

Article

Development of a population pharmacokinetic model of busulfan in children and evaluation of different sampling schedules for precision dosing

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Table S1. Parameter estimates using the base PopPK model.

PK parameter	NONMEM Estimation			Bootstrap Analysis			
	Estimate	SE	RSE%	Mean	SD	CV%	CI (2.5%–97.5%)
CL (L/h)	4.99	0.348	6.97	4.94	0.365	7.38	4.35-5.69
V ₁ (L)	13.9	1.37	9.86	13.98	1.48	10.57	11.3-17.18
V ₂ (L)	3.69	0.466	12.63	3.88	0.71	18.24	2.95-5.88
Q (L/h)	1.55	0.130	8.39	1.51	0.16	10.56	1.19-1.80
CL IIV	0.60	0.0358	5.97	59.2	0.03	5.68	0.53-0.65
V ₁ IIV	0.67	0.0703	10.49	77.5	0.08	9.90	0.63-0.91
Cor. CL-V ₁	0.94	0.0268	2.85	0.94	0.03	2.68	0.89-0.99
CL IOV	0.11	0.0150	13.64	11.5	0.01	12.99	0.09-0.14
V ₁ IOV	0.18	0.0648	36.00	17.9	0.06	32.77	0.07-0.29
Prop. RE*	0.114	0.00977	8.57	0.11	11.2	9.73	0.08-0.13
Add. RE*	0.0229	0.011	48.03	0.03	0.01	35.52	0.01-0.04

*RE= residual error.

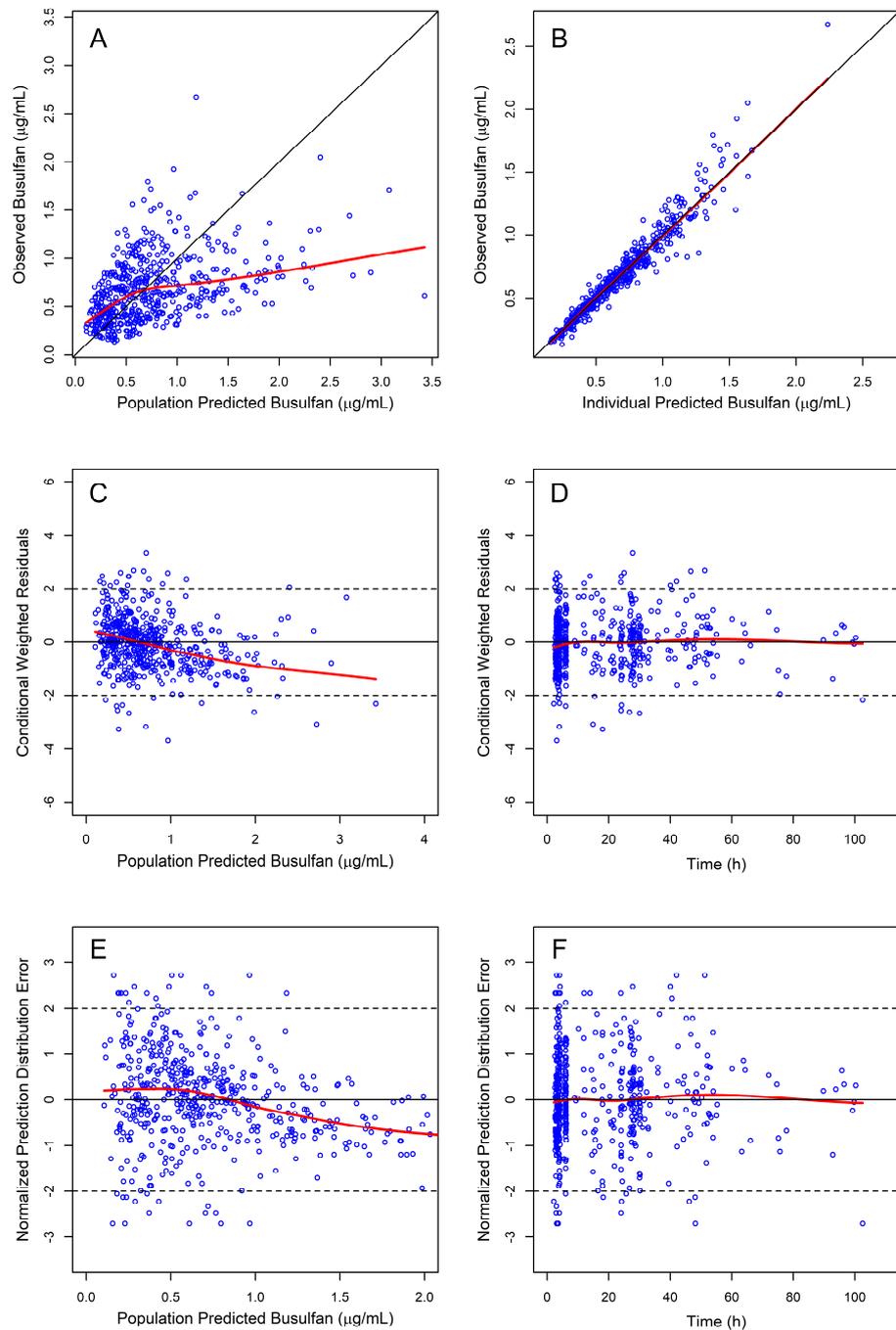


Figure S1. Diagnostic plots for the Base PopPK model. Observed vs population predicted plasma concentrations (A) and individual predicted plasma concentrations (B) plots (black and red lines represent the identity and cubic spline smooth lines, respectively). Conditional weighted residuals vs population predicted plasma concentrations (C) and vs TIME (D) (solid line $y = 0$, dashed lines $y = 2$ and $y = -2$). Normalized Prediction Distribution Error vs population predicted plasma concentrations (E) and vs Time (F).

NONMEM Control script

```

$PROBLEM Busulfan Final Model
$INPUT ID TIME DV EVID AMT TLAG RATE BW MDV OCC

$DATA Busulfan_Data.csv IGNORE=#
$SUBROUTINES ADVAN3 TRANS4

$PK
  IF(NEWIND.LT.2) THEN
    IFL=0
    TAD=0.0
  ENDIF

  IF(EVID.EQ.1.OR.EVID.EQ.4) THEN
    TDOS=TIME
    TAD=0.0
    IFL=1
  ENDIF

  IF(IFL.EQ.1.AND.EVID.NE.1.AND.EVID.NE.4)TAD=TIME-TDOS

  OC1 = 0
  OC2 = 0
  OC3 = 0
  OC4 = 0
  OC5 = 0
  IF (OCC.EQ.1) OC1=1
  IF (OCC.EQ.2) OC2=1
  IF (OCC.EQ.3) OC3=1
  IF (OCC.EQ.4) OC4=1
  OCC1 = OC1*ETA(3) + OC2*ETA(4) + OC3*ETA(5)

  TCL=THETA(1)
  A=(BW/70)**THETA(5)
  CL=TCL * A * EXP(ETA(1))* EXP(OCC1)
  TV1=THETA(2)*(BW/70)**THETA(6)
  V1=TV1*EXP(ETA(2))
  V2=THETA(3)*(BW/70)
  Q=THETA(4)*(BW/70)**THETA(5)

  ALAG1=Tlag
  S1=V1

$THETA (0 11)
  (0 41)
  (0 3.77)
  (0 1.49)
  (0 0.75) FIX
  (0 1) FIX

$OMEGA BLOCK(2) 0.0697 0.0662 0.106

$OMEGA BLOCK(1) 0.0125
$OMEGA BLOCK(1) SAME
$OMEGA BLOCK(1) SAME

```

```
$$SIGMA 0.0136
```

```
$ERROR
```

```
  IPRED=F
```

```
  Y=F+F*EPS(1)
```

```
  IRES=DV-IPRED
```

```
  IWRES=IRES/IPRED
```

```
$ESTIMATION METHOD=1 INTERACTION MAXEVAL=9999 PRINT=2
```

```
$TABLE ID TIME AMT IPRED EVID MDV IWRES CWRES NPDE NOPRINT ONEHEADER  
FILE=sdtab1
```

```
$TABLE ID CL V1 V2 Q NOPRINT ONEHEADER FILE=patab1
```