Integration of Multiple Biomarkers (BM), Translation to Surrogate/Outcomes and Their Application in Early Drug Development – A Case Study to Support Phase IIa Design

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Introduction

- It's challenging to evaluate the potential of a first-in-class drug at early stage.
- Multiple BMs/surrogates data may be available from nonclinical experiments
  - Signals from multiple BMs/surrogates, although potentially different, are considered to be more informative than a signal from a single BM.
  - It's challenging to validate, integrate and analyze multiple BMs/surrogates data.
- Clinical BMs may be useful to support early decisions when clinical surrogate/outcome data are not available.

➔Case: drugX, a receptorY antagonist, first-in-class under development for treatment of diseaseZ

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Case Situation, Objective and Methods

- Situation
  - Known: positive nonclinical data (in rhesus monkeys):
    - BM1: receptor binding response
    - BM2: monocyte shape change
    - Surrogate: monocyte recruitment (MR)
    - Outcomes: behavior/joint movement
  - Known: Limited clinical PK and BM2 data from SAD
  - Unknown: Clinical surrogate/outcomes?
- Objective
  - To simulate effective clinical dose range for Phase II
- Methods
  - Integrate nonclinical BM1, BM2, surrogate and outcomes data to validate BM2
  - Develop exposure-response relationship for clinical BM2
  - Simulate dose-response relationship for clinical MR from BM2 based on mechanism of disease (MOD) and mechanism of action (MOA)

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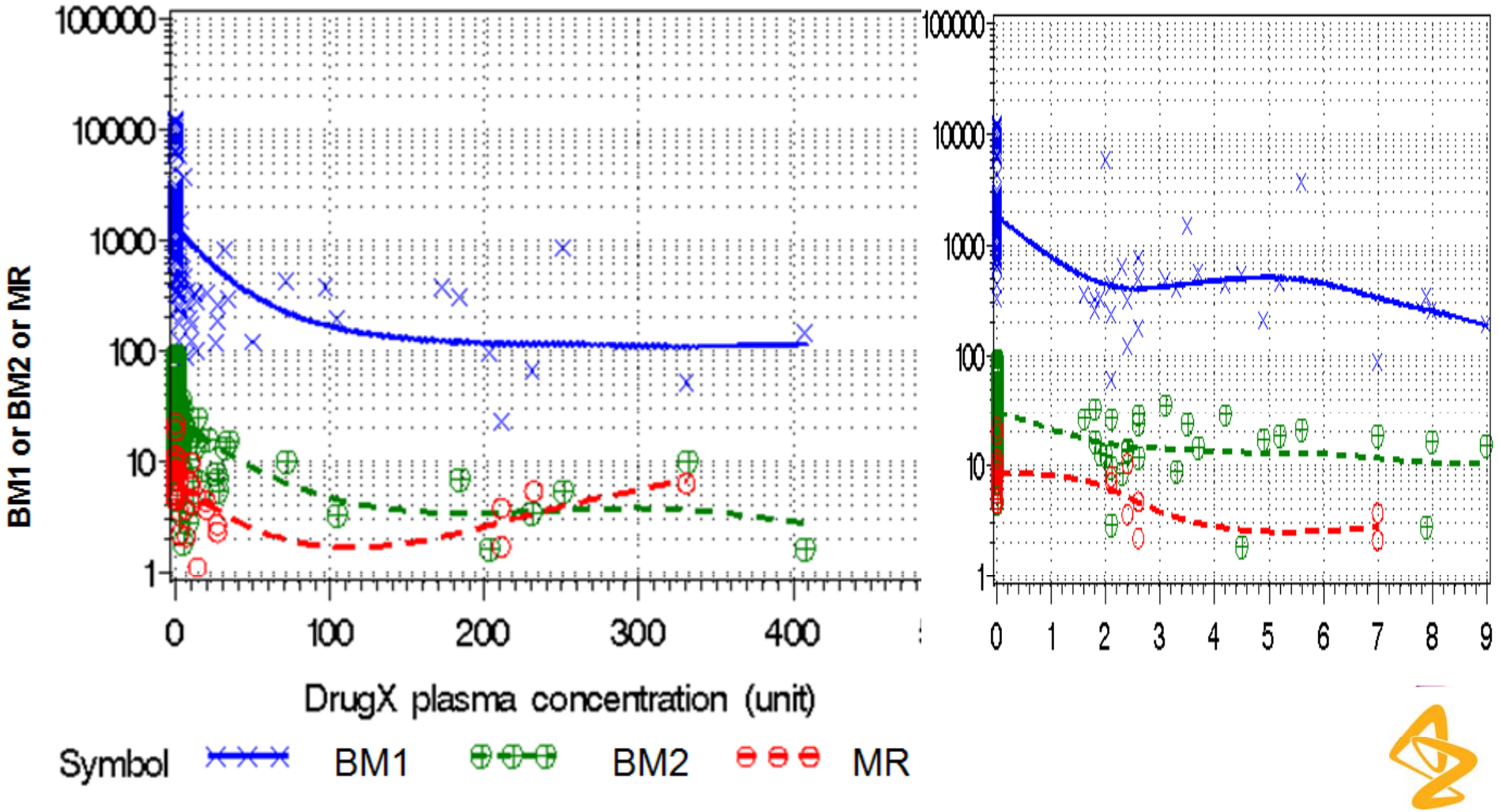
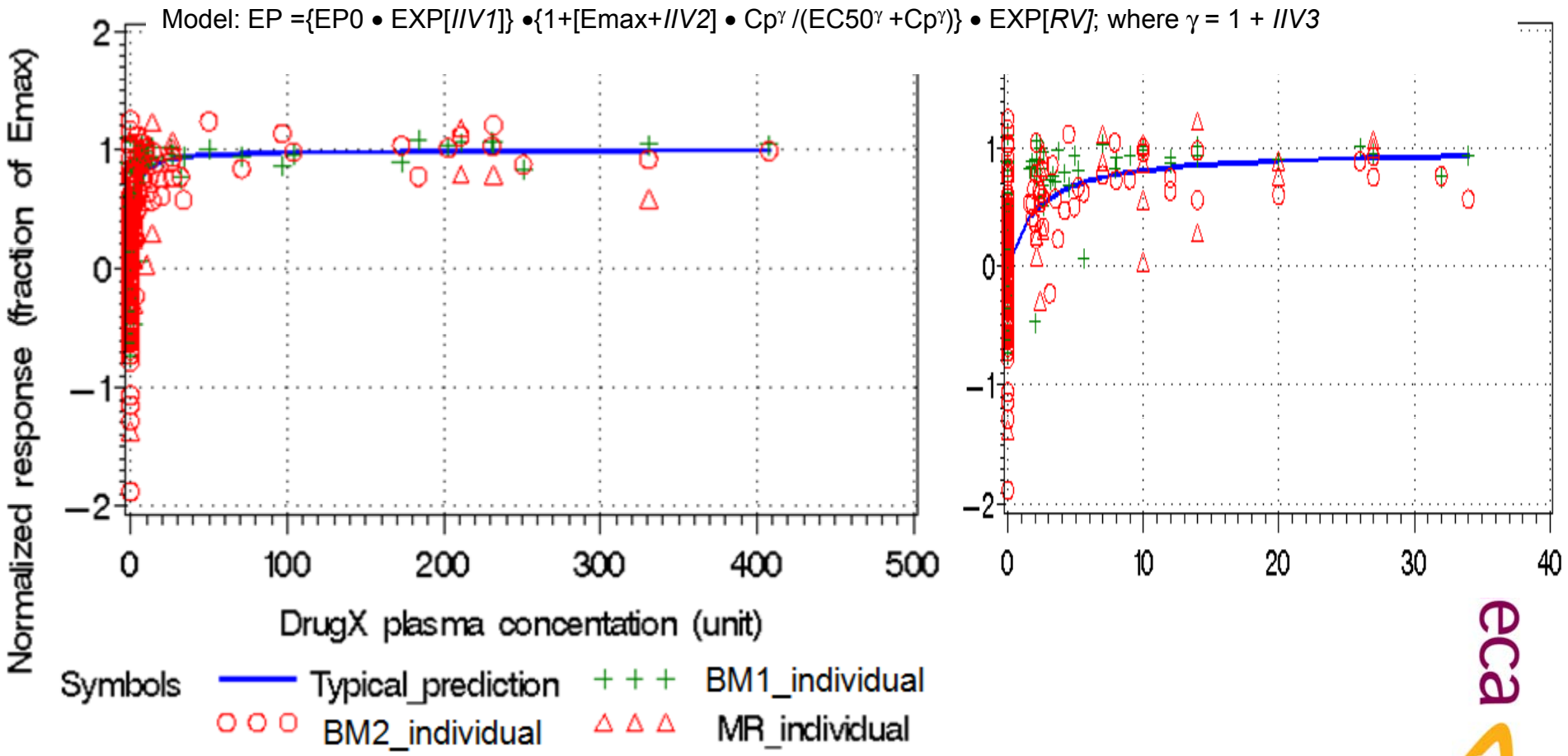
Nonclinical BM/Surrogate/Outcome Data



Outcome: 1 monkey became able to self-feed after administration of DrugX

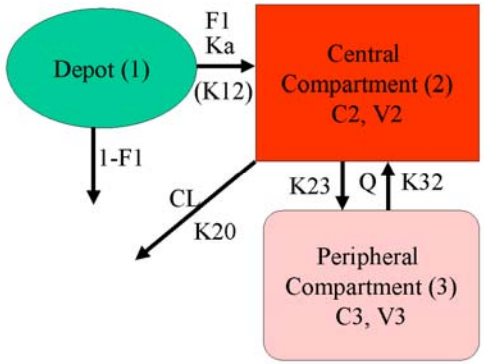
Consistent Normalized E-R Relationship Expressed by BM1, BM2 and MR



- Confirmed by the outcomes

➔ BM2 appeared to be predictive?

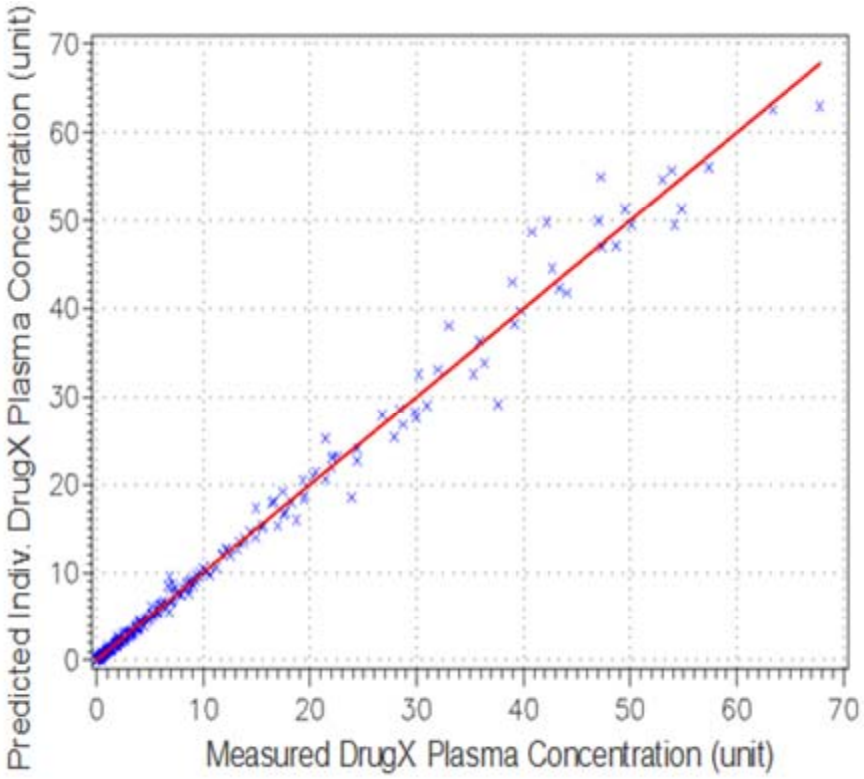
Clinical PK/PD Model and Goodness-of-Fit

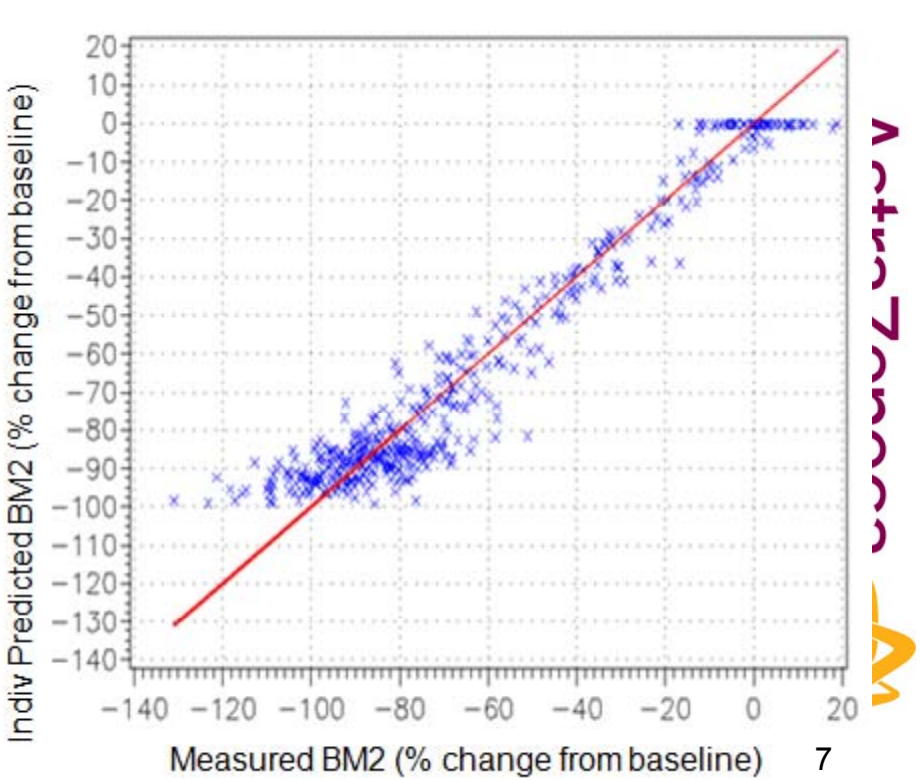


- PKPD model:

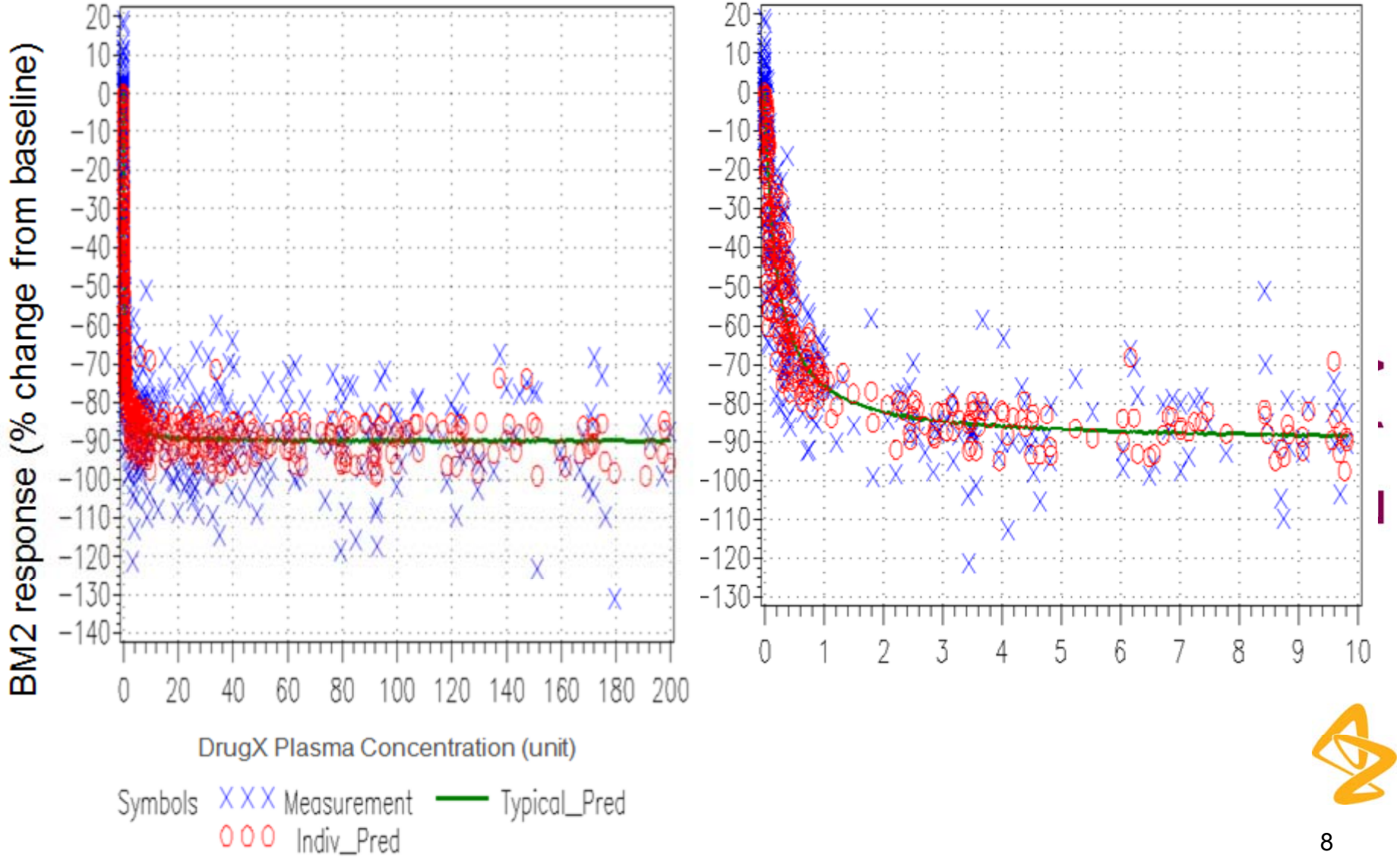
E=[Emax+*IIV*]•Cp/(EC50+Cp) + *RV*

- Variabilities were estimated where possible





Clinical PK/PD Model Fit to BM2



Mechanism-based BM2➔MR Translation

Monocyte recruitment in 24 hours (one dosing interval at steady state)

=Number of monocytes migrating from blood to tissue in 24 hours

= integral of {availability of monocytes at the surface to be recruited • ability of monocytes to be recruited • monocyte transmigration rate} over time (from 0 to 24 hours)

➔ Integral of {monocyte shape change} over time (0-24 hours)

Assuming

- Availability of monocytes at the surface to be recruited at steady state does not significantly vary with time and administration of DrugX.
- Ability of monocytes to be recruited at steady state is proportional to monocyte shape change.
- Monocyte transmigration rate at steady state does not significantly vary with time and administration of DrugX.

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Simulation Assumption

- Single-dose PK of the 1-300 *unit* dose range in healthy young subjects reasonably predicts steady-state PK in the 0.2-100 *unit* dose range in the target patient population.
- PK/PD model on BM2 developed from the 1-300 *unit* dose range reasonably predicts PD response from 0.2 to 100 *unit*.
  - Preclinical BM2-to-MR translation is applicable to clinical
  - Preclinical surrogate MR-to-outcomes translation is applicable to clinical
  - Time integral of BM2 reasonably reflects MR
- Variabilities in PK and PKPD were used as estimated

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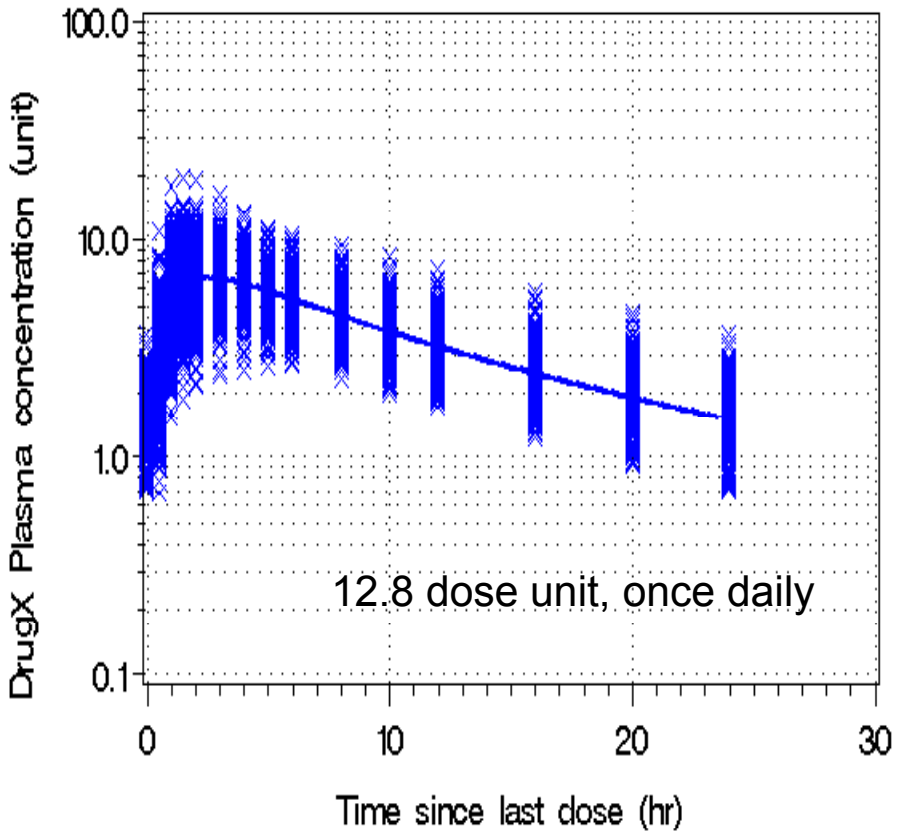
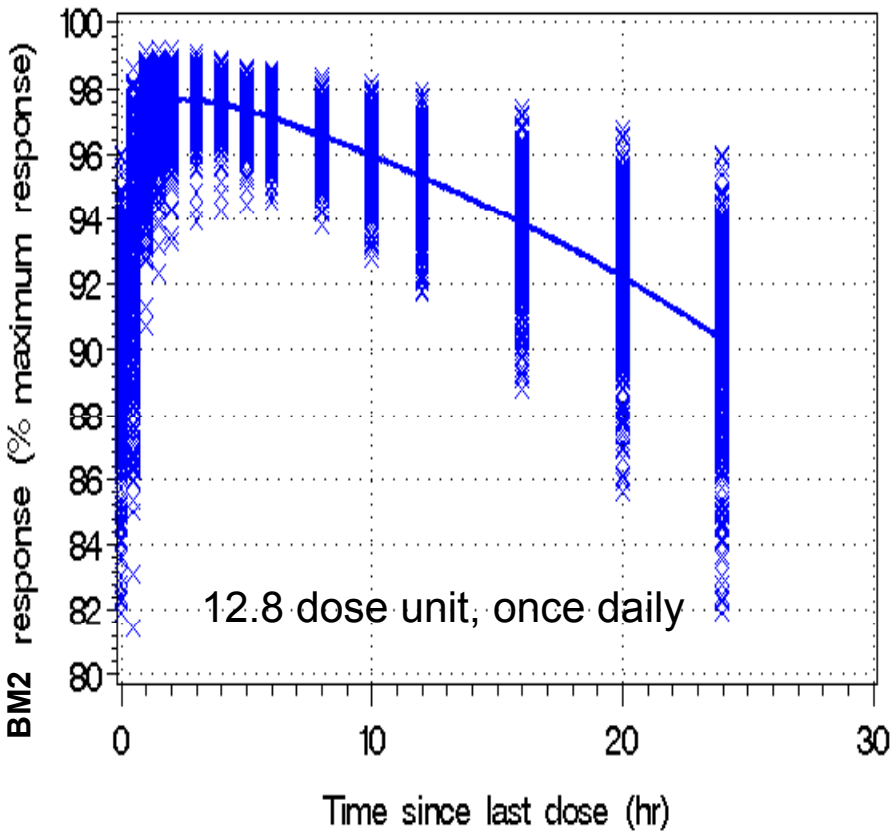
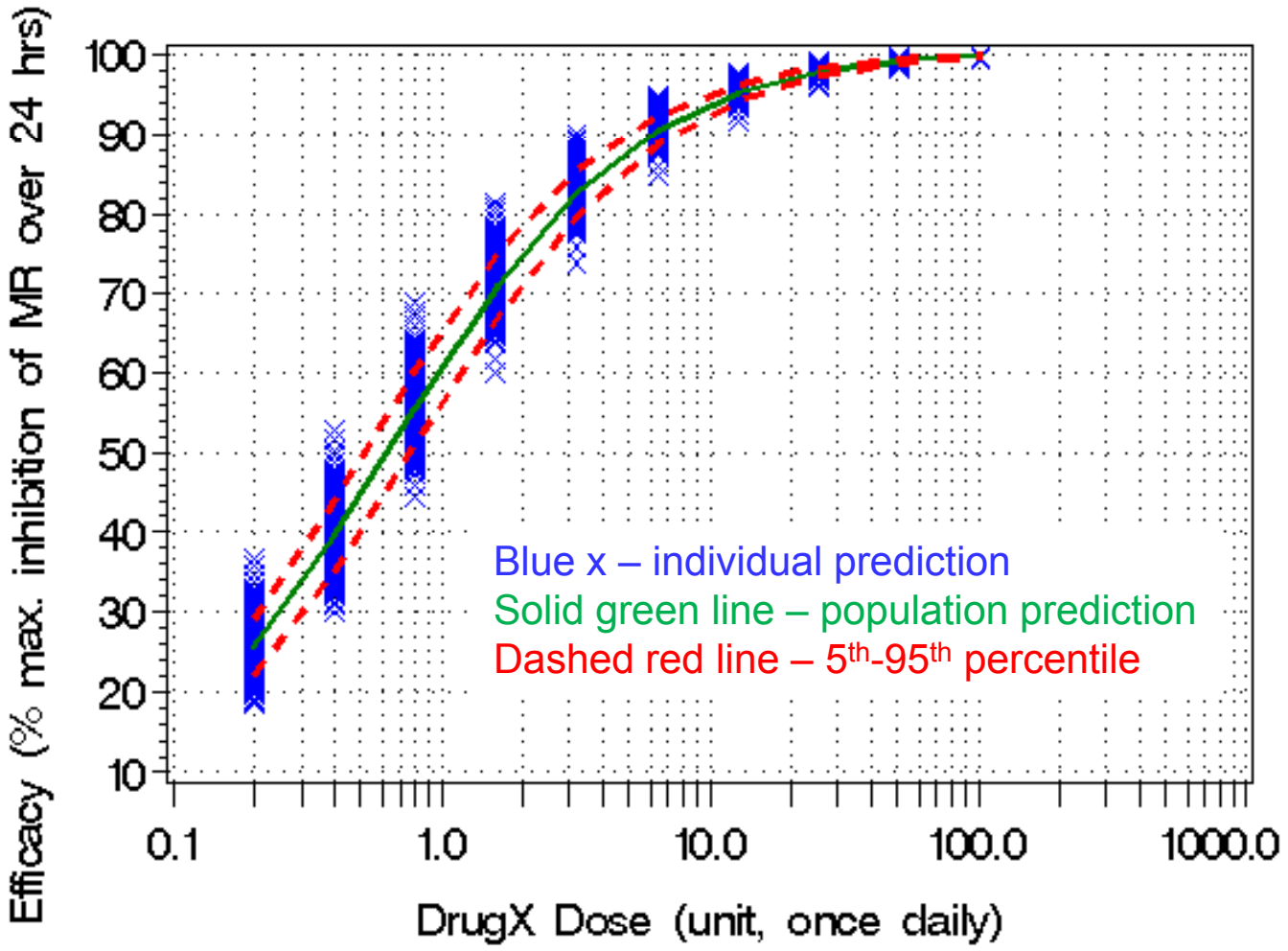
Simulated Steady-State DrugX Plasma Concentration- & BM2-Time Profiles





Simulated Efficacy† (MR) – Dose Profile



† Efficacy is defined as the percentage of the maximal inhibition of MR over 24 hours

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Summary

- BM1, BM2 and MR were well described with one pseudo-sigmoid PKPD model in rhesus monkeys.
  - BM1 and BM2 PKPD were consistent with surrogate MR PKPD and confirmed with outcomes.
- BM2 in healthy young subjects was well described with a pseudo-sigmoid PKPD model.
- The results of the simulation suggested:
  - ~6 unit of DrugX once daily would achieve ~90% maximal inhibition of MR in about 50% subjects
  - ~13 unit of DrugX once daily would achieve >90% maximal inhibition of MR in >90% population

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Conclusions, Outcomes and Lessons Learned

- This population PKPD analysis helped:
  - Strengthen certainties around BMs in preclinical before using it in clinical
    - BM PKPD and surrogate PKPD can be well linked with MOA and MOD and consistent with preclinical outcomes
    - Integration of preclinical multi-BM and surrogate PKPD are useful and could guide clinical simulation to help decision-making in early drug development
  - Support a "GO" decision to Phase II
    - Dosing regimen for a Phase IIa study: 100 unit, QD, highest safe dose
- Outcomes
  - Clinical surrogate results: negative
  - Clinical POC outcomes: negative
- Challenges in first-in-class drug development
  - Target relevance?
  - BM validation?
  - preclinical-to-clinical translation?
  - clinical BM-to-outcomes translation?

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Backups

BOS 1 Topic 3 Position Statement

- M&S should be used to make optimal use of all available information including in vitro, preclinical (translational M&S), literature and in house data to optimize clinical development and help early selection of safe and efficacious drugs.

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BOS 1 Topic 3 Open Questions

- What is the role of M&S in translation from in vitro-preclinical data to human?
- Sharing data, database development for translational M&S.
- What are the expectations from Regulators on M&S to support IPoM and PoP/C study design documentation and for their regulatory decision making?
- Is success or failure in early development an internal issue for Pharma companies or is there a role for the regulators?
- How can regulators help Pharma companies make better internal decisions that ultimately result in faster access for patients to safe and effective new medicines?
- What are the standards expected for use and reporting if M&S is used as a platform to compile data and optimize development and candidate drug selection?

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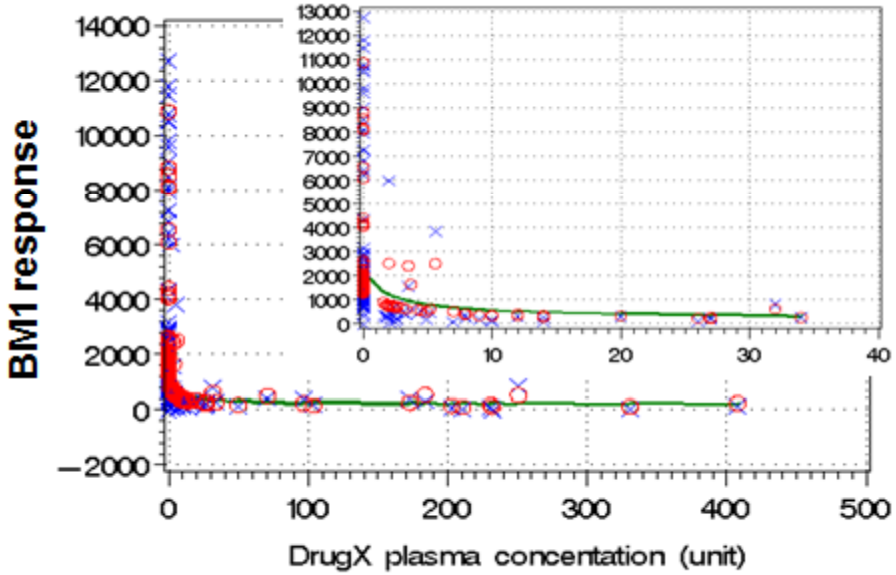
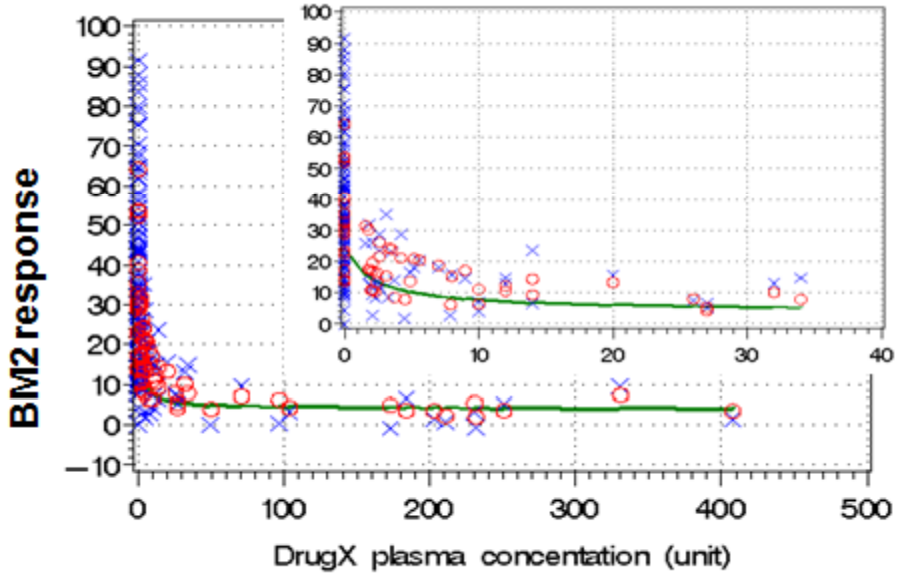
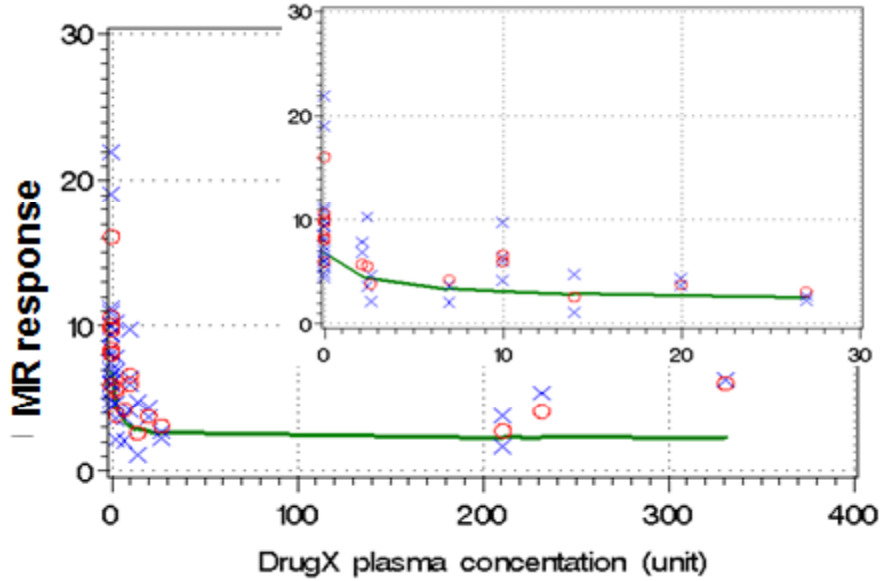
Model-predicted vs. Measured E-R (Non-clinical)







Simulation Data

- 5000 “healthy” subjects/dose
- 15 PK/PD sampling points per subject over 24 hours post dose at steady state
- 10 dose levels: 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, 12.8, 25.6, 51.2 & 102.4 *unit*

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