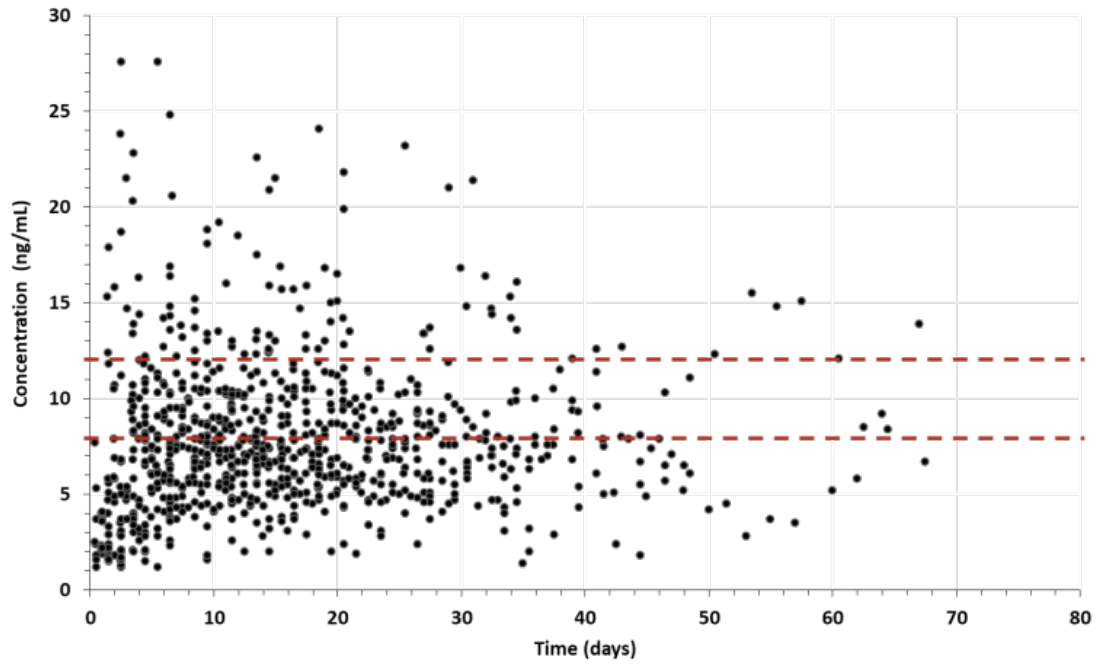


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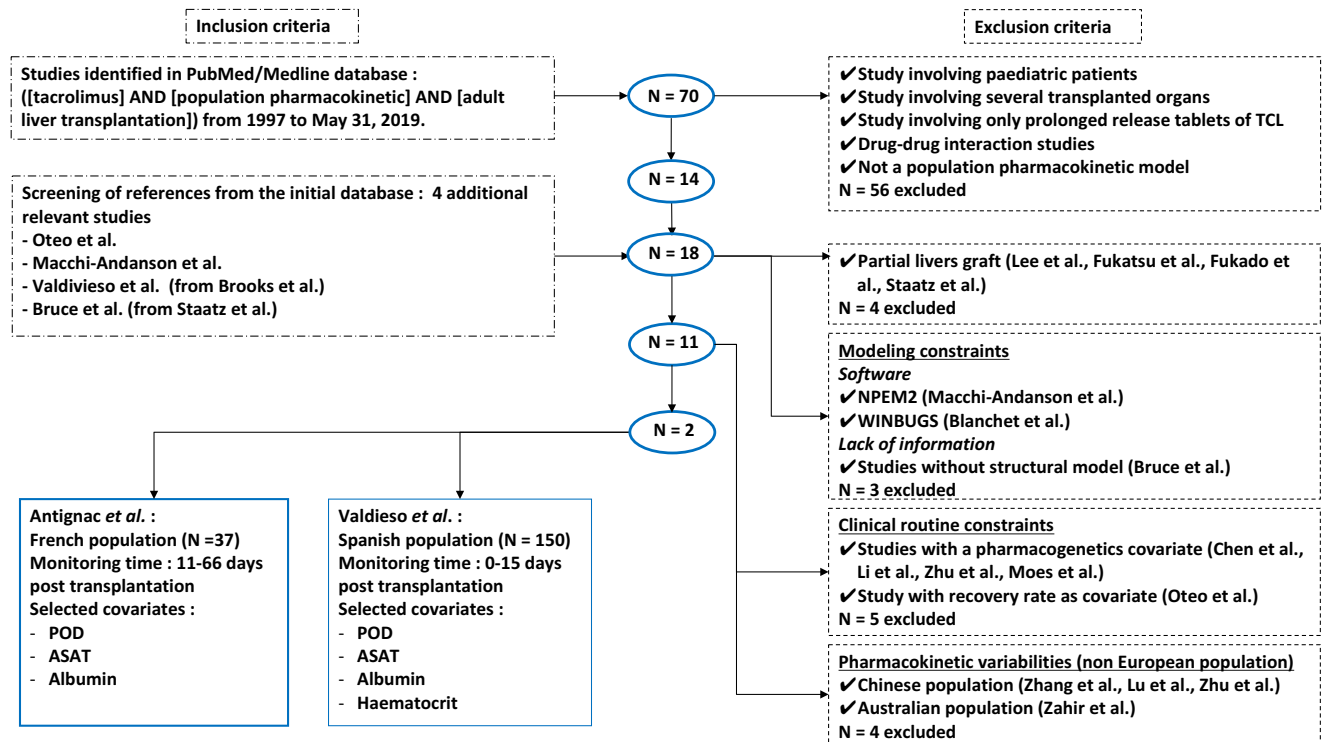
SupData_Document1. Observed concentrations versus time (851 observations, 79 patients). Therapeutic interval is represented by dashed lines.



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SupData_Document2. Selection procedure for articles considered in the current review, with N = number of selected or removed articles at each step or sub-step.



Among the 18 reviewed models, five established a PopPK model with rich samples (Blanchet et al., 2008; Chen et al., 2017; Lu et al., 2015; Staatz et al., 2003; Zhu et al., 2014). The PopPK structure model was linear one-compartment (Antignac et al., 2005; Bruce et al., 1995; Fukatsu et al., 2001; Fukudo et al., 2003; Li et al., 2007; Macchi-Andanson et al., 2001; Moes et al., 2016; Oteo et al., 2013; Staatz et al., 2003; Valdivieso et al., 2013; Zahir et al., 2005; Zhang et al., 2012; Zhu et al., 2015) or two-compartment (Blanchet et al., 2008; Chen et al., 2017; Lu et al., 2015; Zhu et al., 2014) with first-order absorption and elimination. Several covariates were found to have a significant effect on the pharmacokinetics of TCL. The most frequently identified covariate was POD, influencing CL/F and sometimes apparent volume of distribution (V/F) (Antignac et al., 2005; Chen et al., 2017; Fukatsu et al., 2001; Fukudo et al., 2003; Lee et al., 2006; Oteo et al., 2013; Valdivieso et al., 2013; Zhu et al., 2014, 2015). Other identified covariates were haematocrit, ALB, total bilirubin, haemoglobin, ASAT, ALAT, total protein, factor V, serum creatinine, creatinine clearance, TCL daily dose, age, height, CYP3A5 genotype of both recipients and donors, recipient genetic polymorphisms of ABCB1, co-medication (diltiazem, fluconazole or sulfonylurea), graft to recipient body weight ratio (GRWR = Weight of transplant liver/Total body weight) and recovery rate.

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SupData_Document3. Control files.

```
$PROBLEM      Literature model of Antignac et al. for Bayesian predictions
$INPUT        ID TIME DV AMT MDV CMT POD ASAT ALB MOL POD1 NBDV
$SUBROUTINE   ADVAN2 TRANS2
$PK

      ETCLMAX  = ETA(1)
      ETV      = ETA(2)
      ETTCL50  = ETA(3)

TVCLMAX =THETA(1) * EXP(ETA(1))
V =THETA(2) * EXP(ETA(2))
TVTCL50 =THETA(3)* EXP(ETA(3))
KA =THETA(4)
GAMMA =THETA(5)
THASAT =THETA(6)
THALB =THETA(7)

TCL50=TVTCL50*(ASAT/46)**THETA(6)
CLMAX=TVCLMAX*(ALB/38)**(-THETA(7))

CL=(CLMAX*(POD)**GAMMA)/((TCL50)**GAMMA+(POD)**GAMMA)

;IF(CL.EQ.0) CL = 10

S2=V; SCALE

$ERROR

      Y = F + ERR(1)
      TOTO = 0
      IF (F.EQ.0) TOTO = 1
      W = F
      IPRED = F
      IRES = DV - IPRED
      IWRES = IRES * ( 1 - TOTO ) / ( W + TOTO )

$THETA 36 FIX
$THETA 1870 FIX
$THETA 6.3 FIX
$THETA 4.48 FIX
$THETA 4.9 FIX
$THETA 0.28 FIX
$THETA 0.64 FIX
$OMEGA BLOCK(2) FIX
0.19
0.116 0.24
$OMEGA BLOCK(1) FIX
0.11
$SIGMA 5.93172 ; estimated SIGMA on ds_est
$ESTIMATION METHOD=1 MAXEVAL=0 PRINT=5 NOABORT NSIG=3
```

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```
$PROBLEM      Tweaked model F for Bayesian predictions
$INPUT        ID TIME DV AMT MDV CMT POD ASAT ALB MOL POD1 NBDV
$SUBROUTINE   ADVAN2 TRANS2
$PK

      ETCLMAX   = ETA(1)
      ETV       = ETA(2)
      ETTCL50   = ETA(3)

TVCLMAX =THETA(1) * EXP(ETA(1))
V =THETA(2) * EXP(ETA(2))
TVTCL50 =THETA(3)* EXP(ETA(3))
KA =THETA(7)
GAMMA =THETA(4)
THASAT =THETA(5)
THALB =THETA(6)

TCL50=TVTCL50*(ASAT/46)**THASAT
CLMAX=TVCLMAX*(ALB/38)**(-THALB)

CL=(CLMAX*(POD)**GAMMA)/((TCL50)**GAMMA+(POD)**GAMMA)

;IF(CL.EQ.0) CL = 10

S2=V; SCALE

$ERROR

      Y = F + ERR(1)
      TOTO = 0
      IF (F.EQ.0) TOTO = 1
      W = F
      IPRED = F
      IRES = DV - IPRED
      IWRES = IRES * ( 1 - TOTO ) / ( W + TOTO )

$THETA (0,33.0893) ; TVCLMAX
$THETA (0,1867.55) ; V
$THETA (0,6.05626) ; TVTCL50
$THETA (0,3.09924) ; GAMMA
$THETA (0,0.0807805) ; THASAT
$THETA (0,0.0064) ; THALB
$THETA 4.48 FIX ; KA
$OMEGA BLOCK(2)
      0.286419
      0.236591 0.492555
$OMEGA 0.123674
$SIGMA 6.21781

$ESTIMATION METHOD=1 MAXEVAL=0 PRINT=5 NOABORT NSIG=3
```

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```
$PROBLEM      Tweaked model 0 for Bayesian predictions
$INPUT        ID TIME DV AMT MDV CMT POD ASAT ALB MOL POD1 NBDV

$DATA         tdm_pred_0.csv IGNORE=@
$SUBROUTINE   ADVAN2 TRANS2 ; 1 cpt voie orale
$PK

      ETCLMAX  = ETA(2)
      ETV      = ETA(3)
      ETTCL50  = ETA(1)

CLMAX =THETA(1) * EXP(ETA(2))
V      =THETA(2) * EXP(ETA(3))
TCL50  =THETA(3) * EXP(ETA(1))
KA      =THETA(5)
GAMMA  =THETA(4)

CL=(CLMAX*(POD)**GAMMA)/((TCL50)**GAMMA+(POD)**GAMMA)

;IF(CL.EQ.0) CL = 10

S2=V; SCALE

$ERROR

      Y = F + ERR(1)
      TOTO = 0
IF (F.EQ.0) TOTO = 1
      W = F
      IPRED = F
      IRES = DV - IPRED
      IWRES = IRES * ( 1 - TOTO ) / ( W + TOTO )

$THETA (0,24.652) ; TVCLMAX
$THETA (0,1098.51) ; V
$THETA (0,4.85118) ; TVTCL50
$THETA (0,2.8745) ; GAMMA
$THETA 4.48 FIX ; KA
$OMEGA BLOCK(2)
      0.244481
      0.154323 0.460293
$SIGMA 6.15874

$ESTIMATION METHOD=1 MAXEVAL=0 PRINT=5 NOABORT NSIG=3
```

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```
$PROBLEM      Model with Full informative priors to tweak the model on the estimation
dataset (ds_est) and get the tweaked model F
$INPUT        ID TIME DV AMT MDV CMT POD ASAT ALB MOL POD1 NBDV
$PRIOR        NWPRI
$$SUBROUTINE  ADVAN2 TRANS2
$PK

      ETCLMAX  = ETA(1)
      ETV      = ETA(2)
      ETTCL50  = ETA(3)

TVCLMAX =THETA(1) * EXP(ETA(1))
V =THETA(2) * EXP(ETA(2))
TVTCL50 =THETA(3)* EXP(ETA(3))
KA =THETA(7)
GAMMA =THETA(4)
THASAT =THETA(5)
THALB =THETA(6)

TCL50=TVTCL50*(ASAT/46)**THASAT
CLMAX=TVCLMAX*(ALB/38)**(-THALB)

CL=(CLMAX*(POD)**GAMMA)/((TCL50)**GAMMA+(POD)**GAMMA)

;IF(CL.EQ.0) CL = 10

S2=V; SCALE

$ERROR

      Y = F + ERR(1)
      TOTO = 0
IF (F.EQ.0) TOTO = 1
      W = F
      IPRED = F
      IRES = DV - IPRED
      IWRES = IRES * ( 1 - TOTO ) / ( W + TOTO )

$THETA  (0,36) ; TVCLMAX
$THETA  (0,1870) ; V
$THETA  (0,6.3) ; TVTCL50
$THETA  (0,4.9) ; GAMMA
$THETA  (0,0.28) ; THASAT
$THETA  (0,0.64) ; THALB
$THETA  4.48 FIX ; KA
$OMEGA  BLOCK(2)
      0.19
      0.116 0.24
$OMEGA  0.11
$SIGMA  9.4

; =====
; PRIOR INFORMATION
; =====
$THETAP 36 FIX
      1870 FIX
```


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```
6.3 FIX
4.9 FIX
0.28 FIX
0.64 FIX
$THETAPV BLOCK(6) FIX
3
0 295
0 0 0.6
0 0 0 1.1
0 0 0 0 0.12
0 0 0 0 0 0.66
$OMEGAP BLOCK(2) FIX
0.19
0.116 0.24
$OMEGAP 0.11 FIX
$OMEGAPD 19 FIX
7.72 FIX
; =====
$ESTIMATION METHOD=1 MAXEVAL=9999 PRINT=5 NOABORT NSIG=3
$COVARIANCE MATRIX=R PRINT=E UNCONDITIONAL
```

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```
$PROBLEM      Model with Optimization by minimization of the prior information to
tweak the model on the estimation dataset (ds_est) and get the tweaked model O
$INPUT       ID TIME DV AMT MDV CMT POD ASAT ALB MOL POD1 NBDV
$PRIOR       NWPRI
$DATA        ds_est.csv IGNORE=@
$SUBROUTINE  ADVAN2 TRANS2 ; 1 cpt voie orale
$PK

ETCLMAX      = ETA(2)
ETV          = ETA(3)
ETTCL50      = ETA(1)

CLMAX =THETA(1) * EXP(ETA(2))
V =THETA(2) * EXP(ETA(3))
TCL50 =THETA(3) * EXP(ETA(1))
KA =THETA(5)
GAMMA =THETA(4)

CL=(CLMAX*(POD)**GAMMA)/((TCL50)**GAMMA+(POD)**GAMMA)

;IF(CL.EQ.0) CL = 10

S2=V; SCALE

$ERROR

Y = F + ERR(1)
TOTO = 0
IF (F.EQ.0) TOTO = 1
W = F
IPRED = F
IRES = DV - IPRED
IWRES = IRES * ( 1 - TOTO ) / ( W + TOTO )

$THETA (0,36) ; TVCLMAX
$THETA (0,1870) ; V
$THETA (0,6.3) ; TVTCL50
$THETA (0,4.9) ; GAMMA
$THETA 4.48 FIX ; KA
$OMEGA 0.11
$OMEGA BLOCK(2)
0.19
0.116 0.24
$SIGMA 9.4

; =====
; PRIOR INFORMATION
; =====
$OMEGAP 0.11 FIX
$OMEGAPD 2 FIX
; =====
$ESTIMATION METHOD=1 MAXEVAL=9999 PRINT=5 NOABORT NSIG=3
$COVARIANCE MATRIX=R PRINT=E UNCONDITIONAL
```

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SupData_Document4. Comparison of population pharmacokinetic parameters of the literature model (by Antignac et al.) and the tweaked models F and O. SE: standard error of the estimate; TV(CLmax), TV(V), TV(TCL50) and TV(γ): typical values of CLmax, V, TCL50, and γ , respectively; θ ALB and θ ASAT: influential factors for ALB and ASAT, respectively; ω^2 : inter-subject variance; $r\{CL\max, V$: correlation coefficient between $\omega^2(CLmax)$ and $\omega^2(V)$.

Parameter	Literature model		Tweaked model F		Tweaked model O	
	Mean	SE	Mean	SE	Mean	SE
Structural model						
TV(CLmax) (l/h)	36	3	33*	1.5	25	1.8
TV(V) (l)	1,870	295	1,870*	17.2	1,100	146
Ka, fixed (h ⁻¹)	4.48	–	4.48	–	4.48	–
TV (TCL50) (day)	6.3	0.6	6.1*	0.4	4.9	0.5
TV (γ)	4.9	1.1	3.1*	0.8	2.9	0.6
θ ASAT	0.28	0.12	0.08*	0.09	–	–
θ ALB	0.64	0.66	0.01*	10⁻⁷	–	–
Statistical model						
Residual variance, σ^2	9.4	1.9	6.2*	0.5	6.2	0.4
$\omega^2 \{CL\max$	0.19	0.04	0.29*	0.05	0.25	0.05
$\omega^2 V$	0.24	0.08	0.49*	0.10	0.46	0.12
ω^2 TCL50	0.11	0.06	0.12*	0.04	0.18**	0.08
$r\{CL\max, V$	0.55	0.24	0.24*	0.06	0.15	0.06

*estimated with informative priors

**estimated with non informative priors

Significant numbers are those of the published literature model