Electronic Supplemental Materials

Title: A Model-Informed Method for the Purpose of Precision Dosing of Isoniazid in Pulmonary Tuberculosis

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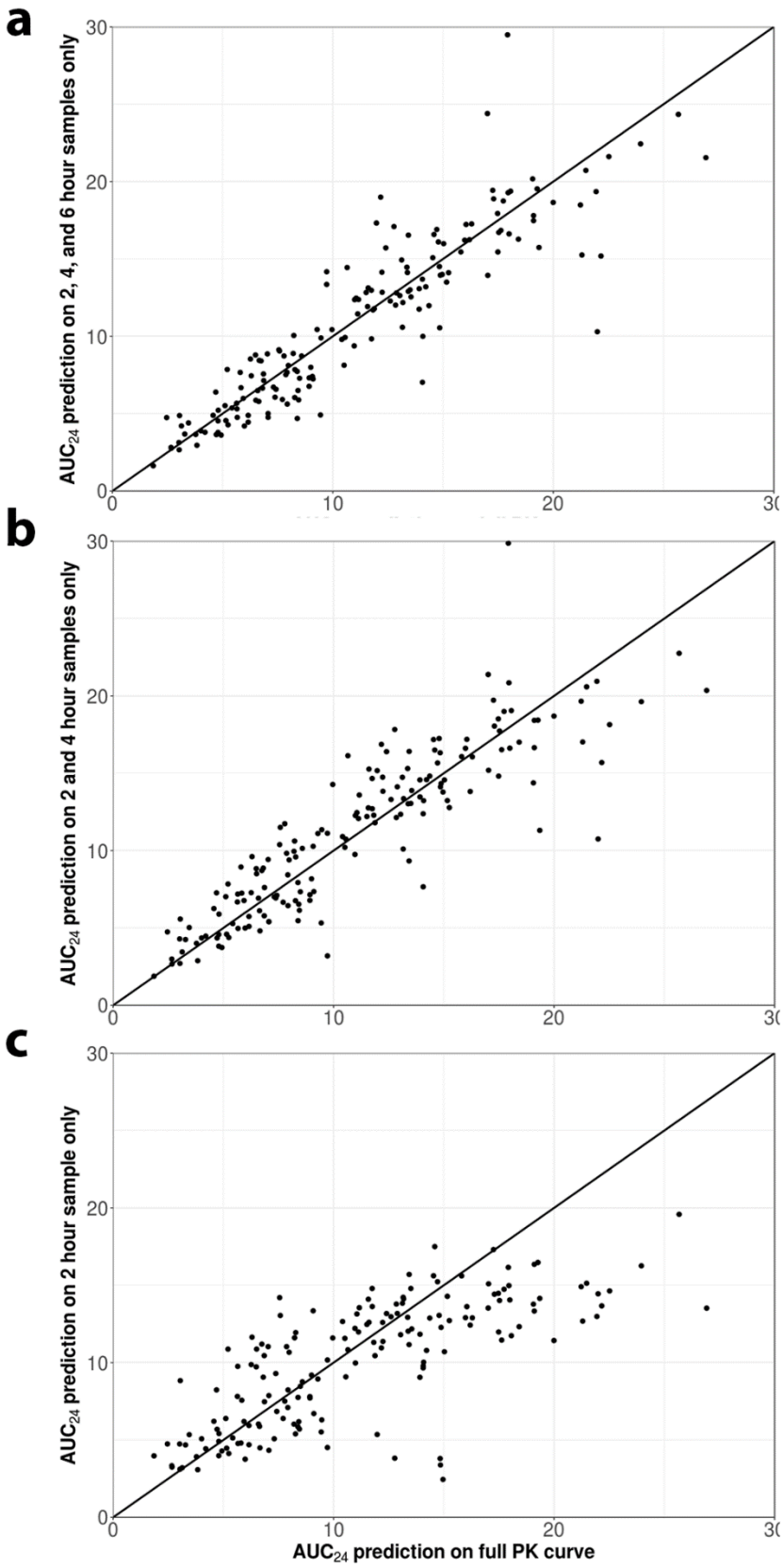
Captions:

ESM 1. Scatterplots of the AUC_{24} prediction versus the prediction on the full pharmacokinetic curve for the limited sampling strategies using sampling **(a)** at 2, 4 and 6 hours after dosing, **(b)** at 2 and 4 hours after dosing, and **(c)** at 2 hours after dosing.
AUC_{24} area under the concentration time curve from 0 to 24 hours after dosing, *PK* pharmacokinetic

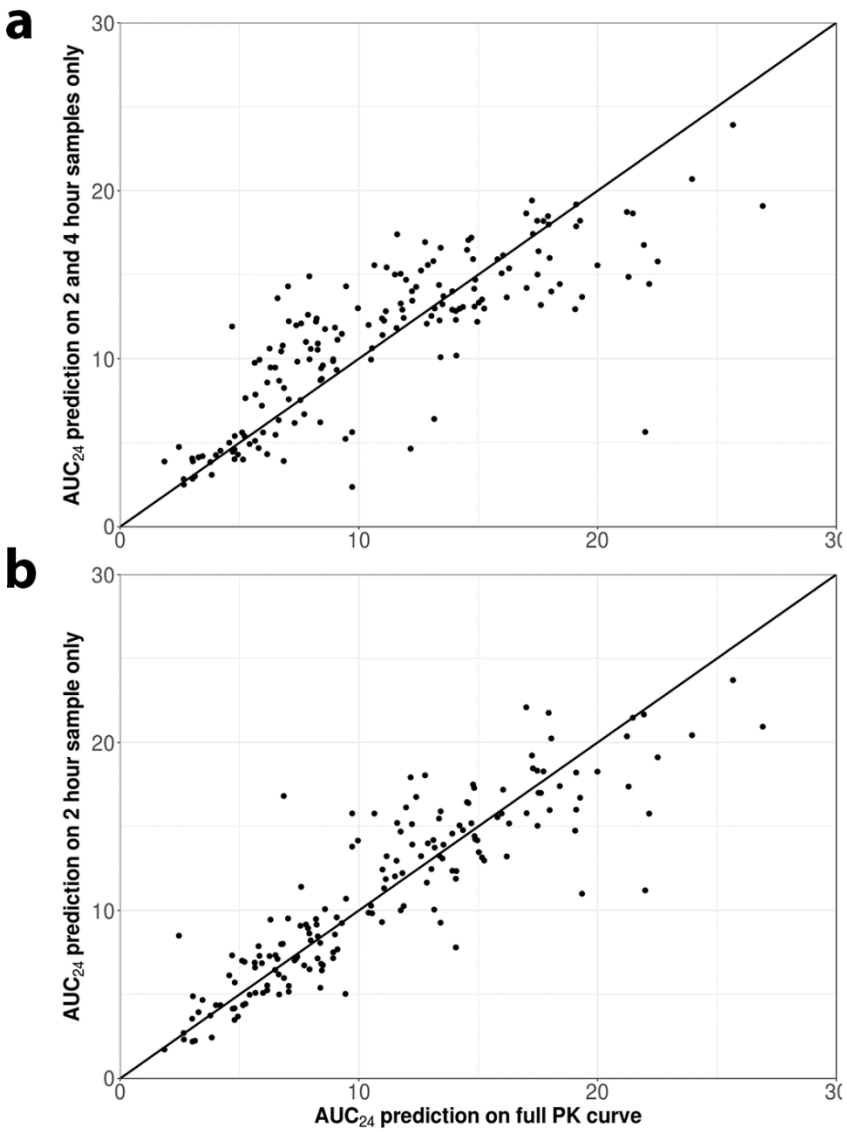
ESM 2. Prediction of the AUC_{24} using the 2 and 4 hour sampling strategy versus AUC_{24} prediction on the full pharmacokinetic curve for **(a)** the final model without acetyl-isoniazid data, and **(b)** the re-estimated model without mixture component.
AUC_{24} area under the concentration time curve from 0 to 24 hours after dosing, *PK* pharmacokinetic

ESM 3. NONMEM control stream of the population pharmacokinetic model of isoniazid and acetyl-isoniazid

ESM 1


a
b
c
AUC24 prediction on 2, 4, and 6 hour samples only
AUC24 prediction on 2 and 4 hour samples only
AUC24 prediction on 2 hour sample only
AUC24 prediction on full PK curve
0
10
20
30

ESM 2


a
b
AUC24 prediction on 2 and 4 hour samples only
AUC24 prediction on 2 hour sample only
AUC24 prediction on full PK curve
0
10
20
30

ESM 3

```
$SUBROUTINE ADVAN5

$MODEL
COMP=(DOSE,DEFDOSE)
COMP=(CENTRAL,DEFOBS)
COMP=(TRANSIT1)
COMP=(TRANSIT2)
COMP=(TRANSIT3)
COMP=(TRANSIT4)
COMP=(PERIPH)
COMP=(LIVER)
COMP=(ACINH)

$MIX
NSPOP=2
P(1) = THETA(8)
P(2) = 1-THETA(8)

$PK
FFM2= FFM
IF(FFM.EQ.-99) FFM2 = 45

FCL = (FFM2/45)**0.75
FV  = (FFM2/45)**1

TVV     = THETA(1) * FV
TVCLF   = THETA(2) * FCL
TVCLS   = THETA(9) * FCL
TVKA    = THETA(3)
TVV2    = THETA(4) * FV
TVQ     = THETA(5) * FCL
TVVM    = THETA(6) * FV
TVCLM   = THETA(7) * FCL
TVCLO   = THETA(10)* FCL

V                       = TVV*EXP(ETA(1))
IF(MIXNUM.EQ.1) CL      = TVCLF*EXP(ETA(5))
IF(MIXNUM.EQ.2) CL      = TVCLS*EXP(ETA(5))
MIX                     = MIXNUM
KA                      = TVKA*EXP(ETA(2))
V2                      = TVV2
Q                       = TVQ
VM                      = TVVM*EXP(ETA(4))
CLM                     = TVCLM*EXP(ETA(3))
CLO                     = TVCLO*EXP(ETA(6)

VH          = 1 * FV
QH          = 0.55 * 90 * FCL
FU          = 0.9
```

```
CLINT           = CL+CLO
EH              = ( CLINT * FU ) / ( ( CLINT * FU ) + QH )
CLH             = EH * QH

EH_ACINH        = ( CL * FU ) / ( ( CL * FU ) + QH )
CL_ACINH        = EH_ACINH * QH

K13     = KA
K34     = KA
K45     = KA
K56     = KA
K68     = KA
K27     = Q/V
K72     = Q/V2
K82     = (QH*(1-EH))/VH
K28     = QH/V
K89     = CL_ACINH/VH
K90     = CLM/VM
K80     = CLO/VH

$ERROR

IF(STDY.EQ.1) THEN
        ALT_BLQ = 1
ELSE
        ALT_BLQ = 0
ENDIF

IF(CMT.EQ.2) THEN
        ERR_BLQ = ( ALT_BLQ * ERR(3) ) + ( ( 1-ALT_BLQ ) * ERR(4) )
        ERRORS= ERR(1)
        IPRED=A(2)/V
ELSE
        ERR_BLQ = ERR(5)
        ERRORS= ERR(2)
        IPRED=A(9)/VM
ENDIF

IF(BLQ.EQ.0) THEN
        Y = IPRED + IPRED*(ERRORS)
ELSE
        Y = IPRED + IPRED*(ERRORS) + ERR_BLQ
ENDIF

IRES = DV - IPRED
IWRES = IRES/IPRED

$THETA
(0, 57.5) ;1 V
(0, 32.7) ;2 CL FAST
(0, 5.42) ;3 KA
(0, 18.7) ;4 V2
```

```
(0, 2.48) ;5 Q
(0, 39.2) ;6 VM
(0, 6.65) ;7 CLM
(0, 0.434,1) ;8 PROP FAST
(0, 4.31) ;9 CL SLOW
(0, 12.1) ;10 CL OTHER

$OMEGA
 0.0697  ;1 IIV V
 0.692  ;2 IIV KA
 0 FIX  ;3 IIV F
 0.135  ;4 IIV CLM
 0.0107  ;5 IIV VM
$OMEGA BLOCK(2)
 0.331  ;6 IIV CL
 0.0312  0.144 ;7 IIV CLO

$SIGMA BLOCK(2)
 0.141  ;1 Proportional error parent
 0.0525  0.0544  ;2 Proportional error metabolite
$SIGMA
 0.000002  FIX  ;3 additive BLQ error parent analytical method 1
 0.00000008  FIX  ;4 additive BLQ error parent analytical method 2
 0.0000002  FIX  ;5 additive BLQ error metabolite

$ESTIMATION METH=1 INTER PRINT=1
```