

Putting science to work for better, faster TB cures

PK/PD Support for a Phase 1 Study of TBA-7371



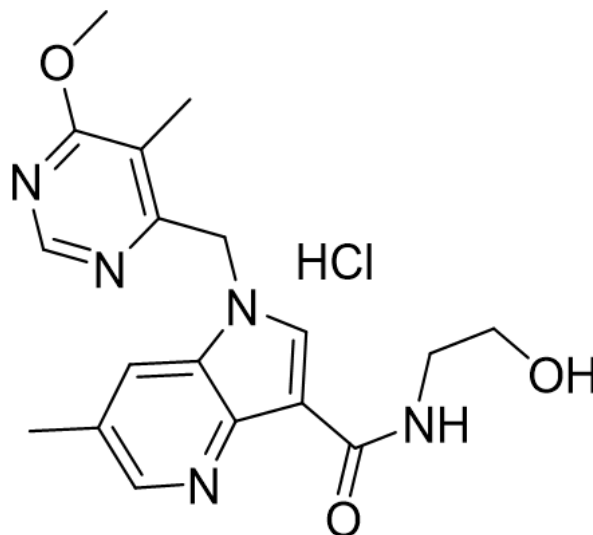
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Fran Pappas, Angelo Del Parigi, Bridget K. Rawls, TJ Yang**

Main Themes

- TBA-7371
- First-in-Human Study
- Pharmacometrics

TBA-7371: Background

- Potent, non-covalent inhibitor of DprE1, an essential enzyme for cell-wall synthesis



TBA-7371 HCl

Mol Wt: 391.85

Preclinical Insights going into Phase 1: Efficacy

- Target AUC:
 - Chronic mouse model: 73 $\mu\text{g}\cdot\text{h}/\text{mL}$
 - Dose fractionation study: 37 $\mu\text{g}\cdot\text{h}/\text{mL}$
- Human efficacious dose projection: 500 – 1000 mg

Preclinical Insights going into Phase 1: Safety

- Induction of CYP2B6 and CYP3A4
- Heart Rate
 - 9.3 $\mu\text{g}/\text{mL}$: HR \uparrow in dogs
 - 17 $\mu\text{g}/\text{mL}$: HR --- in monkeys
 - 20 $\mu\text{g}/\text{mL}$: HR \uparrow in monkeys
- Weak PDE inhibition -> Visual effects?

First-in-Human Study: SAD/MAD/DDI

- SAD (Single Ascending Dose): n = 6 active / 2 placebo per cohort
 - 5 cohorts planned: 100, 250, **500, 1000**, 1500 mg
- MAD (Multiple Ascending Dose, 14 days): n = 9 / 3 per cohort
 - Three dose amounts TBD based on SAD
- DDI (Drug-Drug Interaction): n = 14 / 0 (one cohort)
 - One TBA-7371 dose amount TBD based on SAD and MAD
 - Bupropion: probe substrate for CYP2B6
 - Midazolam: probe substrate for CYP3A4

SAD Cohort 1, 100 mg, results

- Safe and well tolerated

- PK

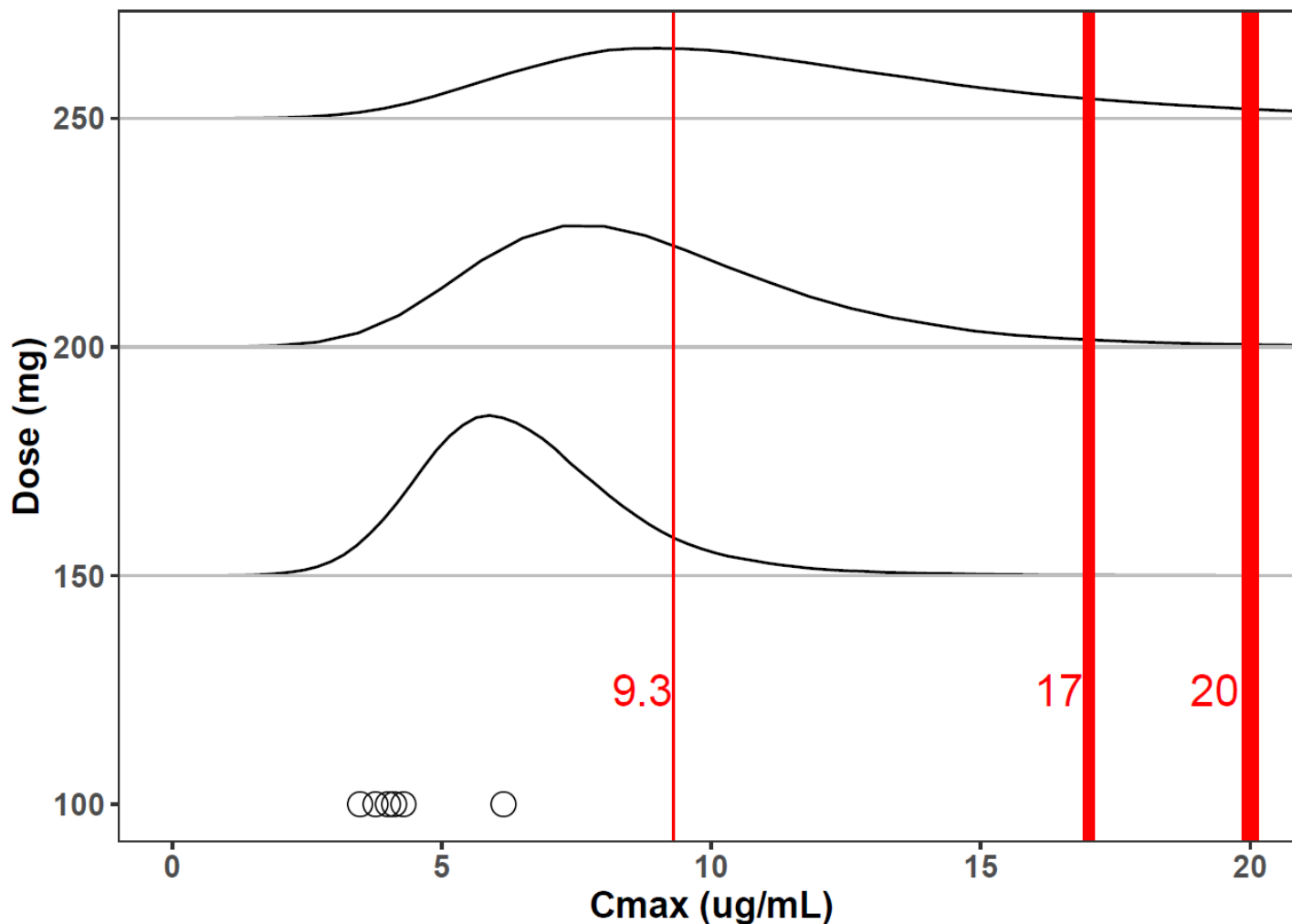
	Observed	Target / Threshold
AUC ₀₋₂₄	44 µg.h/mL	37 – 73 µg.h/mL
C _{max}	4.3 µg/mL	9.3 – 17 – 20 µg/mL

- Human efficacious dose projection: ~~500 – 1000 mg~~ 100 – 200 mg?

- Next dose?

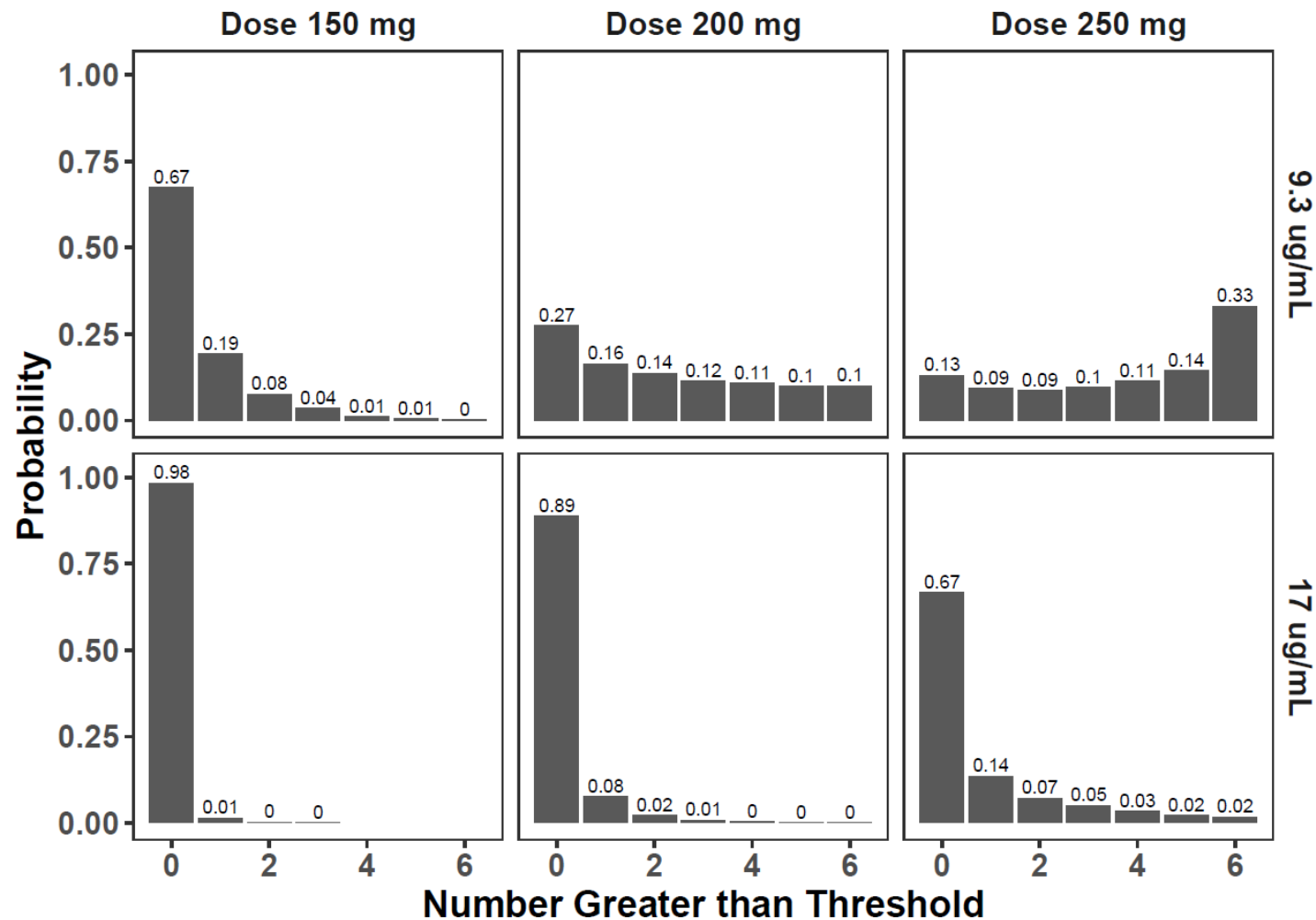
Planned next Dose: 250 mg. Change?

Data at 100 mg + Bayesian predictive distributions at 150, 200, and 250 mg



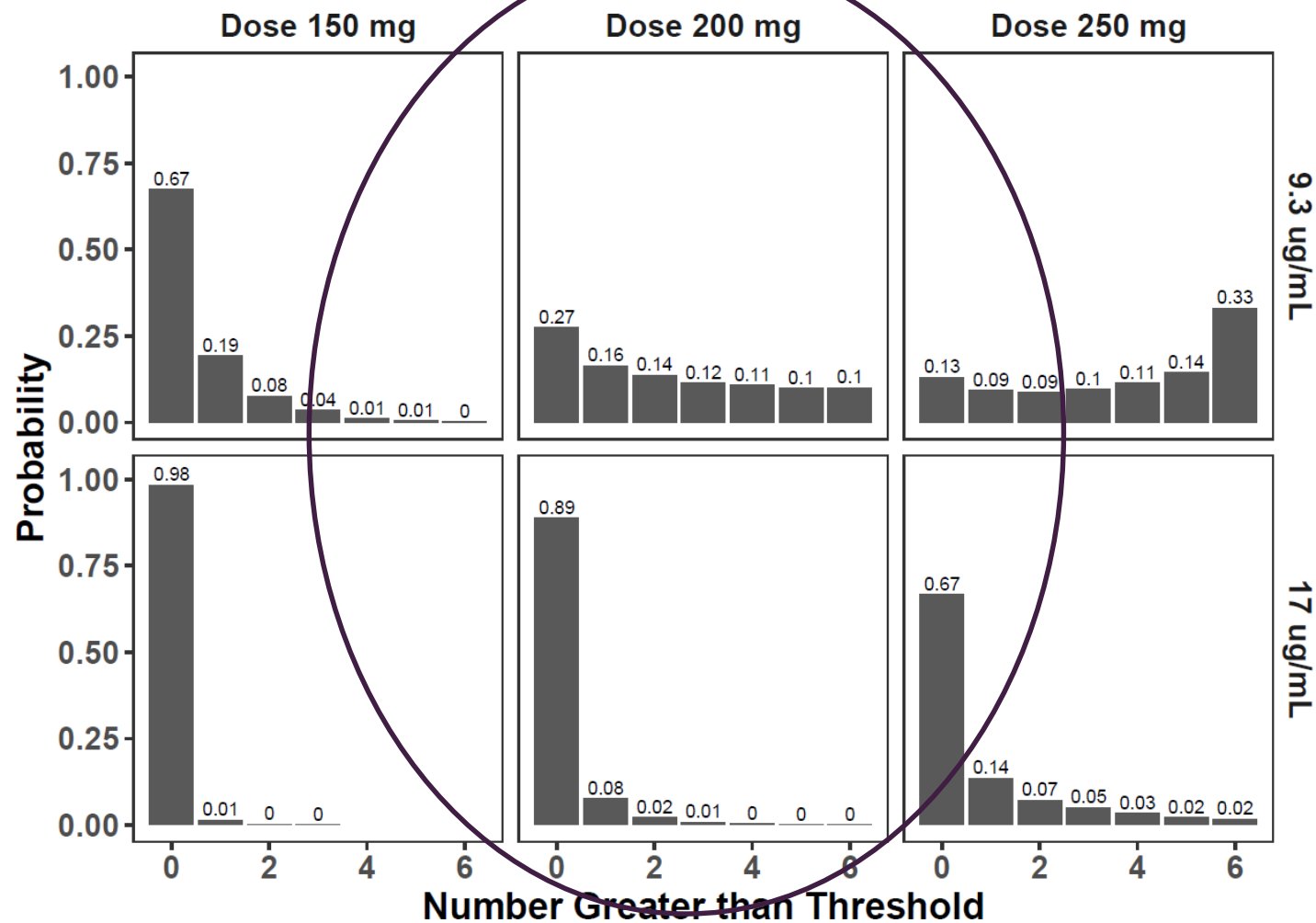
Planned next Dose: 250 mg. Change?

How many out of six will exceed threshold? Bayesian predictive distribution.

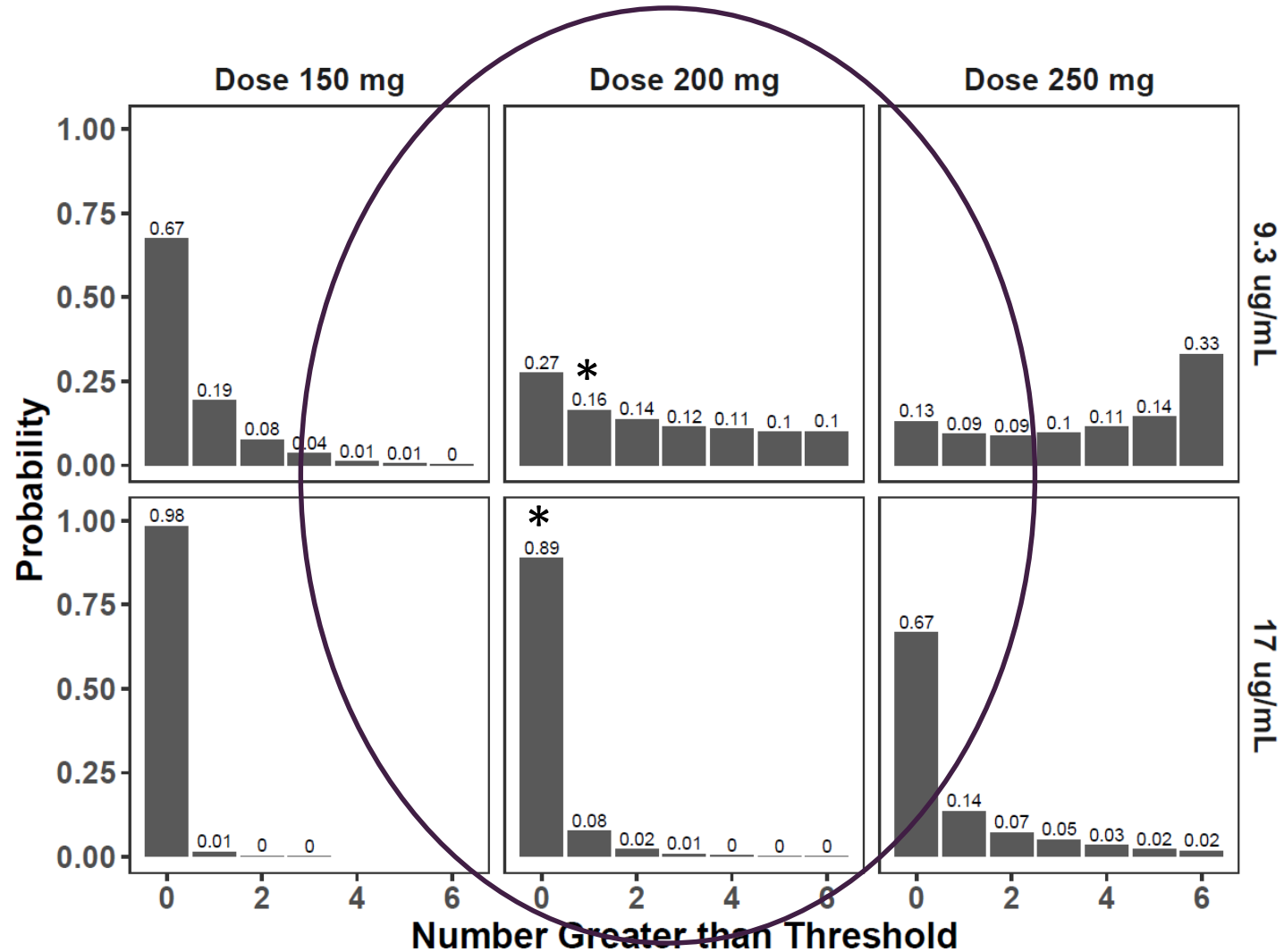


Planned next Dose: ~~250 mg~~ 200 mg

How many out of six will exceed threshold? Bayesian predictive distribution.



Results: Cmax = 6.9, 7.5, 8.0, 9.0, 10 µg/mL



Ultimate SAD

- Planned doses: ~~100 – 250 – 500 – 1000 – 1500 mg.~~
- Actual doses: 100 – 200 – 400 – 800 mg

	100 mg	200 mg	400 mg	800 mg
AUC ₀₋₂₄ (µg.h/mL)	44	87	175	440
T _{max} (hr)	2.0	2.0	2.0	3.0
C _{max} (µg/mL)	4.3	8.4	15.	33.

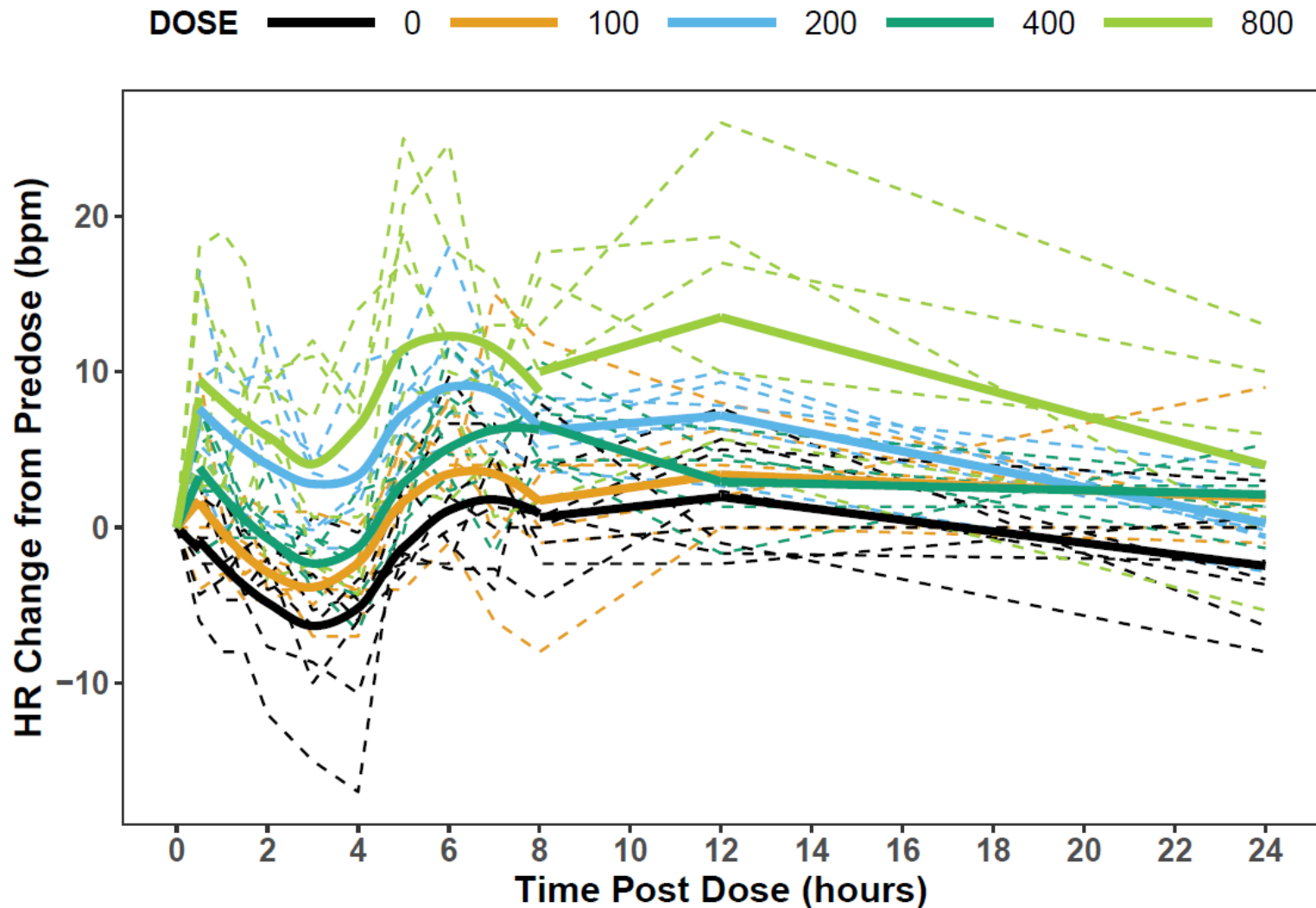
Preclinical Heart-Rate Thresholds Crossed

- Planned doses: ~~100 – 250 – 500 – 1000 – 1500 mg.~~
- Actual doses: 100 – 200 – 400 – 800 mg

	100 mg	200 mg	400 mg	800 mg
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Heart Rates?

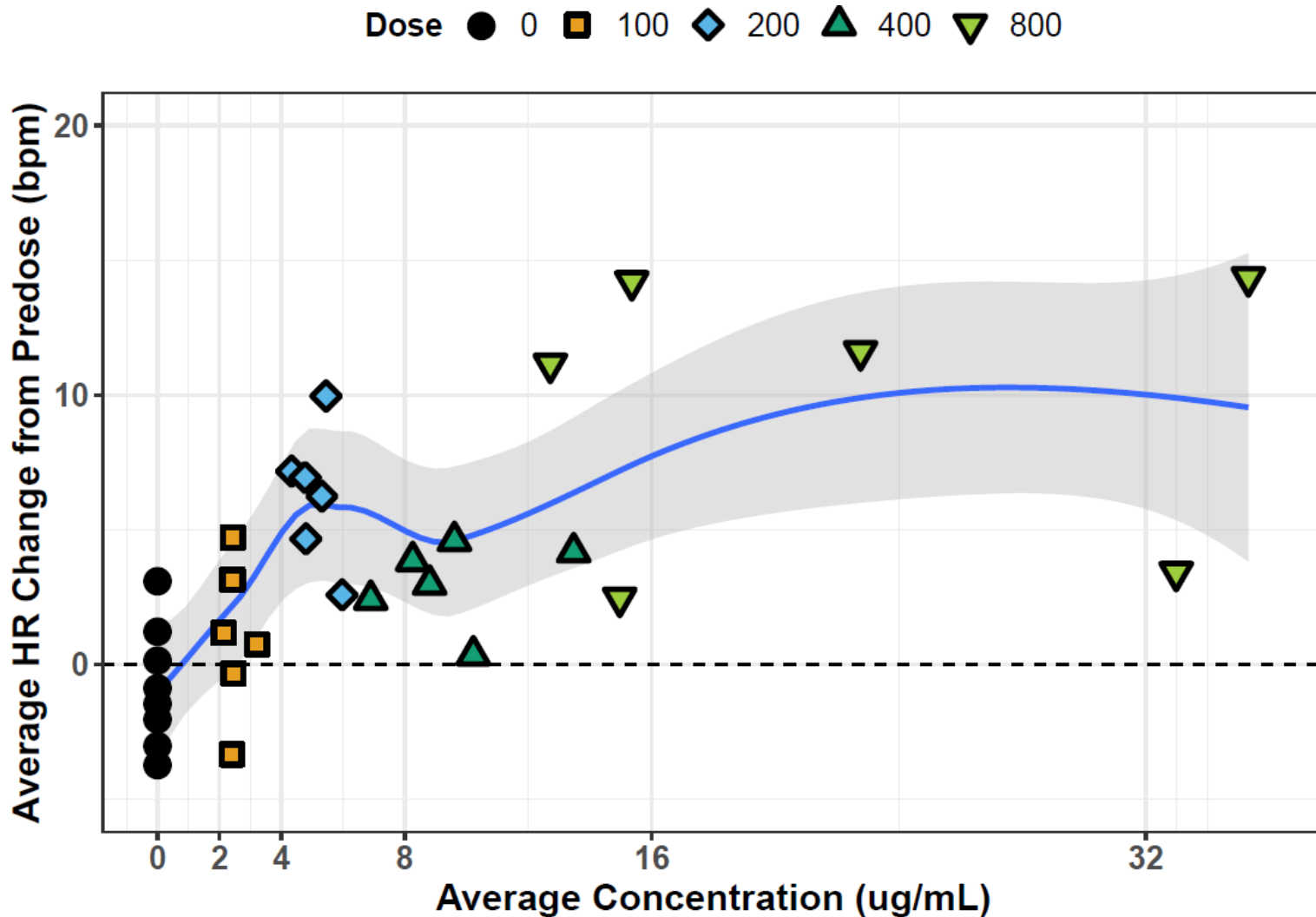
Holter Heart-Rate Changes from Predose, SAD



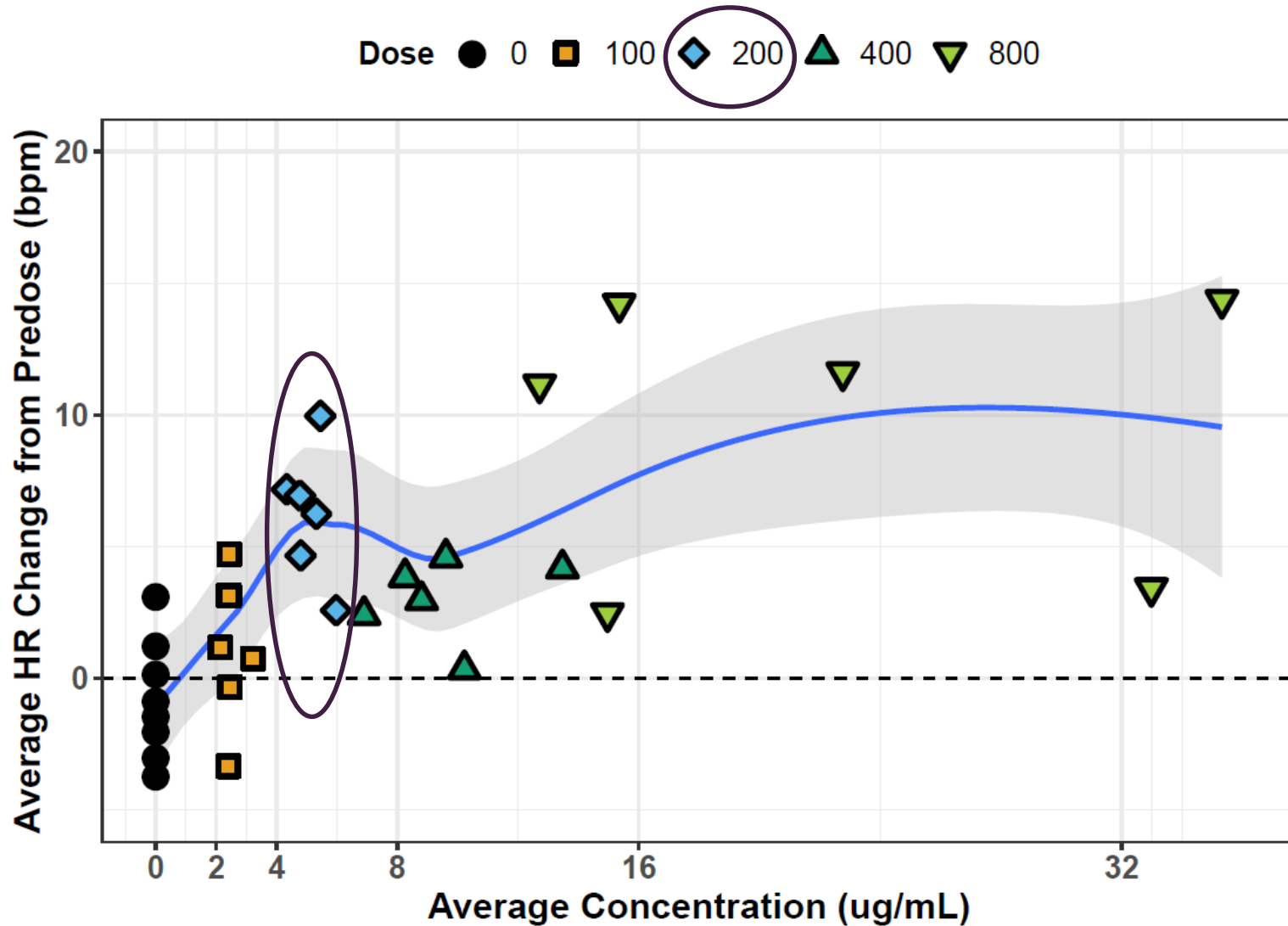
Simplification #1: Time Averages

- T = time duration, 12 or 24 hours.
- Average Concentration = AUC_{0-T}/T
- Average Heart Rate Change from Predose = $AU(\Delta HR)_{0-T}/T$

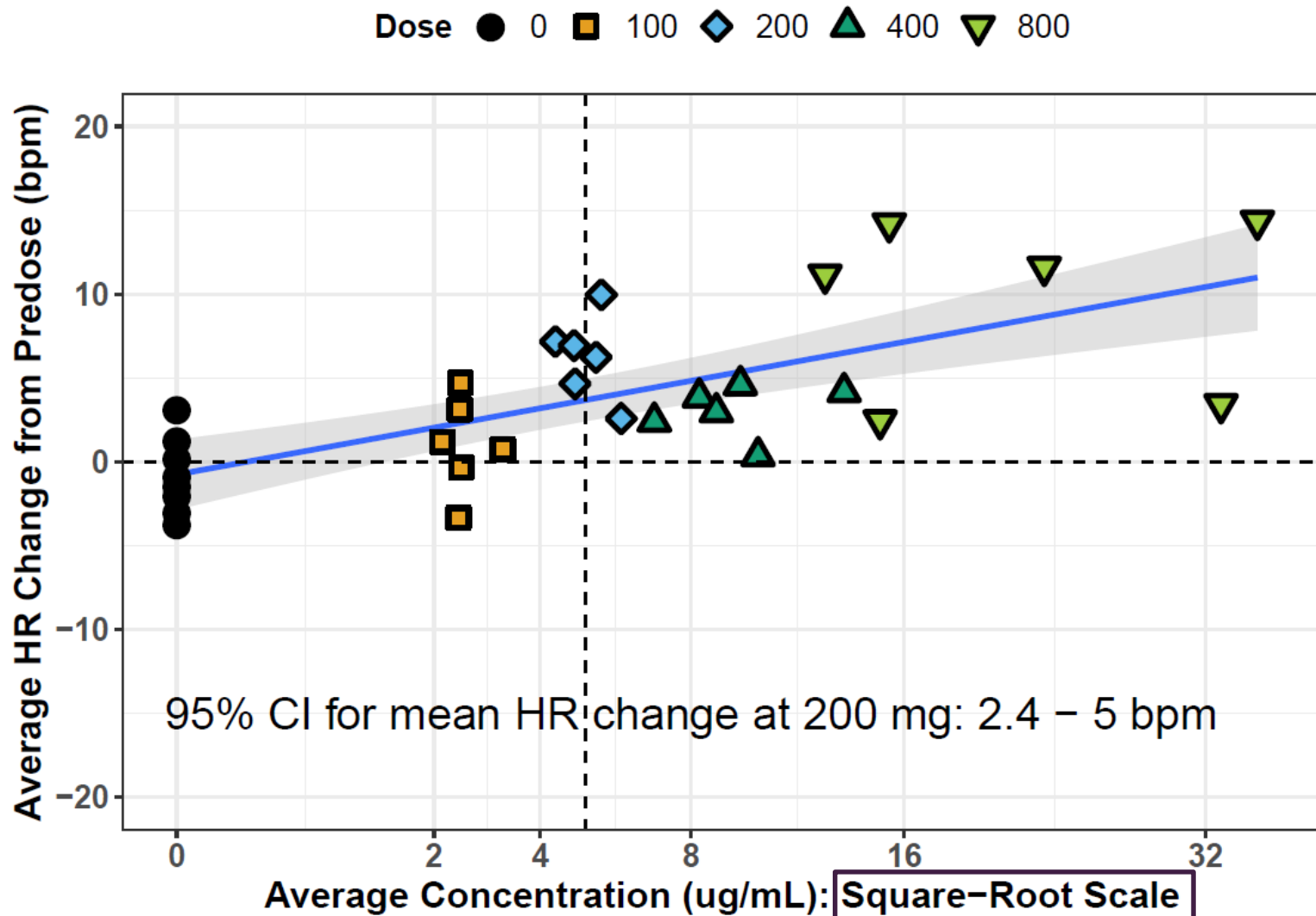
Simplification #1: Time Averages



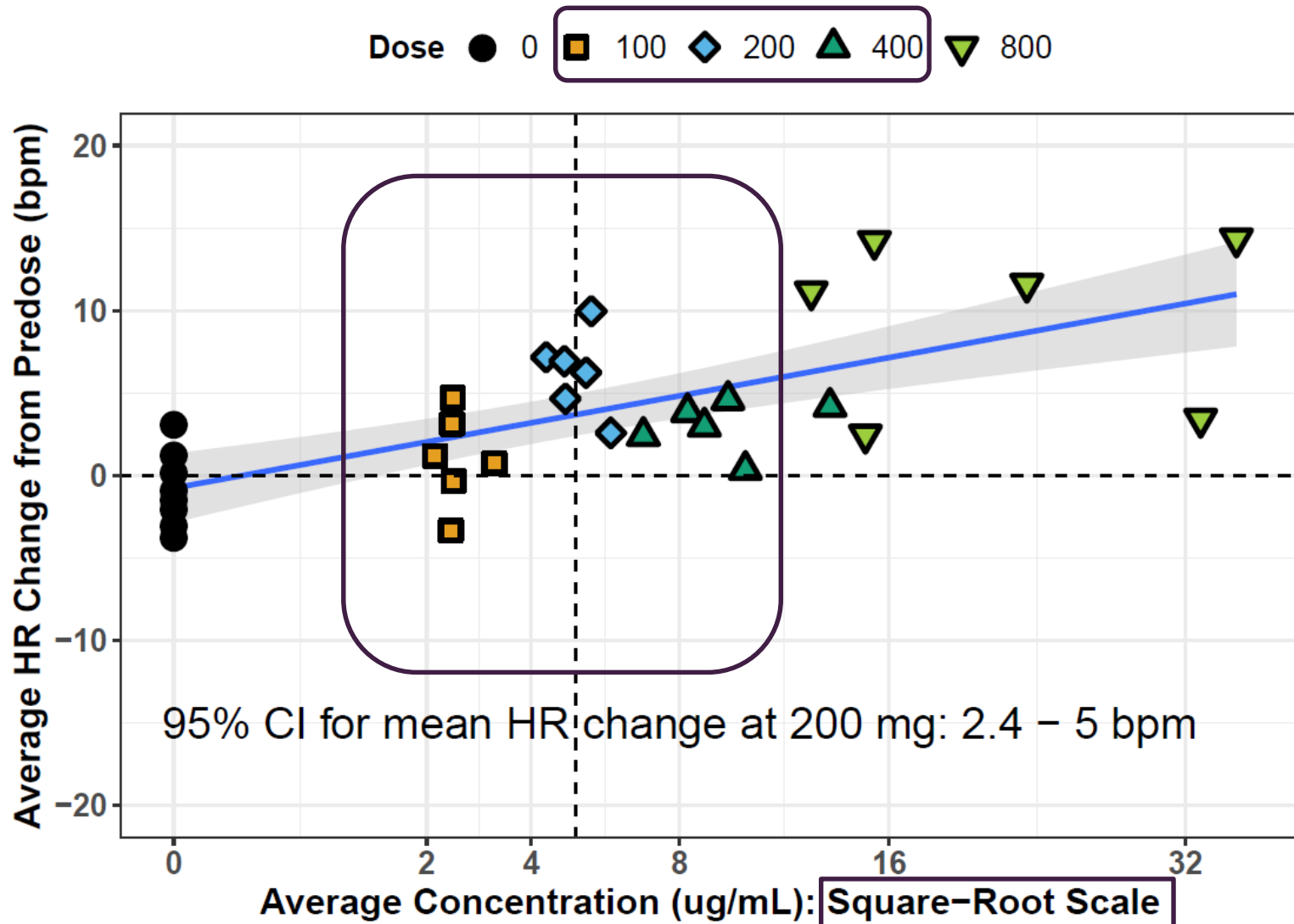
Primary Interest: 200 mg



Simplification #2: Transform to Linearity



Take into MAD: 100 – 200 – 400 mg

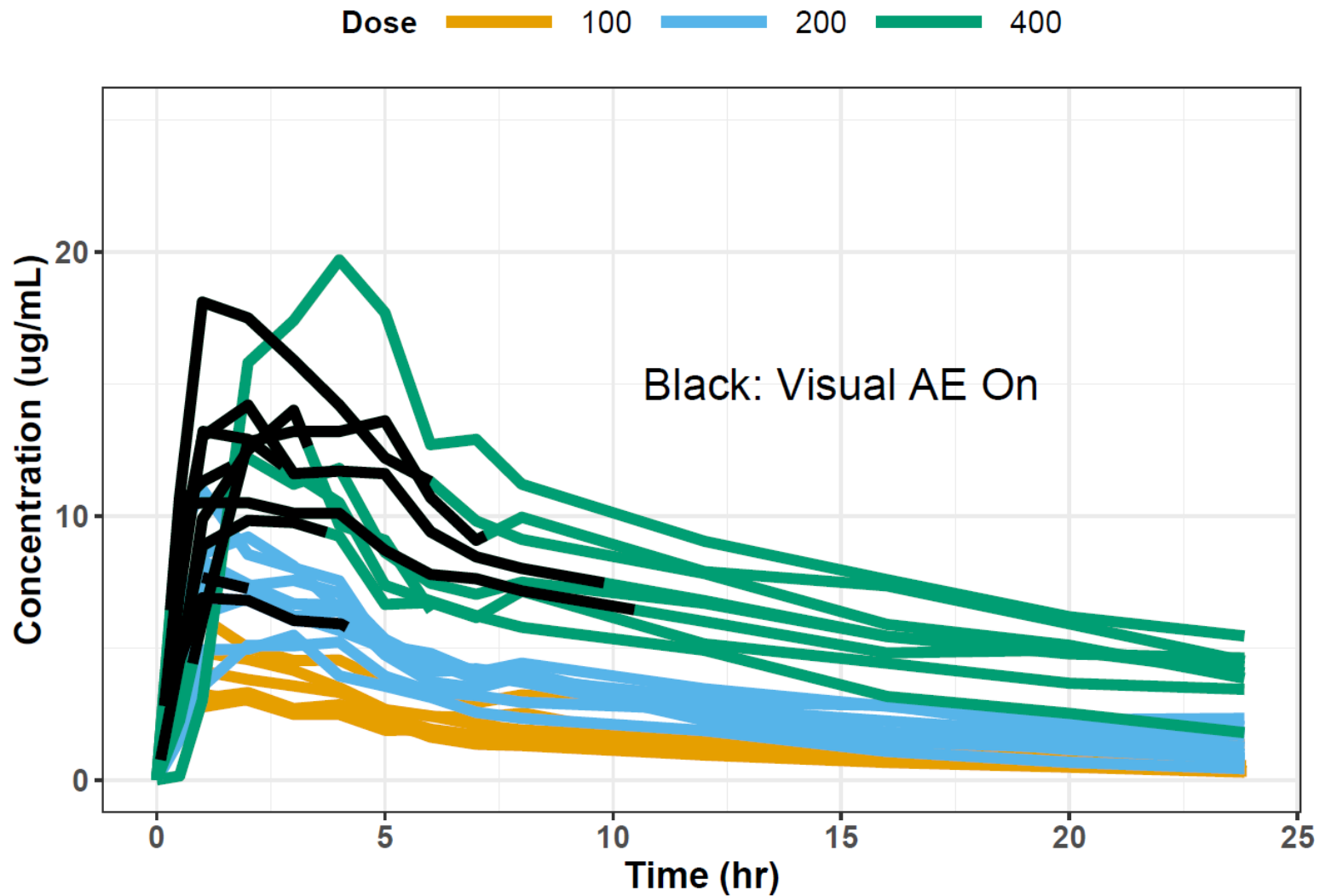


Visual AEs in the SAD and MAD

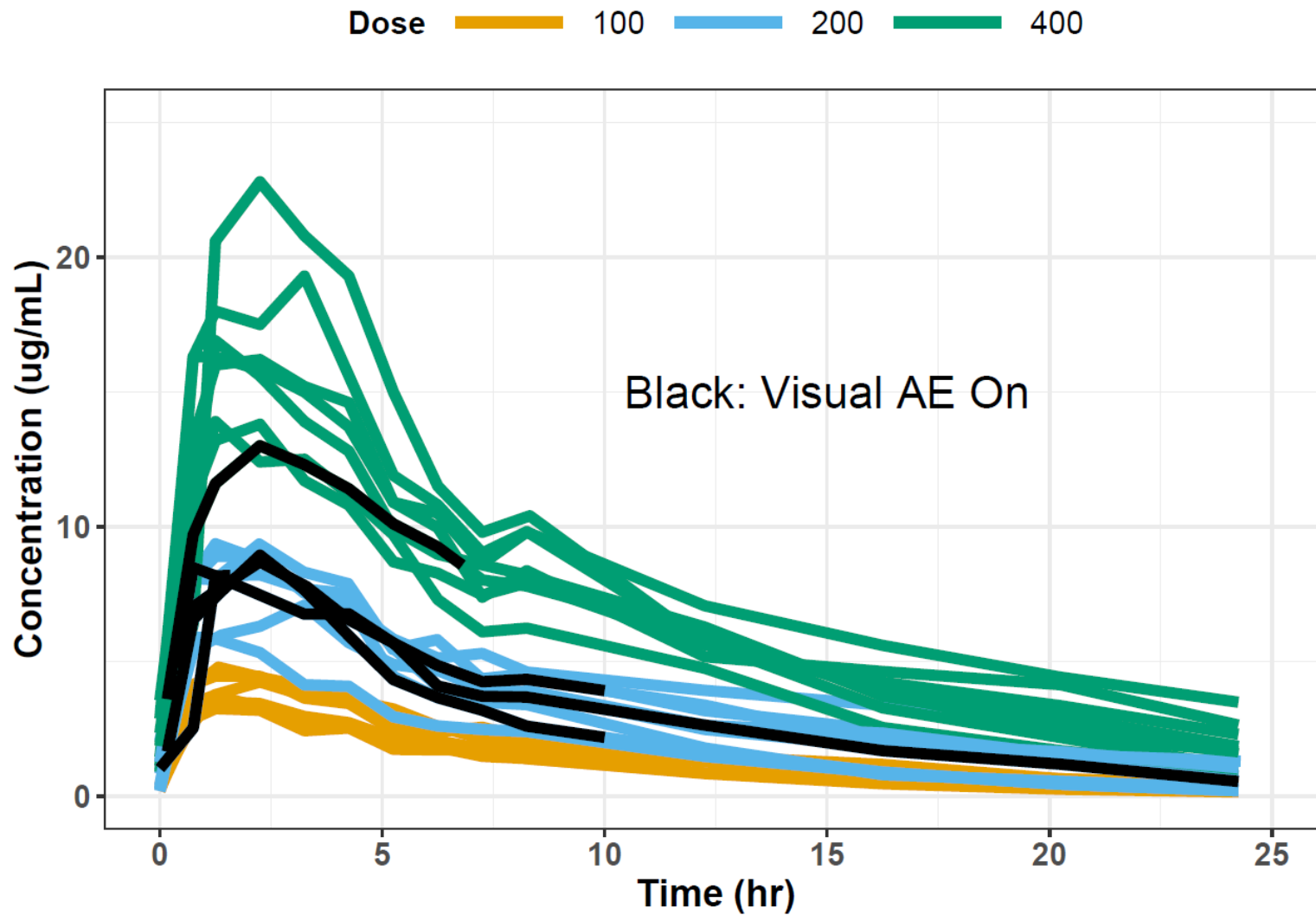
Adverse Event*	DOSE (mg)						
	SAD (n=6 per dose)				MAD (n=9 per dose)		
	100	200	400	800	100	200	400
Photophobia							1
Blurred Vision			1	2			1
Altered Color Perception				1			1
Photophobia & Blurred Vision						3	3
Photophobia & Altered Color Perception						1	
Altered Color Perception & Blurred Vision							2
TOTAL	0	0	1	3	0	4	8

All events were mild in severity.

Day 1 of MAD



Day 14 of MAD



DDI PK: Induction of Probes @ 200 mg TBA-7371

Geometric mean ratio: AUC_{0-inf} after 14 days TBA-7371 / AUC_{0-inf} Day 1	
Probe	Ratio (90% Confidence Interval)
Bupropion (2B6)	0.64 (0.53 – 0.76)
Midazolam (3A4)	0.60 (0.53 – 0.68)

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Thank You

