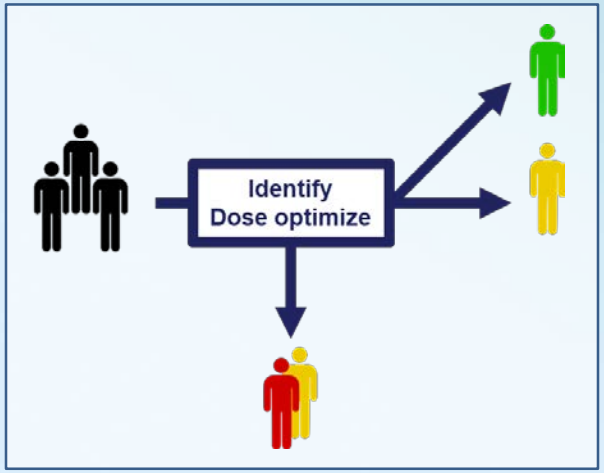
Presenter: Rob van Wijk, PhD

Team Members:
Sebastiaan Goulooze, MSc
Linda Aulin, MSc
Sinziana Cristea, MSc
Michiel van Esdonk, MSc

IDOSE: identification of and dose optimization for drug D-sensitive patients

Leiden PMX

Rob van Wijk, Linda Aulin, Sînziana Cristea, Michiel van Esdonk, Sebastiaan Goulooze



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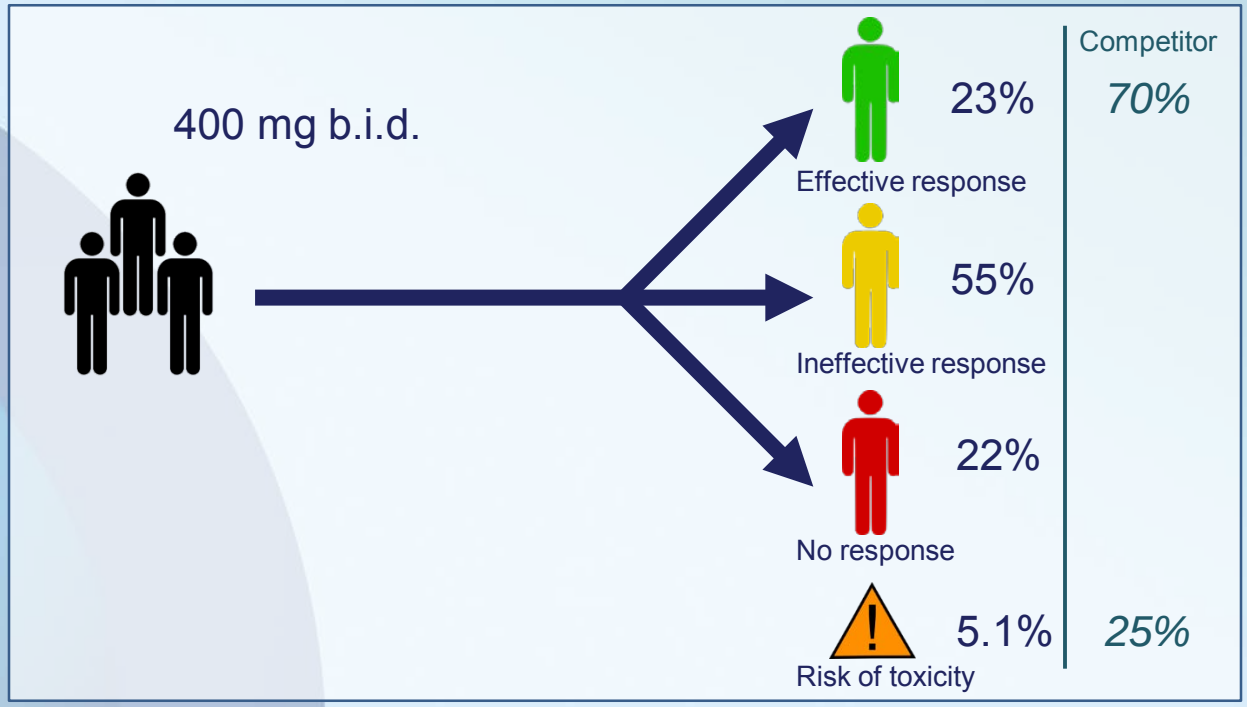
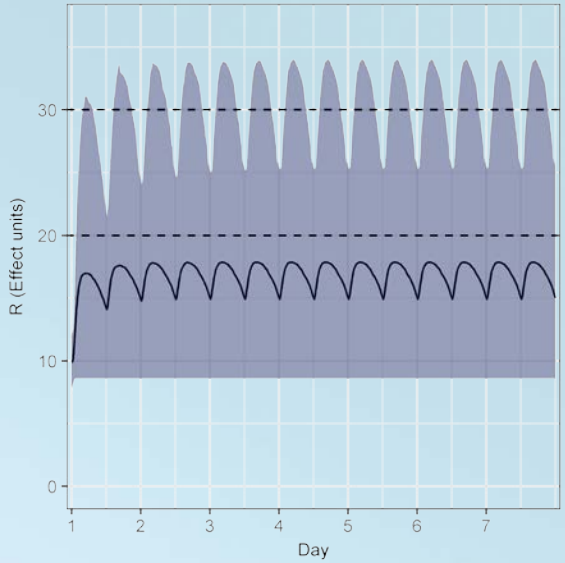
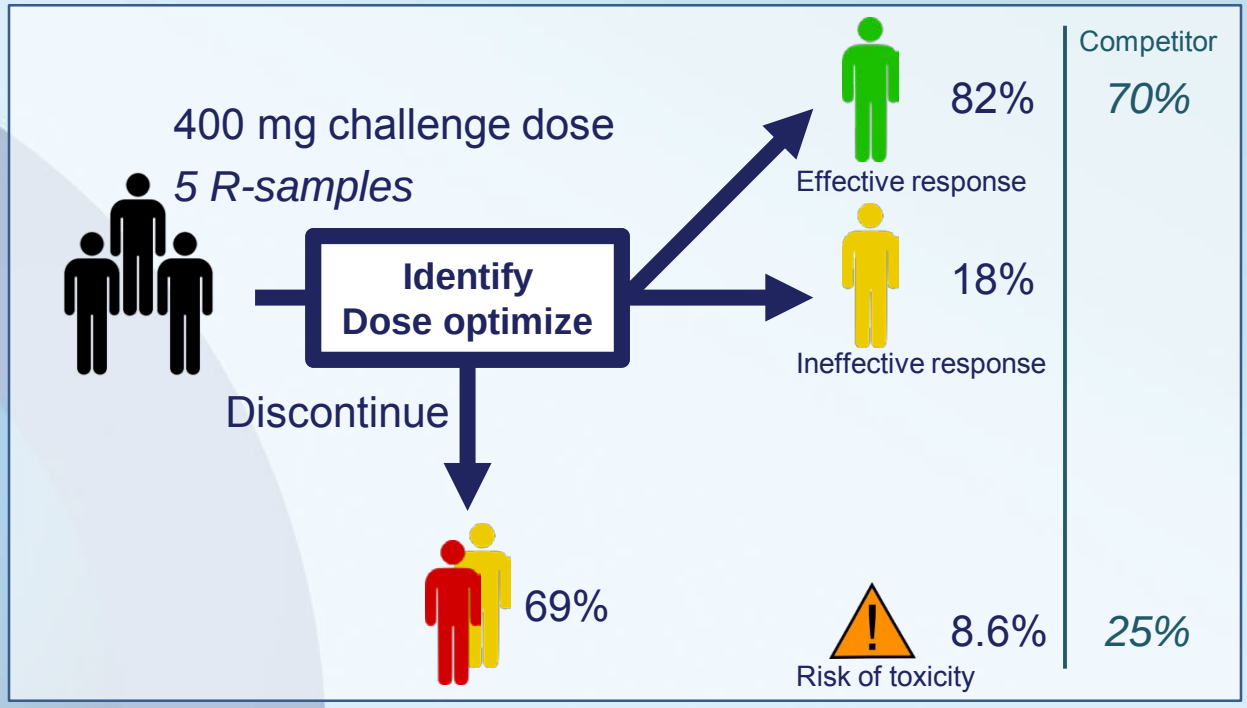
Fixed dose of drug D only treats 23%

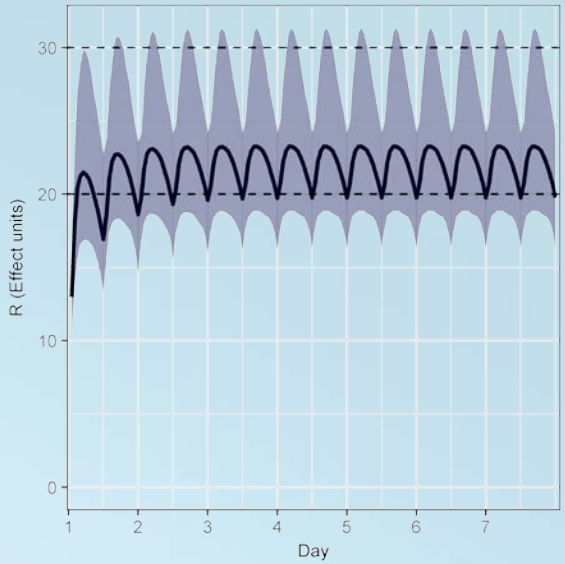




Drug D-sensitive patients need to be identified

Select drug D-sensitive patients





Identify and Dose Optimize SEnsitive patients (IDOSE)

IDOSE

This IDOSE application was developed to identify and optimize dosing in sensitive patients for drug D.

Insert a patients albumin, GFR (MDRD) and observed R levels and the dosing algorithm will start.

Patient characteristics:

Albumin (g/100mL)

3.1

GFR MDRD (mL/min)

23

Insert observations below:

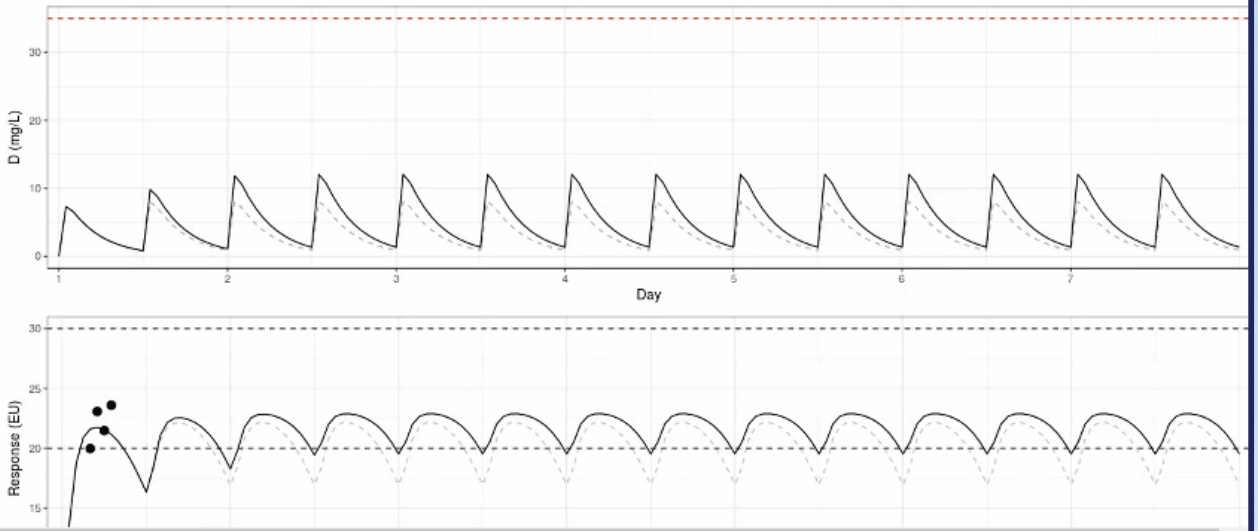
Time after dose (h)	Response (EU)
-0.5h	10.66

Introduction | Dosing recommendations | Model fit results

Main conclusions:
A new dose of 600 mg was estimated for this individual!
The percentage of time within the therapeutic window with the new dosing regimen was 86.9 % of the 7 day period.
The risk on adverse events was only 5.9 %.

Continue treatment of this individual with a dose of 600 mg b.i.d.

Simulations with an up-titration of 100 mg per dose have been performed and are shown in black below, if applicable.



Model informed advice

Commercial viability

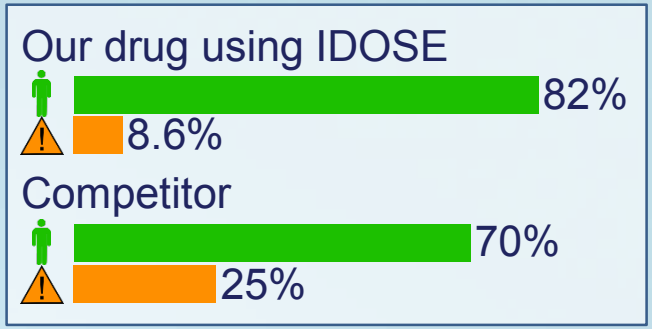
- Substantial clinical benefit necessary

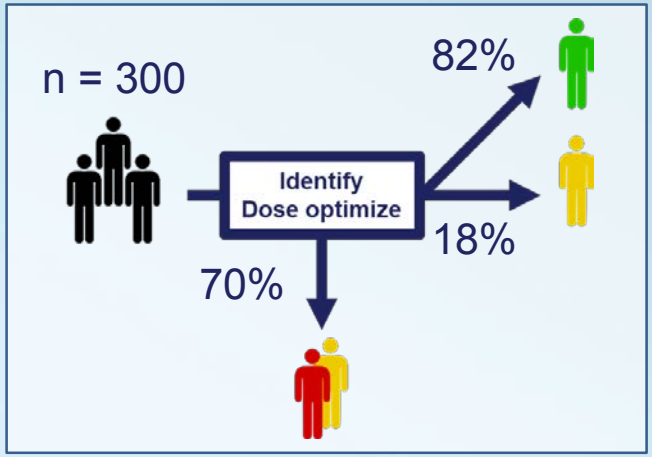
Phase IIb study using IDOSE application

- 300 patients, 7 days treatment

Knowledge gap

- Mechanism of action
- Drug-drug interactions





Trainee Team 2: Team Maryland

Presenter: Alejandro Perez Pitarch, PhD

Team Members:

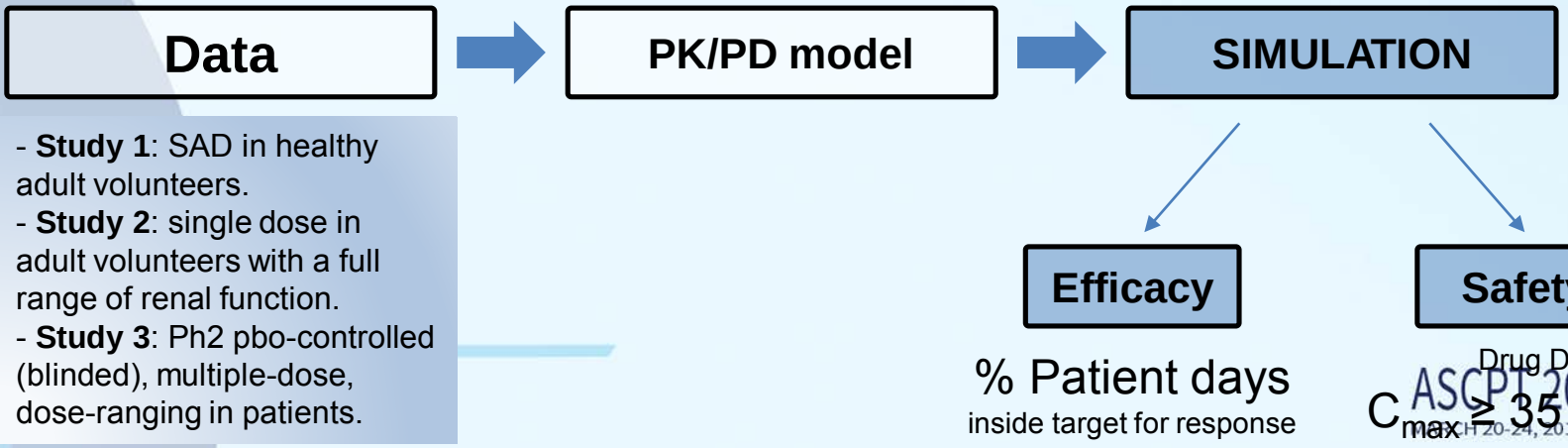
Ken Ogasawara, PhD

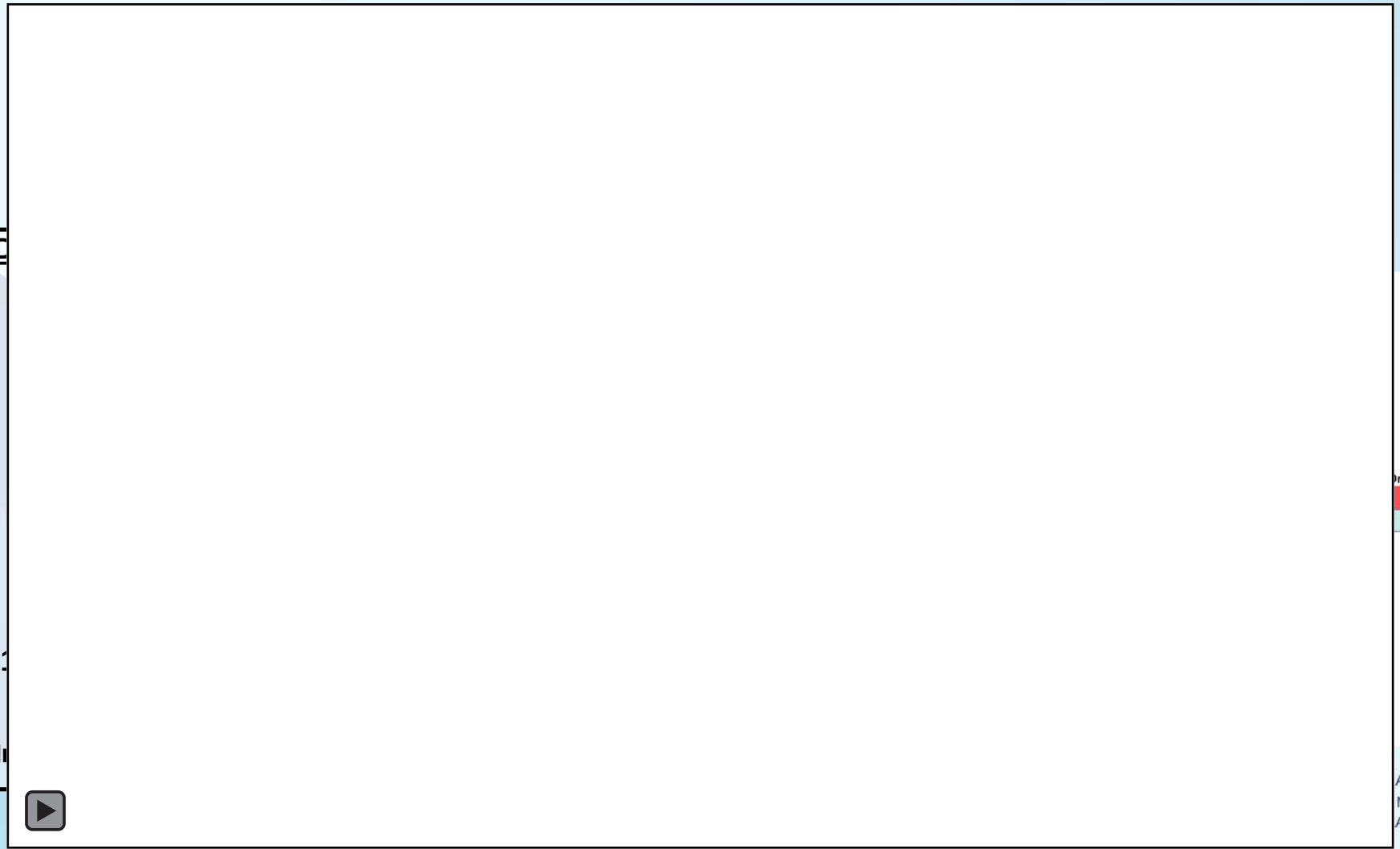
Beatriz Guglieri Lopez, PhD

Outline

OBJECTIVES

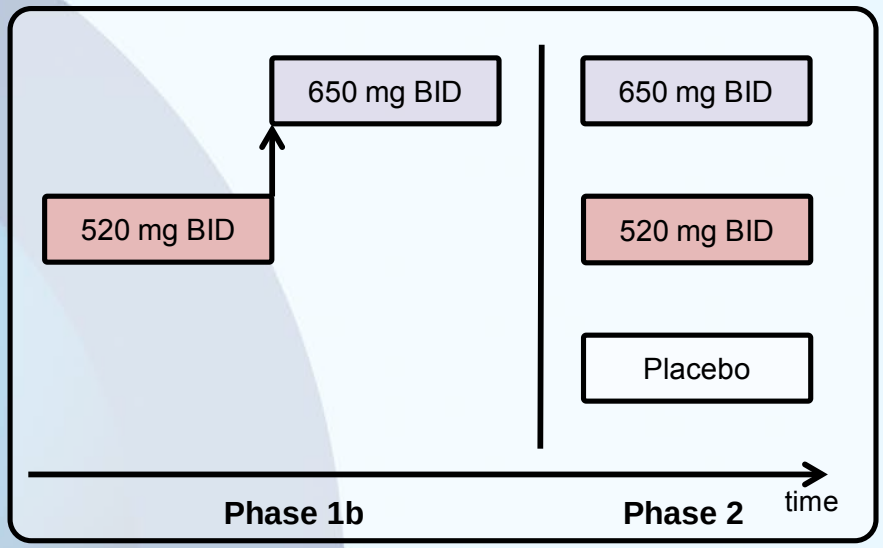
1. Propose dosing guidelines for Drug D.
2. Propose next study design.
3. Identify critical gaps in knowledge that might affect the success of Drug D in this disease.
4. Assess the commercial viability of Drug D relative to the SOC.




rug D Cmax
>= 35 mg/L
< 35 mg/L

2) Next Study Design & 3) Critical Gap

Next Study Design



Critical Gap

A subpopulation of **non-responders** to Drug D has been identified (~20%)

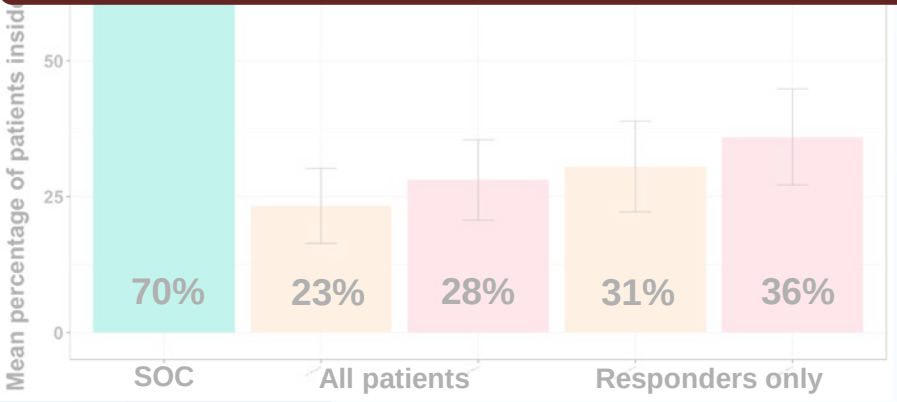
Pharmacogenomic analysis

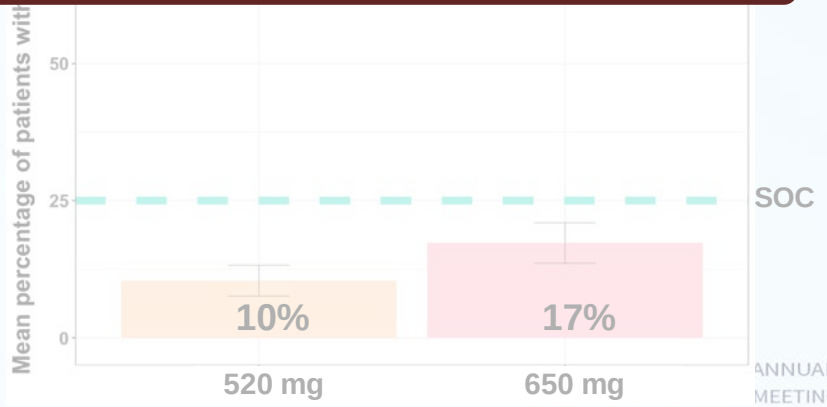
4) Commercial Viability of Drug D

Efficacy

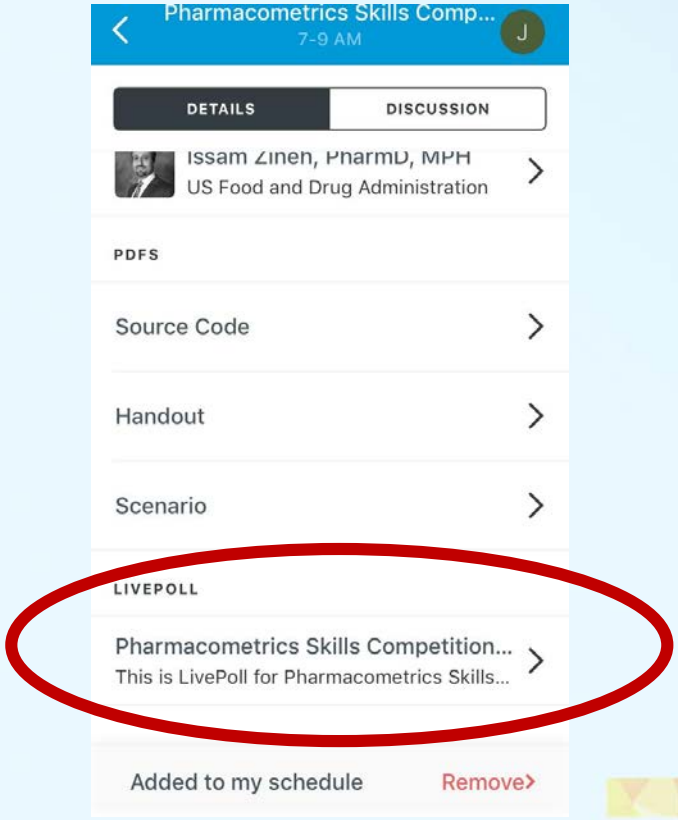
Safety

The commercial viability of Drug D relative to the standard of care is limited based on the available information.





Cast your Vote Now



Professional Team Presentations

Professional Team 1: GEMS (Genentech Modelers)

Presenter: Kenta Yoshida, PhD

Team Members:
Vidya Ramakrishnan, PhD
Matts Kagedal, PhD
Michael Dolton, PhD
Phyllis Chan, PhD

Model-Informed Assessment of Development Strategy for Drug D

Executive Summary

- Current assessment of commercial viability for Drug D is low
  - Non-responders and need of treatment individualization to match the efficacy profile with D0
- Key knowledge gaps:
  - Exposure-response at expected therapeutic dose levels for efficacy & safety
  - Drivers of efficacy and safety (parent/metabolite)
  - Mechanism of variable drug response among patients
- Phase 2 study and in vitro/preclinical mechanistic studies are recommended to:
  - Fill the knowledge gaps and provide better assessment of commercial viability
  - Optimize treatment individualization strategies to achieve better balance of efficacy/safety

Team GEMS (GEnentech ModelerS) - March 24, 2018

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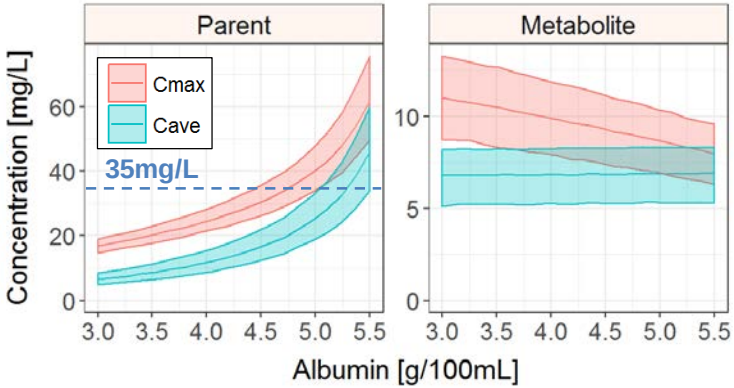
Key learnings from PKPD analysis

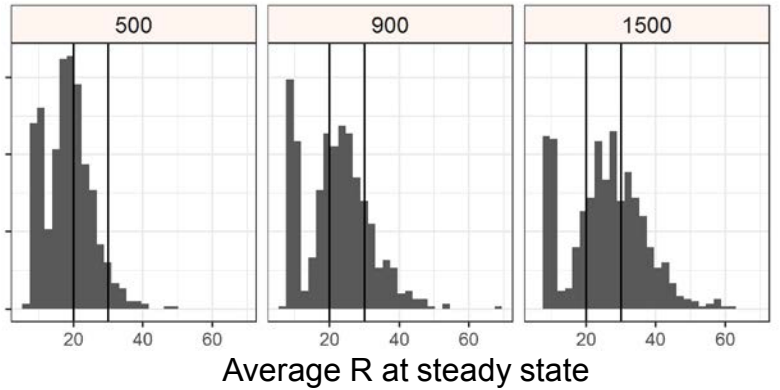
- Population PK analysis
  - Linear PK observed across dose levels
  - High albumin levels steeply increase total parent concentration, but not metabolite
  - Limited understanding of unbound parent drugs
  - Uncertainty in drivers of safety makes it difficult to directly translate the finding into recommendations

- Population PK/PD analysis
  - Metabolite seemed to drive response (R)
  - R<20 for most patients in study 3
  - Large inter-individual variability (IIV) in drug effect
  - Subset of population (~20%) did not appear to respond to the treatment

Simulated exposures with 900mg BID dosing



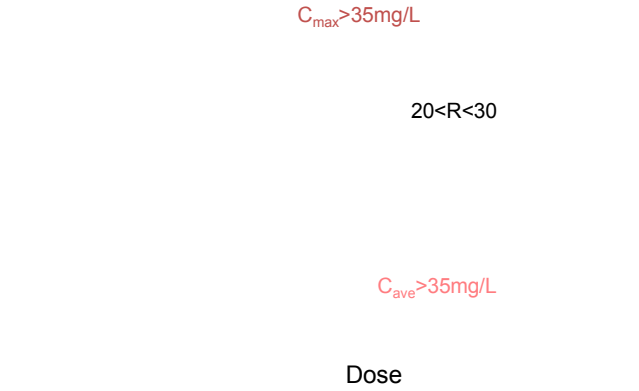
Simulated PD response (R) at different dose levels



Optimal dose explored by clinical trial simulations

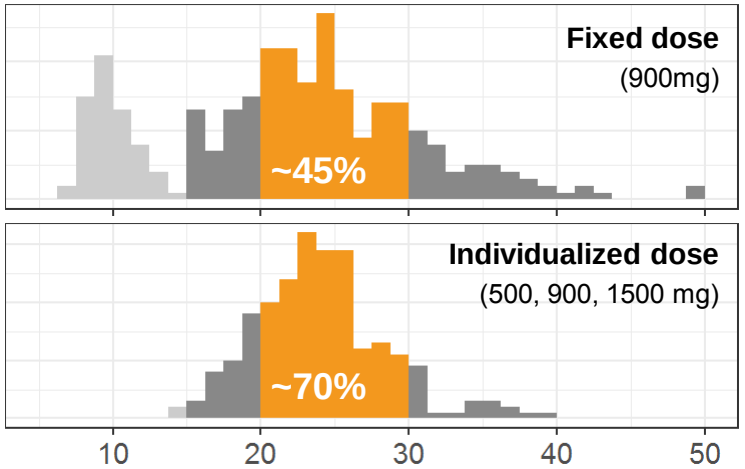
- 900mg BID is most likely to maximize target attainment (20<R<30)
  - Uncertainty in “best dose” due to paucity of data from therapeutic dose levels
  - Increased proportion of exceeding safety threshold (R>35 and parent>35 mg/L) with higher dose

Proportion of patients achieving 20<R<30



- Dose individualization expected to improve target attainment
  - Large variability in drug effect warrants dose individualization based on measured R after one dose
  - Target attainment similar to D0 can be achieved

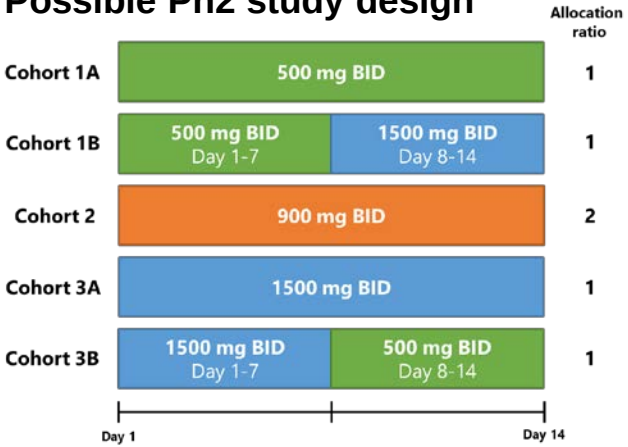
Simulated average R at steady state



Recommended next steps for drug D

- Additional Ph2 study
  - Characterize E-R at exposures covering expected therapeutic dose levels
  - Dose-switching cohorts (1B/3B) to inform feasibility/accuracy of dose individualization strategy
  - Analysis of outcome to optimize Ph3 dose including individualization
- Biomarkers for PD effect
  - Explore biomarkers that can explain inter-individual variability in drug response and identify non-responder population
- In vitro / preclinical studies
  - Establish active compound responsible for efficacy/safety
  - Mechanism of albumin effect, measure unbound parent drug in plasma
- Evaluate other factors that influence clinical utility of D
  - Properties of AE (severity, frequency) and relative importance of disease control vs minimizing AEs
  - Need of treatment individualization for the Drug D0

Possible Ph2 study design



Recommendations

- Current assessment of commercial viability for Drug D is low
  - Non-responders and need of treatment individualization to match the efficacy profile with D0
- Key knowledge gaps:
  - Exposure-response at expected therapeutic dose levels
  - Drivers of efficacy and safety (parent/metabolite)
  - Mechanism of variable drug response among patients
- Phase 2 study and in vitro/preclinical mechanistic studies are recommended to:
  - Fill the knowledge gaps and provide better assessment of commercial viability
  - Optimize treatment individualization strategies to achieve better balance of efficacy/safety

Acknowledgement

- Event organizers
- Team GEMS

Phyllis Kenta Matts Michael Vidya

Professional Team 2: Supermodels

Presenter: Akekemi Taylor, PhD

Team Members:
Leon Pheng, PhD
Benjamin Rich, PhD
Thomas Peyret, PhD

Drug D

DOSING RECOMMENDATIONS AND ASSESSMENT OF COMMERCIAL VIABILITY

Supermodels Team (Certara)

Thomas PEYRET
Leon PHENG
Ben RICH
Adekemi TAYLOR
Yuan XIONG

CAN WE SUCCESSFULLY MARKET DRUG D?

DRUG D

- Under development to treat disease X
- M is it's major metabolite
- Increasing doses of D increases concentrations of endogenous R

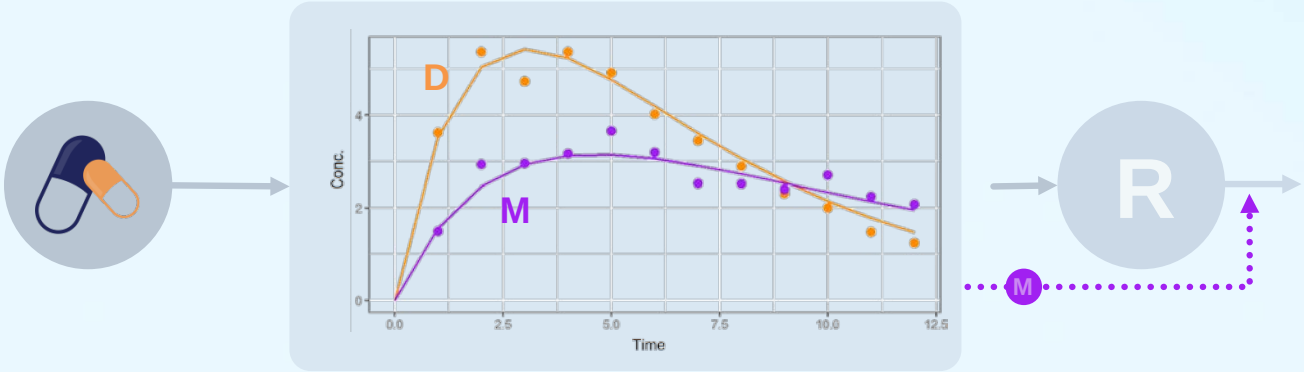
BID DOSING OF THE D0 (SOC) ACHIEVES PD TARGET IN 70% OF PATIENTS, WITH AES IN 25%

TARGETS

- PD: R = 20 – 30 units
- Safety: D ≤ 35 mg/L

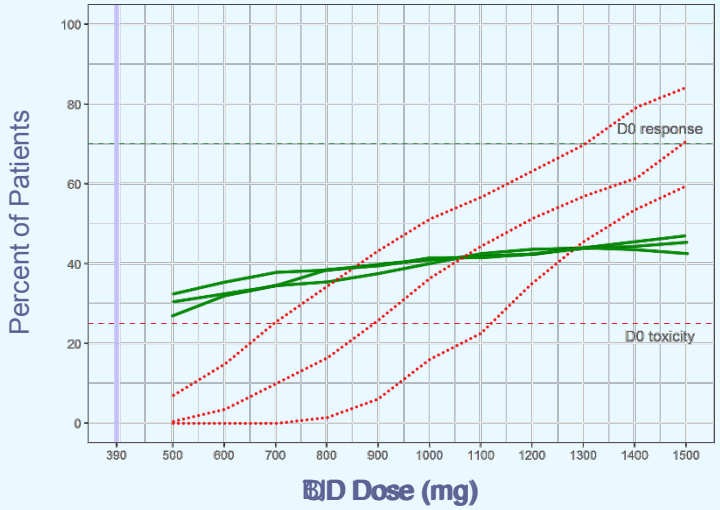
WHAT WE HAD
AND WHAT WE DID

STUDY	POPULATION	DOSING	SUBJECTS	DATA
1	Normal adult volunteers	21 to 84 mg (single ascending dose)	21	Plasma D&M, Urine D
2	Normal & impaired renal function	70 mg (single dose)	35	Plasma D&M, Urine D
3	Phase 2 blinded placebo-controlled study	Placebo, 130, 260, 390 mg (multi-dose)	130	Plasma D&M, Serial R



Maximum inhibition = 52.5%
IC50 = 1.53 mg/L M
Mean Cmax = 4.5 mg/L M

AT SAFE DOSES, <50% OF PATIENTS ACHIEVED THE TARGET RESPONSE



- % experiencing target response
- % experiencing AEs (exceed the safety threshold of 35 mg/L of D).
- maximum dose tested in clinical studies (390 mg once daily)

THE MODEL PREDICTS A DRUG-INDUCED MAXIMUM INCREASE IN R OF 111% ⟶ ~21 EFFECT UNITS.

DRUG D IS NOT READY YET
FOR PHASE 3 PRIME TIME

Drug D is currently **not commercially viable**

None of the dose regimens studied or simulated **beat D0 PD**

Increasing D dose increases the risk of safety issues

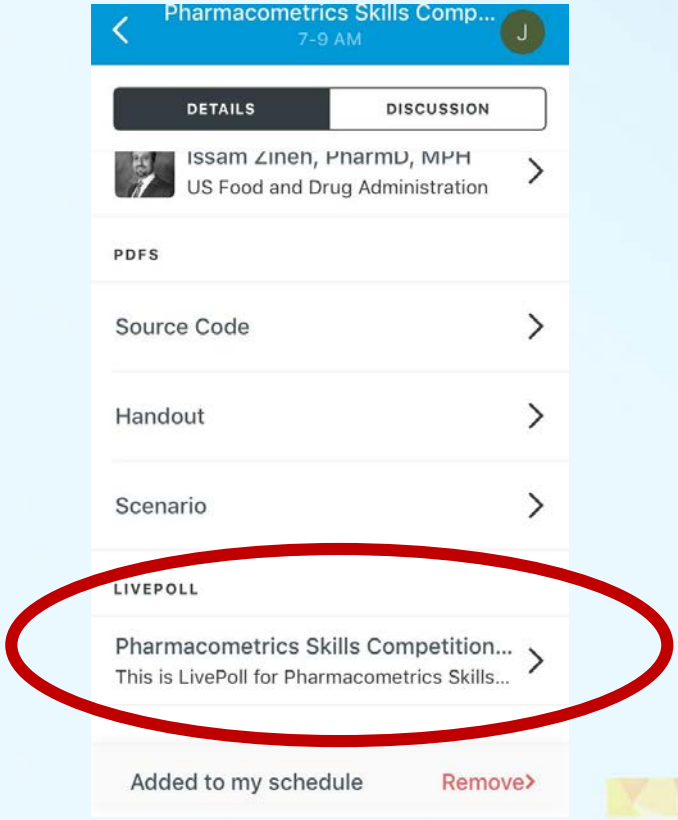
Next steps

Higher doses need to be tested in Phase 1 and 2 PK/PD studies

Investigate whether a high-responding subpopulation can be identified

Run a special population trial in high-responding subjects

Cast your Vote Now



Judges' Decisions

Awards Presentation

Questions?

Back-Up Slides

The Case: Drug D

- Data from three clinical studies
  1. Single ascending oral dose, healthy volunteers
  2. Single oral dose, healthy + end-stage renal disease
  3. Phase 2, multiple-dose, dose-ranging, placebo-controlled, patients
- Drug (D), metabolite (M) in plasma (1, 2. 3)
- D in urine (1, 2)
- Pharmacodynamic response (R, 3)

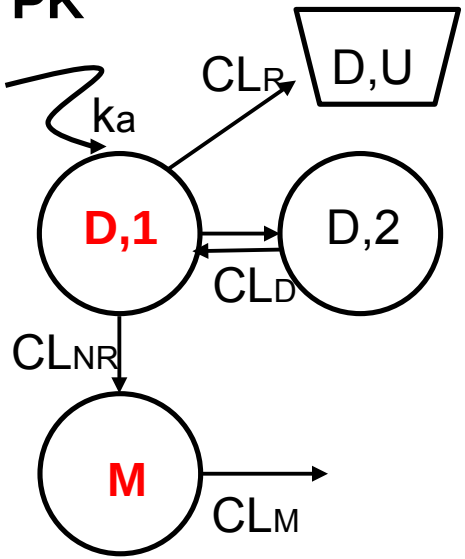
Drug D: Known Properties

- D is ~ 80% bound, mainly to albumin
- M is cleared by nonrenal routes, not highly bound
- PD is an increase in an endogenous molecule R
  - Baseline: 6-12 units
  - Target: 20-30 units
    - 25% of animals experience toxicity at 25-35 units
- D > 35 mg/L associated with significant toxicity risk

Drug D Clinical Studies: Technical Details

- Handout available in the ASCPT Meeting

PK

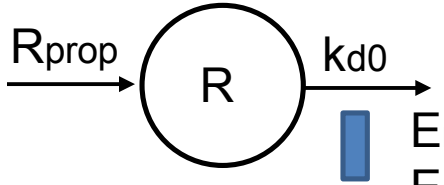


Significant covariates:
CrCL on CL_R
Age on CL_{NR}

D: restrictive binding,
f_u linear with albumin

D and M are both active

PD



$k_{d0} = R_{prop}/R(0)$

$C_{pd} = RP*f_u*\mathbf{D,1} + \mathbf{M}$