ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Use of Exposure-Response Modeling in Early Development

Steve Riley

Pfizer Inc, Groton, CT

01OCT13

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Why Should We?

- Facilitates quantitative bridging of nonclinical and clinical data
  - Need to design experiments appropriately to be informative for this purpose
- Allows for early and data-driven decision making
- Can aid in interpretation of clinical study results and facilitate study design

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Examples

- Proof of Mechanism Biomarker Translation from Nonclinical to Clinical
- Analysis of Early Clinical Data to Drive Decisions
- Model-based Analysis of POC Trial in Schizophrenia

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

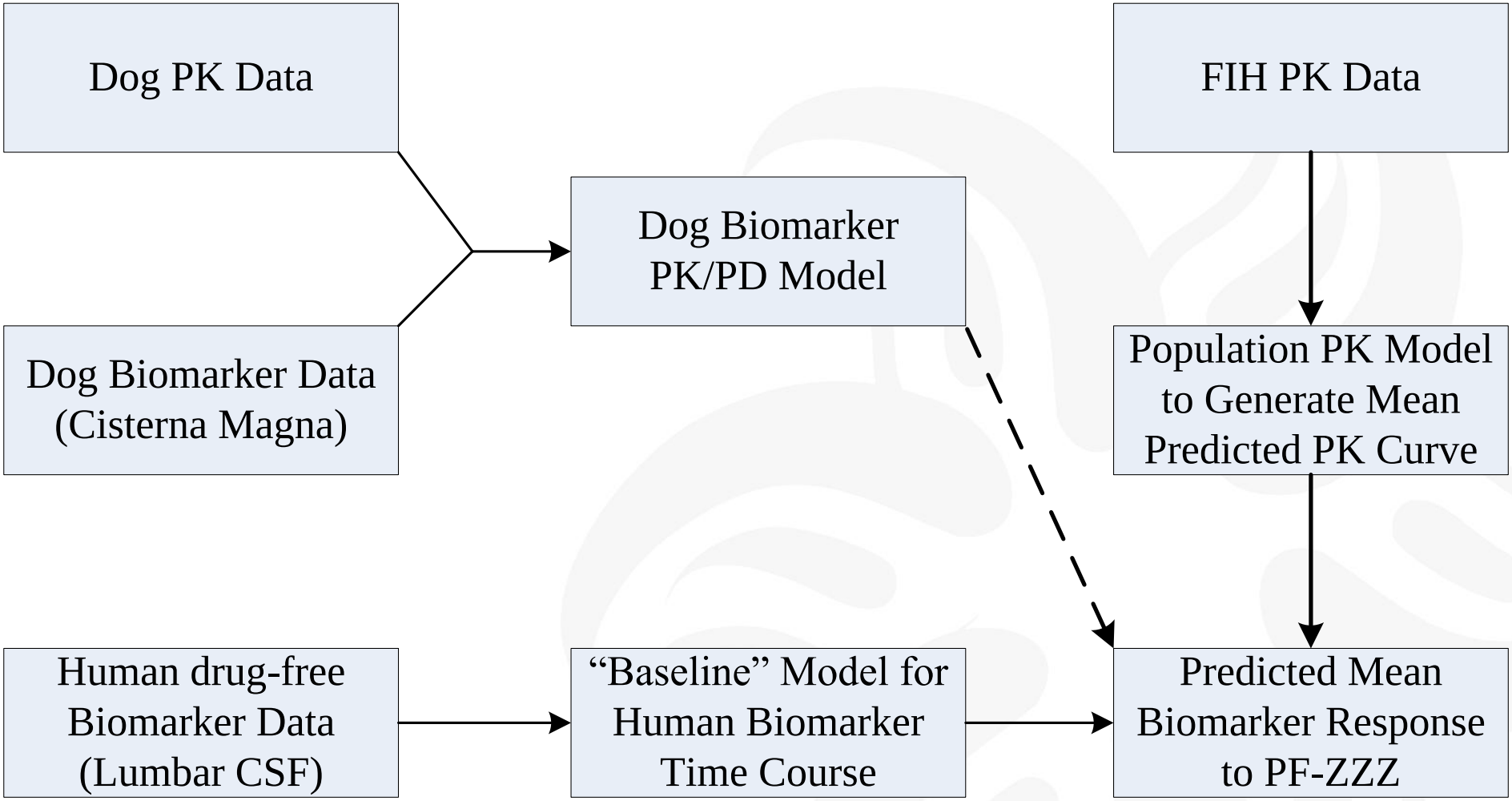
Proof of Mechanism

- Objective: Design a clinical study to demonstrate the effect of PF-ZZZ on a mechanism biomarker in human CSF
- Some of the Challenges
  - Novel MOA; novel biomarker
  - High variability in basal biomarker concentrations
  - Dose selection

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Proof of Mechanism

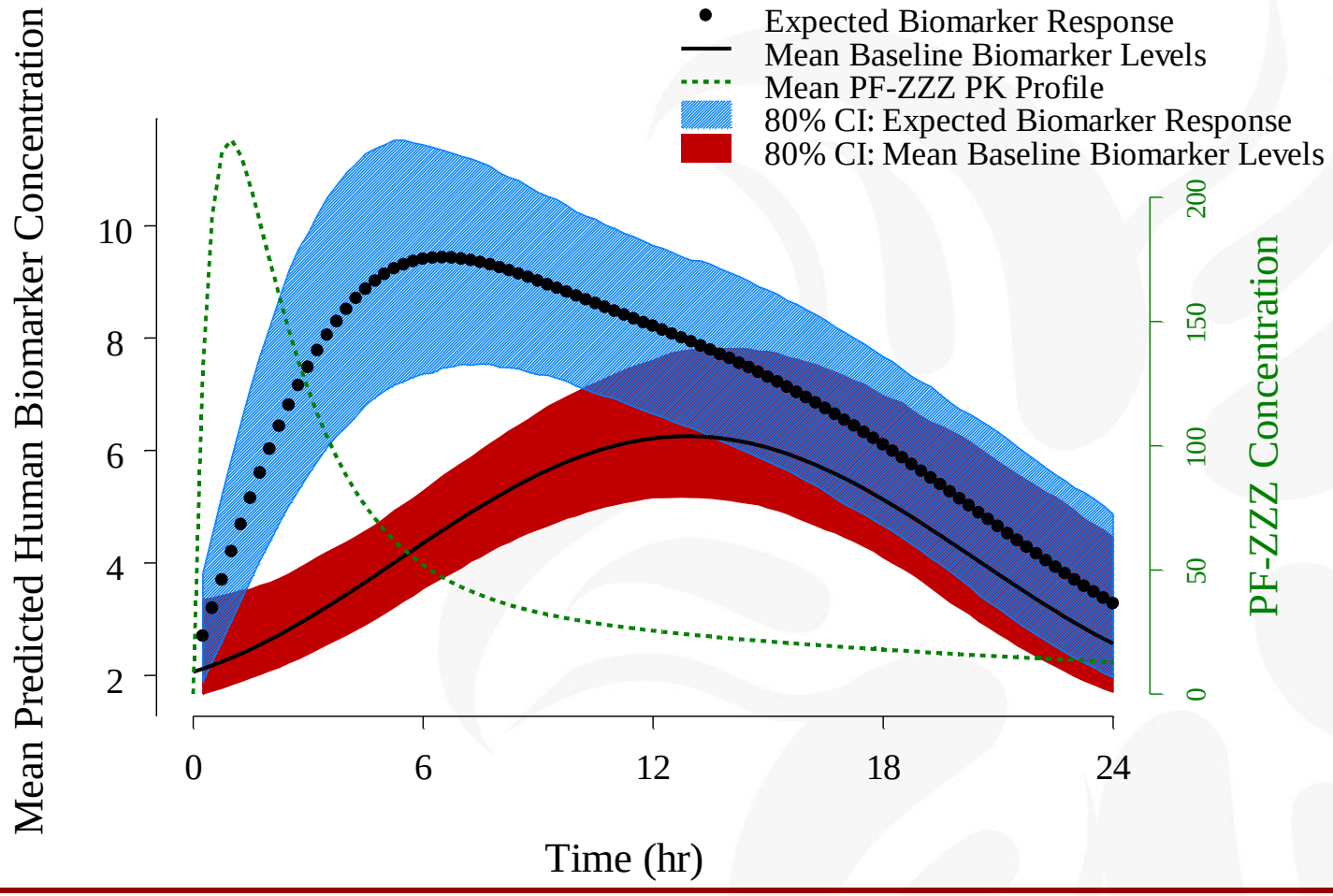
- Road map to predicting human drug response



ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

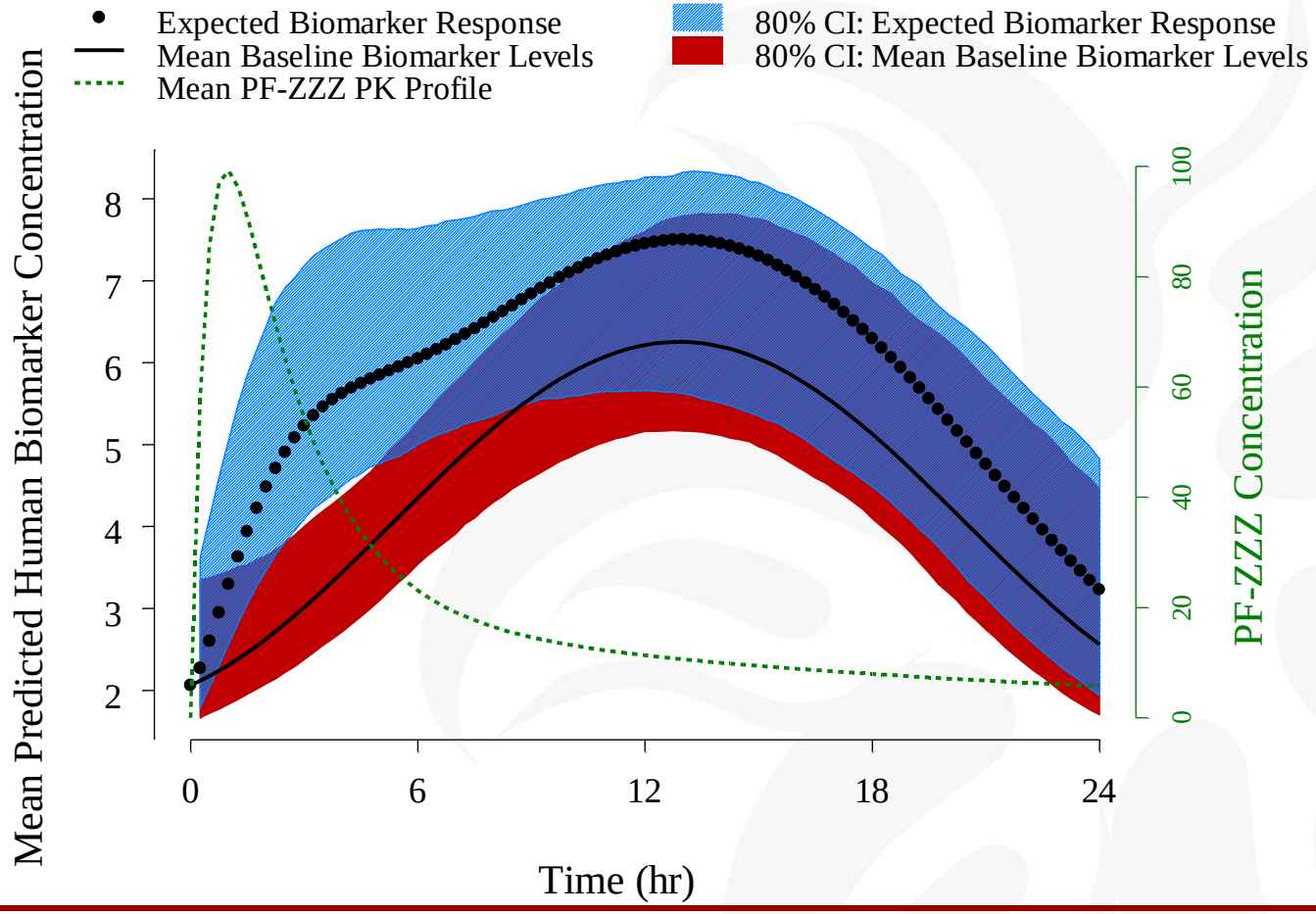
Proof of Mechanism

- 25 mg predicted to show good separation, but that dose was not feasible



Proof of Mechanism

- 10 mg was a tolerable dose for this study
  - Lower chance of showing separation from background



ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Proof of Mechanism

- Study Results
  - Contrary to expectations based upon the mechanism, lumbar biomarker actually decreased in PF-ZZZ group
- What could have went wrong?
  - Unprecedented mechanism/biomarker
  - PF-ZZZ dose not high enough?
  - Dog to human translatability assumption incorrect?
  - Model mis-specification?
  - Sample size too small?

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Go/No Go Decisions Using First-In-Human Data

Thanks to Jack Cook for supplying these slides

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Go/No-Go Decision

- Indication: Schizophrenia
- Key differentiating features:
  - Improved safety: **Reduced QT liability**
  - **Superior treatment** of depressive, anxiety, cognitive symptoms relative to olanzapine
- Evaluated 2 different compounds, PF-AAA and PF-BBB

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Go/No-Go Decision

- Data
  - Single dose data from first-in-human studies of PF-AAA (2-100 mg) and PF-BBB (2-400 mg)
  - Both studies included 10 mg olanzapine as an active comparator
- Pharmacodynamic Endpoints
  - Both Studies: Drug Effect Questionnaire – Strength (DEQ-S), Prolactin, QTc
  - PF-AAA: Psychomotor Vigilance Task – Median Reaction Time (MRT)
  - PF-BBB: Stanford Sleepiness Scale (SSS)

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Go/No-Go Decision

PD Marker	Estimated Daily Dose Equivalent to 10 mg Olanzapine	
	PF-AAA	**PF-BBB**
Prolactin	65 mg[1]	108 mg[1]
PVT-MRT	35 mg[2]	NA
DEQ-S	140 mg[1]	326 mg[1]
SSS	NA	304 mg[1]
Rat LMA	20 – 50 mg[3]	54 mg[3]

[1] Based on EC50 potency ratio and AUC(0-tlqc) results relative to olanzapine

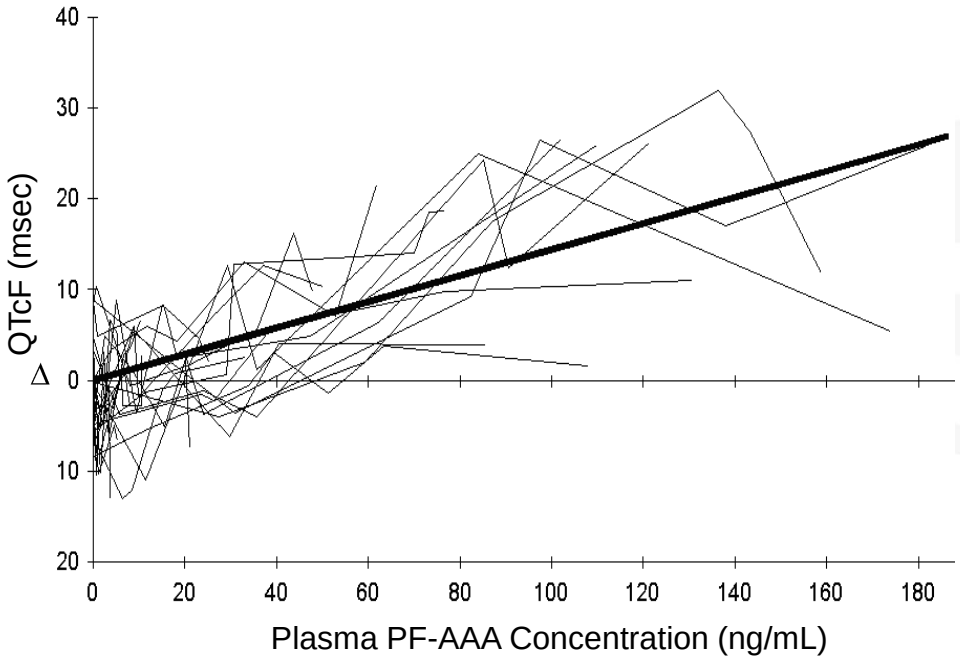
[2] Based on comparison between population predicted mean MRT values of PF-AAA and median MRT at Cmax of olanzapine

[3] Dose range projected to have similar efficacy of ziprasidone 20 – 80 mg BID

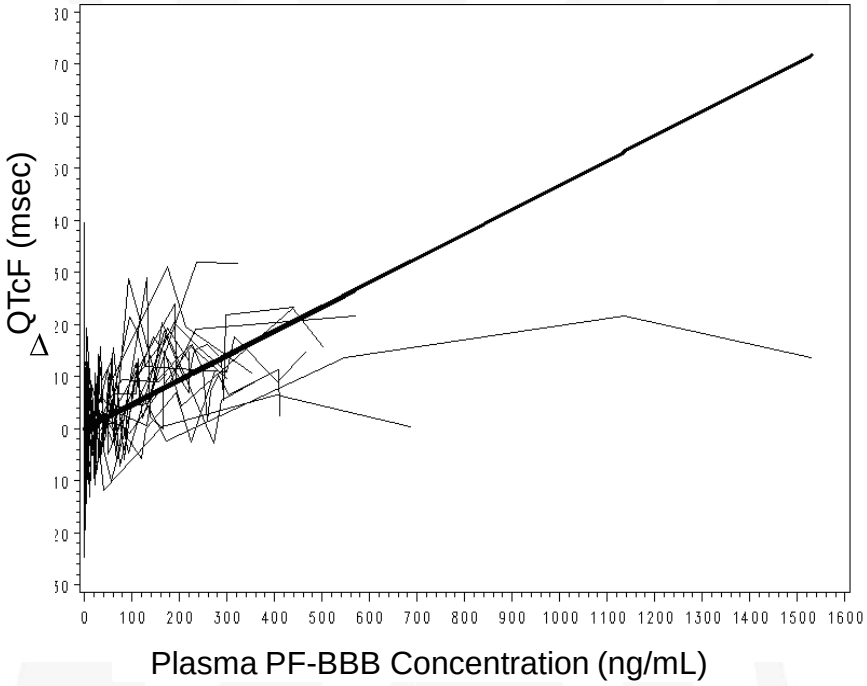
Effect on QTcF

- Exposure-response analysis of ΔQTc vs concentration demonstrated a clear signal for both compounds

PF-AAA



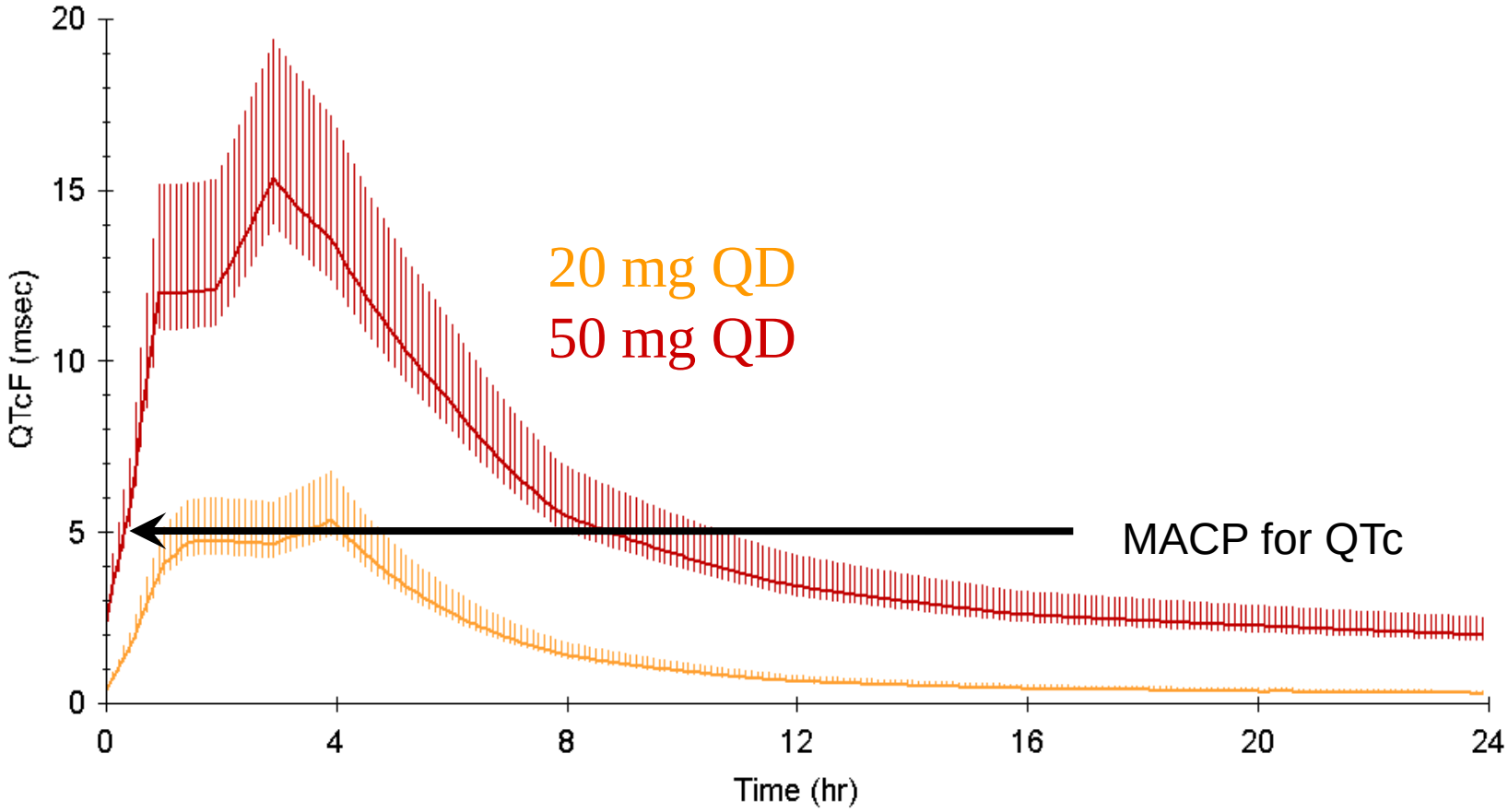
PF-BBB



ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Go/No-Go Decision

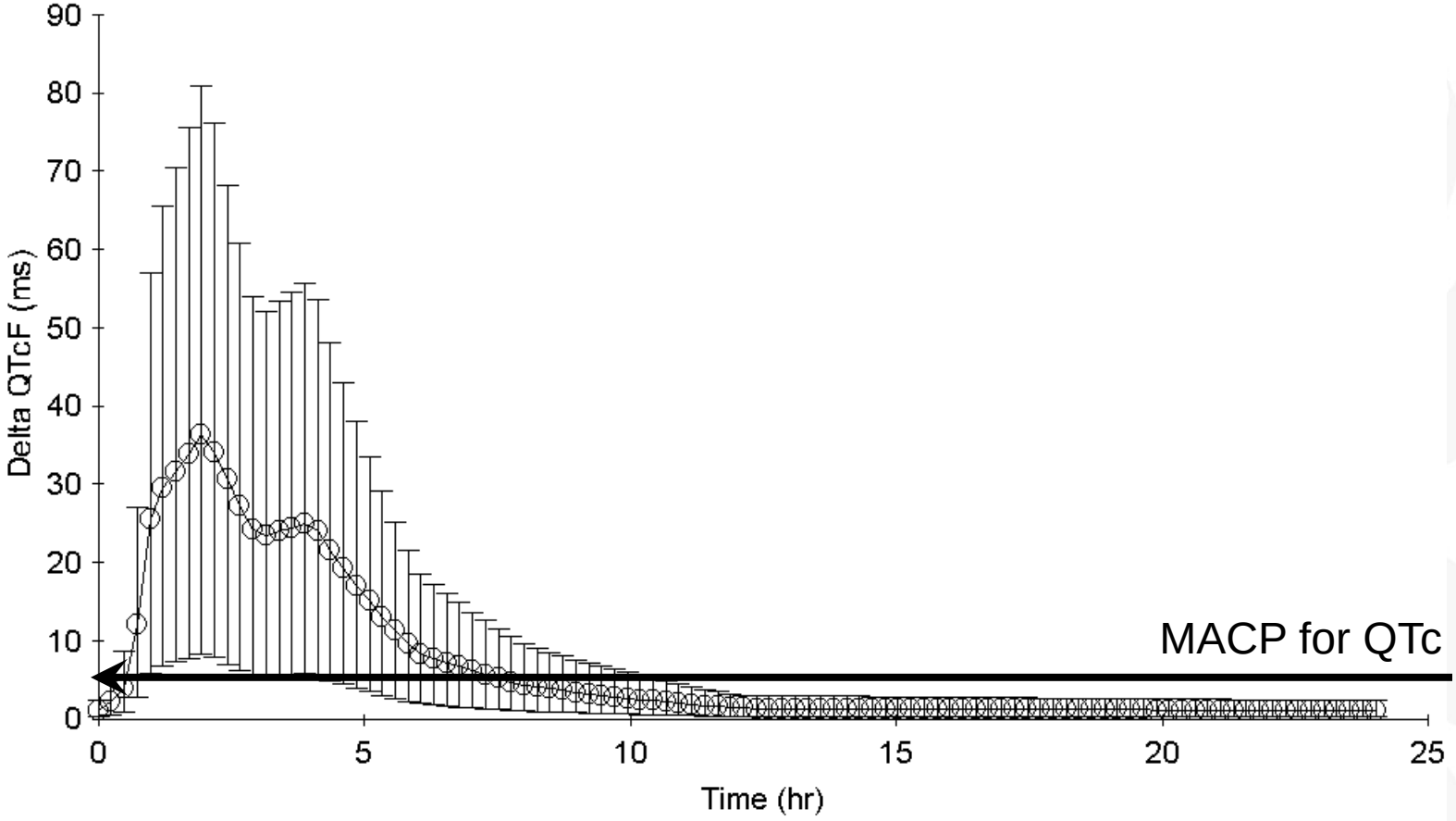
- PF-AAA QTc Changes At Likely Minimally Effective Doses



ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Go/No-Go Decision

- PF-BBB QTc Changes At Likely Minimally Effective Dose



ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Go/No-Go Decision

- Conclusions
  - Results from exposure-CNS activity markers and -QTcF modeling were sufficient to allow a decision to stop further development of both compounds

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Model-based Analysis of POC Trial in Schizophrenia

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

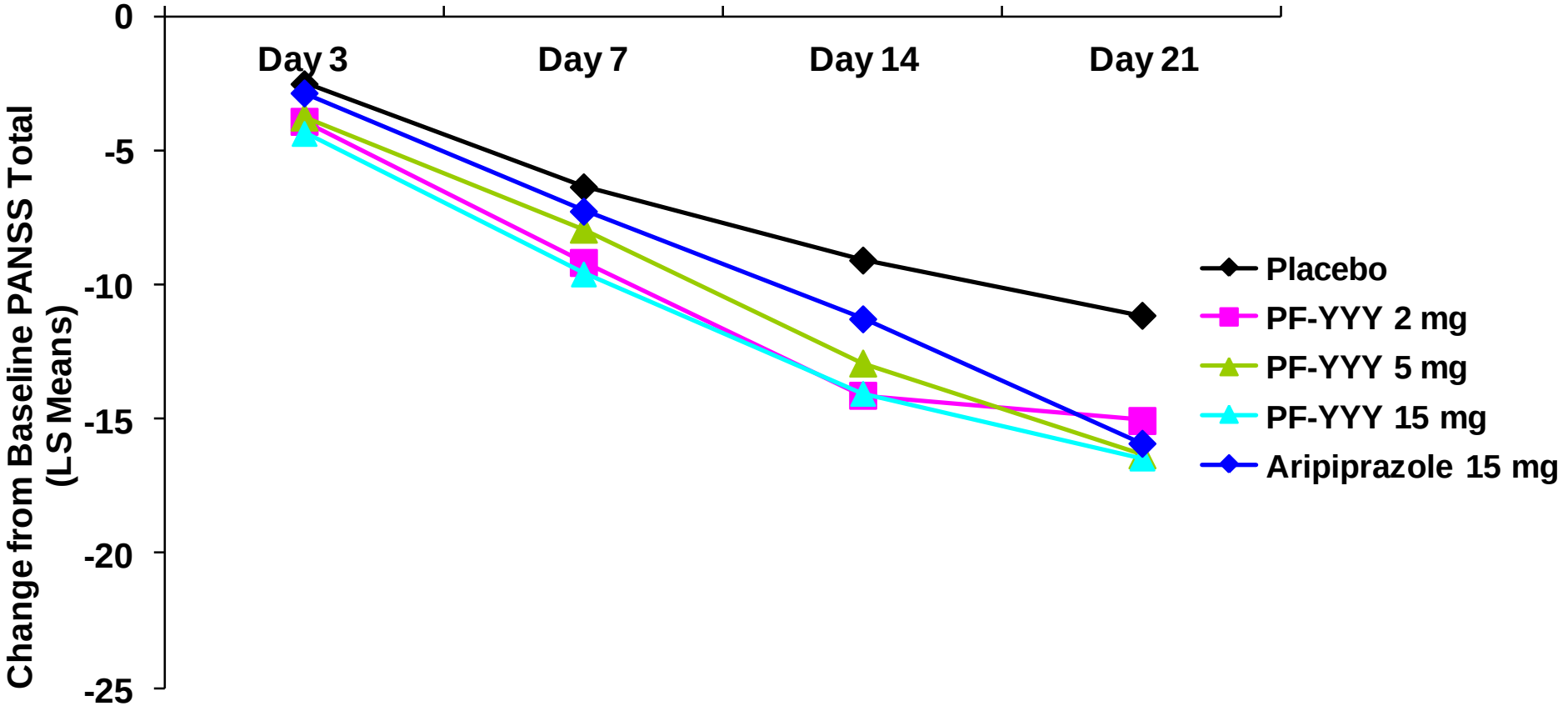
Schizophrenia POC

- Background
  - PF-YYY was being developed as a treatment for schizophrenia
- POC Study
  - **Objective:** Evaluate **dose-response for PF-YYY** (2 mg, 5 mg, and 15 mg) in the treatment of acute exacerbation of schizophrenia
  - **Design:** **3-week** double-blind, placebo and active-controlled study
  - **Primary Endpoint:** Change from baseline **PANSS total compared to placebo**.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Schizophrenia POC

- Longitudinal Analysis of PANSS Total across treatment groups



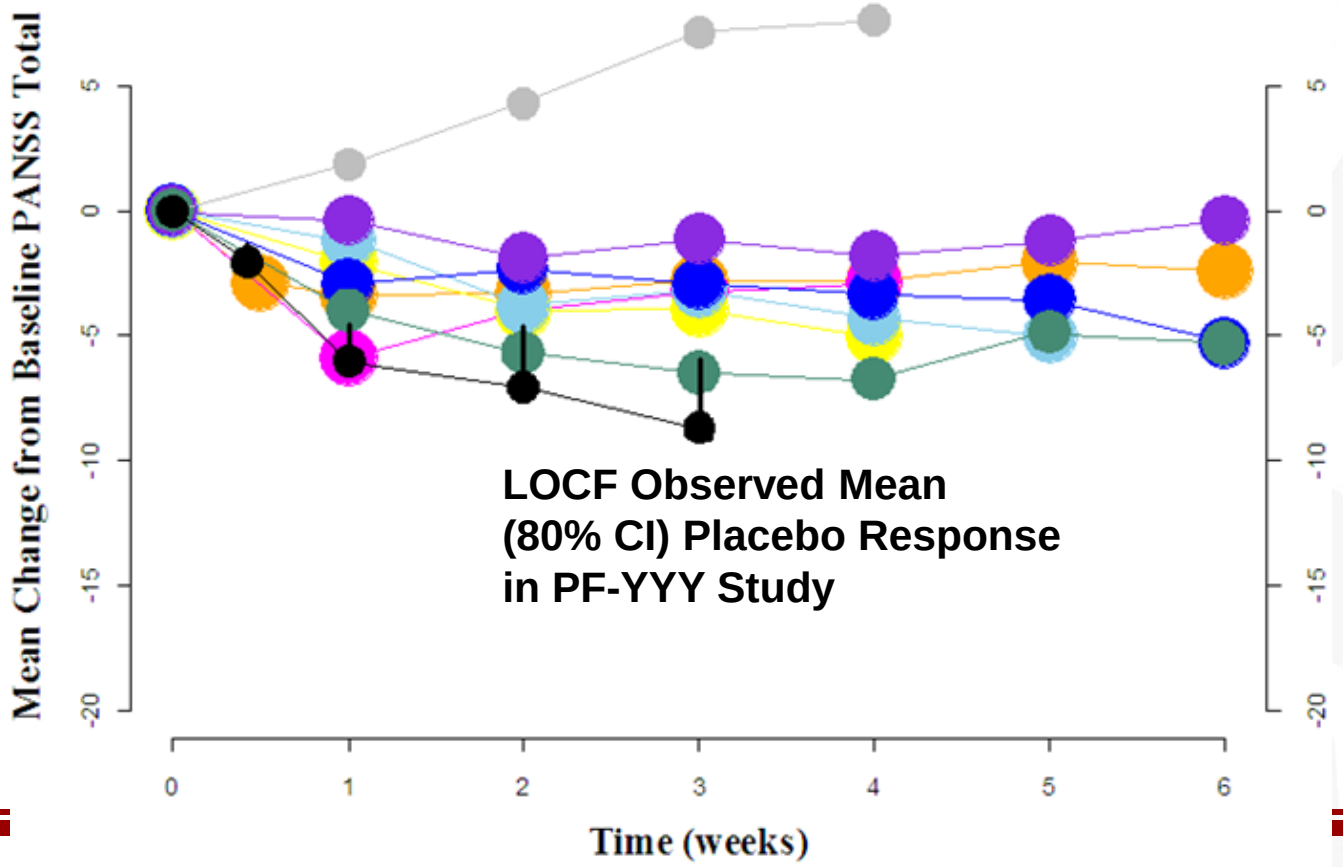
ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Schizophrenia POC

- The a priori-defined linear trend test did not provide the pre-specified level of evidence for a dose-response relationship
- Aripiprazole was not statistically significantly better than placebo
- What happened?

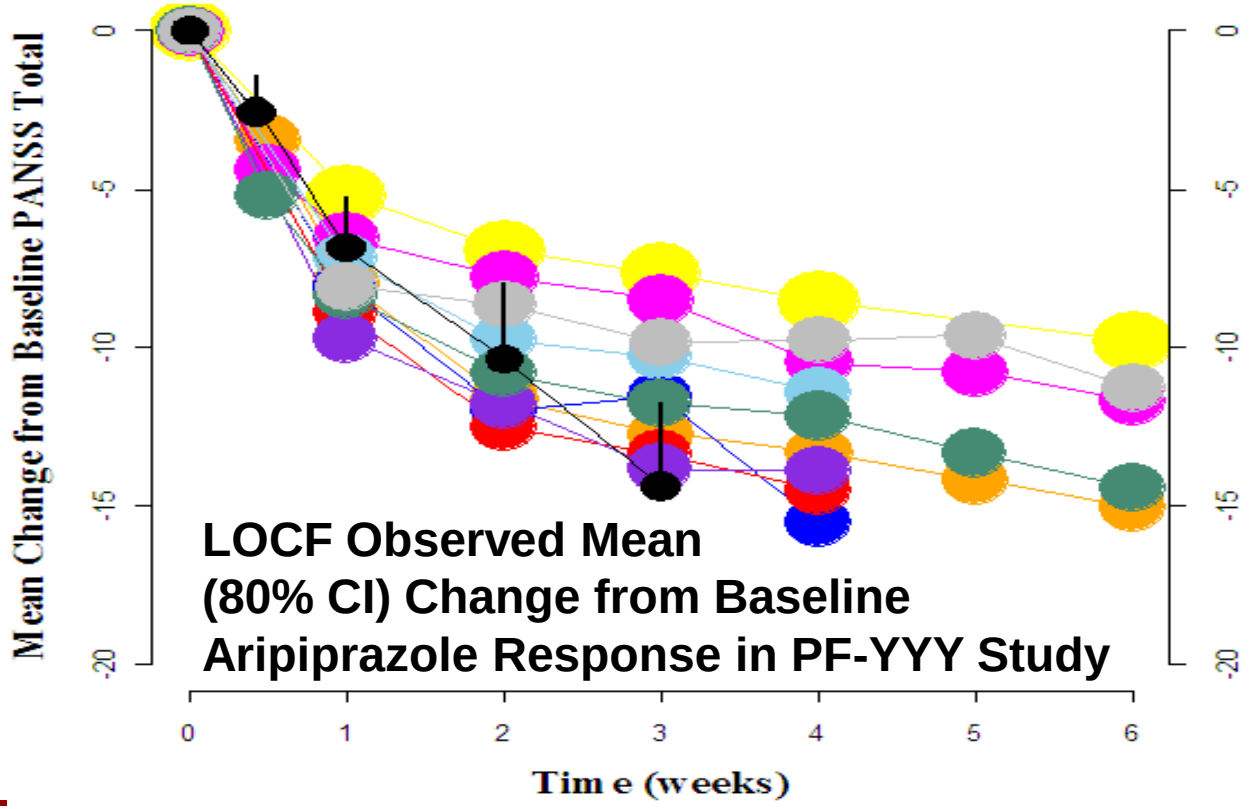
Schizophrenia POC

- Model-based meta analysis (MBMA) of LOCF placebo data from 8 acute schizophrenia trials (n = 710; individual arms n = 34-108)
- Symbol size is a function of sample size for each trial
- **Placebo response was consistent with prior data**



Schizophrenia POC

- MBMA of LOCF aripiprazole data from 8 acute schizophrenia trials (n = 690; individual study arm n = 33-154; 10-30 mg aripiprazole)
- Symbol size is a function of sample size for each trial
- **Aripiprazole response was consistent with prior data**



ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Schizophrenia POC

- Exposure-Response Results
  - Bayesian analysis of PANSS total score vs PF-YYY trough concentrations
  - Baseline and Day 21 PANSS total score included in analysis dataset
  - Estimated parameters included baseline PANSS total score, placebo effect, and an Emax model for drug effect

Parameter	Mean	95% Credible Interval
Baseline Score	99.7	96.9, 102
Placebo Score	88.7	84.9, 92.4
Maximum Drug Effect	**-6.63**	**-1.35, -13.6**
EC50 (ng/mL)	**101**	**7.07, 339**
Residual Error (Std Dev)	16.4	15, 17.6

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Schizophrenia POC

- Lessons Learned?
  - Small studies can result in variable point estimates and have diminished power.
  - Linear trend test may not be sufficiently powerful for certain dose-response shapes
    - Dose responses are not always linear → violated assumption responsible for low power?
- Failed study, but did we learn something?
  - Relying on a p-value in a POC study is not the best use of resources
  - Model-based analyses supported study results (placebo and aripiprazole) and identified deficiencies in the dataset, which could be used to inform future study design

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Conclusions

- Employing model-based analyses in drug development can:
  - Identify and bridge knowledge gaps when they exist
  - Inform quantitative, data-driven decisions
  - Inform study design
  - Provide answers to the “right” questions…the key is deciding what those questions are before the study is designed

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Closing Thought…

"Far better an approximate answer to the right question, which is often vague, than the exact answer to the wrong question, which can always be made precise."

John Tukey