

# SUMMER INTERN PRESENTATION



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2020.8

# What I learn...



Basic SAS  
Programming



Exposure-Response  
Relationship



Visualization of  
ER Relationship



Conclusions &  
Acknowledgments

# 1. Basic SAS Programming

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# SAS Programming Skills



- Tables
  - ADSL
  - ADAE
- Data tabulation: derive SDTM datasets
  - DM domain
- Data analysis: derive ADaM datasets
  - ADSL
  - ADAE
  - ADLBC
- Related skills: Macro, Data step, Proc Step, Proc Report, Proc Sort, Proc Mean, Proc SQL, Proc Transpose, Proc Tabulate, Proc Compare, ODS, Proc Univariate...



# 2. Exposure-Response Relationship

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# Introduction



- Two exposure-response relationships: **efficacy** and **toxicity**
- Purposes:
  - How to use a drug most effectively
  - Develop the drug label (i.e., prescribing information)
  - Quantifying the relationships for a new or modified drug intended for marketing
- Selection of exposures and responses
  - Exposure: the **closer get to the effect site**, the more predictive of response; not often the does
  - Ideal: analyzing the plasma, base exposure-response on plasma concentration data



# Study Design Considerations



- Have an **adequate domain of the exposure measure**. The most practical way to get a wide domain is to study a broad range of doses in phase 1 and phase 2 studies.
- **Ethical** issues.
- Collect **accurate dosing data**. Accurate dosing history is as important in pharmacokinetics as is the accurate recording of sampling times.
- Other problems: a limited range of exposure, variability among subjects, a lag time in effects, a dose titration effect.

# Measure Exposure and Response



- Measuring **Exposure**
  - **AUC**: compare exposure after **multiple doses** to that following a single dose
  - **C<sub>max</sub>**: useful when examining **rapid-onset endpoints** such as toxicity. But due to the potential for large interindividual variability, consideration must be given to expected differences in PK profiles due to demographics, disease states and food effects.
  - **C<sub>min</sub>**: measured just before administration of the next dose, is less commonly used, but useful in objective like **determining the lowest effective dose**; does not reflect drug absorption processes and is often proportional to AUC
  - **Combining population PK analysis and Bayesian estimation methods** can be used to generate an exposure variable that can be correlated to response



# Measure Exposure and Response



- Measuring **response**
  - Both positive (efficacy) and negative (safety) responses can be measured by **clinical outcomes, biomarkers, surrogate markers**
    - **Biomarkers:** blood pressure, cholesterol, viral load, magnetic resonance imaging (MRI) measures
    - **Surrogate markers:** When biomarkers are accepted for use in clinical trials as a substitute for clinically meaningful endpoints (i.e., as predictors of therapeutic effect), they are classified as surrogate markers (e.g., blood glucose, C-peptide, Alzheimer's plaques).
    - **Continuous** and **categorical** outcomes (occurrence of AEs)

# Measure Exposure and Response



- Type of response variable: continuous, categorical, time-to-event data
  - **Continuous**: nonlinear least-squares;
  - **Categorical**: same type with continuous; but data are logit-transformed to apply logistic regression
  - **Time-to event**: proportional hazards model or Kaplan-Meier plots for subjects in different exposure quantiles or placebo



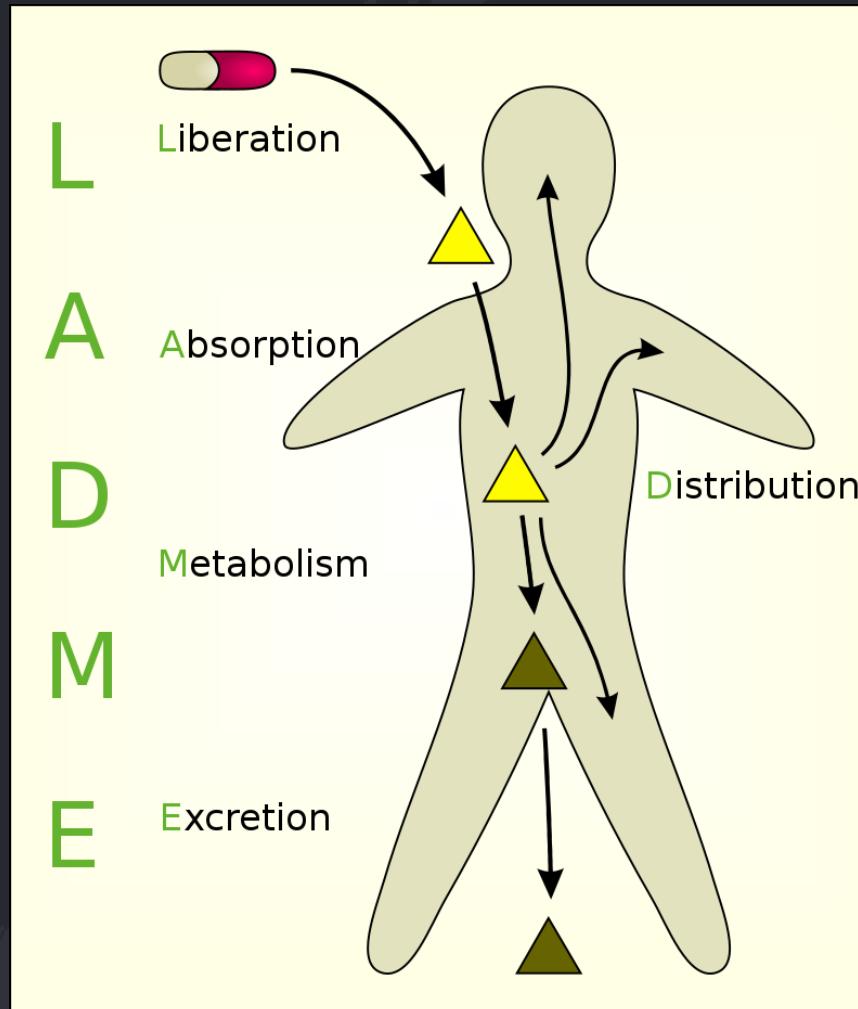
# Statistical Models



- **Empirical** ER model
  - Relationship between exposures and responses
  - Focus more on data
  - Not derived from the biological or medical mechanism
  - e.g. log-dose and other factors: such as age and weight as covariates
- **Mechanistic** ER models
  - specify assumptions
  - attempt to incorporate known factors about the systems surrounding the data into the model, while describing the available data

# Pharmacological Mechanisms

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- **Liberation** – the process of release of a drug from the pharmaceutical formulation.
- **Absorption** – the process of a substance entering the **blood circulation**.
- **Distribution** – the **dispersion** or dissemination of substances throughout the fluids and tissues of the body.
- **Metabolism** (or biotransformation, or inactivation) – the recognition by the organism that a foreign substance is present and the irreversible transformation of **parent compounds** into **daughter metabolites**.
- **Excretion** – the **removal** of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.



# 2.1 Models Based on Pharmacological Mechanisms

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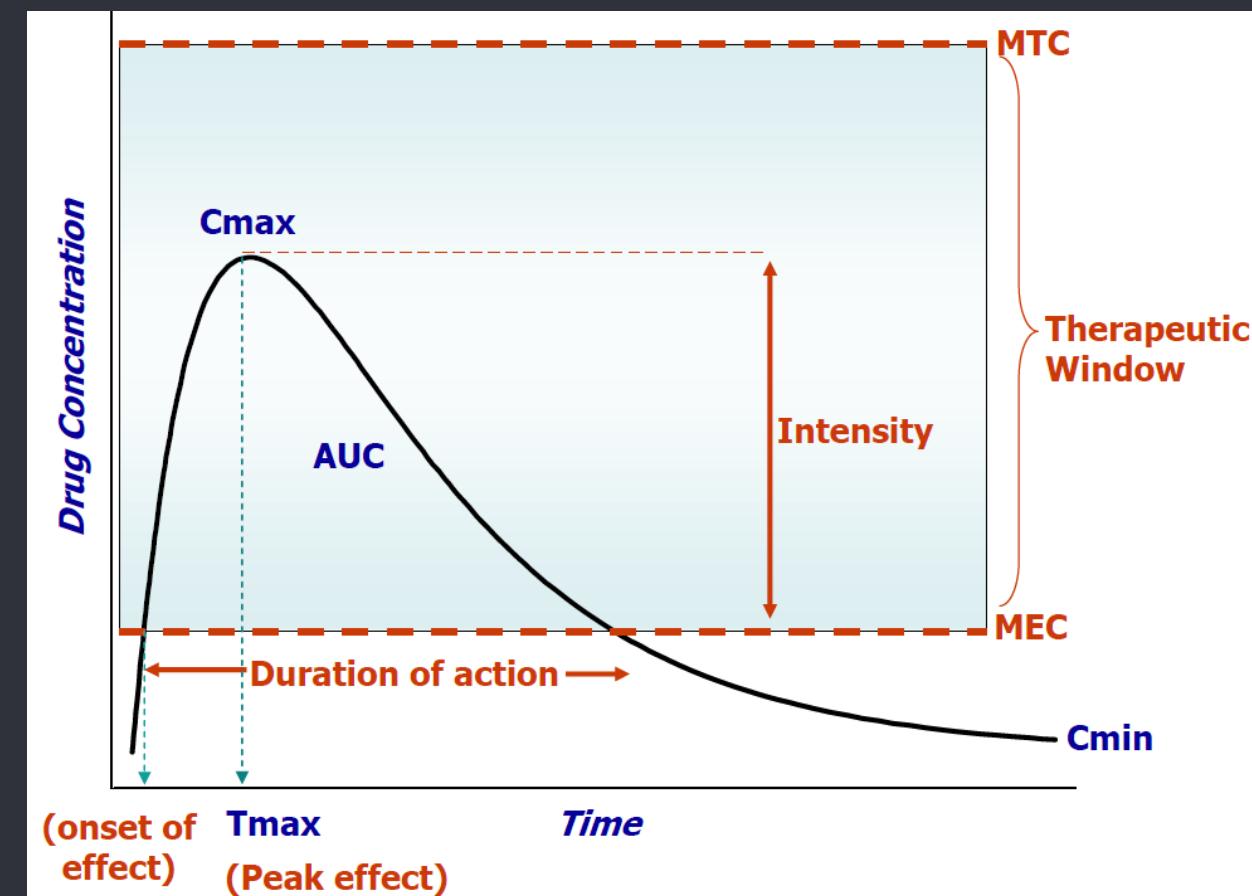
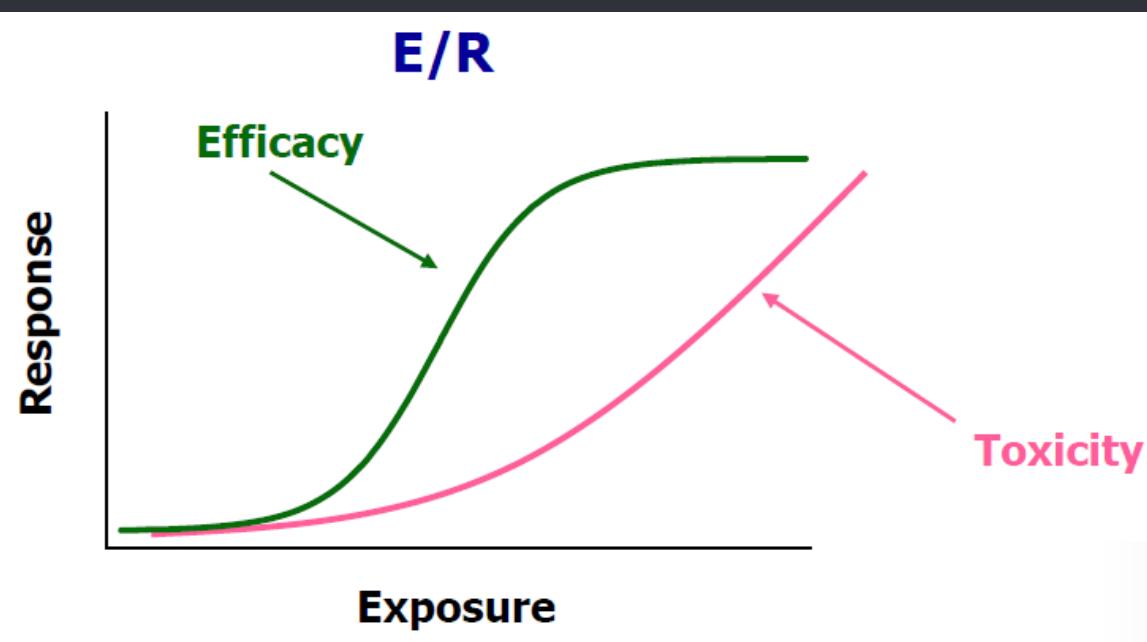
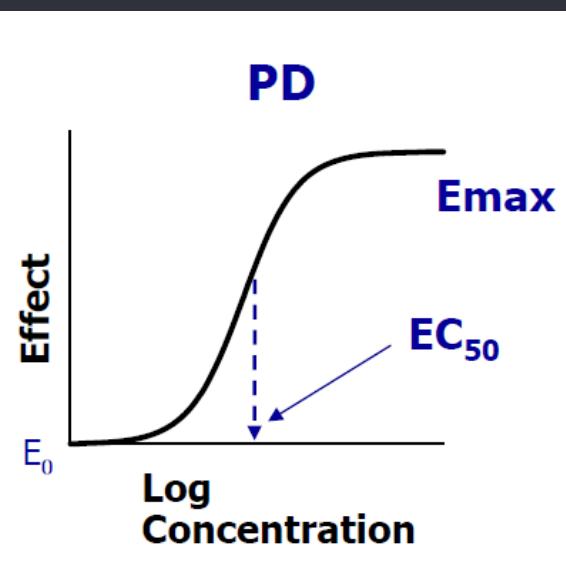
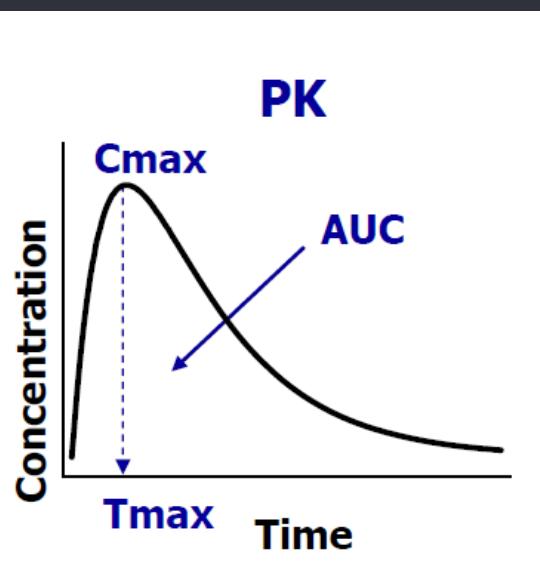
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# Overview of PKPD Models



- Derived: from the **drug receptor occupancy** theory
- Two processes (simultaneously)
  - Free receptors and drug molecules bind to **form the complex**
  - Complex dissociates **back to** free receptors and drug molecules
- Characteristics: **dynamic** and **temporal**
- **PK**: what the **human body does** to a given pharmaceutical, by assessing PK of a biological drug **in different matrices**
- **PD**: what the **drugs' effects** on the body, involves receptor binding, post-receptor effects, and chemical interactions





- PK and drug effect
- Determining therapeutic window

## 2.2 Statistical Models

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# Linear & Nonlinear Models



- The ER model for a particular analysis mainly depends on **the type of response**
  - **Linear models:**
    - $y_i = \beta c_i + X_i + \varepsilon_i$
    - Simple least squares (LS)
    - Key assumption:  $c_i$  and  $\varepsilon_i$  are independent
  - **Nonlinear models:** PKPD models (often)
    - $y_i = g(c_i, X_i, \beta) + \varepsilon_i$
- **Transformations**
  - **Log-transformation:** the most commonly used one
  - Reason: to make the distribution of the response easy (normal)

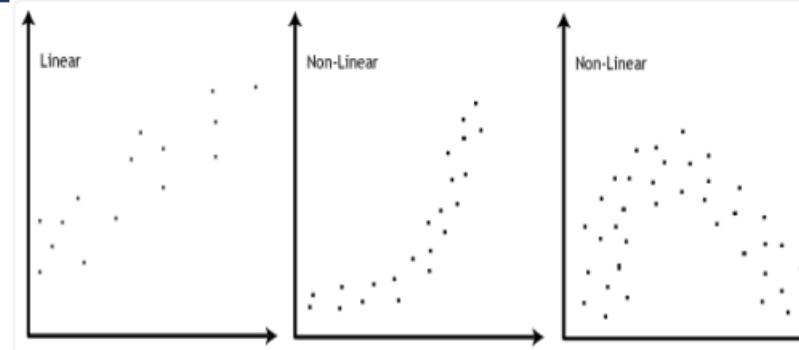
# Linear & Nonlinear Models



## Linear vs non linear

### Linear

- Linear scatter plot
- No curves in residual plot
- Correlation between variable is significant



### Non-linear

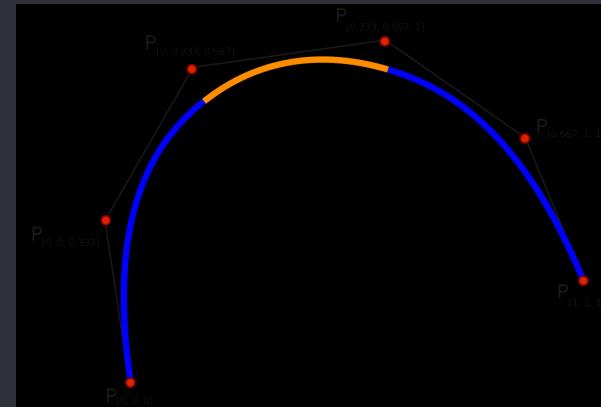
- Curves in scatter plot
- Curves in residual plot
- No significant correlation between variables



# Semiparametric & Nonparametric Models



- Reason: empirical models may consider **less certain of the correctness** and sometimes may **not fit the data well**
- **Spline function:**
  - Piecewise polynomial functions connected at a number of **points (knots)** where the value and derivatives up to a certain order are continuous
  - Curve is sufficiently **smooth**
  - Main purpose in ER: **predict the response** at different exposure levels



# 2.3 ER Models for Longitudinal Data

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# Introduction



- Terminology: dose-exposure (DE); exposure-response (ER)
- ER models assumption
  - Response and exposures are measured at the same time
- Longitudinal data: repeated measures form multiple individuals



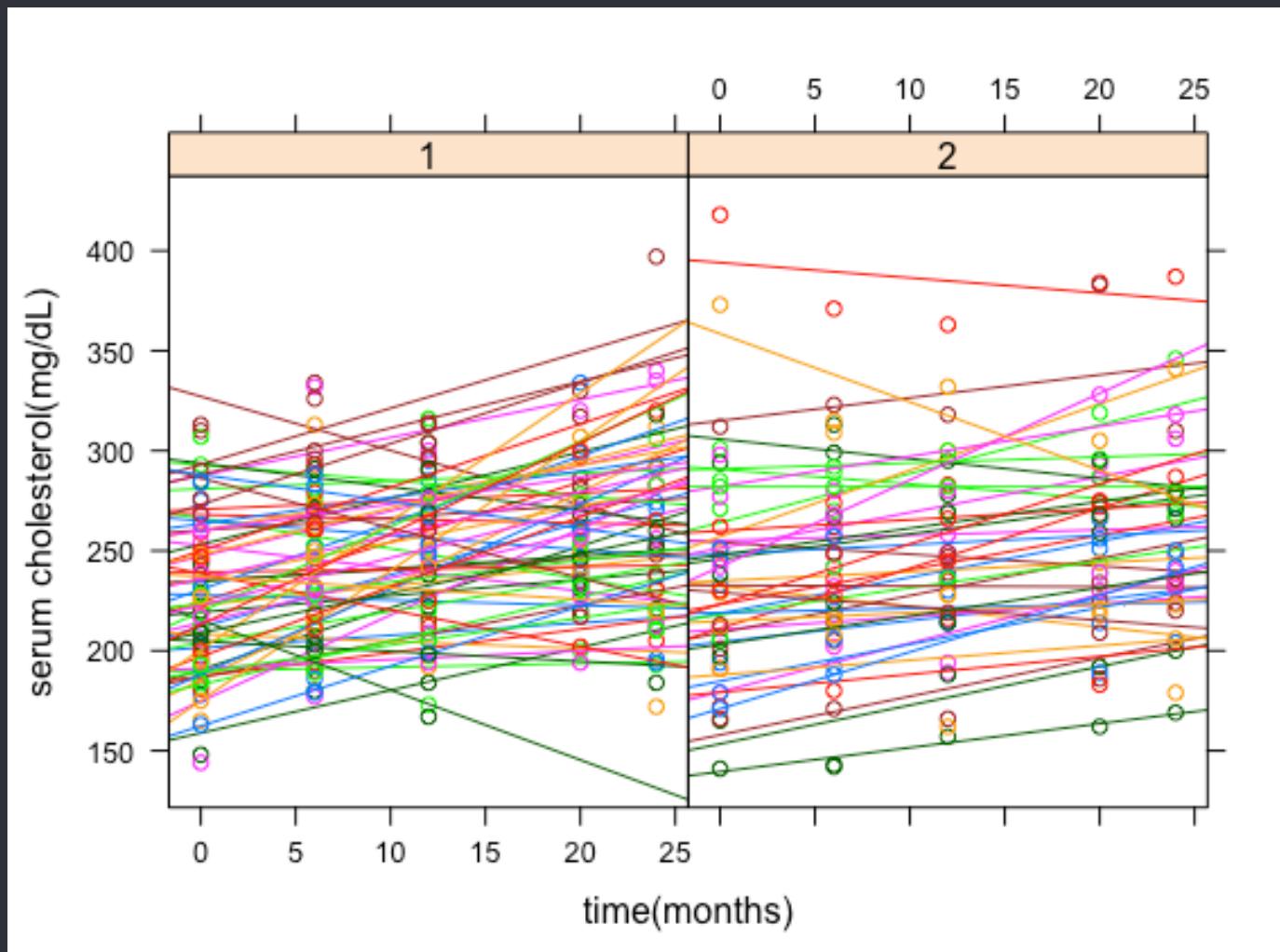
# Linear Mixed Models



- **Linear mixed models (LMM)**
  - Some factors considered as fixed and some others considered as random, referred to as **fixed and random effects** (multi-level)
  - $y_{ij} = \beta_1 + \beta_2 c_{ij} + u_i + \epsilon_{ij}$
  - $y_{ij}$  and  $c_{ij}$  be the response and concentration at **time  $t_j$** ,  $j = 1, \dots, r$  from **patient i**.
  - $u_i$  is a latent variable representing an individual's variability in response, and  $\epsilon_{ij}$  represents **within-patient variation** in response
  - Model selection
    - Hypothesis test
    - Statistically significant difference for component
    - AIC/ BIC: the lower, the better
- Programming
  - R:library lme4



- Linear mixed models (LMM) for two treatments' groups



# Nonlinear Mixed Models



- **Nonlinear mixed models (NLMM)**
  - $y_{ij} = g(c_{ij}, \beta_i) + \varepsilon_{ij}$
  - $y_{ij}$ ,  $i = 1, \dots, n$ ,  $j = 1, \dots, r$ , be the response (e.g., a biomarker measure) and  $c_{ij}$  be the exposure measured (e.g., the trough concentration) at time  $t_{ij}$  (e.g., at day 1 of treatment cycle  $j$ ) from subject  $i$ .
  - $g(c_{ij}, \beta_i)$  is a nonlinear function based on a pharmacological mechanism or as an empirical model
  - $\beta_i$  is a set of parameters for subject  $i$ ,  $\varepsilon_{ij} \sim N(0, \sigma^2 \varepsilon)$  is a within-subject measurement error
- Programming
  - SAS: proc NL MIXED

# Population PK Models



- **popPK modeling:** study of variability in drug concentrations **within a patient population** receiving clinically relevant doses of a drug of interest
  - Usefulness: guide decision-making across all phases of drug development; provide support for efficacy and safety in marketing applications
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- Typical models: compartmental models
  - In NLMM for ER modeling
    - Needs to introduce random effects into the parameters, since they vary between subjects



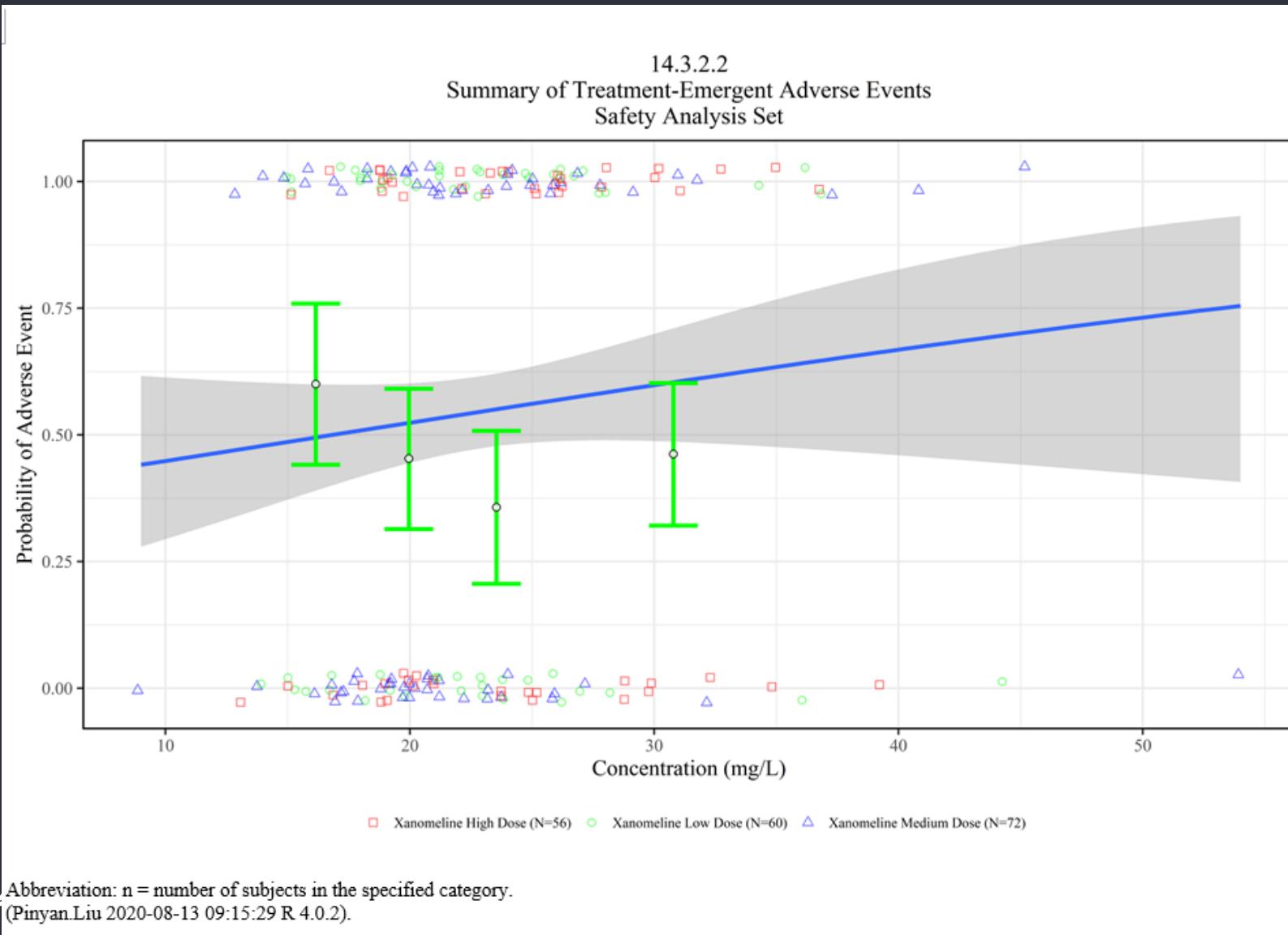
# 3. Visualization of ER Models

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# Binary outcomes (Safety example)



- Scatter plots
- Logistic regression smooth line
- 95% confidence intervals
- Quartiles with mean and 95% error bar

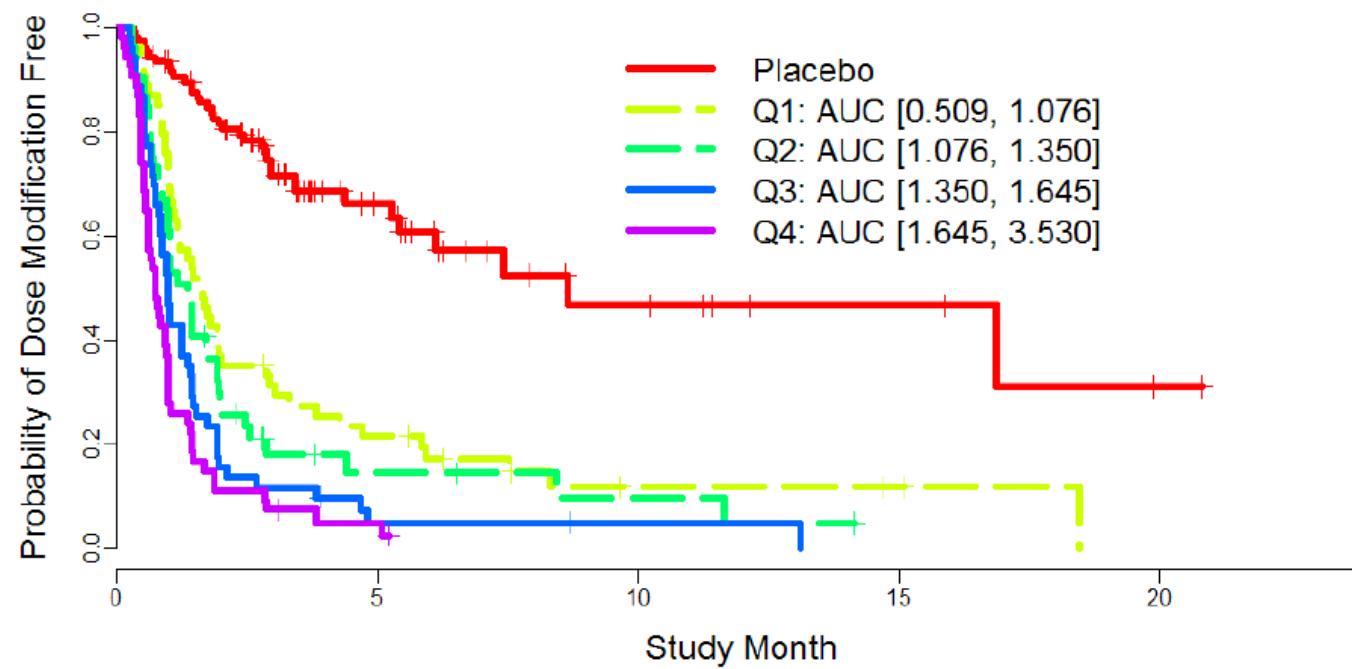
# Result Interpretation



- $\text{logit}(\text{event} | \text{concentration}) = 0.299 - 0.019 * \text{concentration}$
- Scientific interpretation:
  - **Slope:** -0.019 is the difference in the log odds. For a one-unit increase in the concentration, the expected change in log odds of having adverse events is -0.019.
  - **Intercept:** when concentration is 0, the log odds of having adverse events is 0.299.

# PFS (Efficacy example)

**Figure 3: ER Relationship for Time to First Dose Modification Stratified by  $AUC_{ss, pred}$  (mg\*day/L) quartiles for Cabozantinib Treated Patients (Trial XL184-301).**



- PFS: progression-free – survival probability
- Indicating an exposure-response relationship
- Indicating censoring data

[https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/203756Orig1s000ClinPharmR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203756Orig1s000ClinPharmR.pdf)



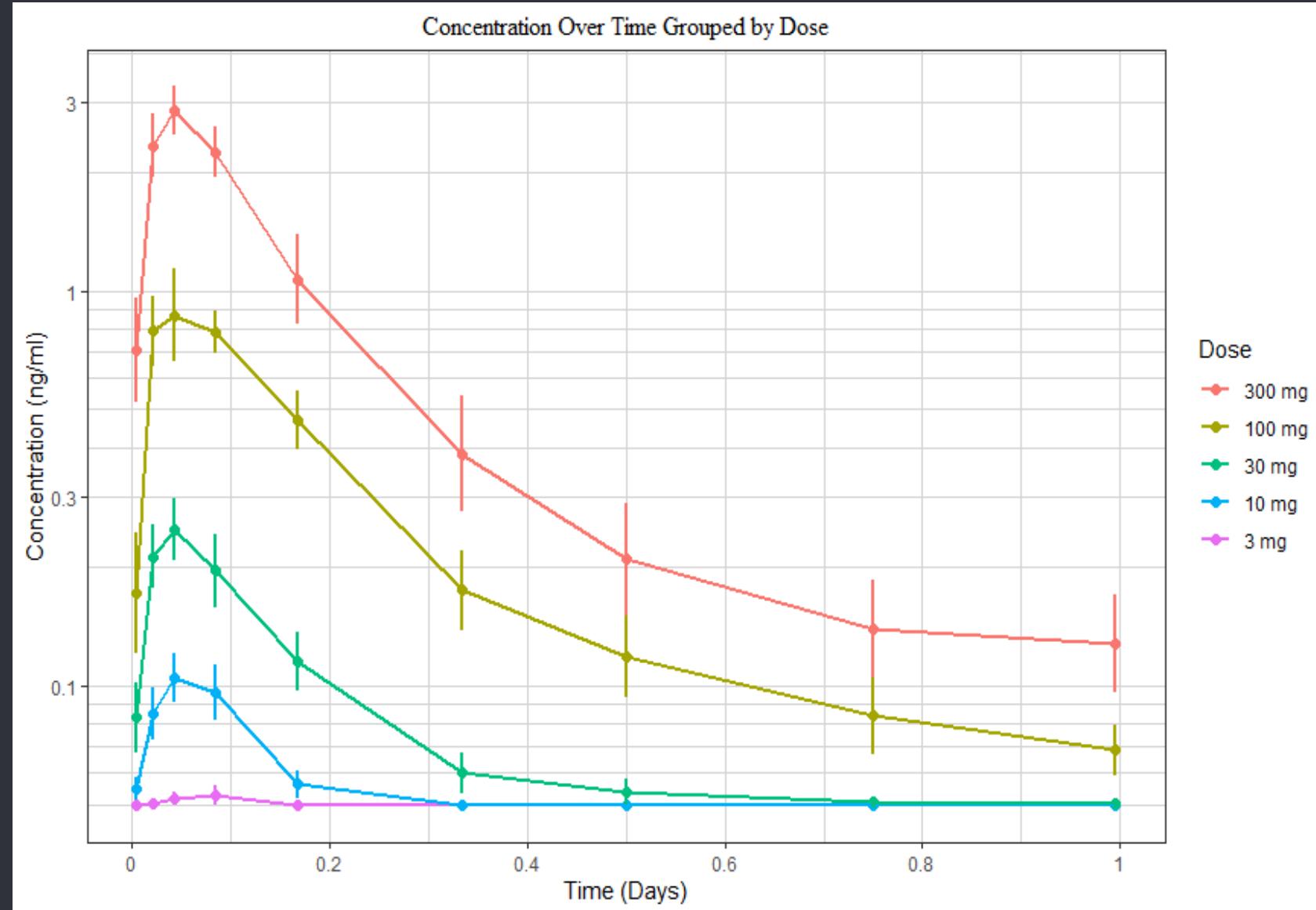
# PKPD Single Ascending Dose

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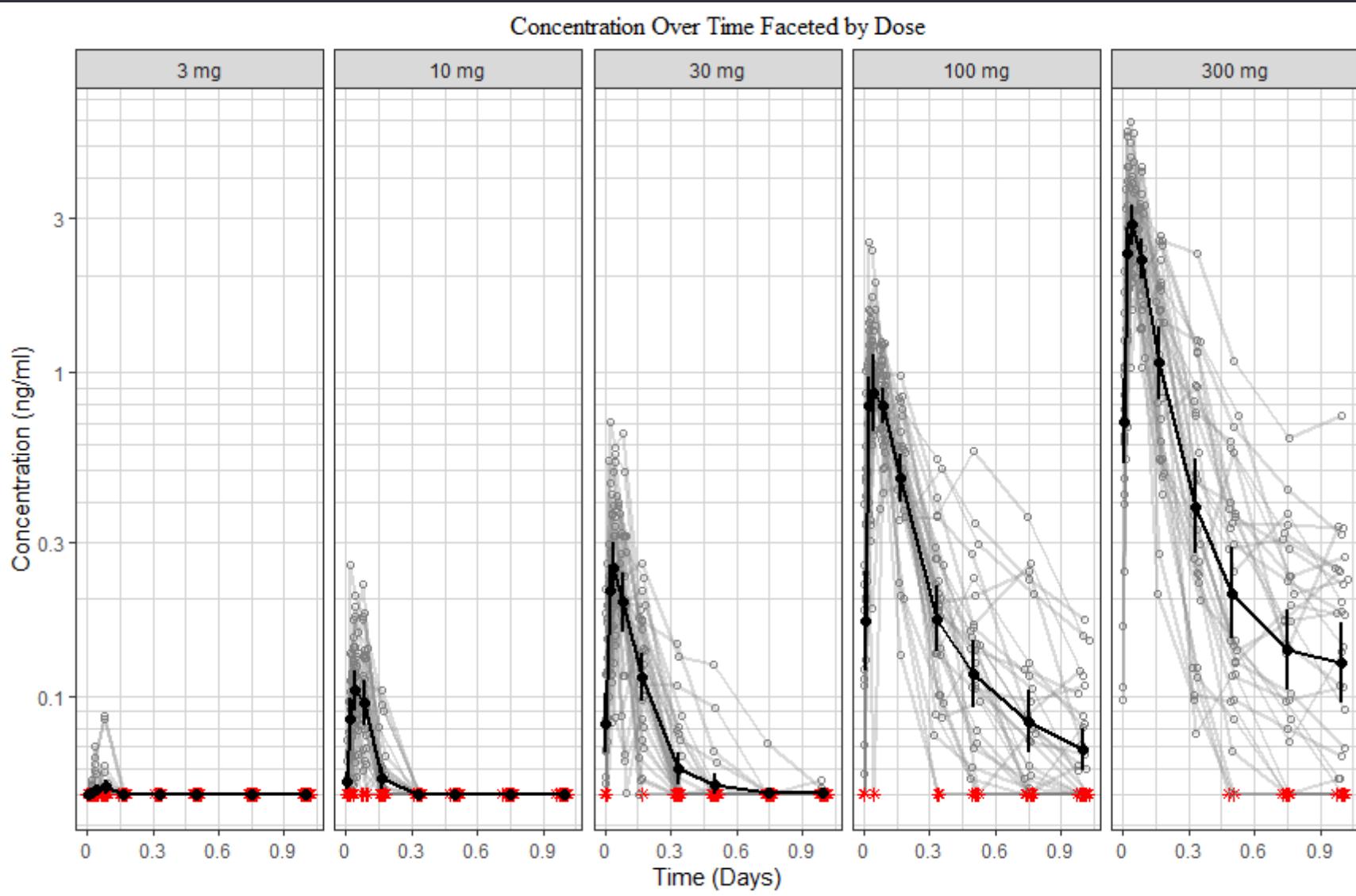
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# Summaries of PK Over Time



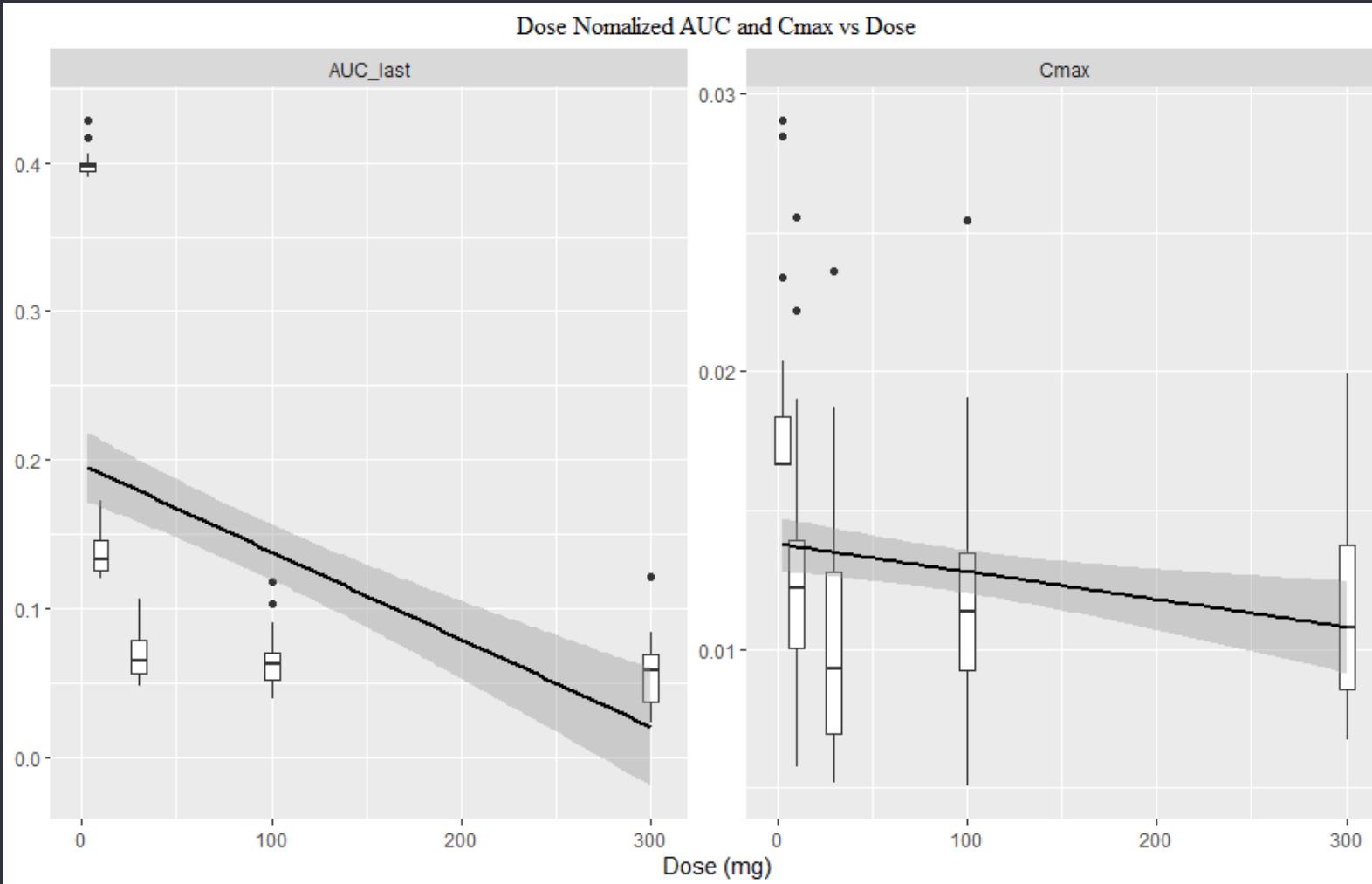
- Overall shape
- Cmax
- Tmax

# Summaries of PK Over Time



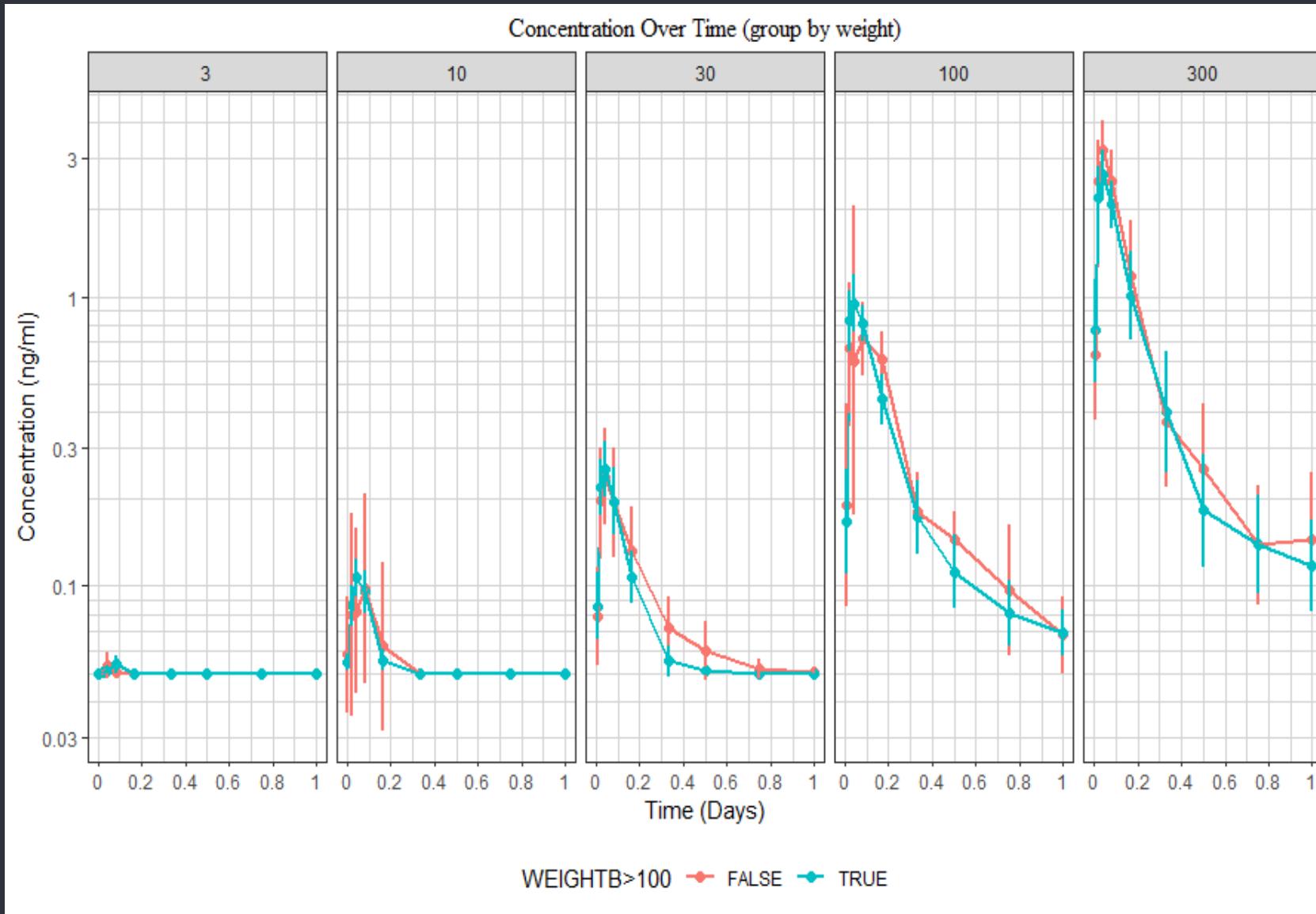
- Faceted by dose
- Group
  - Grey: individuals
  - Black: overall
  - Red: censored
- Cmax increases

# Summaries of PK Over Time



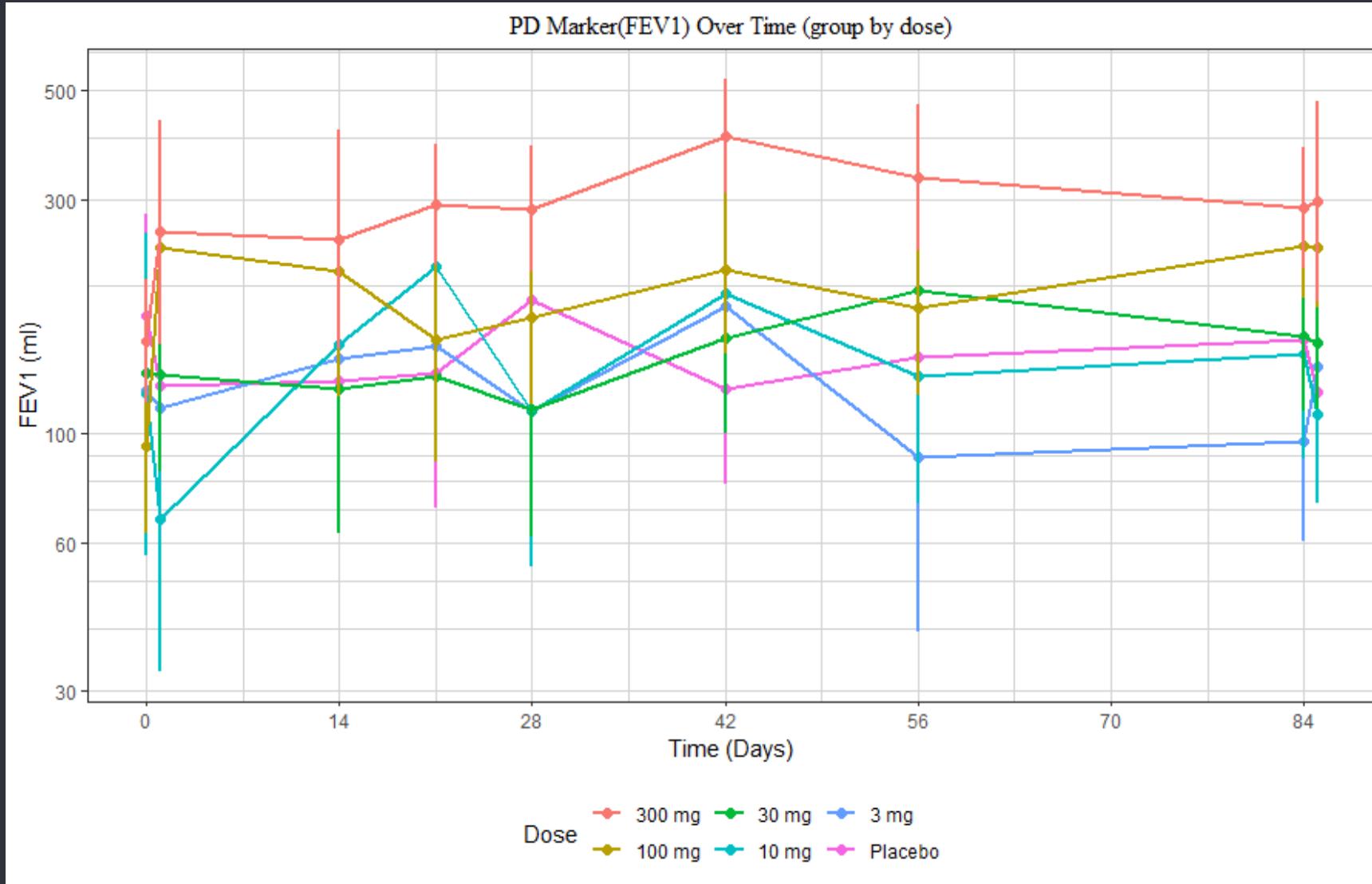
- Parameters decrease linearly and proportional to the dose
- Non-linear pharmacokinetics (PK)

# Summaries of PK Over Time



- Weight effects
- No obvious difference

# Summaries of PD Over Time



- FEV1: PD marker, the forced expiratory volume in one second, showing the amount of air a person can forcefully exhale in one second
- 300mg is the most stable

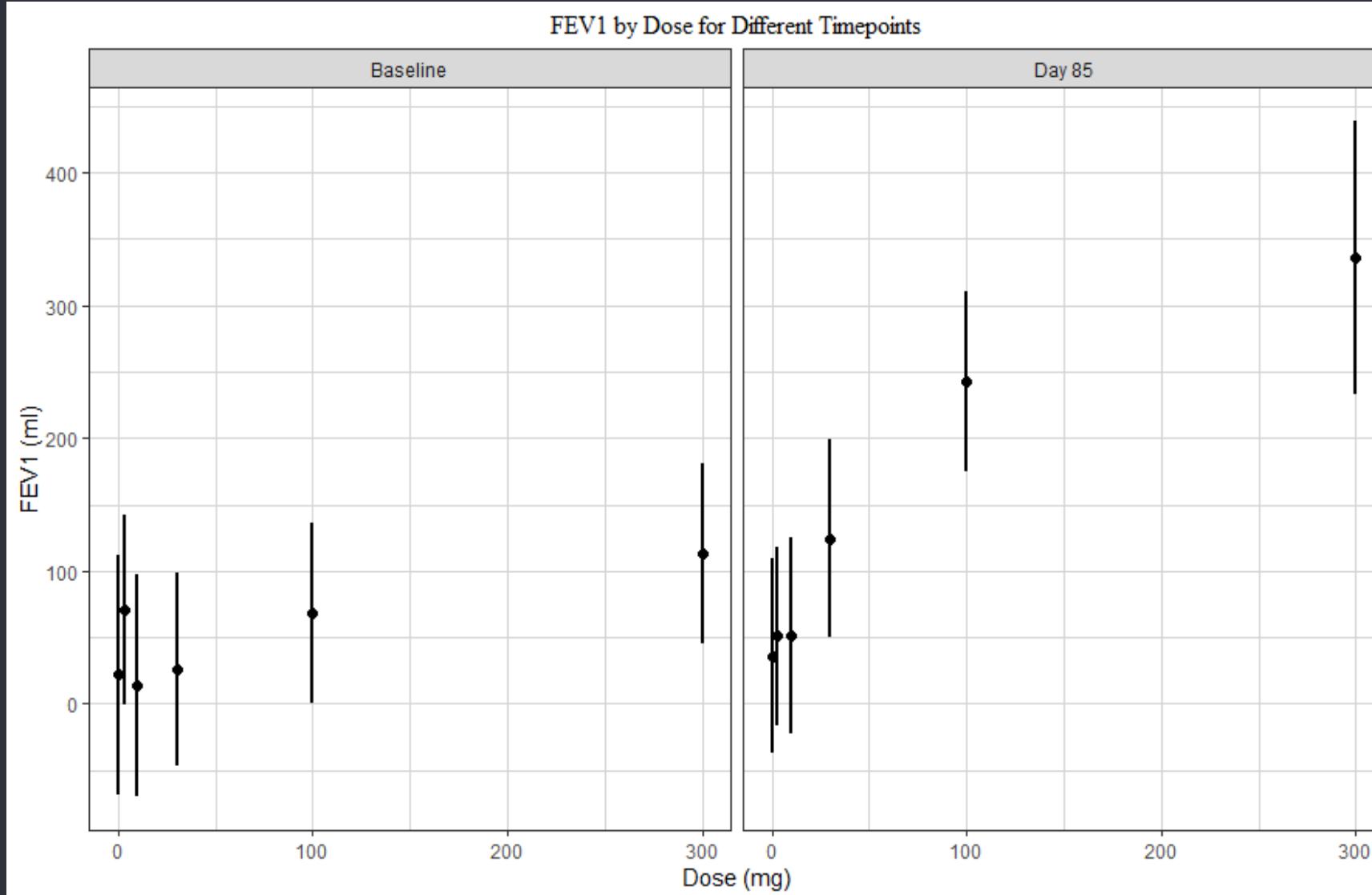
# Explore Dose-Response Relationship

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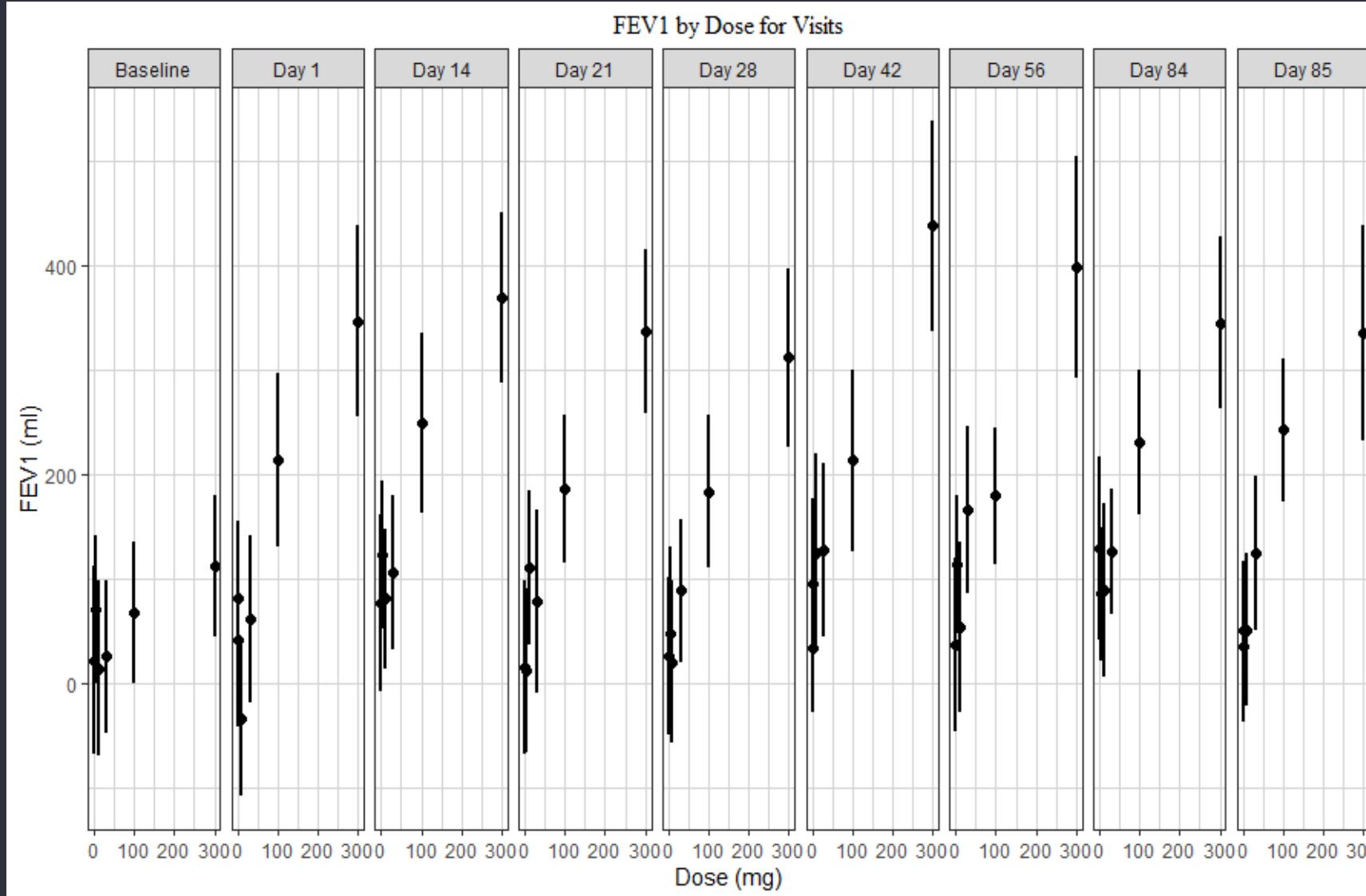
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# Summaries of PD Over Time



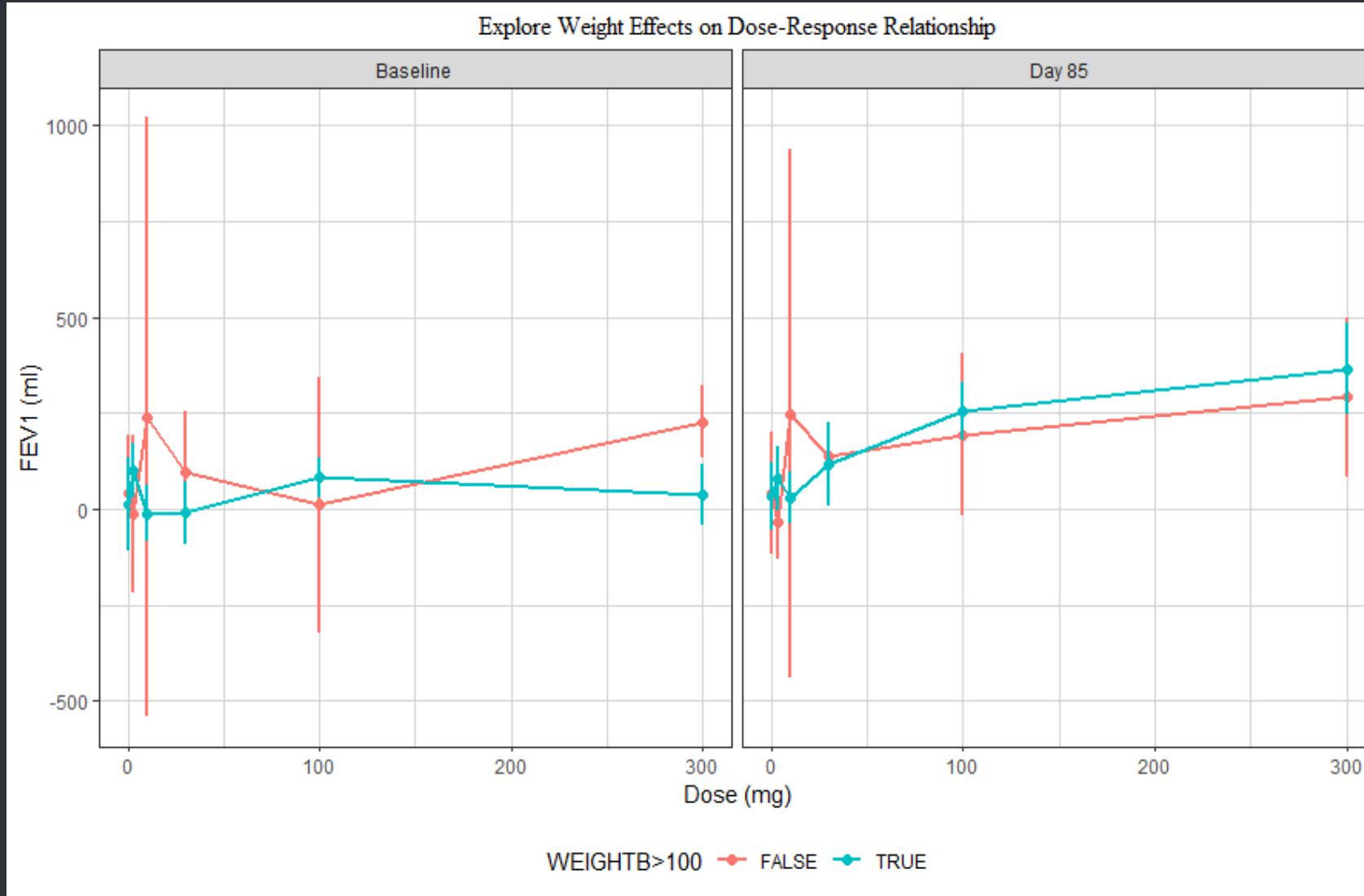
- Dose-response relationship is important to PD markers
- Compared baseline with day 85
- Obvious increases in FEV1 for dose 30,100 and 300mg

# Summaries of PD Over Time



- Explore the steady state

# Summaries of PD Over Time



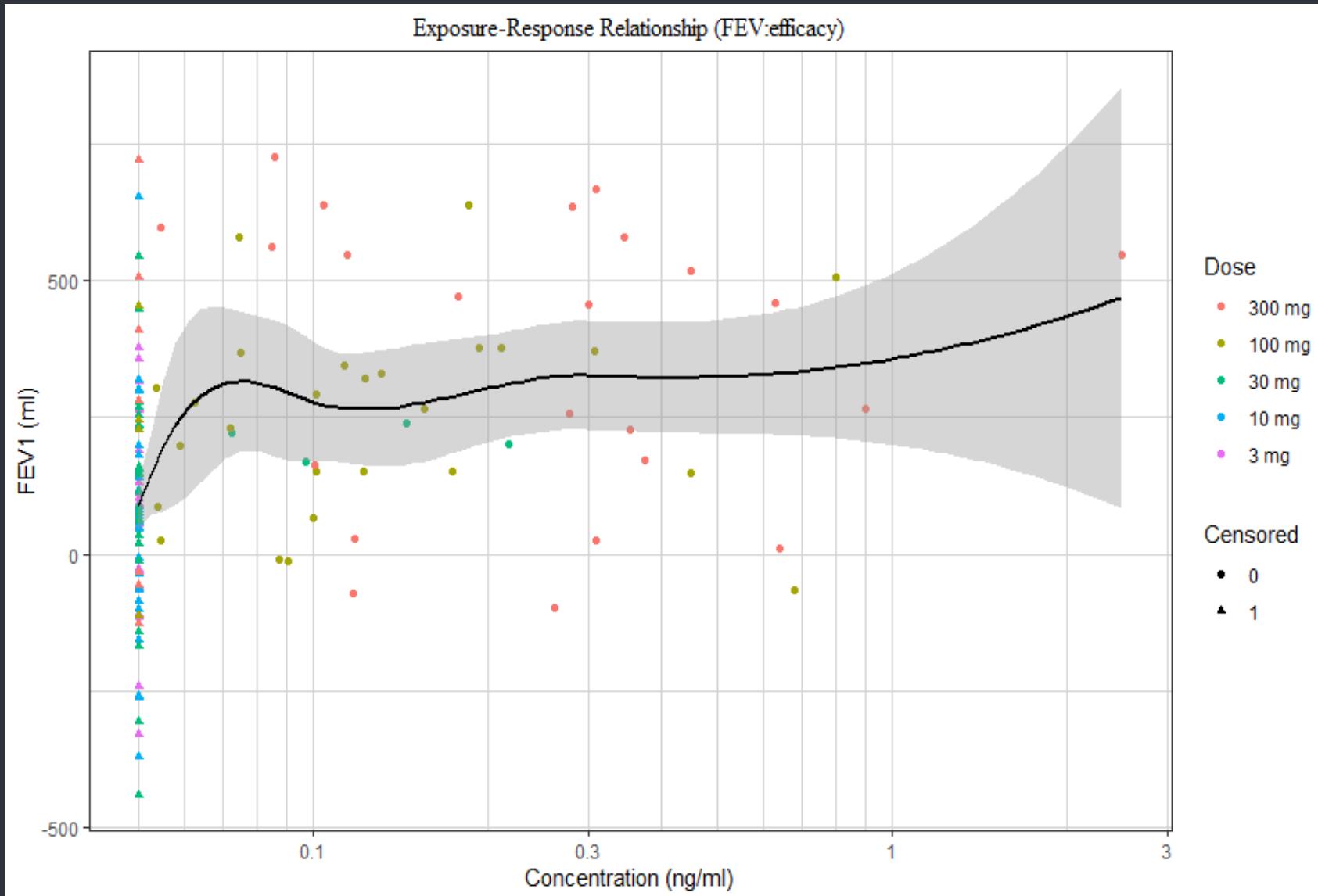
# Explore exposure-Response Relationship

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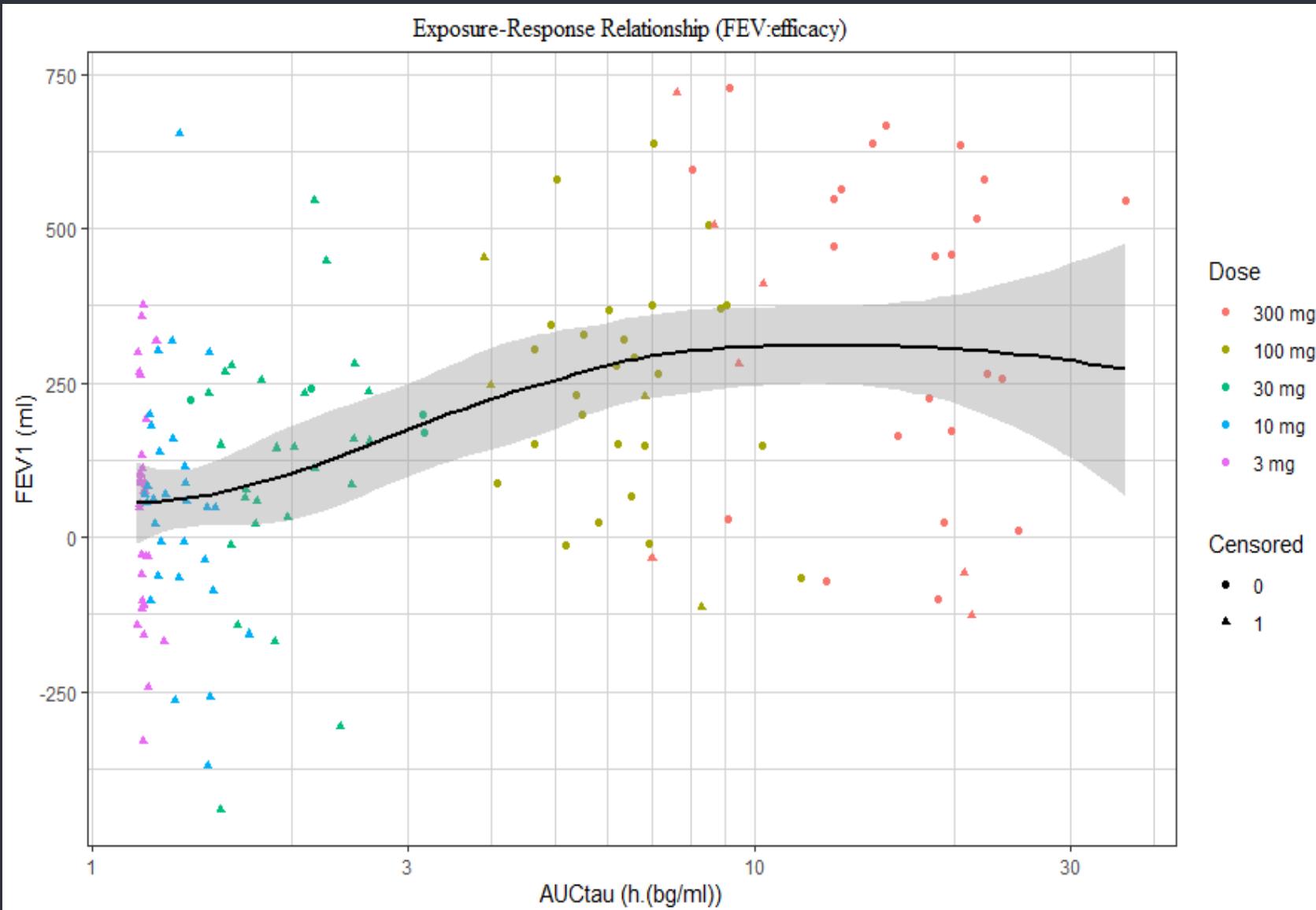
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# Summaries of PD Over Time



- Concentration is proportional to the intensity of efficacy
- Different distribution for different doses
- Emax is not clear

# Summaries of PD Over Time



- AUCtau
- Emax is approximately 300ml for FEV1

# 4. Conclusions

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# Step Progress



**Exposure-Response Data  
Visualization by R and SAS**



**Statistics**



**CDISC Guidelines**



**SAS Skills**



**Protocol Review**



**Biopharmaceutical  
Research  
& Clinical Trial**



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# Acknowledgment



- Dizal Pharma
- Dizal Statistical Programming Group  
(especially for Huadan & Zhiping)

# THANKS FOR YOUR ATTENTION

