

Population Pharmacokinetic Modeling of Abacavir/Dolutegravir/Lamivudine to Support a Fixed-Dose Combination in Children with HIV-1

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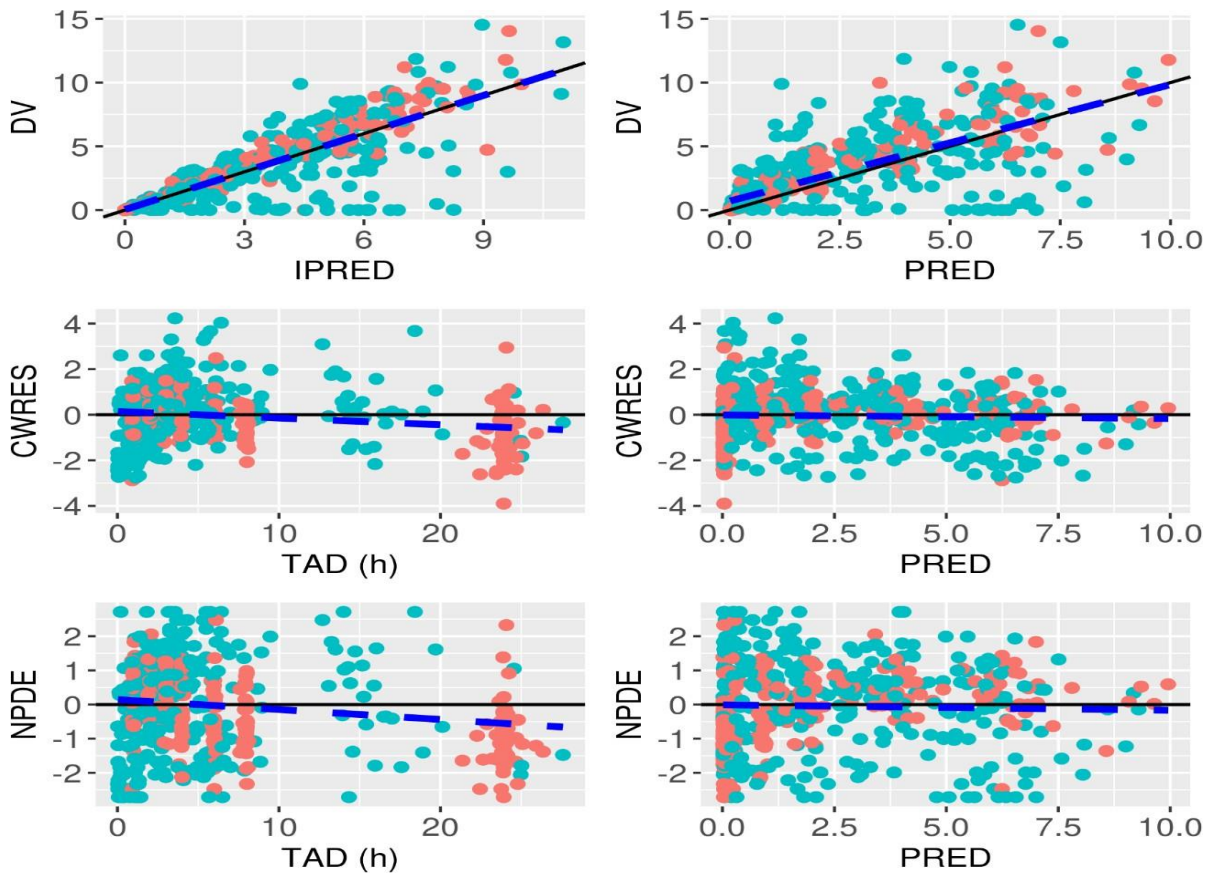
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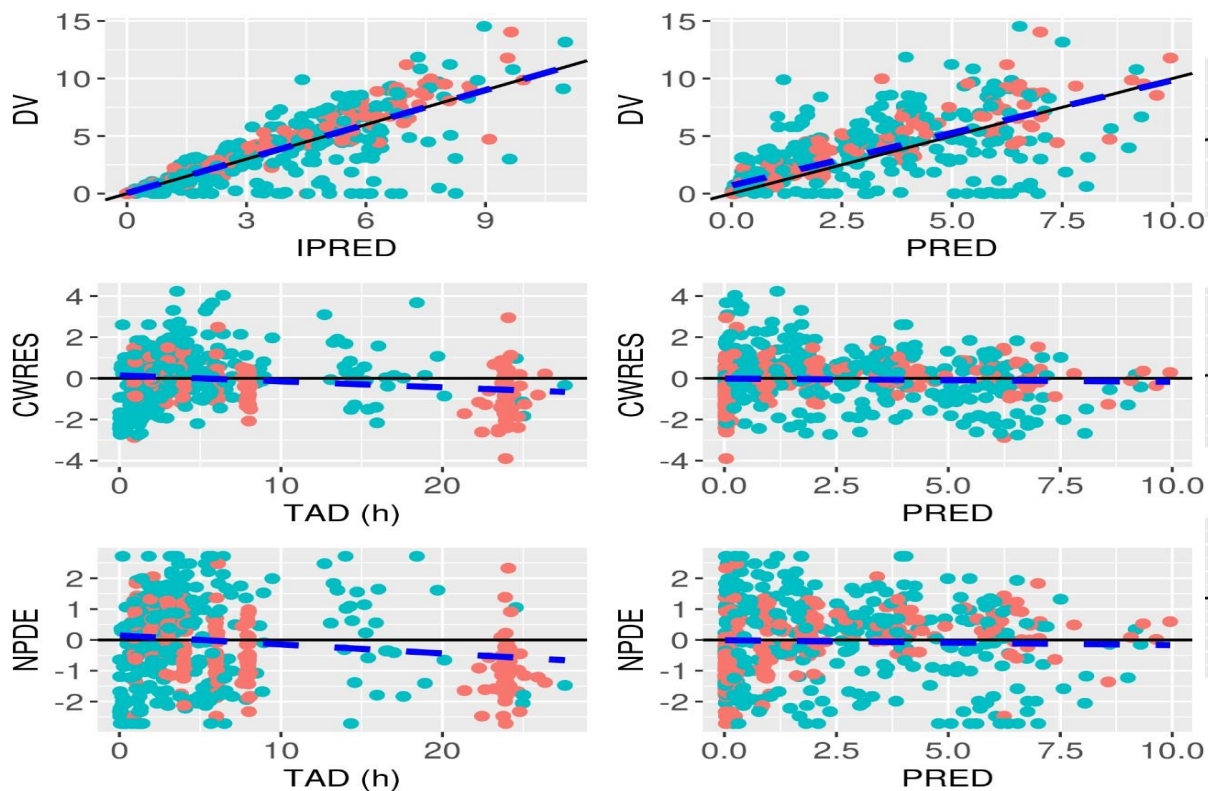
Supplementary Figures

Fig. S1. Goodness-of-fit Plot for the ABC Model



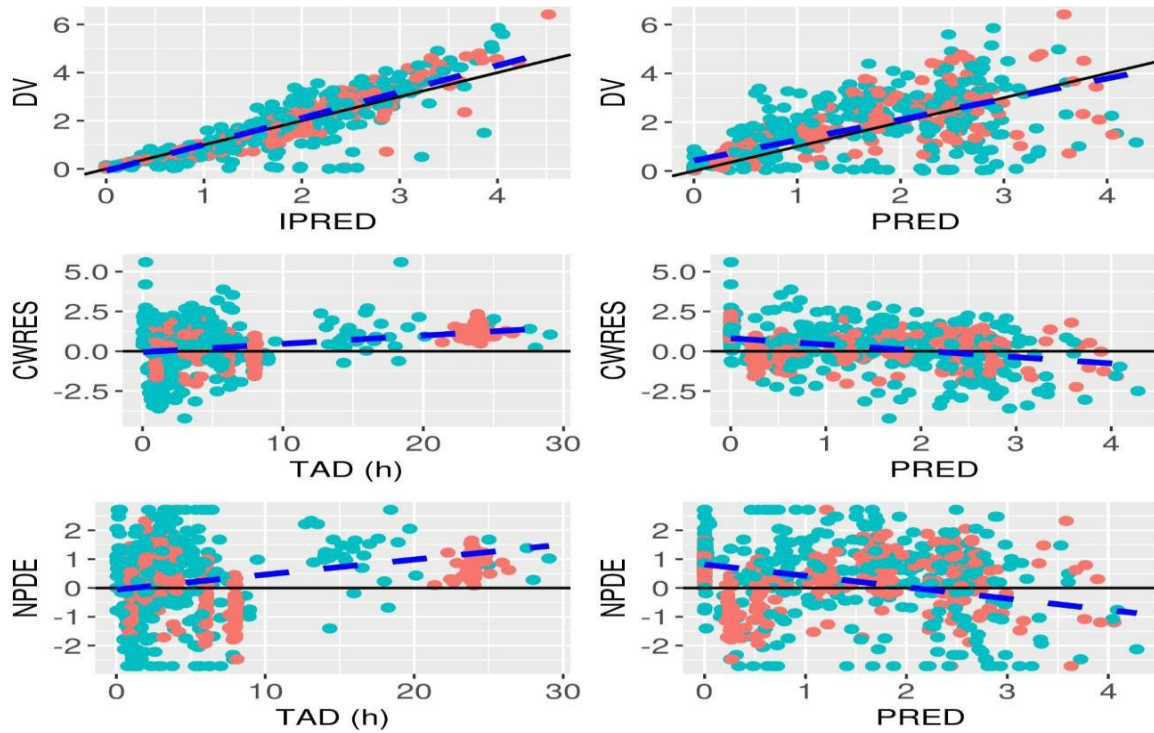
The colored symbols represent individual observations. The dashed blue line is a trend line (for population and individual predictions vs observations) or regression line (for CWRES vs population predictions and time after dose & NPDE vs population predictions and time after dose). DV= Observed concentrations ($\mu\text{g/mL}$), IPRED= Individual Predicted Concentrations ($\mu\text{g/mL}$), PRED= Population Predicted Concentrations ($\mu\text{g/mL}$), TAD= Time after Dose, CWRES: conditional weighted residuals. NPDE: Normalized prediction distribution errors. Notes: Colors of circles represent different sampling scheme, red = Serial sampling, cyan = Sparse sampling

Fig. S2. Goodness-of-fit Plot for the DTG Model



The colored symbols represent individual observations. The dashed blue line is a trend line (for population and individual predictions vs observations) or regression line (for CWRES vs population predictions and time after dose & NPDE vs population predictions and time after dose). DV= Observed concentrations ($\mu\text{ g/mL}$), IPRED= Individual Predicted Concentrations ($\mu\text{ g/mL}$), PRED= Population Predicted Concentrations ($\mu\text{ g/mL}$), TAD= Time after Dose, CWRES: conditional weighted residuals. NPDE: Normalized prediction distribution errors. Notes: Colors of circles represent different sampling scheme, red = Serial sampling, cyan = Sparse sampling

Fig.S3. Goodness-of-fit Plot for the 3TC Model



The colored symbols represent individual observations. The dashed blue line is a trend line (for population and individual predictions vs observations) or regression line (for CWRES vs population predictions and time after dose & NPDE vs population predictions and time after dose). DV= Observed concentrations ($\mu\text{g/mL}$), IPRED= Individual Predicted Concentrations ($\mu\text{g/mL}$), PRED= Population Predicted Concentrations ($\mu\text{g/mL}$), TAD= Time after Dose, CWRES: conditional weighted residuals. NPDE: Normalized prediction distribution errors. Notes: Colors of circles represent different sampling scheme, red = Serial sampling, cyan = Sparse sampling

Supplementary Tables

Table S1. ABC/DTG/3TC (DTs & Tablets) Dosing in IMPAACT 2019 Study and US-FDA Approved Individual Component Dosing in Children ≥ 6 kg

Drug	Weight Bands	ABC/DTG/3TC FDC Dose in IMPAACT 2019 Study	Approved Individual Component Dose
ABC	≥6 to <10 kg	180 mg DT	16 mg/kg Solution (96 - 160 mg)
	≥10 to <14 kg	240 mg DT	16 mg/kg Solution (160 - 224 mg)
	≥14 to <20 kg	300 mg DT	300 mg Tablet
	≥20 to <25 kg	360 mg DT	450 mg Tablet
	≥25 to <40 kg	600 mg Tablet	600 mg Tablet
DTG			
	≥6 to <10 kg	15 mg DT	
	≥10 to <14 kg	20 mg DT	
	≥14 to <20 kg	25 mg DT	
	≥20 to <25 kg	30 mg DT	
	≥25 to <40 kg	50 mg Tablets	
3TC			
	≥6 to <10 kg	90 mg DT	10 mg/kg Solution (60 - 100 mg)
	≥10 to <14 kg	120 mg DT	10 mg/kg Solution (100 - 140 mg)
	≥14 to <20 kg	150 mg DT	150 mg Tablet
	≥20 to <25 kg	180 mg DT	225 mg Tablet
	≥25 to <40 kg	300 mg Tablet	300 mg Tablet

IMPAACT 2019 doses are aligned with WHO weight band-based doses

Table S2. IMPAACT 2019 Participant Characteristics and Demographic

Covariate	(N=55)
Baseline Age (years)	
Mean (SD)	5.53 (3.1)
Median [Min, Max]	6.00 [1.00, 11.0]
Baseline Body Weight (kg)	
Mean (SD)	18.64 (7.4)
Median [Min, Max]	17.00 [8.15, 39.30]
Baseline Height (cm)	
Mean (SD)	109.77 (20.2)
Median [Min, Max]	113.0 [71.0, 153.0]
Baseline Body Mass Index (kg/m²)	
Mean (SD)	14.92 (1.7)
Median [Min, Max]	14.7 [11.7, 21.6]
Baseline Body Surface Area (m²)	
Mean (SD)	0.75 (0.21)
Median [Min, Max]	0.74 [0.42, 1.25]
Baseline Serum Creatinine (umol/L)	
Mean (SD)	33.97 (11.4)
Median [Min, Max]	32.71 [15.0, 68.0]
Baseline Creatinine Clearance (mL/min)	
Mean (SD)	1.92 (0.548)
Median [Min, Max]	1.82 [0.971, 3.85]
Baseline Alanine Aminotransferase (ukat/L)	

Mean (SD)	0.29 (0.10)
Median [Min, Max]	0.28 [0.13, 0.63]
Baseline Aspartame Aminotransferase (ukat/L)	
Mean (SD)	0.55 (0.13)
Median [Min, Max]	0.53 [0.30, 0.95]
Baseline Total Bilirubin (umol/L)	
Mean (SD)	7.04 (4.1)
Median [Min, Max]	6.30 [1.40, 19.84]
Gender (%)	
Male	30 (54.5%)
Female	25 (45.5%)
Race (%)	
Black or African American	37 (67.3%)
Asian	17 (30.9%)
All Others	1 (1.8%)

Table S3. NCA Calculated vs. Individual Post-hoc ABC Steady-State PK Parameters Following Once Daily Oral Dosing of DTG/ABC/3TC FDC doses in IMPAACT 2019 Study (Intensive PK Population Group Only)

Weight Band (kg)	DTG/ABC/3TC Dosage Form	ABC Dose	N	Analysis Method	PK Parameter GM (95% CI)		
					C _{max} (µg/mL)	AUC ₀₋₂₄ (µg*h/mL)	C ₂₄ (µg/mL)
≥6 to <10	DT	180 mg	7	PopPK ^a	5.67 (3.92 -8.19)	15.60 (10.9 -22.20)	0.004 (0.003 -0.006)
					7.30	17.7	0.003

			7	NCA ^b	(6.05 – 8.81)	(13.02 – 23.94)	(0.001 -0.007)
≥10 to <14	DT	240 mg	7	PopPK ^a	8.06 (6.11 -10.60)	19.20 (14.90 -24.80)	0.012 (0.004 -0.040)
			7	NCA ^b	8.36 (5.68 -12.31)	19.8 (12.71 - 30.73)	0.005 (0.002 -0.013)
≥14 to <20	DT	300 mg	7	PopPK ^a	6.30 (5.42-7.32)	14.60 (12.30 - 17.40)	0.004 (0.002 -0.007)
			7	NCA ^b	6.26 (4.73 -8.28)	15.1 (10.54 - 21.61)	0.003 (0.001 -0.006)
≥20 to <25	DT	360 mg	7	PopPK ^a	8.70 (6.18-12.30)	18.30 (14.90 - 22.50)	0.004 (0.003 -0.008)
			7	NCA ^b	6.65 (5.17 -8.56)	17.35 (14.52 - 20.73)	0.004 (0.002 -0.007)
≥25 to <40	Tablets	600 mg	7	PopPK ^a	9.86 (8.01-12.10)	24.40 (20.70 - 28.70)	0.011 (0.005-0.025)
			7	NCA ^b	9.04 (7.40 -11.04)	25.74 (22.51 - 29.44)	0.011 (0.003 -0.037)

^aModel based Individual Post-hoc PK Parameters

^bNCA PK parameters [14]

Table S4. NCA Calculated vs. Individual Post-hoc DTG Steady-State PK Parameters Following Once Daily Oral Dosing of DTG/ABC/3TC FDC doses in IMPAACT 2019 Study (Intensive PK Population Group Only)

Weight Band (kg)	DTG/ABC/3TC Dosage Form	DTG Dose	N	Analysis Method	PK Parameter GM (95%CI)		
					C _{max} (µg/mL)	AUC ₀₋₂₄ (µg*h/mL)	C ₂₄ (µg/mL)
≥6 to <10	DT	15 mg	7	PopPK ^a	6.58 (5.71 -7.59)	76.80 (62.3 -94.80)	0.94 (0.60 -1.49)
			7	NCA ^b	7.40 (5.74 - 9.53)	75.9 (56.0 - 102.8)	0.91 (0.52 -1.61)
			7	PopPK ^a	7.27 (6.57 -8.04)	97.3 (82.1-115.0)	1.63 (1.08 -2.44)

≥10 to <14	DT	20 mg	7	NCA ^b	8.85 (7.28-10.75)	91.0 (65.6 – 126.11)	1.22 (0.65 -2.29)
≥14 to <20	DT	25 mg	7	PopPK ^a	6.59 (5.95-7.30)	74.30 (63.90 -86.40)	0.85 (0.59-1.22)
			7	NCA ^b	7.04 (6.02 -8.23)	71.45 (57.66 -88.53)	0.79 (0.53 -1.16)
≥20 to <25	DT	30 mg	7	PopPK ^a	6.66 (6.13-7.25)	84.50 (71.00-101.00)	1.28 (0.85 -1.93)
			7	NCA ^b	7.29 (6.26 -8.50)	84.44 (66.49 -107.24)	1.35 (0.64 -2.84)
≥25 to <40	Tablets	50mg	7	PopPK ^a	5.86 (5.42-6.33)	78.60 (70.60 -87.50)	1.17 (0.93 -1.46)
			7	NCA ^b	6.25 (5.18 -7.55)	71.80 (63.19 -81.58)	0.98 (0.76 -1.26)

^aModel based Individual Post-hoc PK Parameters

^bNCA PK parameters [14]

Table S5. NCA Calculated vs. Individual Post-hoc 3TC Steady-State PK Parameters Following Once Daily Oral Dosing of DTG/ABC/3TC FDC doses in IMPAACT 2019 Study (Intensive PK Population Group Only)

Weight Band (kg)	DTG/ABC/3TC Dosage Form	3TC Dose	N	Analysis Method	PK Parameter GM (95%CI)		
					C _{max} (µg/mL)	AUC ₀₋₂₄ (µg*h/mL)	C ₂₄ (ng/mL)
≥6 to <10	DT	90 mg	7	PopPK ^a	2.27 (1.75 -2.96)	9.42 (6.53 – 13.60)	0.017 (0.004 - 0.065)
			7	NCA ^b	2.29 (1.61 – 3.27)	10.7 (7.10 – 15.99)	0.055 (0.038 - 0.077)
≥10 to <14	DT	120 mg	7	PopPK ^a	3.22 (2.75 -3.78)	14.10 (11.90 – 16.90)	0.010 (0.003-0.036)
			7	NCA ^b	3.55	14.2	0.046

					(2.99 – 4.21)	(11.39 -17.61)	(0.030 - 0.070)
≥14 to <20	DT	180 mg	7	PopPK ^a	2.67 (2.26 – 3.17)	11.30 (9.71 – 13.2)	0.005 (0.002 - 0.011)
			7	NCA ^b	2.92 (2.36 -3.60)	13.02 (11.28 -15.02)	0.058 (0.042 - 0.081)
≥20 to <25	DT	150 mg	7	PopPK ^a	2.80 (2.11 – 3.72)	12.50 (10.30 –15.10)	0.023 (0.009 - 0.059)
			7	NCA ^b	2.99 (2.24 -3.99)	14.51 (12.46 -16.90)	0.060 (0.051 –0.071)
≥25 to <40	Tablets	300 mg	7	PopPK ^a	3.94 (3.29 – 4.72)	19.20 (15.30 - 24.00)	0.012 (0.003-0.053)
			7	NCA ^b	4.15 (3.18 -5.41)	21.73 (17.13 -27.58)	0.084 (0.061 –0.115)

^aModel based Individual Post-hoc PK Parameters

^bNCA PK parameters [14]

Table S6. ABC PopPK NONMEM Code

\$PROBLEM

\$INPUT

\$DATA

\$SUBROUTINES ADVAN4 TRANS4

\$PK

FLAG=0

OCC1=0

IF (OCC.EQ.1) OCC1 = 1

OCC2=0

IF (OCC.EQ.2) OCC2 = 1

OCCCL = OCC1 * ETA(5) + OCC2 * ETA(6)

TVKA=THETA(1)

TVVQ=THETA(2)

TVV2=THETA(3)

TVV3=THETA(4)

TVCL=THETA(5)

CLW=(WT/15.6)**THETA(6)

V2W=(WT/15.6)**THETA(7)
TVFT=THETA(8) ; F TABLET
TVFS=THETA(9) ; F SOLUTION

IF (FLAG.EQ.0) THEN
TVF=1
ELSE
TVF= (1-FORM)*TVFS + FORM*TVFT
ENDIF

KA=TVKA
Q=TVVQ*EXP(ETA(1))
V2=(TVV2*V2W)*EXP(ETA(2))
V3=(TVV3)*EXP(ETA(3))
CL=(TVCL*CLW)*EXP(ETA(4)+OCCCL)
F1=TVF
S2=V2

\$ERROR
DEL=0
IF (F.EQ.0) DEL=1
W=F+DEL
Y=F*EXP(ERR(1))
IPRED=F
IRES=DV-IPRED
IWRES=IRES/W

Table S7. DTG PopPK NONMEM Code

\$PROBLEM
\$INPUT
\$DATA
\$SUBROUTINES ADVAN2 TRANS2
\$PK

IF (FORM.EQ.3) THEN
FORMK=1
ELSE
FORMK=0
ENDIF

PMA=AGE*52+40
HILL=THETA(7)
TM50=THETA(8)
FMAT=(PMA**HILL/(PMA**HILL+TM50**HILL))

TVCL = THETA(1)
TVV = THETA(2)
TVKA = THETA(3)
TVF1 = THETA(4)

```

CL = TVCL*FMAT*((WT/70)**THETA(5))*EXP(ETA(1)+ETA(4))
V = TVV*((WT/70)**THETA(6))*EXP(ETA(2))
KA = TVKA*(THETA(9)**FORMK)*EXP(ETA(3)+ETA(5))
F1 = TVF1*FORMK + 1*(1-FORMK)
S2 = V
$ERROR
DEL=0
IF (F.EQ.0) DEL=1
W=F+DEL

IPRED=F
IRES=DV-IPRED
IWRES=IRES/W

Y = F + F*ERR(1)+ERR(2)

```

Table S8. 3TC PopPK NONMEM Code

```

$PROBLEM
$INPUT
$DATA
$SUBROUTINES ADVAN2 TRANS2
$PK
ROUTE=1
FORM=1
OCC1=0
IF (OCC.EQ.1) OCC1 = 1
OCC2=0
IF (OCC.EQ.2) OCC2 = 1
OCC3=0
IF (OCC.EQ.3) OCC3 = 1
OCCCL = OCC1 * ETA(4) + OCC2 * ETA(5) + OCC3 * ETA(6)
OCCKA = OCC1 * ETA(7) + OCC2 * ETA(8) + OCC3 * ETA(9)
OCCV = OCC1 * ETA(10) + OCC2 * ETA(11) + OCC3 * ETA(12)
CLW=(WGHT/18.5)**THETA(6) ; wt as covariate
VWT=(WGHT/18.5)**THETA(7)
TVCL= THETA(1)*CLW
TVV=THETA(2)*VWT
TVKA=THETA(3)
CL=TVCL*EXP(ETA(1)+OCCCL)
V=TVV*EXP(ETA(2)+OCCV)
KA=TVKA*EXP(ETA(3)+OCCKA)
ALAG1= THETA(4)

```

```
FSOL = THETA(8) ; F1 SOLUTION
FTAB = THETA(9) ; F1 TABLET
IF (ROUTE.EQ.0) THEN
F1 =1 ; iv
ELSE
F1= (1-FORM)*FSOL + FTAB*FORM
ENDIF
S2=V
$ERROR
DEL=0.015
IF (F.EQ.0) DEL=1
W=F+DEL
WT=THETA(5)**2
ROOT=SQRT(1+WT*(F**2))
Y=F+EPS(1)*ROOT
IPRED=F
IRES=DV-IPRED
IWRES=IRES/W

LQ=0.0025
TDV=DV
IF(TDV.LT.LQ) TDV=LQ
```