

Figure S1. (a) Target mathematical model for the initial dQTcF linear mixed-effects model, and (b) formula (fit in R) describing the final dQTcF model components.

(a)

$$\Delta QTcF_{ijk} = (\theta_0 + \eta_{0,i}) + \theta_1 \cdot TRT_j + \sum_{n=1}^I (\theta_{(2,I)} + \eta_{2,il}) \cdot C_{ijkl} + \theta_3 \cdot TIME_j + \theta_4 \cdot (QTcF_{i,j=0} - \overline{QTcF}_0)$$

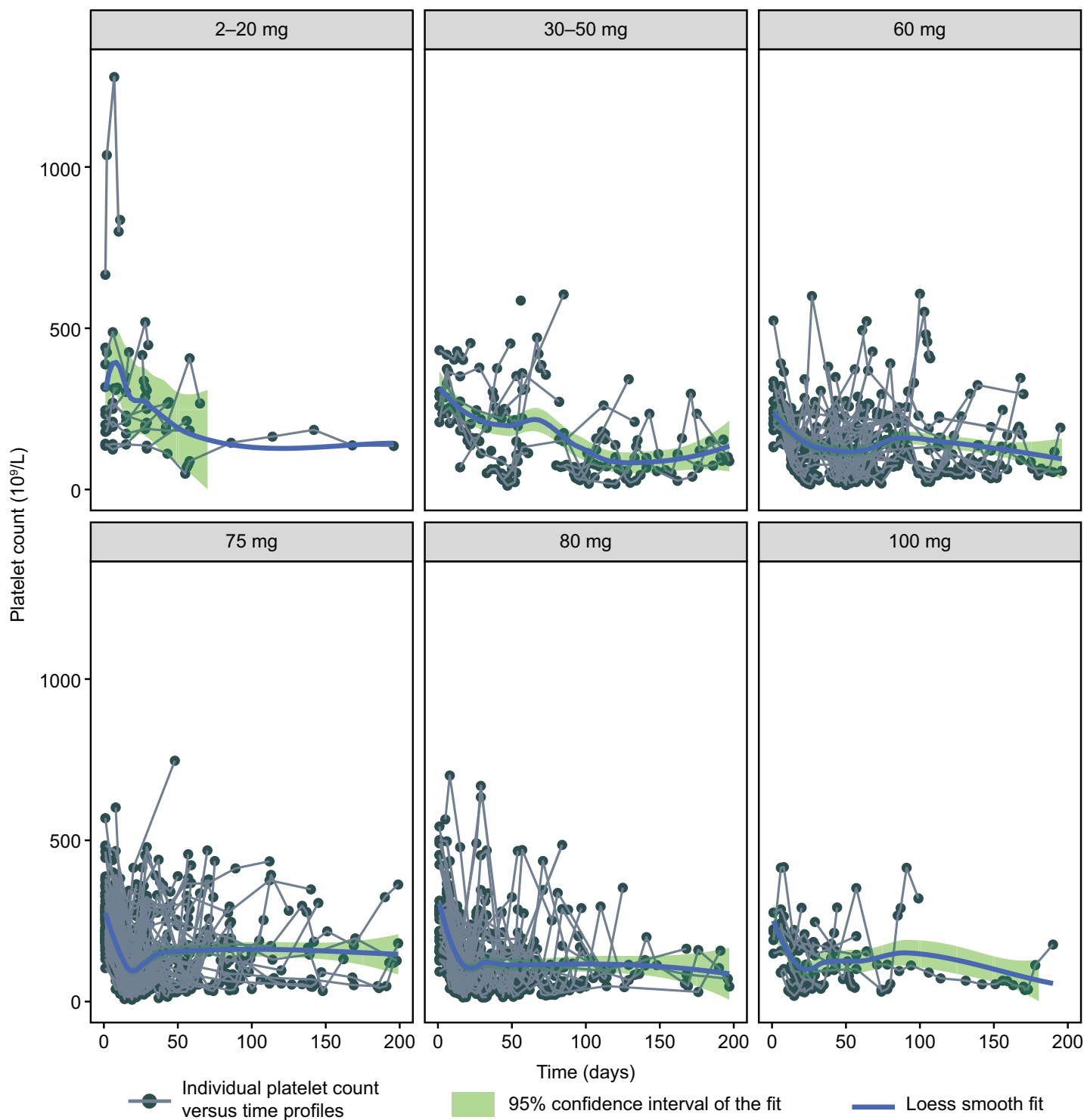
$\Delta QTcF_{ijk}$, change from baseline in dQTcF for patient i receiving treatment j at time k ; θ_0 , population mean intercept in the absence of a treatment effect; $\eta_{0,i}$, random effect associated with the intercept θ_0 ; θ_1 , fixed effect associated with the treatment TRT_j (0=placebo, 1=active drug); $\theta_{2,l}$, population mean slope of the assumed linear association between the concentration of analyte l (molibresib, active metabolite composite [GSK3529246] or TAM) and ΔQTc_{ijk} ; $\eta_{2,il}$, random effect associated with the slope $\theta_{2,l}$; C_{ijkl} , concentration of the analyte l for patient i receiving treatment j at time k ; θ_3 , fixed effect associated with time; θ_4 , fixed effect associated with baseline $QTc_{i,j=0}$; $QTcF_0$, overall mean of $QTc_{i,j=0}$ across patients, i.e., the mean of all the baseline dQTcF values.

(b)

$$DQTcF \sim INT + DM \cdot DMQTcF + GSK3529246^{(P145 \cdot (OCC==1,4,5) + P2 \cdot (OCC==2) + P3 \cdot (OCC==3))}$$

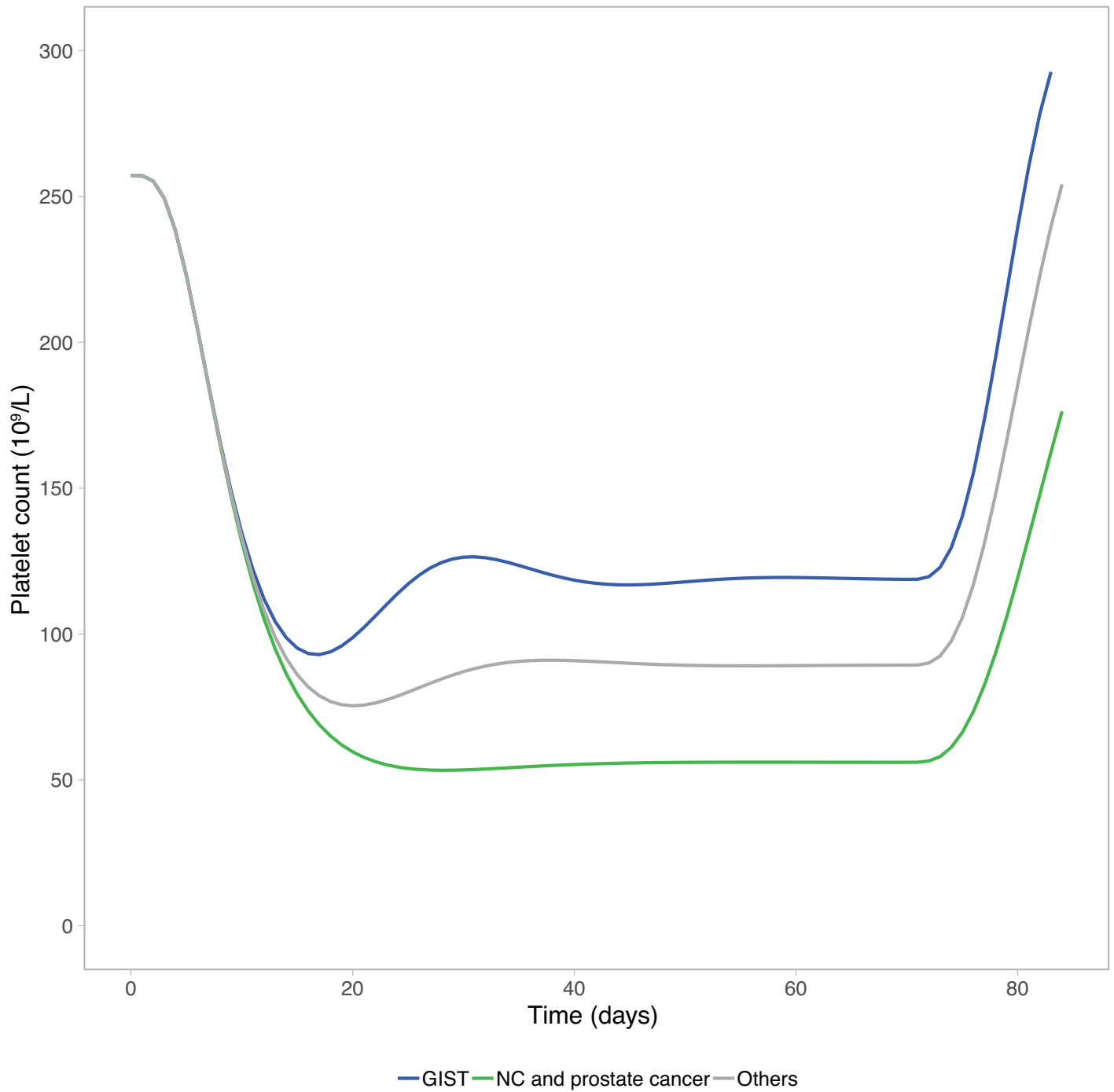
DQTcF, QT interval prolongation corrected by Fridericia formula and by baseline; INT, model intercept; DM, parameter describing the effect of DMQTcF; DMQTcF, the individual specific difference of baseline QTcF from population mean; Px, occasion-specific exponents of the molibresib active metabolite composite (GSK3529246) effect for occasion x .

Figure S2. Observed platelet count versus time profiles (0–200 days) stratified by molibresib dose (FTIH study).



FTIH, first-time-in-human.

Figure S3. Final model simulations of platelet levels following administration of molibresib (75 mg QD) for GIST, NC and prostate cancer.



GIST, gastrointestinal stromal tumor; NC, nuclear protein in testis carcinoma; QD, once daily.

Figure S4. Goodness-of-fit plots for the final platelet model: (a) Conditionally weighted residuals versus time; (b) Distribution of conditionally weighted residuals.

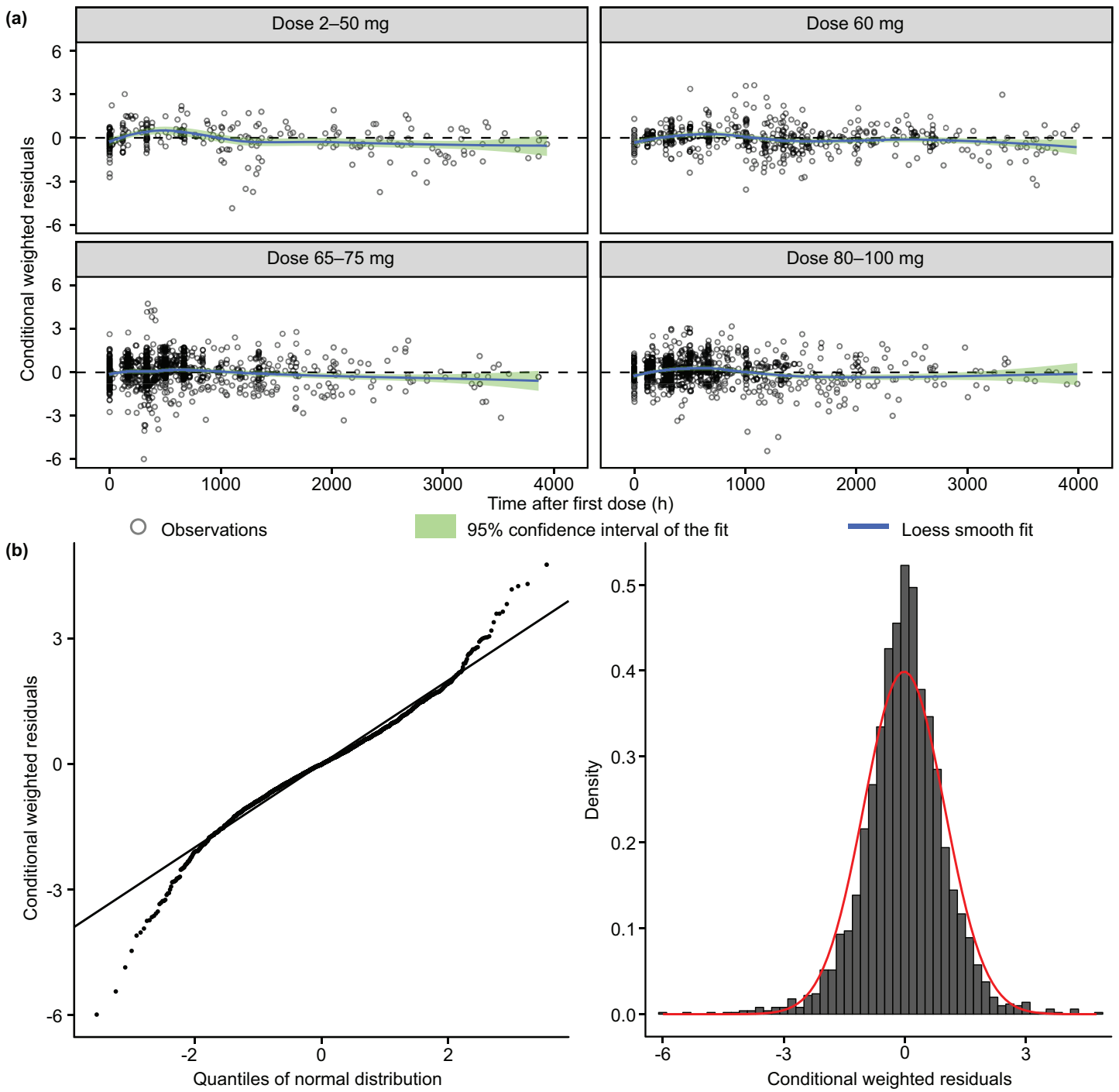


Figure S5. Simulated occurrence of Grade 3 or Grade 4 thrombocytopenia using the final platelet model.

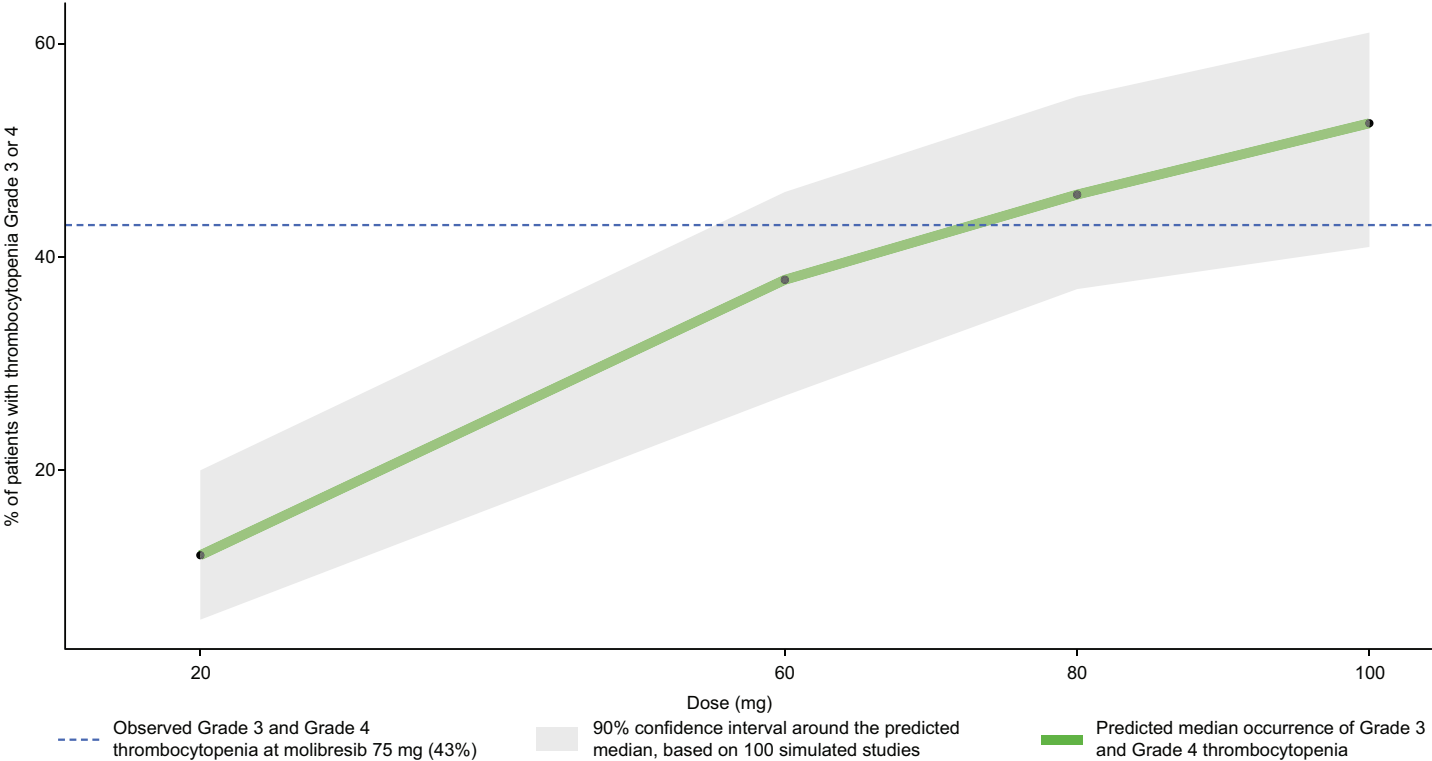
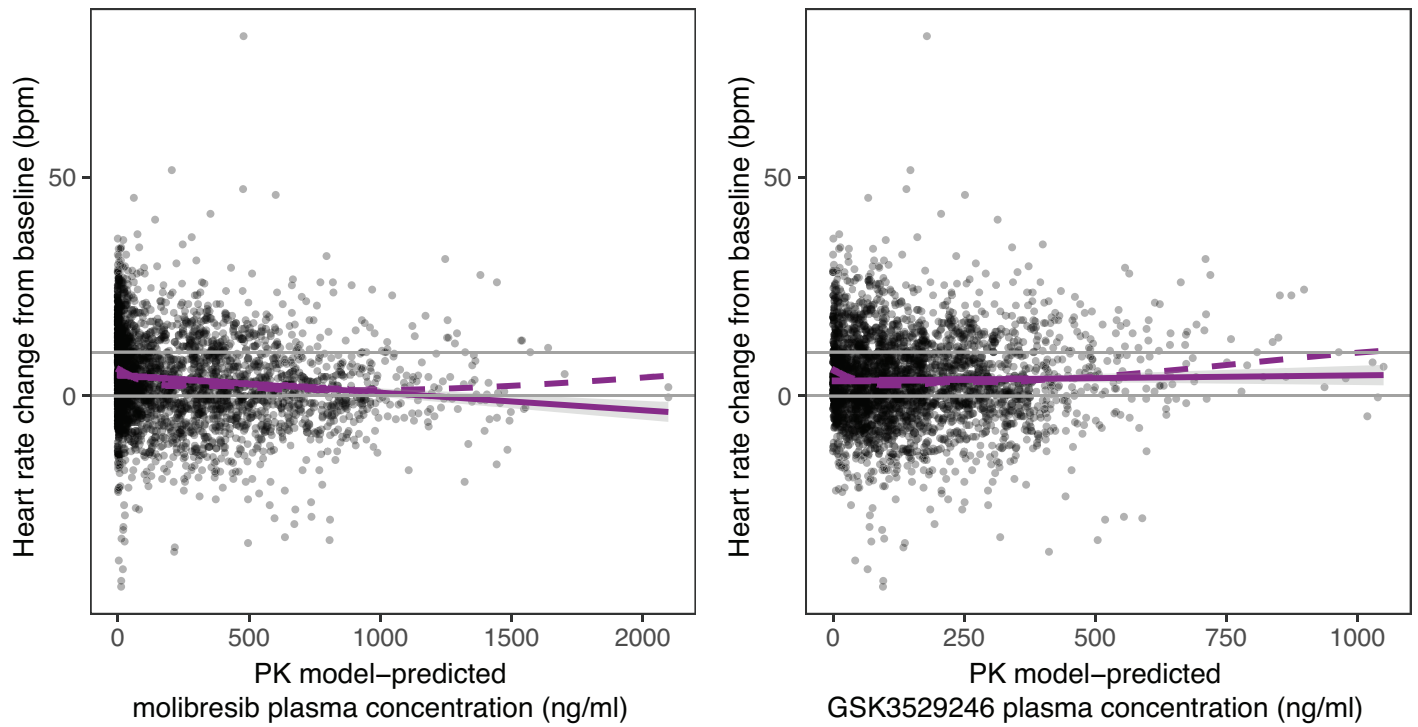


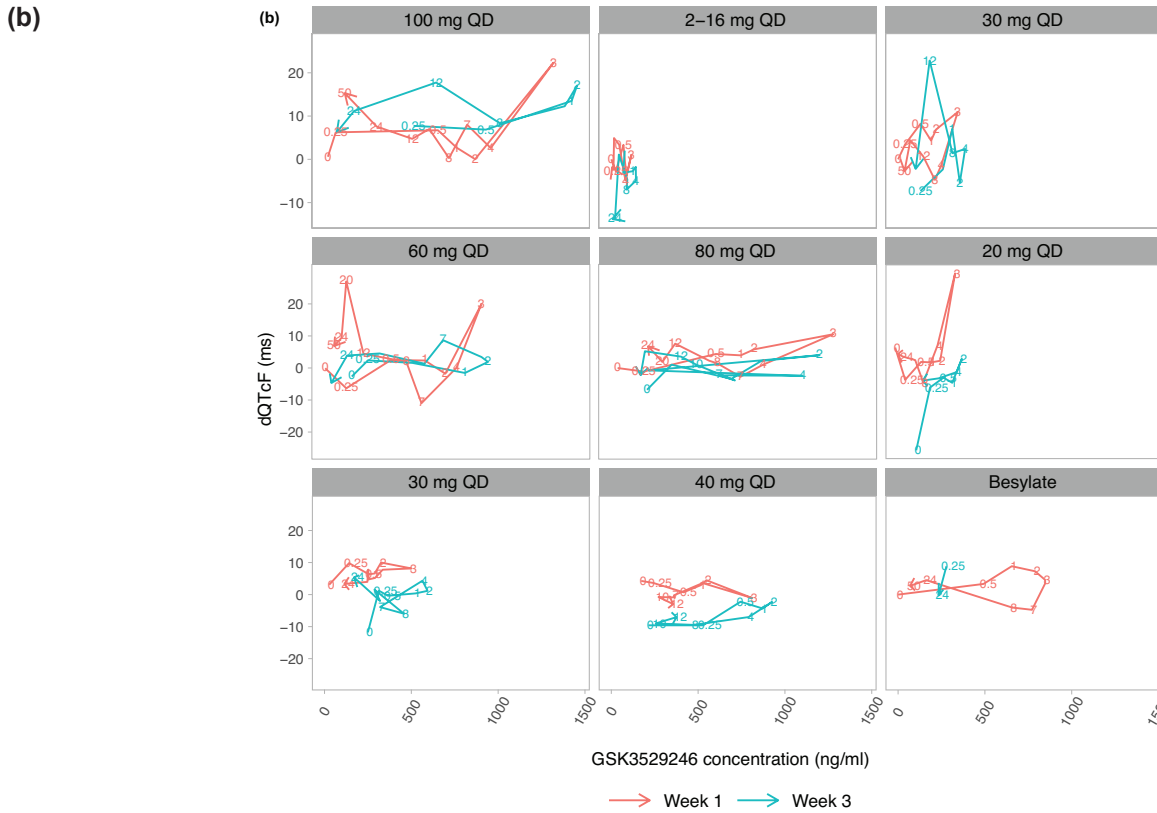
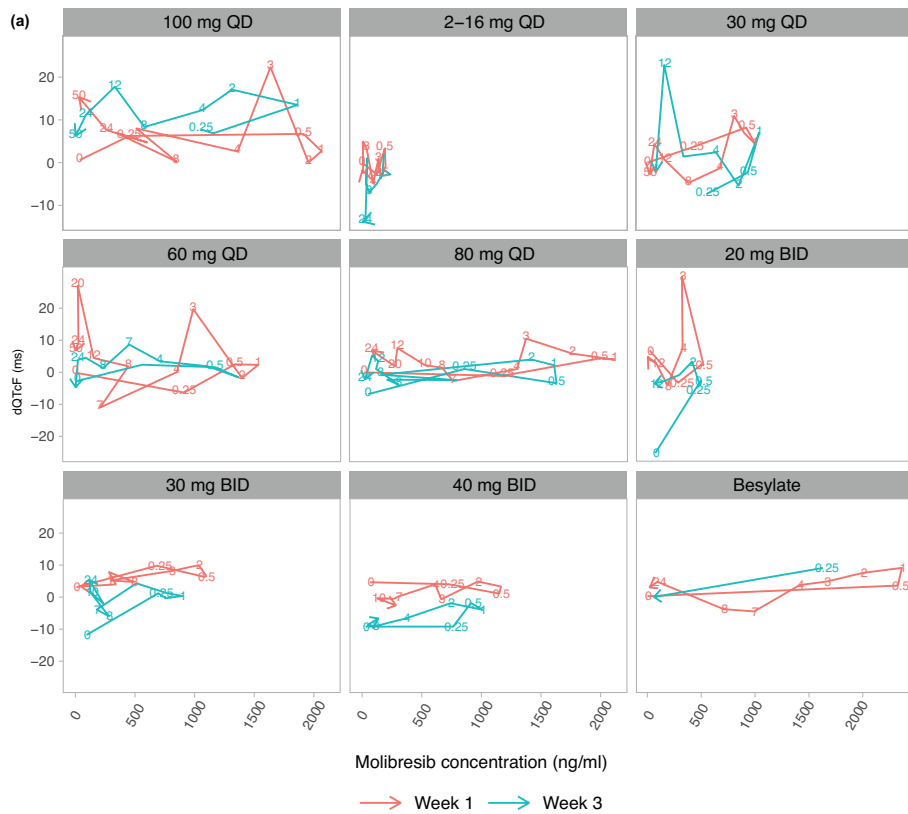
Figure S6. Heart rate change from baseline with molibresib and GSK3529246 plasma concentrations.



Dots represent observations; solid purple line represents the linear model fit; dashed purple line represents smooth through the data; horizontal grey lines indicate 0 and 10 bpm.

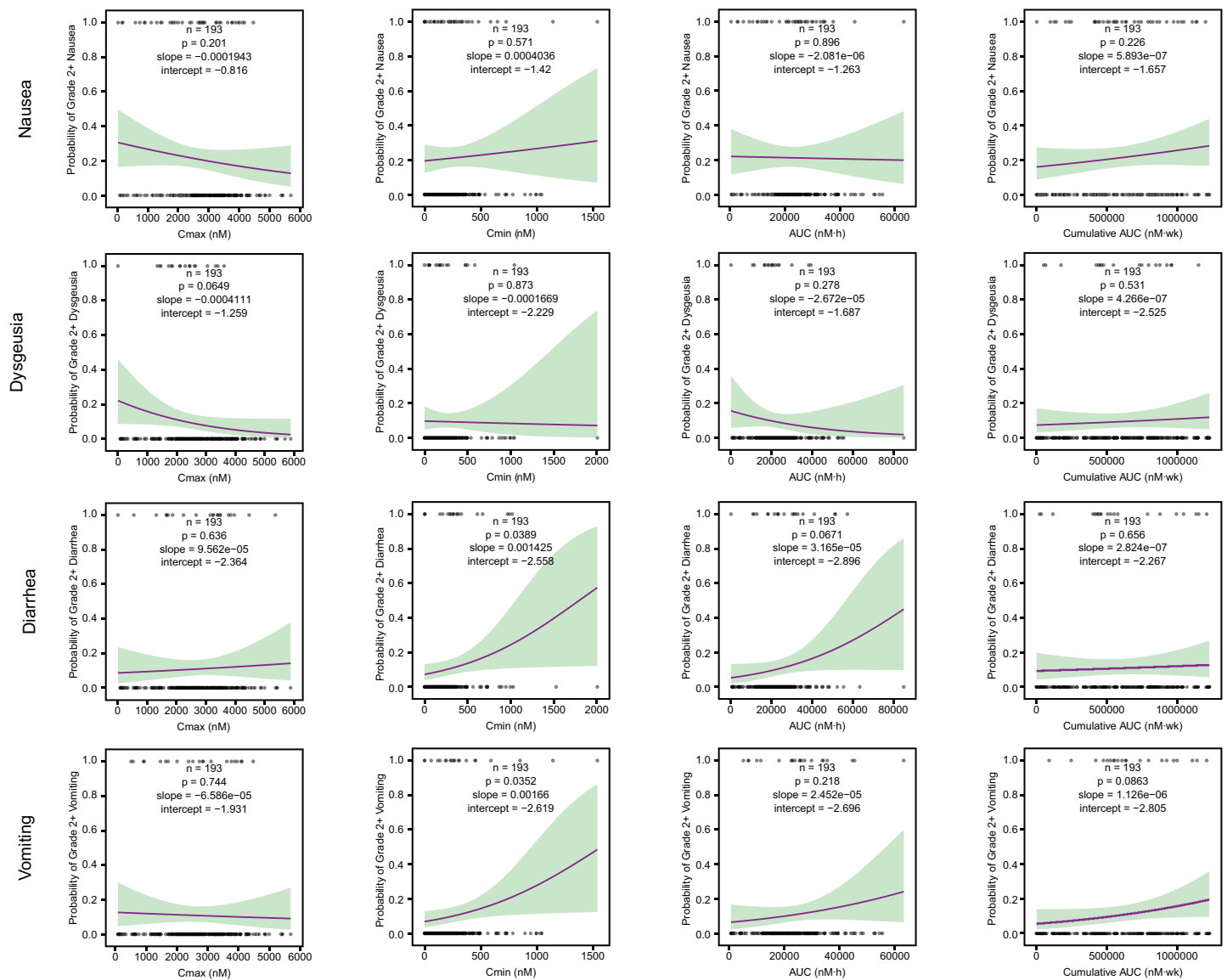
bpm, beats per minute; PK, pharmacokinetics.

Figure S7. Hysteresis plots showing the mean dQTcF change with (A) molibresib and (B) GSK3529246 exposure.



BID, twice daily; dQTcF, QT interval prolongation corrected by Fridericia formula and by baseline; QD, once daily.

Figure S8. Incidence of nausea, dysgeusia, diarrhea, and vomiting versus TAM exposure metrics.



Dots represent individual data points (1.0: nausea/dysgeusia/diarrhea/vomiting Grade 2 or greater, 0.0: No nausea/dysgeusia/diarrhea/vomiting or Grade 1 nausea/dysgeusia/diarrhea/vomiting); solid lines represent the model fits; shaded green areas represent 95% confidence intervals.

AUC, area under the concentration–time curve; C_{max} , maximum plasma concentration; C_{min} , minimum plasma concentration; TAM, total active moiety.

Supplementary Text 1. Final PK/PD Platelet model code.

- :: 1. Based on: 231
- :: 2. Description:
 - :: Final Platelet model
- :: 3. Label:
 - :: Friberg model
- :: 4. Structural model:
 - :: Friberg model
- :: 5. Covariate model:
 - :: Forward step 1
- :: 6. Inter-individual variability:
 - :: Baseline
- :: 7. Inter-occasion variability:
 - :: NONE
- :: 8. Residual variability:
 - :: Proportional
- :: 9. Estimation:
 - :: FOCE+I

\$SIZES PD=-100

\$PROBLEM GSK BET

\$INPUT STUDY ID SUBJID PARTN AMTMG AMTUG AMT II ADDL LINDV DV

BPLT DAY WEEK TIME RTLD ADOSE EVID MDV OCC DOSENUM QDBID

AGE SEX WT HT BBSA BBMI RACEN ETHN CANCER BECOG ECOG

EXFLAG FDARACEN FOOD PPTF PTAX BAST AST HGB BHGB IALAG1

ICL IV IKA IV2 IQ IKIN ISLP NIMCL IMV IMKA IMV2 IMQ IMCL

\$DATA ../nm_pkpd_data_25SEP19_param32.csv IGNORE=@

IGNORE=(EXFLAG.GT.0)

;-----

\$SUBROUTINE ADVAN13 TOL=12

\$MODEL COMP=(ABS,DEFDOSE) COMP=(LIVER) COMP=(METABS)

COMP=(CENT,DEFOBS) COMP=(PERIPH) COMP=(IND) COMP=(METCENT)

COMP=(METPERIPH) COMP=(PROLIFERATING) COMP=(TRANSIT)

COMP=(TRANSIT) COMP=(TRANSIT) COMP=(CIRCULATING)

;-----

\$PK

; Stratification by dose levels for VPC

STRT=1 ; Doses below 50 mg

IF(ADOSE.GE.50) STRT=2 ; Doses 50-60 mg

IF(ADOSE.GT.60) STRT=3 ; Doses 65-75 mg

IF(ADOSE.GT.75) STRT=4 ; Doses 80-100 mg

;----- PLATELETS -----

COVCAN_FB = 1

IF(CANCER.EQ.3) COVCAN_FB = (1+THETA(6))

IF(CANCER.GE.7) COVCAN_FB = (1+THETA(7))

TVBASE = THETA(1)

TVKTRANS = THETA(2)

TVFBPOWER = THETA(3)

TVVEC50 = THETA(4)

TVEMAX = THETA(5)

MU_1 = TVBASE

MU_2 = TVKTRANS

MU_3 = TVFBPOWER

MU_4 = TVVEC50

MU_5 = TVEMAX

BASE = EXP(MU_1 + ETA(1))

KTRANS = EXP(MU_2 + ETA(2))

FBPOWER = COVCAN_FB*EXP(MU_3 + ETA(3))

EC50 = EXP(MU_4 + ETA(4))

EMAX = EXP(MU_5 + ETA(5))

A_0(9) = BASE

A_0(10) = BASE

A_0(11) = BASE

A_0(12) = BASE

A_0(13) = BASE

; ----- PK from run 32 -----

; Parent

KA = IKA

CL = ICL

V = IV

$$QH = \text{EXP}(4.007333)$$

$$VH = \text{EXP}(0.4054651)$$

$$Q = IQ$$

$$V2 = IV2$$

$$ALAG1 = IALAG1$$

$$SLP = ISLP$$

$$KIN = IKIN$$

; Metabolite

$$POWAST = -0.194$$

$$COVAST_MCL = (AST/28)**POWAST$$

$$MKA = IMKA$$

$$MCL = IMCL*COVAST_MCL$$

$$MV = IMV$$

$$MQ = IMQ$$

$$MV2 = IMV2$$

; ---- initialize enzyme CMT -----

$$ENZBASE = 1$$

$$KOUT = KIN/ENZBASE$$

$$A_0(6) = ENZBASE$$

; Rate Constants

$$K42 = QH/V$$

$$K45 = Q/V$$

$$K54 = Q/V2$$

K70 = MCL/MV

K78 = MQ/MV

K87 = MQ/MV²

IF(NEWIND.LT.2) THEN

IFL = 0

TAD = 0.0

ENDIF

IF(EVID.EQ.1) THEN

TDOS = TIME

TAD = 0.0

IFL = 1

ENDIF

IF(IFL.EQ.1.AND.EVID.NE.1) TAD = TIME - TDOS

; -----

\$DES

; Parent

CH = A(2)/VH + 1E-9 ; liver concentrations

IND = SLP*CH ; linear induction of liver enzymes

EH = CL*A(6)/QH ; hepatic extraction ratio

FH = 1 - EH ; fraction escaping first-pass metabolism

$$K24 = QH*FH/VH$$

$$K23 = QH*EH/VH$$

$$DADT(1) = -KA*A(1)$$

$$DADT(2) = KA * A(1) - K24 * A(2) + K42 * A(4) - K23 * A(2)$$

$$DADT(4) = K24 * A(2) - K42 * A(4) - K45*A(4) + K54*A(5)$$

$$DADT(5) = K45*A(4) - K54*A(5)$$

$$DADT(6) = KIN*(1 + IND) - KOUT*A(6)$$

$$A6 = A(6)$$

; Metabolite

$$DADT(3) = K23*A(2) - MKA*A(3)$$

$$DADT(7) = MKA*A(3) - K78*A(7) + K87*A(8) - K70*A(7)$$

$$DADT(8) = K78*A(7) - K87*A(8)$$

; Platelets

$$EFFCONC=(A(4)/V + A(7)/MV)$$

$$DEFF = (EMAX * EFFCONC/(EC50 + EFFCONC))$$

$$RATIO = BASE/A(13)$$

$$FEEDBACK = RATIO**FBPOWER$$

$$DADT(9) = KTRANS*A(9)*(1-DEFF)*FEEDBACK - KTRANS*A(9) ;prol cells$$

$$DADT(10) = KTRANS*A(9) - KTRANS*A(10) ;transit 1$$

$$DADT(11) = KTRANS*A(10) - KTRANS*A(11) ;transit 2$$

$$DADT(12) = KTRANS*A(11) - KTRANS*A(12) ;transit 3$$

$$DADT(13) = KTRANS*A(12) - KTRANS*A(13) ;circ plat$$

;-----

\$ERROR

IPRED = LOG(A(13)+0.0000001)

Y = IPRED + EPS(1)

;-----

\$THETA (2.5,5.55,7.5) ; Baseline Platelet Count; (10⁹/L); LOG

\$THETA (-5,-3.36,-1) ; Platelet Transit Rate; h-1; LOG

\$THETA (-3,-1.94,0) ; Feedback Power; -; LOG

\$THETA (-15,1.57) ; EC50; nM; LOG

\$THETA -0.001 FIX ; EMAX; -; LOG

\$THETA (-0.99,2) ; FEEDBACK~CANCER3; ; LIN

\$THETA (-0.99,2) ; FEEDBACK~CANCER78; ; LIN

;-----

\$OMEGA 0.125 ; Baseline Platelet Count_

\$OMEGA 0.0167 ; Platelet Transit Rate_

\$OMEGA 0.256 ; Feedback Power_

\$OMEGA 0.363 ; EC50_

\$OMEGA 0 FIX ; EMAX_

;-----

\$SIGMA 0.0765 ; Proportional Error

;-----

\$ESTIMATION METHOD=COND MAXEVAL=9999 INTER SIGL=9 NSIG=3 NOABORT FAST

PRINT=1

\$COVARIANCE PRINT=E UNCONDITIONAL SIGL=9

\$TABLE ID TAD DV EVID TIME RTLD IPRED CWRES BASE KTRANS FBPOWER
EC50 EMAX ETAs(1:LAST) BPLT DAY WEEK ADOSE OCC DOSENUM
QDBID AGE SEX WT HT BBSA BBMI RACEN ETHN CANCER BECOG
EXFLAG FDARACEN FOOD NOPRINT ONEHEADER FORMAT=s1PE13.7
FILE=sdtab219

\$TABLE ID BASE KTRANS FBPOWER EC50 EMAX ETAs(1:LAST) NOPRINT
ONEHEADER FORMAT=s1PE13.7 FILE=patab219

\$TABLE ID BPLT ADOSE AGE WT HT BBMI BBSA HGB BHGB NOPRINT
ONEHEADER FORMAT=s1PE13.7 FILE=cotab219

\$TABLE ID PARTN SEX RACEN ETHN CANCER ECOG BECOG PPTF PTAX
NOPRINT ONEHEADER FORMAT=s1PE13.7 FILE=catab219