



EXPERTISE

SAFETY

SOLUTIONS

Pharmacokinetic and Statistical Considerations in First-in-Human Clinical Trials

Joanna Magielse, PhD

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WHEN YOU NEED TO BE SURE

SGS

OVERVIEW

- Introduction
- How to set up the study
- How to analyze the data
- Case study
- Conclusion

■ Goal

- Find best dose and dose regimen for PhII

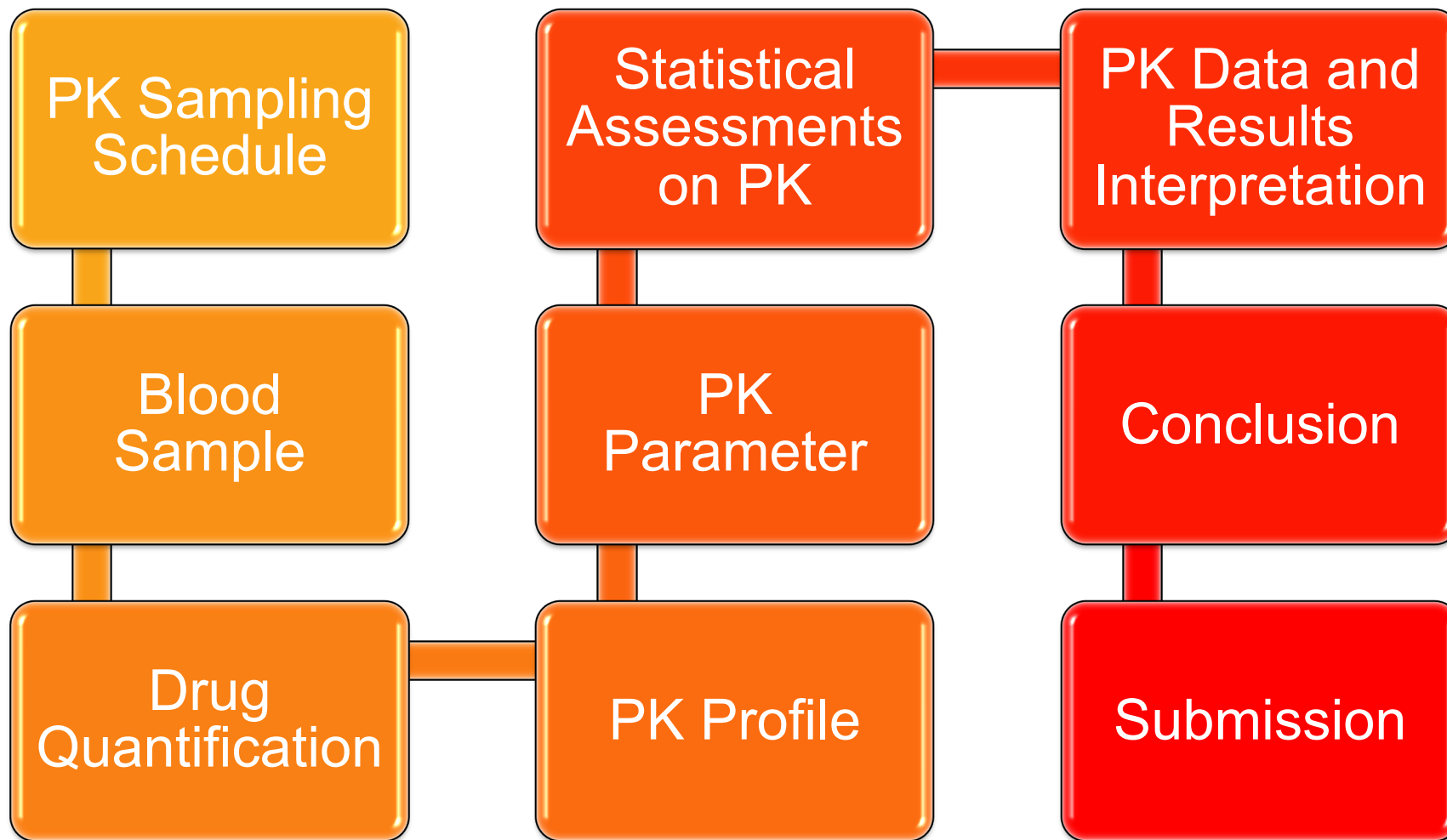
■ Recommendations (limited)

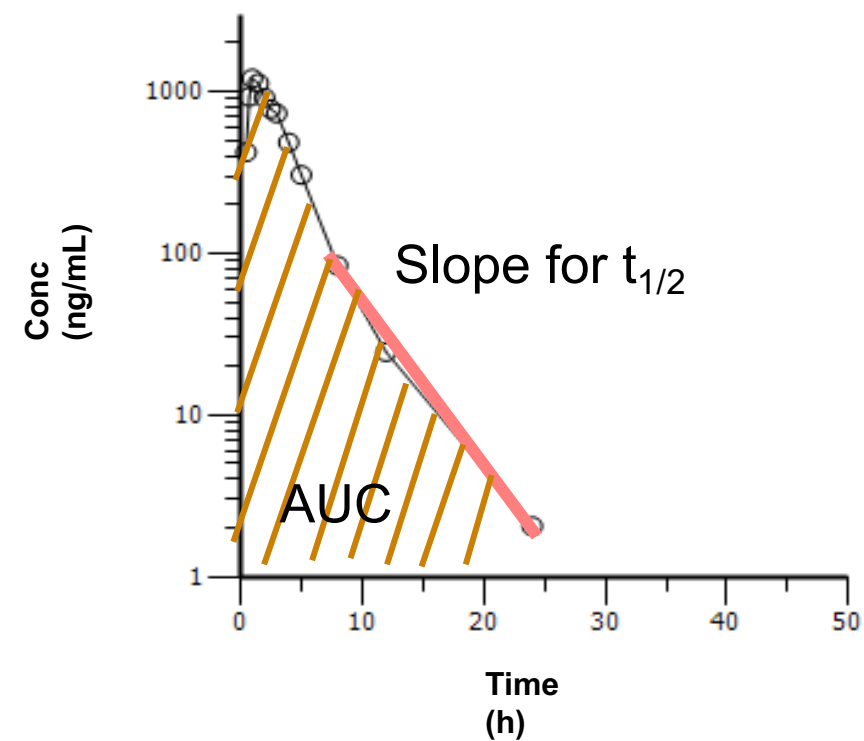
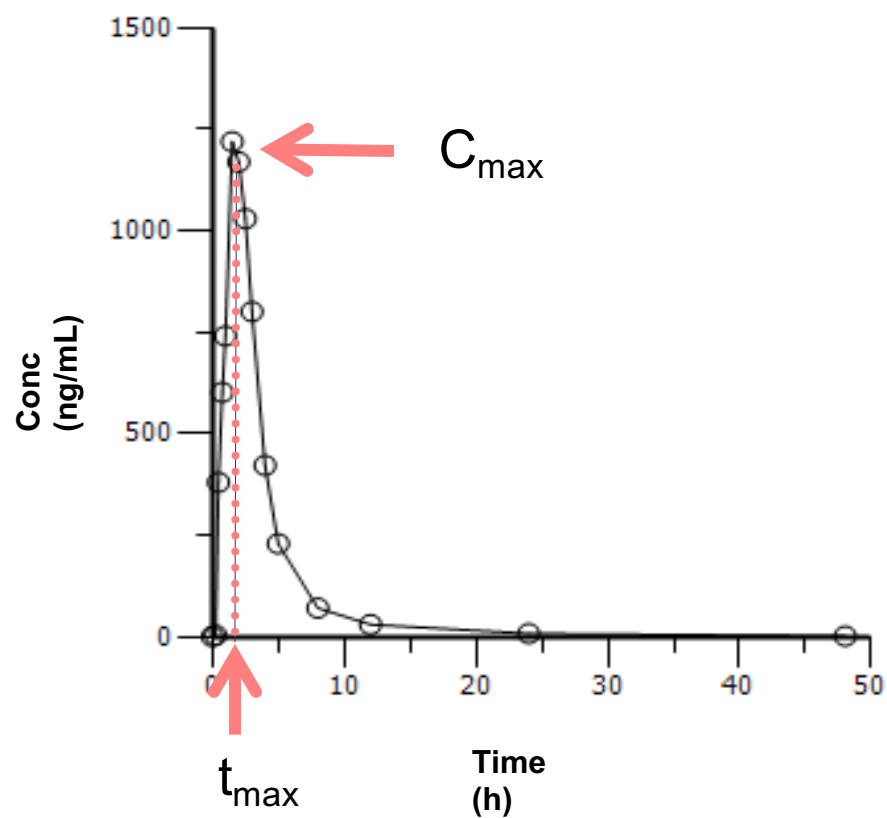
- EMA
- FDA

■ Challenges

- How to plan PK
- How to analyze PK
 - Depends on drug properties and pre-clinical observations

- Type of study
 - SAD: dose proportionality
 - MAD: accumulation/ steady state
 - Integrated protocols
 - Food
 - DDI
 - Age
- $n < 8$ / dose group
 - **EXPLORATORY**





OVERVIEW

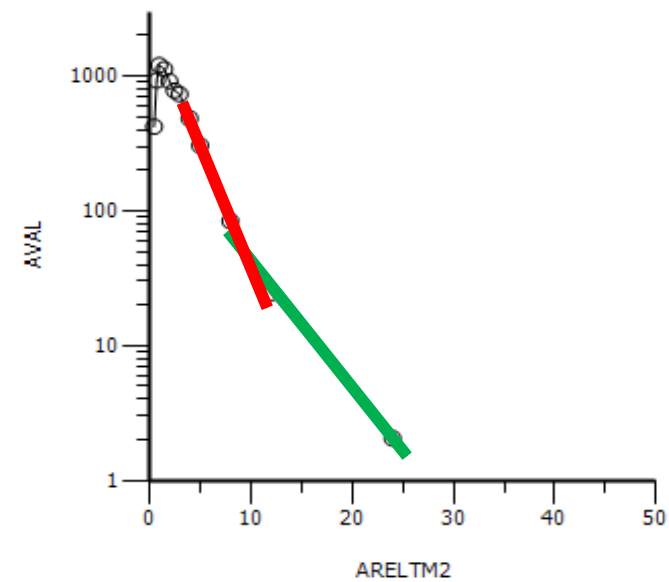
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SAMPLING SCHEME

- Around expected $t_{\max}$
- In elimination phase
 - Min 3 samples after $t_{\max}$
 - About $5 \times t_{1/2}$
- Harmonize PK and PD sampling scheme

- Suitable sensitivity
- Metabolites ?

How to set up the study



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REVIEW OF DATA

- Explanation for unexpected profiles
 - Samples switched
 - Time deviation
 - Concomitant medication
 - Adverse events (vomiting, diarrhea)
 - Pharmacogenomics
- Parameters not estimated correctly
 - Insufficient sampling period
 - Missing data
- Inclusion/exclusion of data
 - As described in analysis plan

OBJECTIVES

- PK profile
- Dose proportionality
- Accumulation
- Steady state
- Food effect
- Gender effect

- Descriptive statistics
 - Mean, SD, CV%, min, median, max
- Graphs
 - PK profile
 - Linear-linear scale: peak
 - Log-linear scale: elimination
- Inferential statistics
 - LSM with CI
 - Ratio with CI
 - Log transformed
 - ! **EXPLORATORY** nature of study
 - quantifying, not proving

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STUDY CHARACTERISTICS

- Randomized, double-blind, placebo-controlled, sequential dose escalation study in healthy subjects.
- Part 1: SAD
 - 5 cohorts of 8 (6:2) subjects
 - Single oral dose of 10, 25, 50, 150 and 300 mg
 - In Cohort 4 (150 mg): food effect
 - 2-period crossover study
- Part 2: MD
 - 1 cohort of 8 (6:2) subjects
 - Oral dose of 300 mg q.d. for 7 days

ANALYSIS PLAN

- List PK parameters with derivation rules
- Descriptive statistics
- Inferential statistics
 - Dose proportionality
 - Steady state
 - Food effect
- List of TLFs

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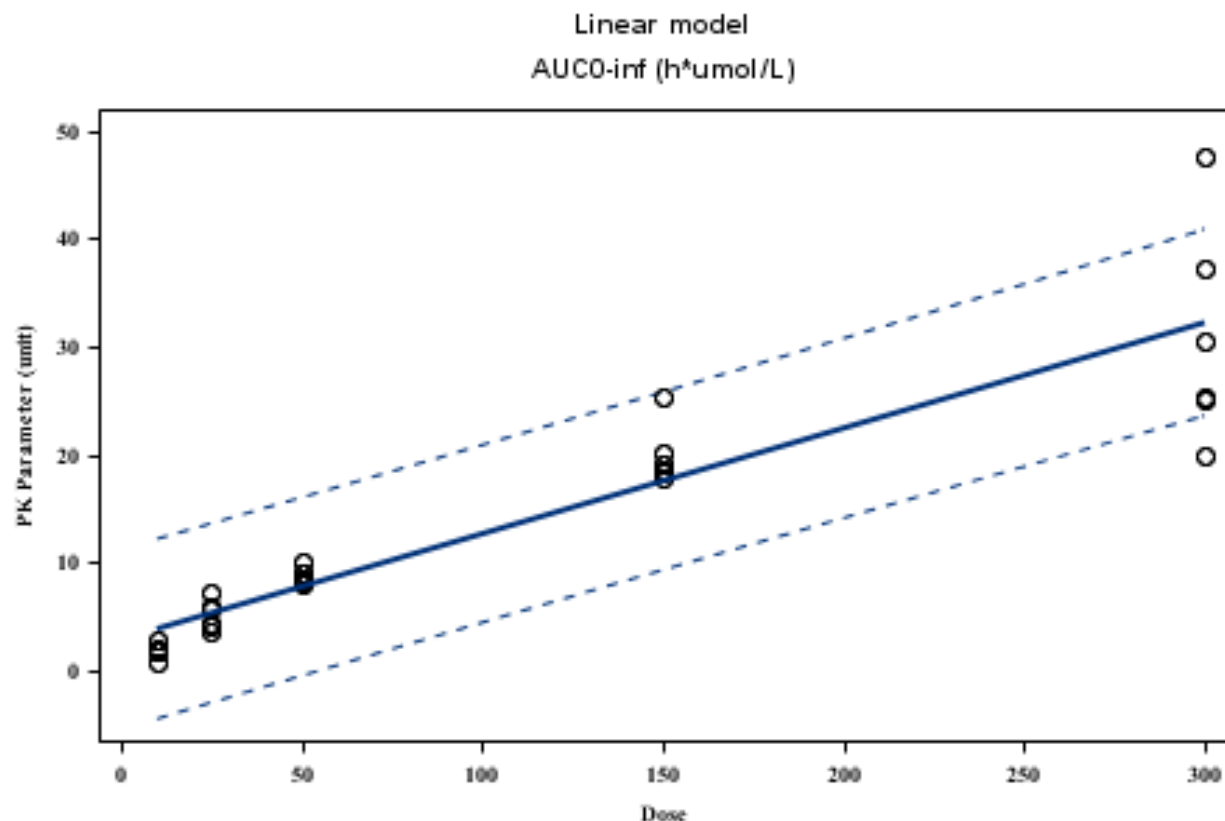
■ Available data

- Part 1: 5 Cohorts, n=6
- Doses: 10 – 300 mg
- AUCinf

■ Proposed analysis methods

- Linear model
- Power model
- Boxplot

LINEAR MODEL



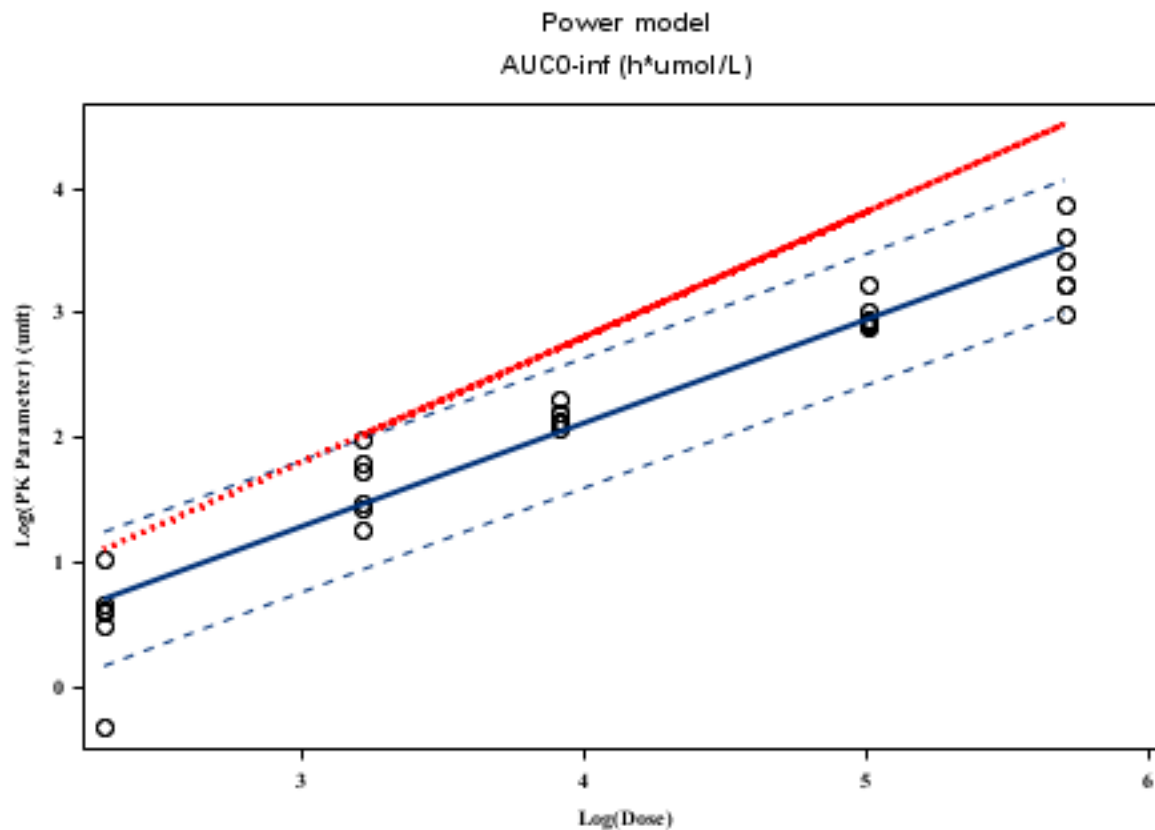
Model: dose and dose² as fixed effects

ANOVA

Significant linear
dose effect
Non-significant
quadratic effect

No conclusion
on dose
proportionality

POWER MODEL



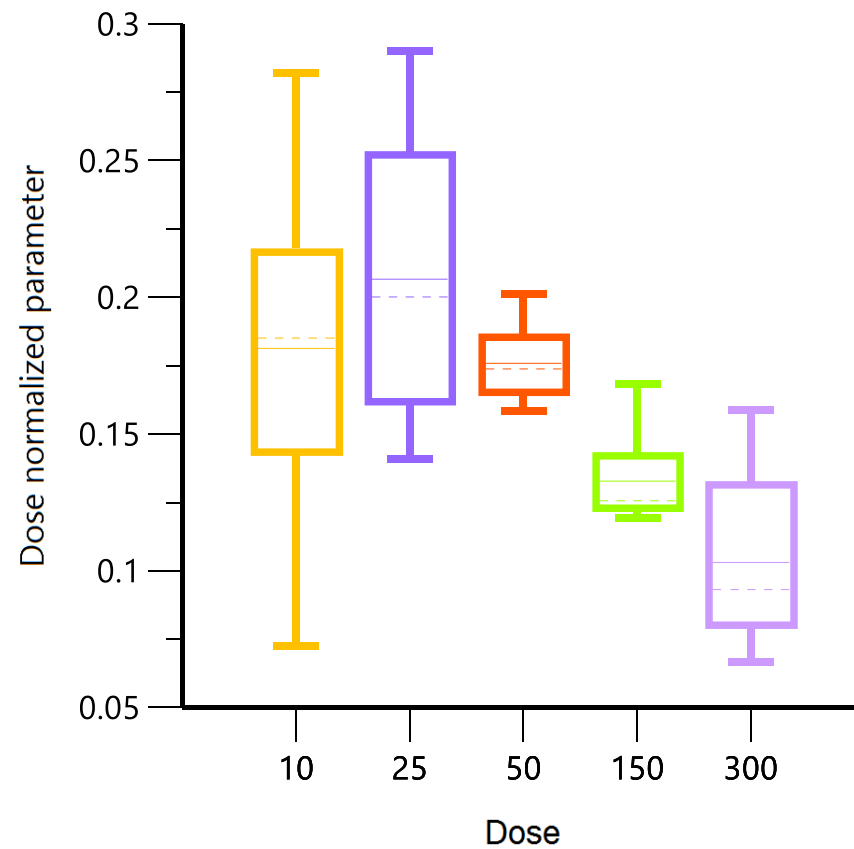
Model: log-dose as fixed effects

ANOVA
Slope = 1

Slope:
0.75 – 0.90

Less than dose
proportional

Case study
Dose proportionality



Less than dose
proportional

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DATA AND METHODS

- Available data
 - Part 2: 1 cohort, n=6
 - Trough concentrations

- Proposed analysis methods
 - Linear trend
 - Pairwise comparison
 - Graphical evaluation
 - Individual and mean data

LINEAR TREND

Period	Slope (95% CI)
Day 2 to 8	0.05 (0.01; 0.09)
Day 3 to 8	0.02 (-0.03; 0.07)
Day 4 to 8	0.01 (-0.07; 0.08)
Day 5 to 8	0.00 (-0.10; 0.10)
Day 6 to 8	0.00 (-0.16; 0.16)

ANOVA
Slope = 0

Steady state
from Day 3

Model: day as fixed effects

PAIRWISE COMPARISON

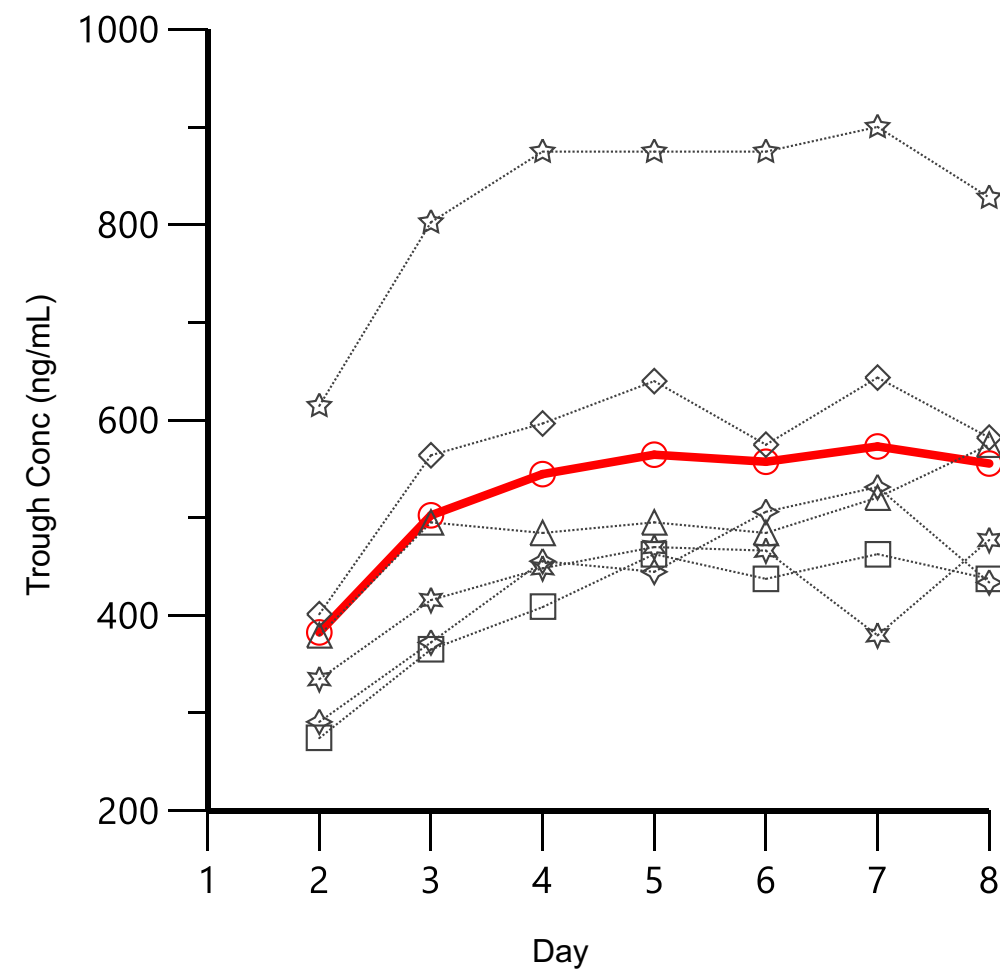
Day	3	4	5	6	7	8
2	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
3		0.4140	0.0718	0.1237	0.0467	0.1262
4			0.9571	0.9901	0.9048	0.9909
5				0.9999	1.0000	0.9999
6					0.9989	1.0000
7						0.9987

ANOVA

Steady state
from Day 4Case study
Steady state

Model: day as fixed effects

GRAPHICAL ASSESSMENT MEAN AND INDIVIDUAL DATA



Steady state
from Day 4

Case study
Steady state

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■ Available data

- Part 1, Cohort 4, n=6
- AUCinf
- 2xCO

■ Proposed analysis methods

- Statistical assessment
- Graphical evaluation
 - Individual and mean data
 - Boxplot

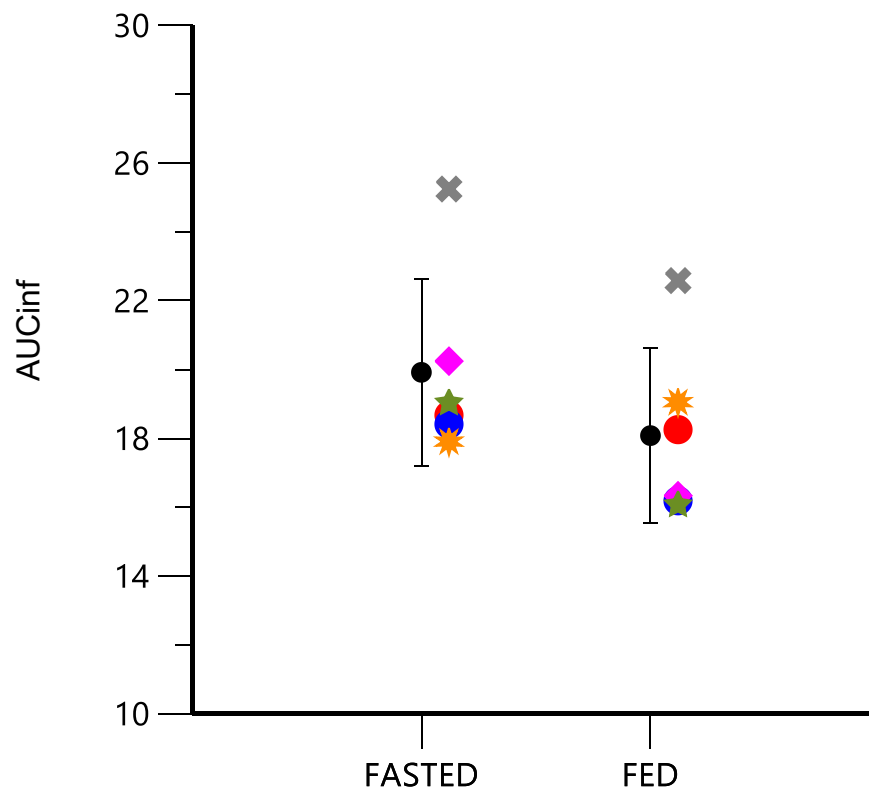
	LSM (95% CI)	LSM ratio (90% CI)	P-value of treatment
Model A			
Fed	18 (16; 21)	90.72	0.0646
Fasted	20 (17; 23)	(83.48; 98.58)	
Model B			
Fed	18 (16; 20)	90.72	0.0971
Fasted	20 (18; 22)	(82.40; 99.88)	

ANOVA

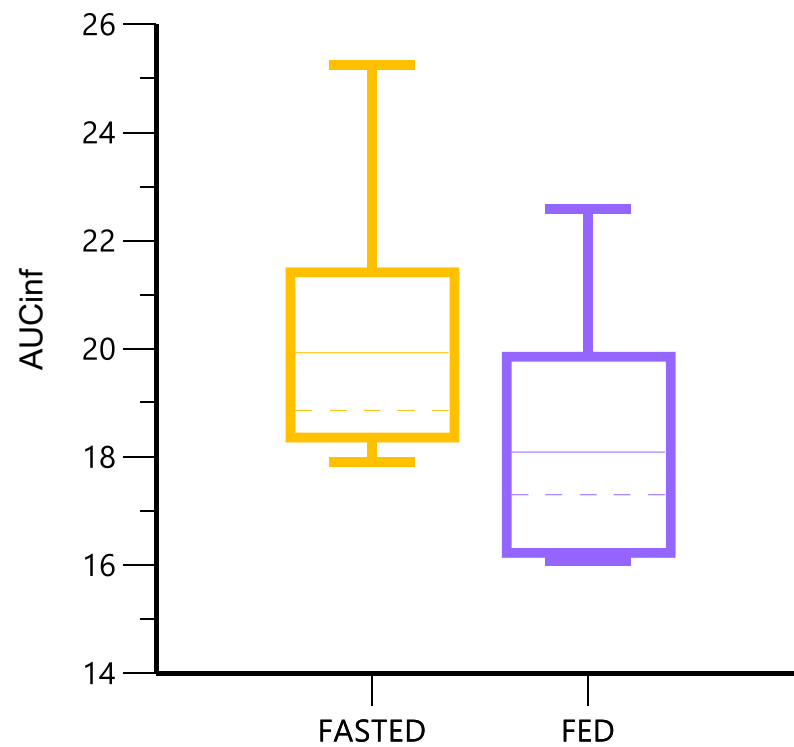
No food effect
LSM ratio within
80-125%

Case study
Food effect

Model A: Treatment as fixed effect and subject as random effect.
 Model B: Treatment, sequence, period and subject within sequence as fixed effects.

GRAPHICAL ASSESSMENT
INDIVIDUAL AND MEAN DATACase study
Food effect

No food effect
Overlap mean
 $\pm$ SD



No food effect
Overlap boxplots

OVERVIEW

- Introduction
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■ How to plan the data

- Sampling scheme
- Analytical method

■ How to analyze the data

- Review the data before analyzing it
- Graphical presentation
 - Preference over inferential statistics
 - ! Exploratory nature
 - Know what you plot (linear vs dose proportional)

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Posted: May 31, 2019



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By: *Narine Baririan, PharmD*

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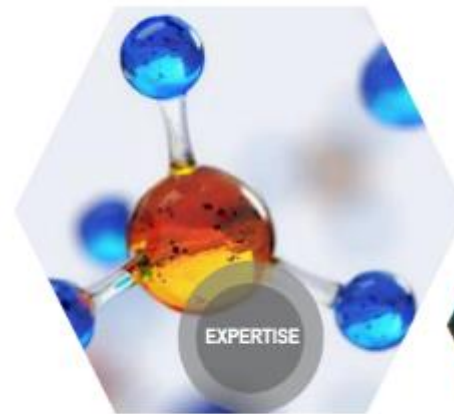
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