A Modeling and Simulation Case Study

Impact on an Early Clinical Development Program

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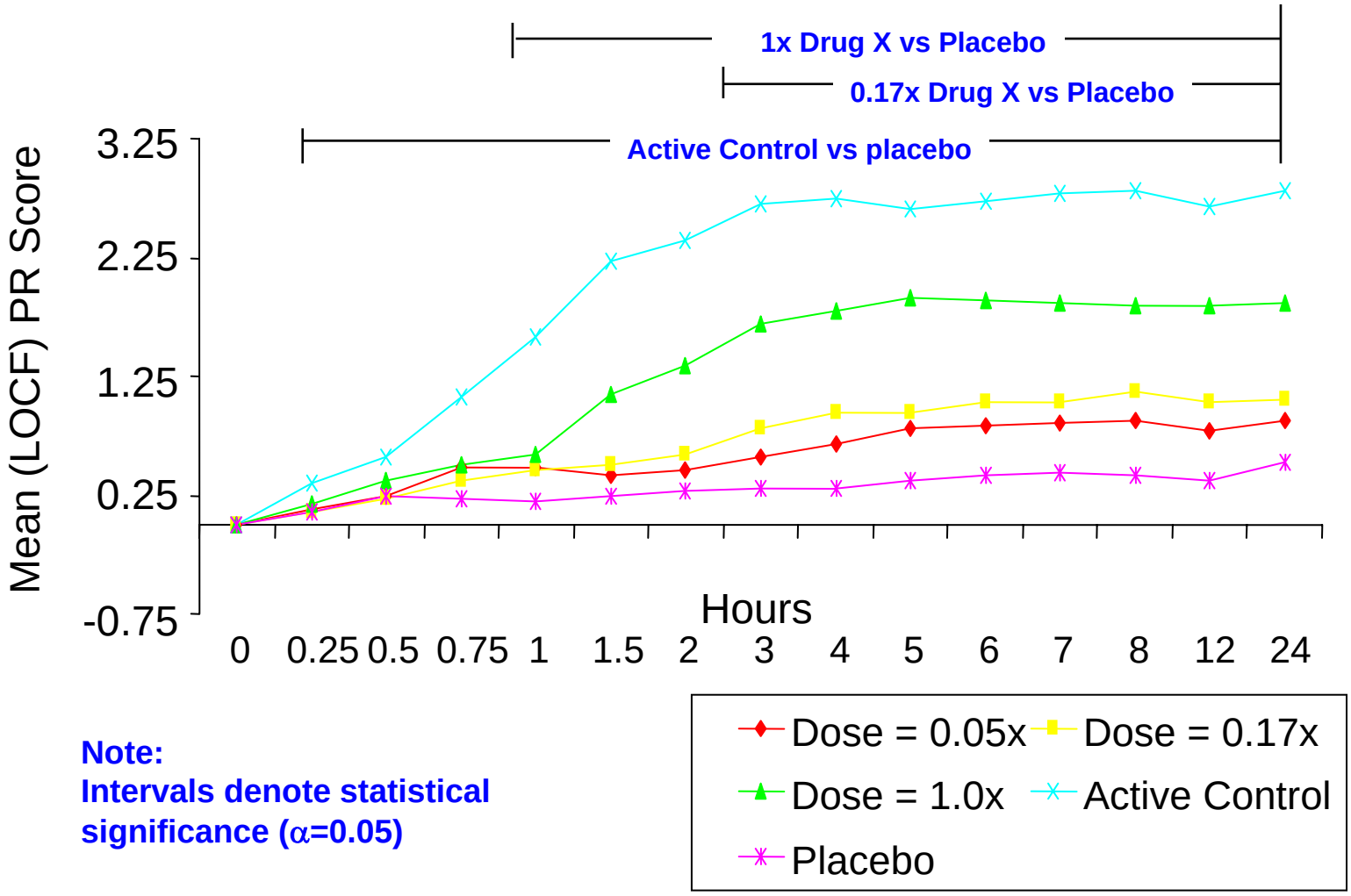
Outline

- Background
- PK/PD Model
- Predictions and Extrapolations
- Clinical Trial Simulations
- Comparison of Predictions vs. Actual Results
- Impact on Drug Development Program
- Final Remarks

Background

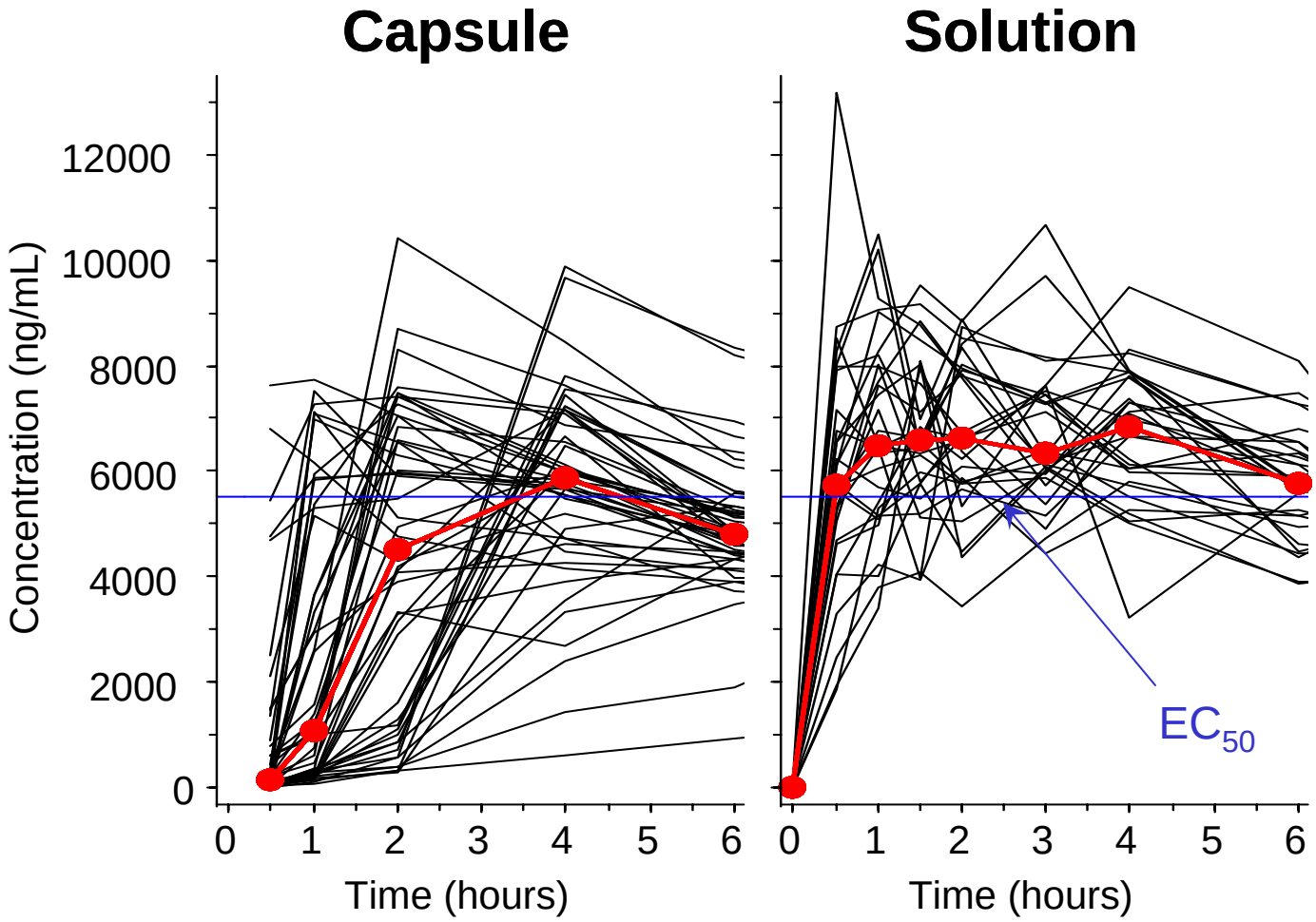
- Drug X is in early clinical development for the treatment of acute pain
- Dose-ranging (20-fold dose range) study conducted using capsule formulation
  - Active control worked as expected
  - Significant pain relief for Drug X relative to placebo
  - Lower than expected pain relief relative to active control

Mean (LOCF) Pain Relief Scores



Note:
Intervals denote statistical significance (α=0.05)

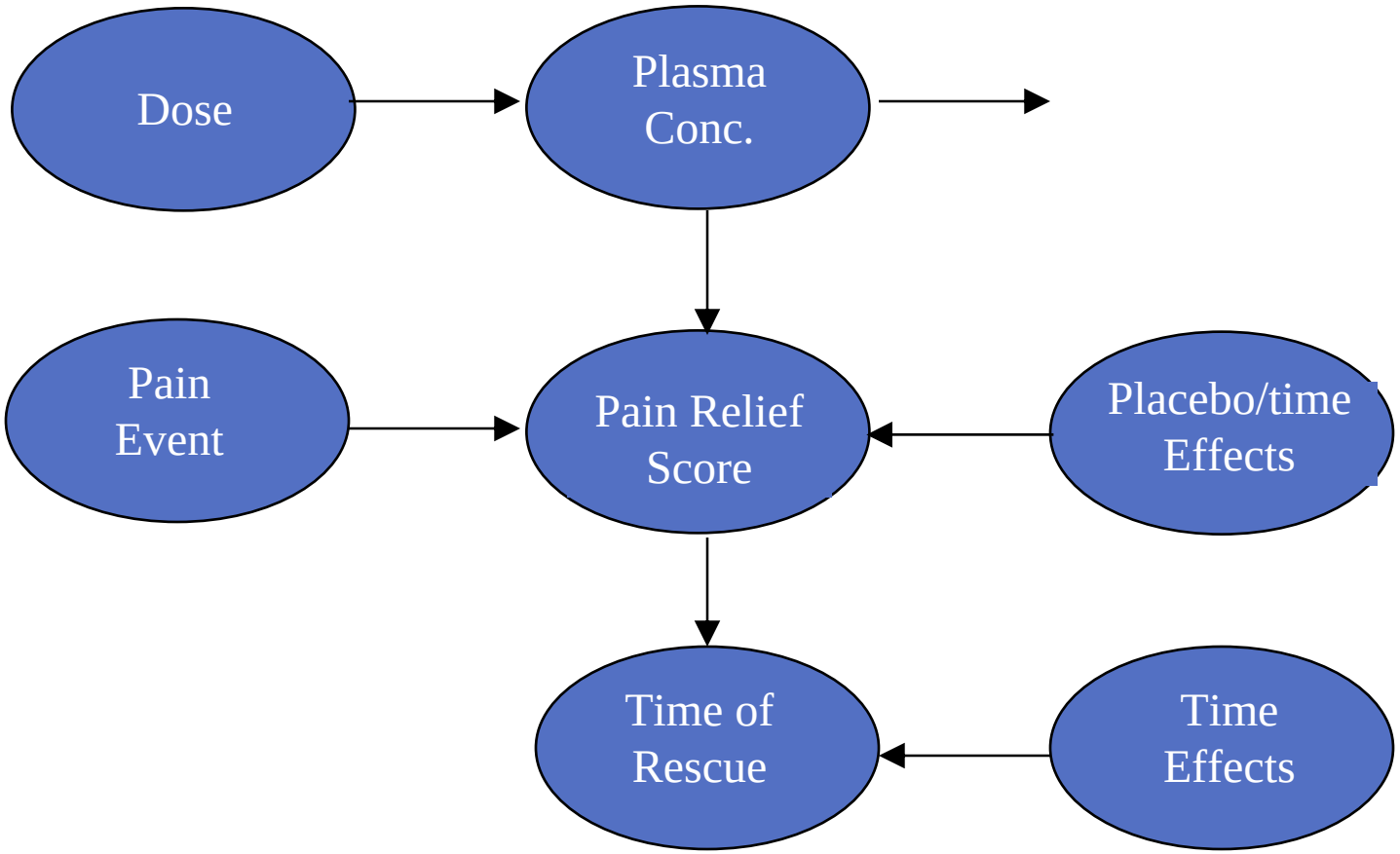
Lower Early Drug Exposure for Capsule



A Formulation Issue

- What would the response have been if absorption had been more like the solution?
  - PK/PD model required
  - Modeling performed to relate drug exposure to PR scores and time of dropout (rescue)

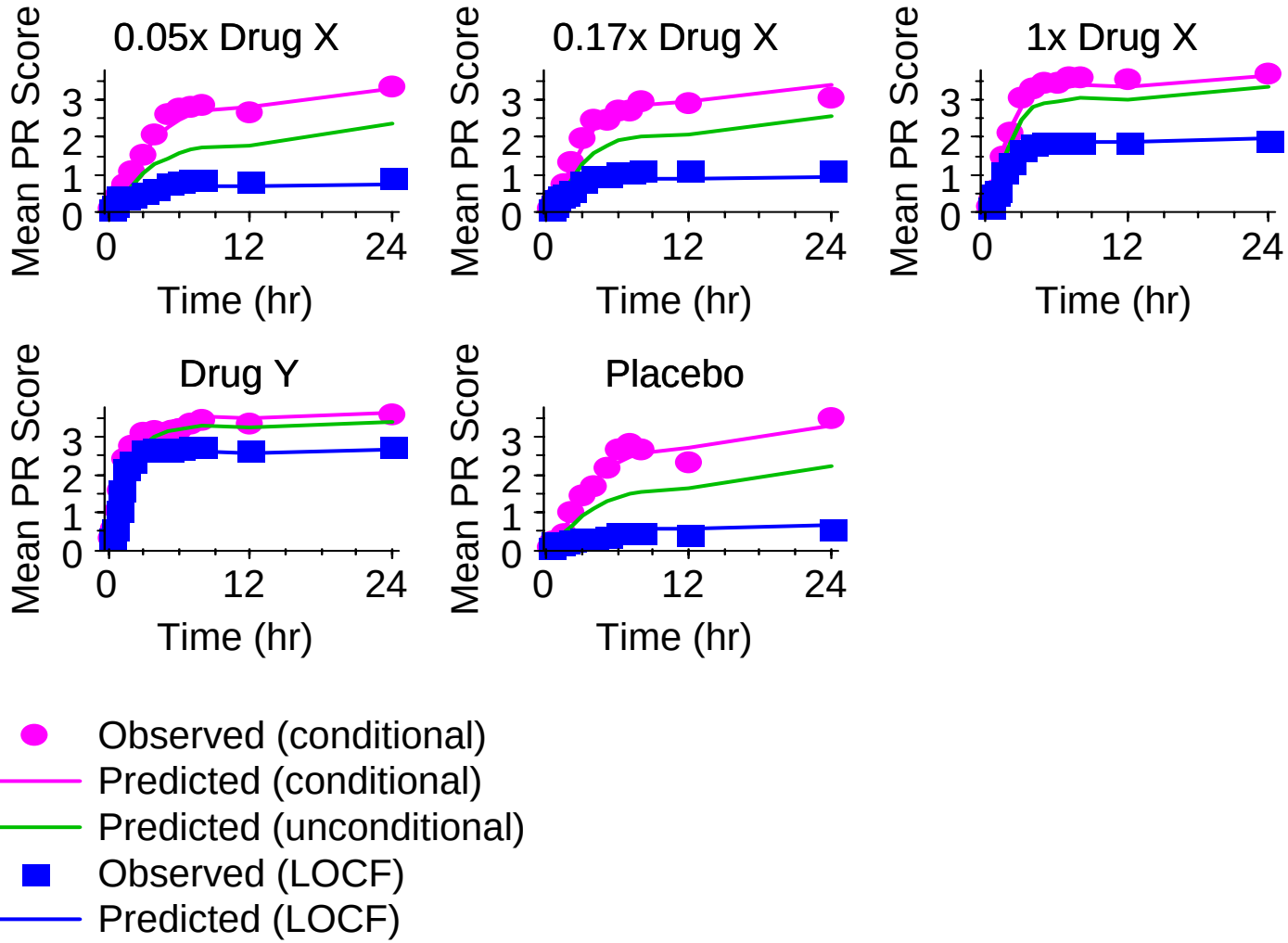
Conceptual PK/PD Model



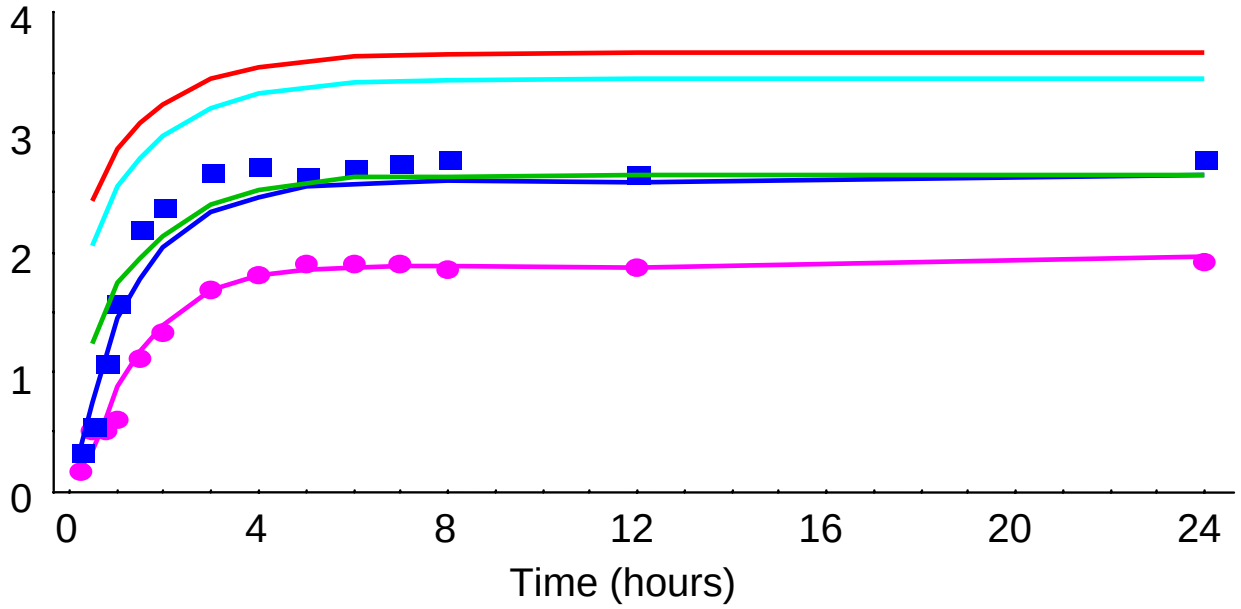
PK/PD Model Equations

- Pain Relief Model (5-point ordinal scale)
  - $\text{Logit}\{P(PR \geq m \mid \eta)\} = f_p(t_j; m, \theta_p) + f_d(C_p; \theta_d) + \eta$
    - f_p denotes placebo effects – exponential asymptote model
    - f_d denotes drug effects – Emax model
    - η denotes interindividual random effect
- Time-to-Rescue Medication (Dropout) Model
  - $P(T_i=t_j \mid T_i \geq t_j, PR_{ij}=m) = 1 - \exp\{-\lambda_m(t_j - t_{j-1})\}, t_j \geq 1$
  - $P(T_i \geq t_j \mid PR_{ij}=m) = \exp\{-\lambda_m t_j\}, t_j \geq 1$
- Methodology
  - Sheiner, CPT 1994;56:309-322
  - Mandema & Stanski, CPT 1996;60:619-635
  - Sheiner, Beal, & Dunne, JASA 1997;92:1235-1255

Observed and Predicted Mean PR Scores



Mean (LOCF) PR Score Predictions/Extrapolations



- Dose = 1x Capsule (observed)
- Dose = 1x Capsule (predicted)
- Active Control (observed)
- Active Control (predicted)
- Dose = 1x Solution (predicted)
- Dose = 3x Solution (predicted)
- Dose = 6x Solution (predicted)

A Plan to Move Forward

- Project team intrigued by these hypotheses
  - Oral solution predicted to have greater efficacy than capsule formulation
  - Higher doses may result in efficacy differentiation relative to active control
- Conduct clinical trial simulations to recommend a design to evaluate doses using the oral solution
- Dose selection could be made based on oral solution without having to wait for development of a new formulation
  - Formulation re-work could be done in parallel
- Validated PK/PD model could be used to evaluate formulations
  - No need to repeat dose-ranging with new formulation

Clinical Trial Simulations

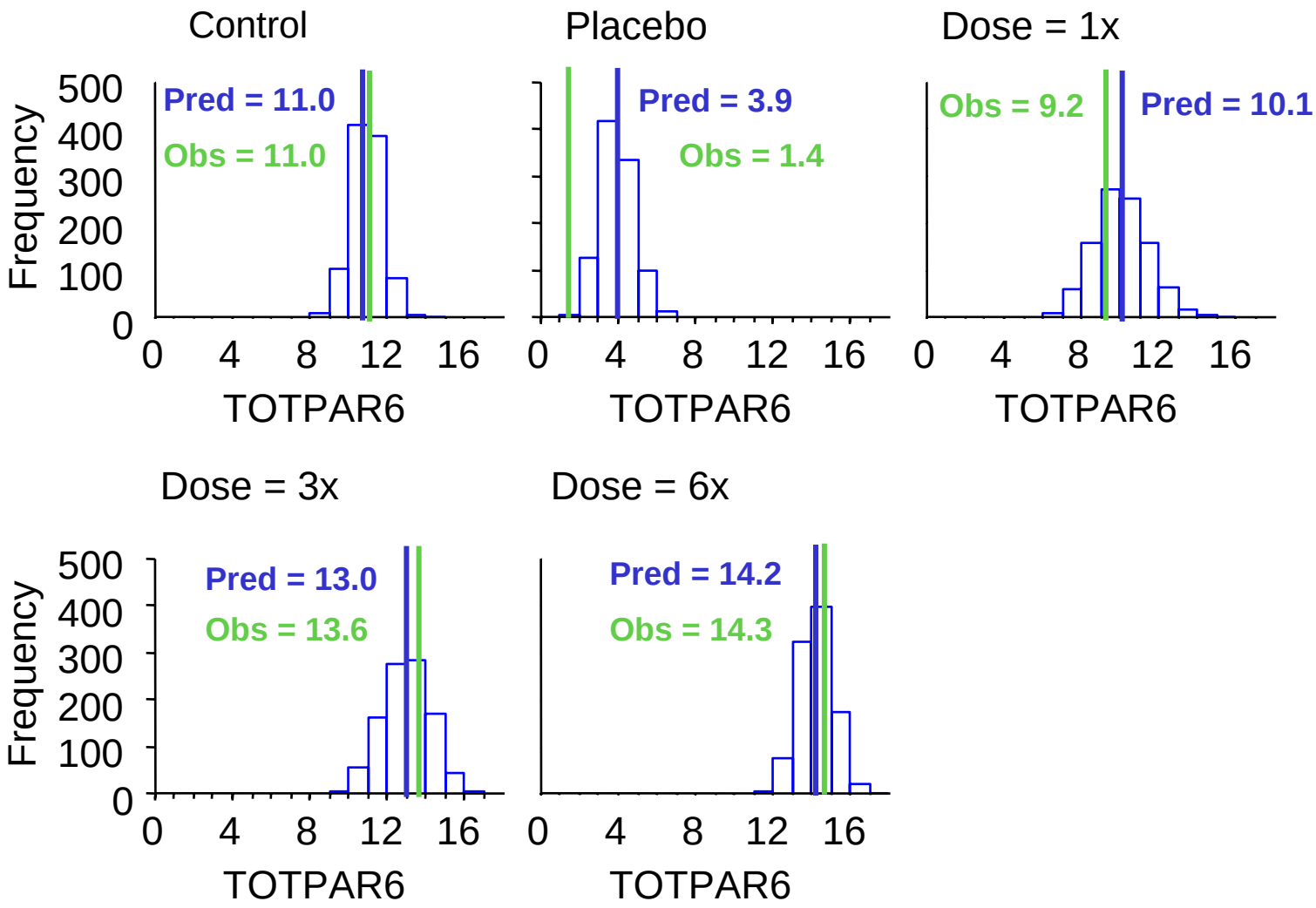
- Simulate PK, PR scores, and rescue (dropout) times for 1000 hypothetical trials for each design
  - Placebo, Drug X oral solution (3 dose levels), Active Control
- Perform a one-way ANOVA on TOTPAR6 for each trial
  - TOTPAR6 = $\sum PR_j(t_j - t_{j-1})$, $t_0=0$, $t_n=6$, $j=1,\ldots,n$
  - Estimate differences between high dose (6x) of Drug X and Active Control
  - Power calculated as the percent of trials where 95% LCL>0 (two-sided unadjusted for multiple comparisons)

Oral Solution Clinical Trial Simulation Results

Dose	TOTPAR6		Design I		Design II		**Design III**		Design IV	
	Est.	Diff.	N	Power	N	Power	**N**	**Power**	N	Power
Placebo	3.9	-7.1	50	---	50	---	**50**	**---**	50	---
1x	10.1	-0.9	50	0.019	50	0.017	**50**	**0.022**	50	0.021
2x	12.1	1.1	---	---	50	0.173	**---**	**---**	---	---
3x	13.0	2.0	50	0.298	---	---	**50**	**0.383**	---	---
4x	13.6	2.6	---	---	---	---	**---**	**---**	50	0.553
6x	14.2	**3.2**	50	0.619	100	0.844	**100**	**0.871**	100	0.863
Control	11.0	0	50	---	100	---	**100**	**---**	100	---

- Design III was approved and recently completed
- ΔTOTPAR6 = 3.0 is assumed to be clinically relevant
  - Approximately a 0.5 increase in PR score over first 6 hours
  - 6x dose is only dose predicted to achieve this difference

TOTPAR6: Predictions Vs. Actual



Impact on Drug Development Program

- Hypotheses generated by the PK/PD model provided the rationale for exploring higher doses
- PK/PD modeling and simulation provided a basis to continue development of the compound without waiting for formulation re-work
- PK/PD modeling and simulation provided guidance for the solid dosage form development
- PK/PD model is being leveraged to provide guidance for other compounds in the same class

Final Remarks

How did we garner the trust and confidence of the team to employ a model-based approach?

- Couched PK/PD modeling results as "hypothesis generating" requiring empirical confirmation
- Explicit and transparent about assumptions
  - Same Emax across all compounds in class
    - All compounds can achieve similar effects assuming comparable exposure relative to their potency
  - Linear PK for Drug X through 6x dose
    - Confirmed in 2nd SDT study prior to conduction oral solution pain study
  - PK similar between HV subjects and patients
- Calibration of model predictions against data-derived (non-model-based) endpoints used in standard statistical analysis
  - LOCF-imputed mean PR scores and TOTPAR6