**Quantification of the time course of CYP3A inhibition, activation, and induction using a population pharmacokinetic model of microdosed midazolam continuous infusion**

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**NONMEM code of the joint midazolam and 1'-hydroxymidazolam population pharmacokinetic model**

```
$INPUT      ID              ;individual number
            SEX
            AGE
            HT              ;height [m]
            WT              ;weight [kg]
            BMI             ;body mass index [kg/m2]
            TIME
            TINF            ;time of midazolam infusion [h]
            RATE            ;rate of midazolam infusion [ug/h]
            AMT             ;amount of midazolam administered [ug]
            ADM             ;order of administration
            EVID
            MDV
            DV
            DVTYPE          ;type of analyte
            CMT             ;compartment identifier
            FLAGMED         ;flag according to perpetrator

$SUBROUTINES ADVAN6 TOL=3

$MODEL   NCOMP=2
COMP=(CENTRAL,DEFOBS)    ;COMPARTMENT FOR MDZ
COMP=(METAB)            ;COMPARTMENT FOR 1'-OH-MDZ

$PK
;------------------------------------------------------------------------
; Covariate impact: Time here is relative to midazolam administration
;------------------------------------------------------------------------
;Placebo/no perpetrator
IF(TIME.LT.2.OR.FLAGMED.EQ.1) CLFLAGMED = 1  ;placebo

;[A] Efavirenz
IF(TIME.GT.2.AND.TIME.LE.4.AND.FLAGMED.EQ.2) CLFLAGMED = ( 1 + THETA(6))
IF(TIME.GT.4.AND.TIME.LE.5.AND.FLAGMED.EQ.2) CLFLAGMED = ( 1 + THETA(7))
IF(TIME.GT.5.AND.TIME.LE.6.AND.FLAGMED.EQ.2) CLFLAGMED = ( 1 + THETA(8))
IF(TIME.GT.6.AND.TIME.LE.7.AND.FLAGMED.EQ.2) CLFLAGMED = ( 1 + THETA(9))
IF(TIME.GT.7.AND.TIME.LE.8.AND.FLAGMED.EQ.2) CLFLAGMED = ( 1 + THETA(10))
IF(TIME.GT.8.AND.FLAGMED.EQ.2) CLFLAGMED            = 1

;[B] Rifampicin
IF(TIME.LE.24.AND.FLAGMED.EQ.3) CLFLAGMED = 1
IF(TIME.GT.24.AND.TIME.LE.26.AND.FLAGMED.EQ.3) CLFLAGMED = ( 1 + THETA(11))
IF(TIME.GT.26.AND.TIME.LE.28.AND.FLAGMED.EQ.3) CLFLAGMED = ( 1 + THETA(12))
IF(TIME.GT.28.AND.TIME.LE.30.AND.FLAGMED.EQ.3) CLFLAGMED = ( 1 + THETA(13))
IF(TIME.GT.30.AND.TIME.LE.32.AND.FLAGMED.EQ.3) CLFLAGMED = ( 1 + THETA(14))
IF(TIME.GT.32.AND.FLAGMED.EQ.3) CLFLAGMED                = ( 1 + THETA(15))

;[C] Voriconazole oral
IF(TIME.GT.2.AND.TIME.LE.3.AND.FLAGMED.EQ.4) CLFLAGMED = ( 1 + THETA(16))
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IF(TIME.GT.3.AND.TIME.LE.4.AND.FLAGMED.EQ.4) CLFLAGMED = ( 1 + THETA(17))
IF(TIME.GT.4.AND.TIME.LE.5.AND.FLAGMED.EQ.4) CLFLAGMED = ( 1 + THETA(18))
IF(TIME.GT.5.AND.TIME.LE.6.AND.FLAGMED.EQ.4) CLFLAGMED = ( 1 + THETA(19))
IF(TIME.GT.6.AND.TIME.LE.7.AND.FLAGMED.EQ.4) CLFLAGMED = ( 1 + THETA(20))
IF(TIME.GT.7.AND.TIME.LE.8.AND.FLAGMED.EQ.4) CLFLAGMED = ( 1 + THETA(21))
IF(TIME.GT.8.AND.TIME.LE.9.AND.FLAGMED.EQ.4) CLFLAGMED = ( 1 + THETA(22))
IF(TIME.GT.9.AND.FLAGMED.EQ.4) CLFLAGMED              = ( 1 + THETA(23))

;[D] Voriconazole i.v
IF(TIME.GT.2.AND.TIME.LE.3.AND.FLAGMED.EQ.5) CLFLAGMED = ( 1 + THETA(24))
IF(TIME.GT.3.AND.TIME.LE.5.AND.FLAGMED.EQ.5) CLFLAGMED = ( 1 + THETA(25))
IF(TIME.GT.5.AND.TIME.LE.6.AND.FLAGMED.EQ.5) CLFLAGMED = ( 1 + THETA(26))
IF(TIME.GT.6.AND.TIME.LE.7.AND.FLAGMED.EQ.5) CLFLAGMED = ( 1 + THETA(27))
IF(TIME.GT.7.AND.TIME.LE.8.AND.FLAGMED.EQ.5) CLFLAGMED = ( 1 + THETA(28))
IF(TIME.GT.8.AND.TIME.LE.9.AND.FLAGMED.EQ.5) CLFLAGMED = ( 1 + THETA(29))
IF(TIME.GT.9.AND.FLAGMED.EQ.5) CLFLAGMED              = ( 1 + THETA(30))


;-------------
; Parent (MDZ)
;-------------
; Parent clearance
TVCL = THETA(1) * CLFLAGMED
CL   = TVCL * EXP(ETA(1))
; Parent volume of distribution
TVV1 = THETA(2)
V1   = TVV1 * EXP(ETA(2))


;----------------------
; Metabolite (1'-OH-MDZ)
;----------------------
; Metabolite clearance
TVCLM = THETA(3)
CLM   = TVCLM * EXP(ETA(3))
; Metabolite volume of distribution
TVV2  = THETA(4)
V2    = TVV2 * EXP(ETA(4))

;Fraction metabolized
FMET = THETA(5)

S1   = V1/1000     ; change from mL to L
S2   = V2/1000


;-------------Rate constants-------------------------
k10 = (1-FMET) * CL/V1
K12 = FMET * CL/V1
K20 = CLM/V2


$DES
DADT(1) = -K10*A(1)-K12*A(1)
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```
DADT(2) =  K12*A(1)*(341.77/325.78)-K20*A(2)      ;(341.77/325.78)
                                                  ; metabolite/parent ratio


$ERROR
IF(CMT.EQ.1) IPRED = A(1)/S1
IF(CMT.EQ.2) IPRED = A(2)/S2

;Proportional RUV
W   = IPRED
Y1  = IPRED + W*EPS(1)      ;parent
Y2  = IPRED + W*EPS(2)      ;metabolite


IF(CMT.EQ.1) TYPE=0   ;parent
IF(CMT.EQ.2) TYPE=1   ;metabolite


Y   = Y2*TYPE + Y1*(1-TYPE)


IRES  = DV-IPRED
DEL   = 0
IF(IPRED.EQ.0)DEL = 0.0001
IWRES = IRES/(W+DEL)

;-------------Initial estimates---------------------------
$THETA (0,44)             ;1. CL_parent [L/h]
$THETA (0.0001,56)        ;2. V_parent [L]
$THETA (0,240)            ;3. CL_metabolite [L/h]
$THETA (0.001,286)        ;4. V2_metabolite [L]
$THETA  0.92 FIX          ;5. Fraction metabolised

;A. cov efavirenz-CLFLAGMED2
(0,0.15)  ; CLFLAGMED2  2-4
(0,0.59)  ; CLFLAGMED2  4-5
(0,0.54)  ; CLFLAGMED2  5-6
(0,0.28)  ; CLFLAGMED2  6-7
(0,0.33)  ; CLFLAGMED2  7-8

;B. cov rifampicin-CLFLAGMED3
(0,0.27) ; CLFLAGMED3  24-26
(0,0.17) ; CLFLAGMED3  26-28
(0,0.23) ; CLFLAGMED3  28-30
(0,0.46) ; CLFLAGMED3  30-32
(0,0.1)  ; CLFLAGMED3  32-36

;C. cov voriconazole oral-CLFLAGMED4
(-1,-0.4,0)   ; CLFLAGMED4  2-3
(-1,-0.3,0)   ; CLFLAGMED4  3-4
(-1,-0.23,0)  ; CLFLAGMED4  4-5
(-1,-0.32,0)  ; CLFLAGMED4  5-6
(-1,-0.64,0)  ; CLFLAGMED4  6-7
(-1,-0.54,0)  ; CLFLAGMED4  7-8
(-1,-0.70,0)  ; CLFLAGMED4  8-9
(-1,-0.7,0)   ; CLFLAGMED4  9-10
```

```
;D. cov voriconazole i.v-CLFLAGMED5
(-1,-0.16,0)   ; CLFLAGMED5   2-3
(-1,-0.11,0)   ; CLFLAGMED5   3-5
(-1,-0.15,0)   ; CLFLAGMED5   5-6
(-1,-0.36,0)   ; CLFLAGMED5   6-7
(-1,-0.39,0)   ; CLFLAGMED5   7-8
(-1,-0.6,0)    ; CLFLAGMED5   8-9
(-1,-0.58,0)   ; CLFLAGMED5   9-10


$OMEGA  0.04      ; IIV_CL_parent
$OMEGA  0.09      ; IIV_V_parent
$OMEGA  0.18      ; IIV_CL_metabolite
$OMEGA  0.15      ; IIV_V2_metabolite

$SIGMA  0.02      ; 1. Parent Prop RUV
$SIGMA  0.05      ; 2. Metabolite Prop RUV

$ESTIMATION METHOD=1 INTERACTION MAXEVAl=9999 SIG=3 NOABORT PRINT=5

$COV
```