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**Supplementary Information for
Population Pharmacokinetic and Concentration-QTc Analysis of Delamanid
in Pediatric Participants with Multidrug-Resistant Tuberculosis**

Supplemental Tables

6 **Table S1. Dosing Regimens and Pharmacokinetic/Pharmacodynamic Sampling Plans**

Trial Number/ Phase	Dosing Regimen	Pharmacokinetic Sampling	Pharmacodynamic (QTc) Sampling
232/ Phase 1	Delamanid 50 mg oral tablet or 25 mg/5 mg dispersible tablet ^c for 10 days <ul style="list-style-type: none"> • Group 1 (ages 12 - 17 years): 100 mg BID + OBR, adult formulation tablet • Group 2 (ages 6 - 11 years): 50 mg BID + OBR, adult formulation tablet • Group 3 (ages 3 - 5 years): 25 mg BID + OBR, dispersible tablet • Group 4 (ages birth - 2 years): dispersible tablet <ul style="list-style-type: none"> ➤ 10 kg: 10 mg BID + OBR ➤ 8 kg and ≤ 10 kg: 5 mg BID + OBR ➤ ≥ 5.5 kg and ≤ 8 kg: 5 mg QD + OBR 	<ul style="list-style-type: none"> • Days 1 to 2 and 10 to 11: <ul style="list-style-type: none"> ➤ Predose and 2, 4, 10, 12^a, 14, and 24 hours postdose • Days 13^a, 15, and 18 (72, 120, and 192 hours, respectively, postdose on Day 10) • Early Termination 	<ul style="list-style-type: none"> • Day -1: Time of day that corresponds to the predose, 4-hour, and 10-hour post morning dose administration on Day 1 • Days 1 and 10: Predose, 4-hour, and 10-hour post morning dose administration • Day 18: 192-hour post dose • Early Termination: Time paired with PK blood sample
233/ Phase 2	Delamanid 50 mg oral tablet or 25 mg/5 mg dispersible tablet ^c for 6 months Dosing regimen is same as 242-12-232	<ul style="list-style-type: none"> • Predose on Days 1, 56, 154, and 182 • Theoretical predose on Day 210^b (Sampling timing is same as other predose samples, but no delamanid dose is planned) • Any time point on Days 14, 98, 189, 196, 203, and 238^b • Early Termination 	<ul style="list-style-type: none"> • Day -1 • Predose on Days 28, 84, and 126 • Days 1, 56, 154, and 182: Predose, time paired with PK blood sample • Day 210: Theoretical predose, time paired with PK blood sample • Early Termination

7 ^a The samples at 12 hours postdose and Day 13 are only available for Groups 1 and 2. ^b Last dose of delamanid on Day 182.

8 ^c 25 mg and 5 mg dispersible tablet are delamanid pediatric formulations. QD=Once a day. BID=Twice a day.

10 **Table S2. Combination of Scenario Tested in Structural Model Development**

Compartmental Model	Absorption Order	Lag Time for Absorption	Residual Error Model
One Two Three	Transit compartment First-order	Yes No	Additive Proportional Additive and Proportional

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12 **Table S3. Planned Evaluation of Covariate in Analyses**

Covariate	Pharmacokinetic Parameters		
	Absorption Rate/Extent	Volume of Distribution	Clearance
Dose	X		
Formulation	X		
Dose timing	X		
Age Group number	X		
Age	X	X	X
Body weight		X	X
Body surface area		X	X
BMI	X	X	X
Sex	X	X	X
Race	X	X	X
Country	X	X	X
Clinical laboratory values ^a	X ^b	X ^b	X

13 ^a Clinical laboratory values include estimated glomerular filtration rate using Schwartz equation, albumin, alanine
 14 aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, and total protein.

15 ^b only albumin was tested.

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17 **Table S4. Parameter Estimates of the Linear Mixed Effects Model for Delamanid/ Δ QTcB**

Parameter	Estimate	SE	90% CI
Fixed Effects			
θ_0 , Intercept (ms)	1.47	1.67	-1.80, 4.75
θ_1 , Slope (ms/[ng/mL])	0.00792	0.00471	-0.00132, 0.0172
θ_2 , Baseline QTcB effect	0.0318	0.0739	-0.113, 0.177
Inter-Individual Variability (shown as variance)			
η_0 , Random effect for the intercept	63.5	NE	
η_1 , Random effect for the slope	0.0000937	NE	
Residual Variability (shown as variance)	180	NE	

18 NE: not estimated

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20 **Table S5. Parameter Estimates of the Linear Mixed Effects Model for DM-6705/ Δ QTcB**

Parameter	Estimate	SE	90% CI
Fixed Effects			
θ_0 , Intercept (ms)	0.923	1.61	-2.22, 4.07
θ_1 , Slope (ms/[ng/mL])	0.0613	0.0231	0.016, 0.107
θ_2 , Baseline QTcB effect	0.0309	0.0728	-0.112, 0.174
Inter-Individual Variability (shown as variance)			
η_0 , Random effect for the intercept	59.9	NE	
η_1 , Random effect for the slope	0.00446	NE	
Residual Variability (shown as variance)	174	NE	

21 NE: not estimated

22

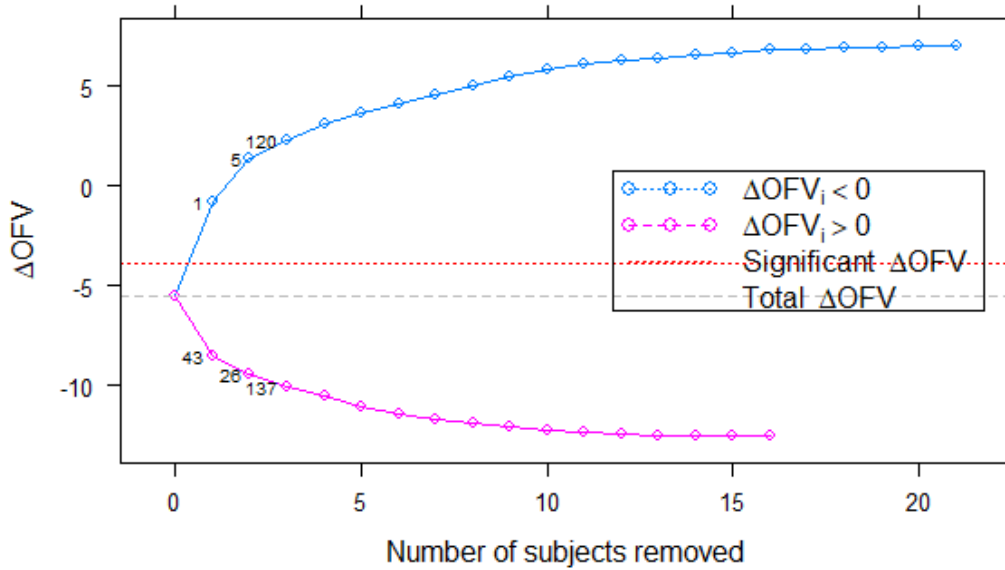
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Supplemental Figures

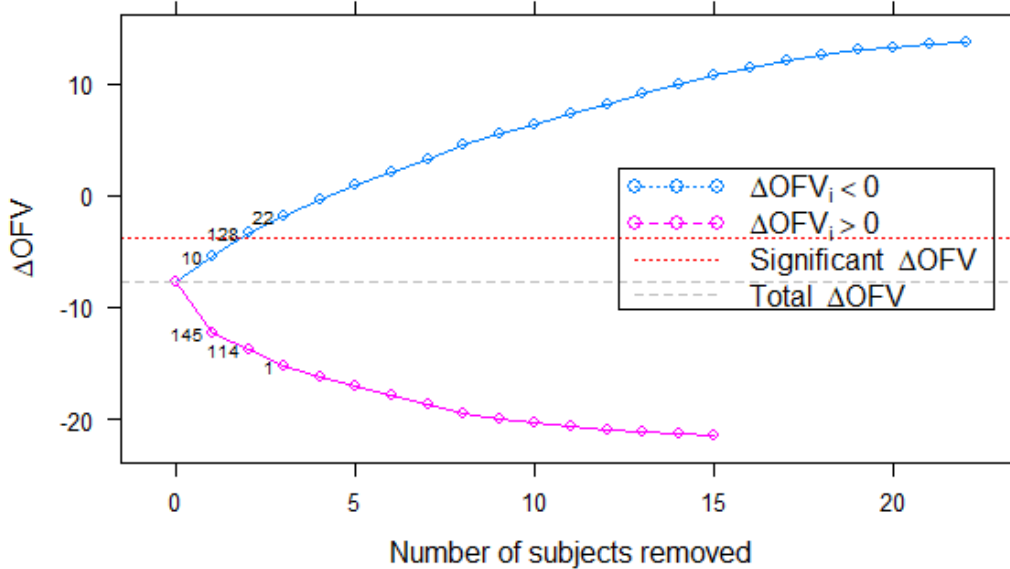
26 **Figure S1. Impact by Removing Individuals on Significance of Covariates (Upper:**
27 **Albumin, Lower: Sex)**

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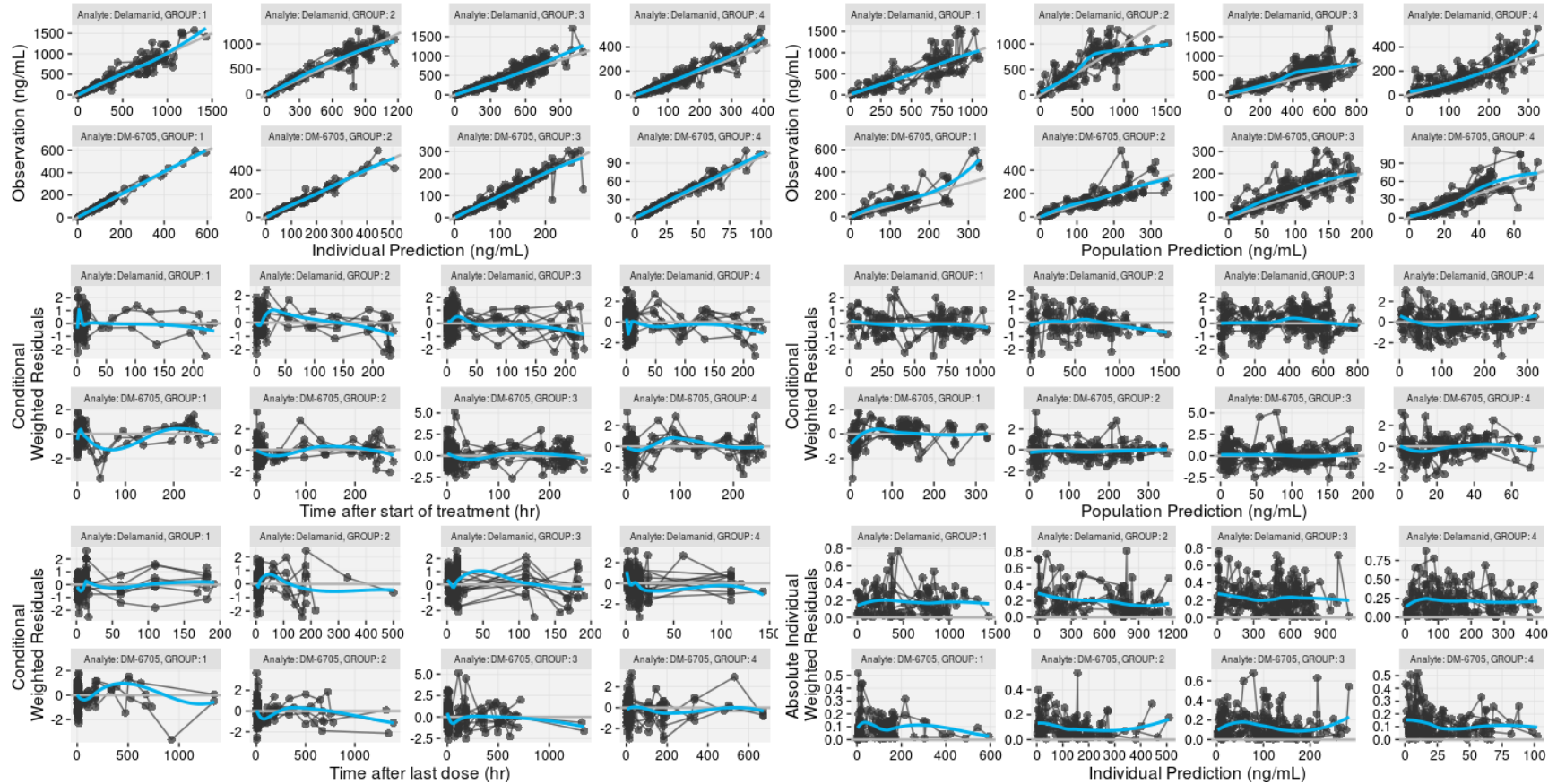
31

32 Each plot represents ΔOFV (OFV with covariate [albumin or sex] - OFV without covariate) by removing
 33 individuals. Blue or pink line represents runs with increased or decreased ΔOFV by removing subjects.
 34 Red line represents the significance threshold for ΔOFV with $P < 0.05$ and degree of freedom = 1.

35 Gray line represents Δ OFV by using all data. Each number is ID of subject removed.
36

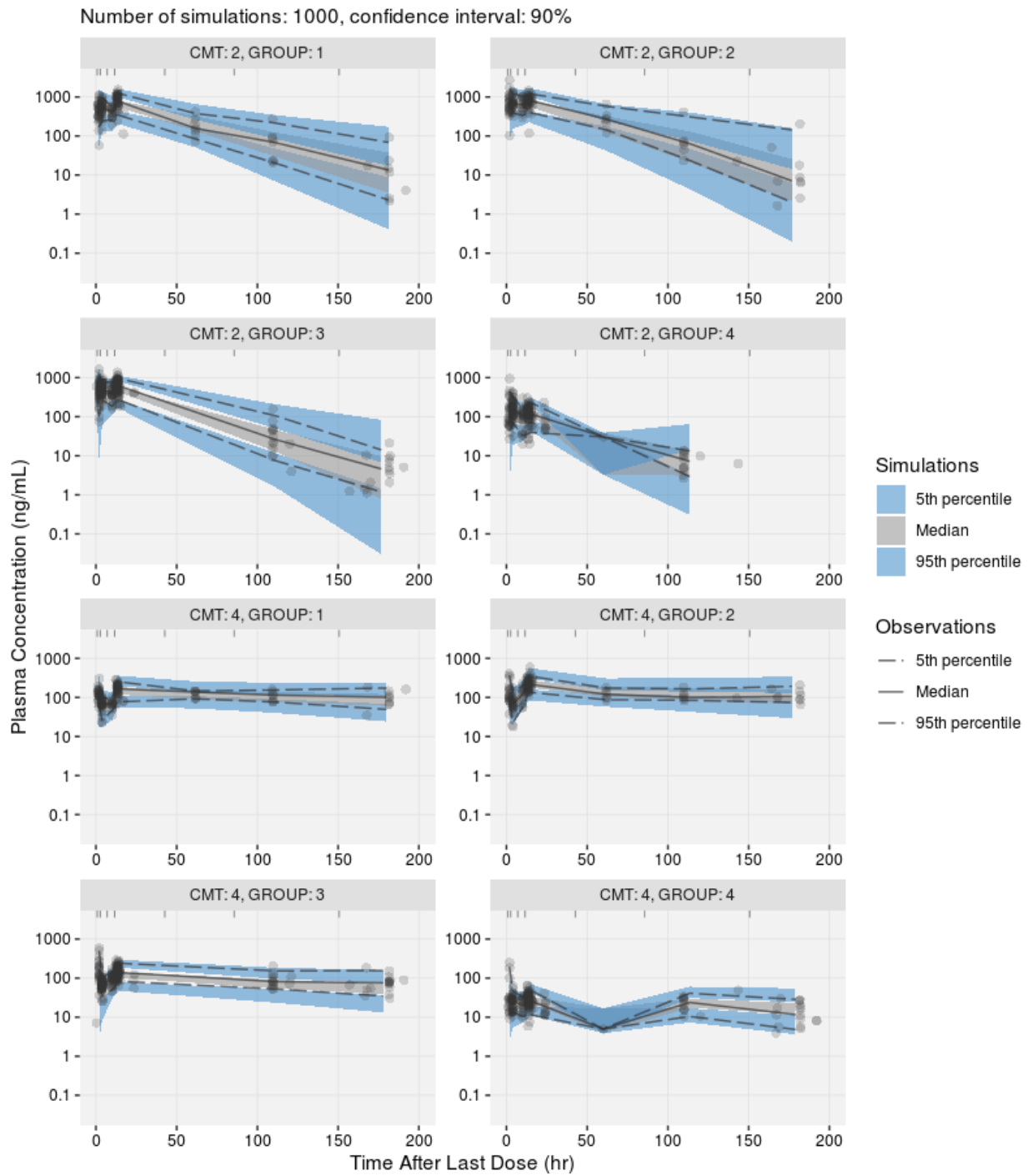
37 **Figure S2. Goodness of Fit Plot of Final Model Stratified by Analyte and Age Group**

GOF plot | Run 207, Ofv=10344.853



- 38
- 39 Black circle represents individual data. Connected line means data from same individual.
 40 Gray line represents line of identity ($y=x$) or $y=0$. Blue line shows smoothing line of data.
 41 Group 1: ages 12 - 17 years, Group 2: ages 6 - 11 years, Group 3: ages 3 - 5 years, Group 4: ages birth - 2 years.
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43 **Figure S3. Prediction-Corrected Visual Predictive Check Plots by Age Group and Analyte**



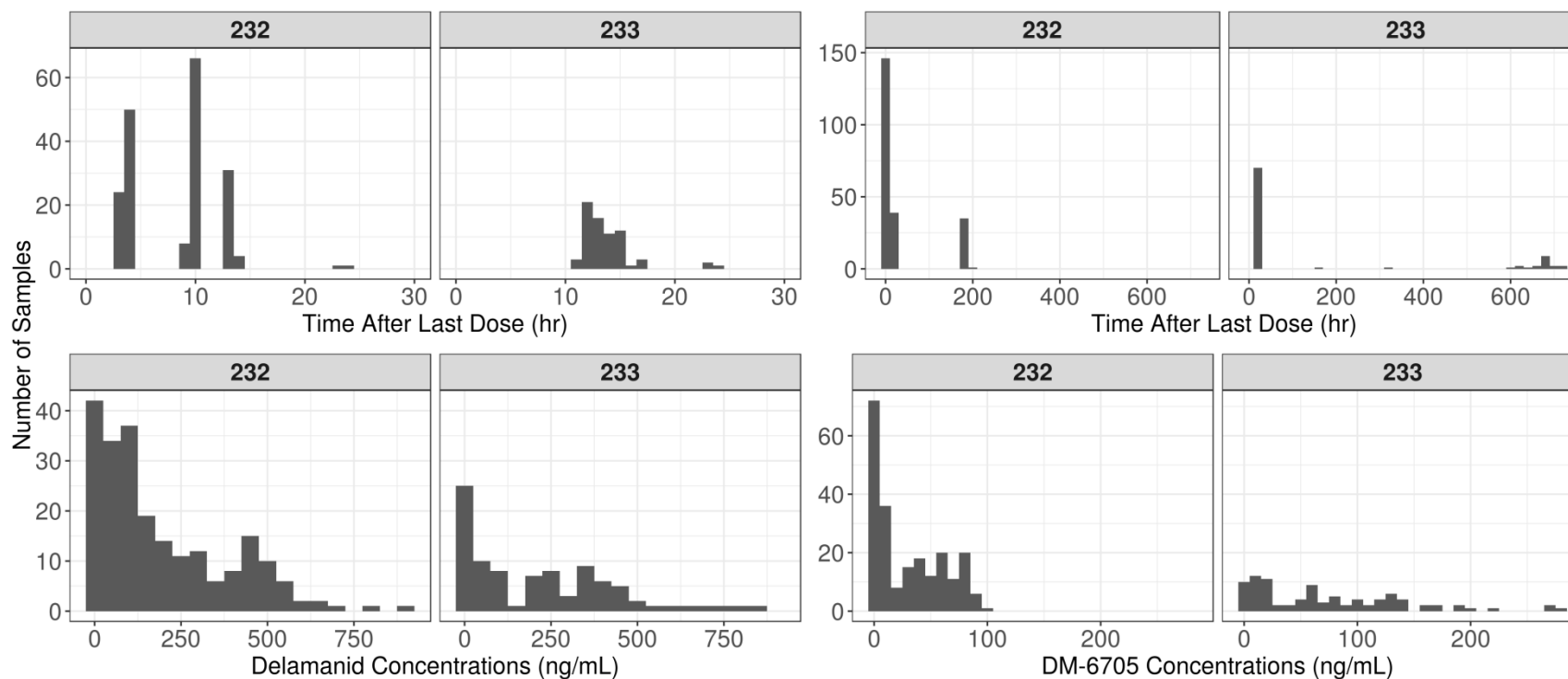
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45 CMT: 2 represents delamanid and CMT: 4 represents DM-6705.

46 Group 1: ages 12 - 17 years, Group 2: ages 6 - 11 years, Group 3: ages 3 - 5 years, Group 4: ages birth - 2 years

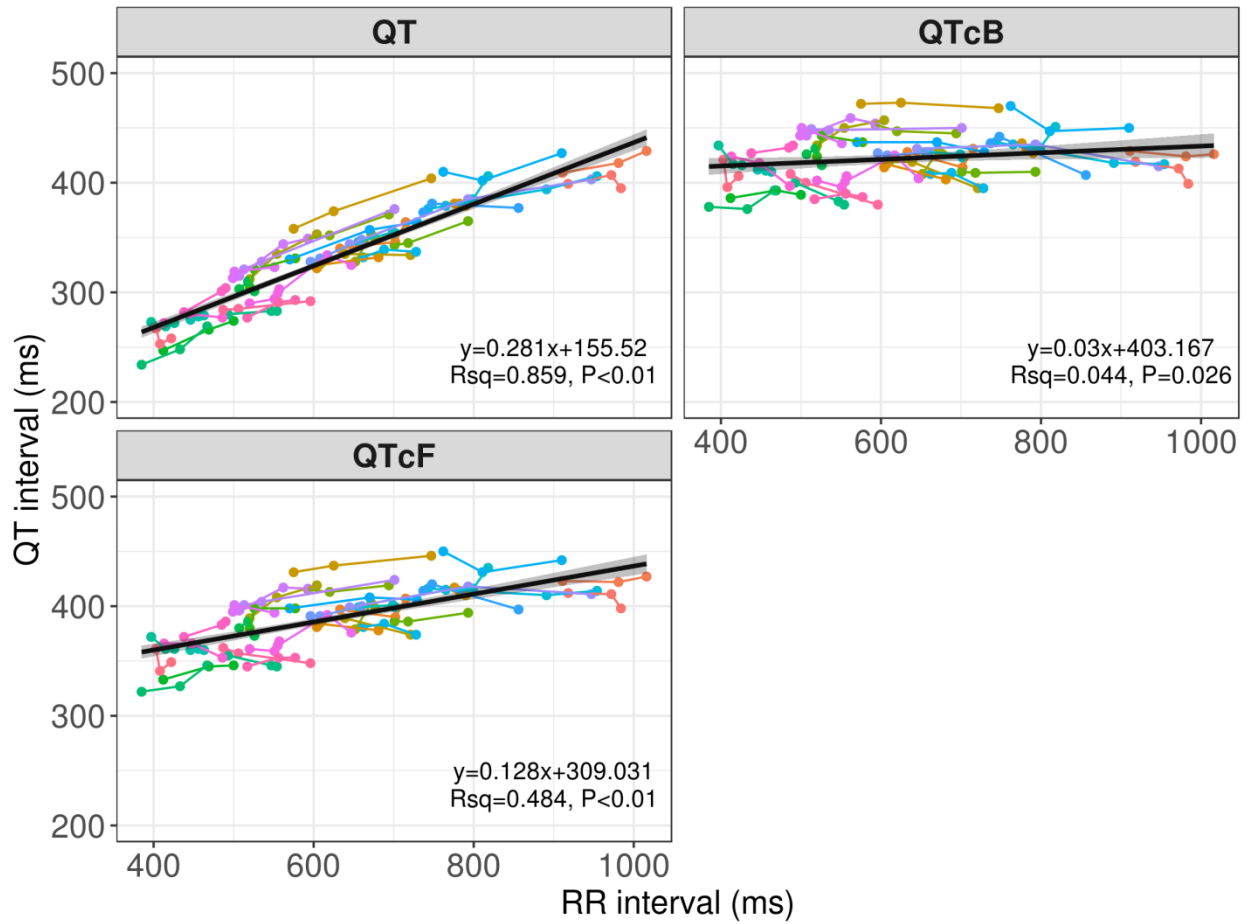
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48 **Figure S4. Distributions of QT Samples Stratified by Study**



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50 Left top figure and right top figure are basically same figures, but zoomed in 30 hr after dose for left top one.
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52 **Figure S5 QT/QTc versus RR Plots**



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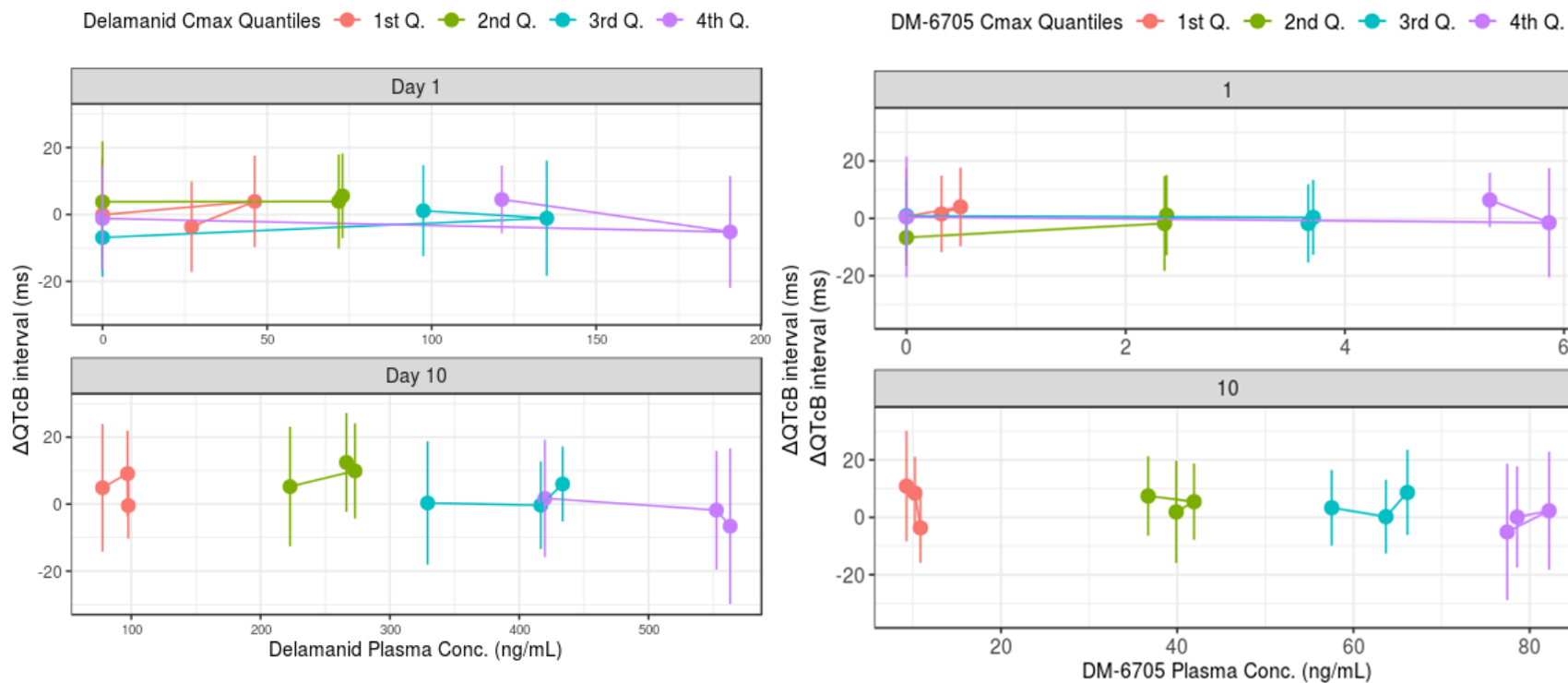
54 Closed circles represent observed data.

55 Each line represents data from one subject.

56 Black solid line with grey shaded area represent linear regression line with 90% CI.

57 Rsq: R squared.

58 **Figure S6 Hysteresis Plot: Mean Δ QTcB versus Mean DM-6705 Concentration by Cmax Quantiles of Delamanid (Left)/DM-**
 59 **6705 (Right) Stratified by Study Day**



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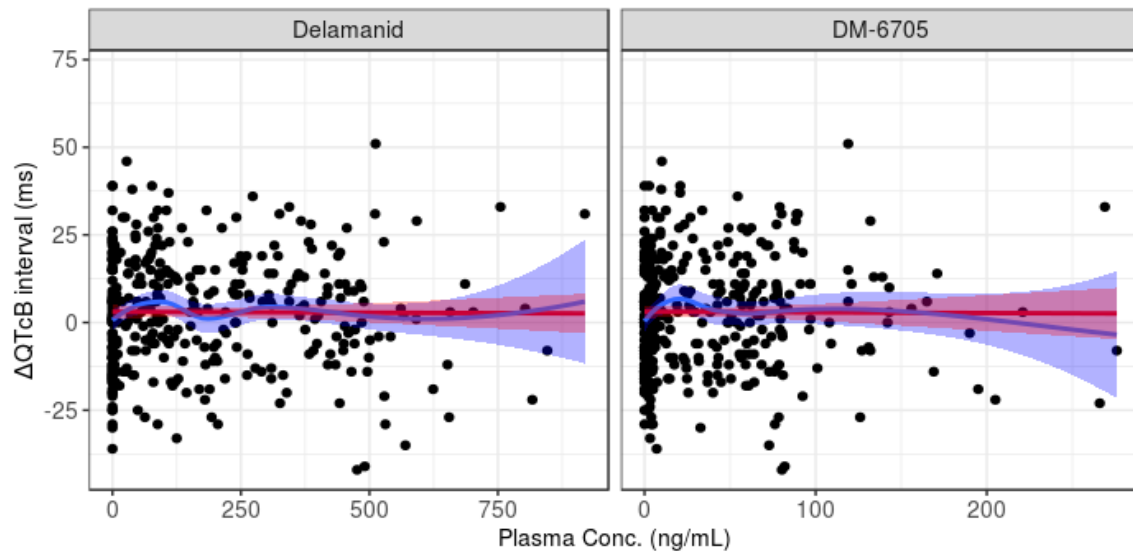
61 Data are shown as mean \pm SD.

62 Δ QTcB is baseline-corrected QTcB.

63 Q: quantile.

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65 **Figure S7 Scatter Plot of Δ QTcB vs Concentration**



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67 Closed circles represent observed values.

68 Red solid line and shaded area represent linear regression line and its 90% CI.

69 Blue solid line and shaded area represent loess smoothing curve and its SE.

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