Supplementary Materials

Comparable Bioavailability and Disposition of Pefloxacin in Patients with Cystic Fibrosis and Healthy Volunteers Assessed via Population Pharmacokinetics

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Table 1. Estimates from the original dataset compared to the median and 95% confidence intervals from nonparametric bootstrapping (200 replicates) for the final population PK model.

PK Parameters	Symbol	Unit	Population Mean		Between Subjects Variability (CV)	
			Original Dataset	Median (95% CI) (2.5^{th} to 97.5^{th} percentile)	Original Dataset	Median (95% CI) (2.5^{th} to 97.5^{th} percentile)
Pefloxacin						
Oral bioavailability	F_{BIO}	-	1.00 [a] 1.03 [b]	1.01 (0.909–1.11) [a] 1.03 (0.934–1.10) [b]	0.146 [a] 0.127 [b]	0.140 (0.0548–0.210) [a] 0.119 (0.0478–0.160) [b]
Absorption lag-time	T_{lag}	min	13.3	13.4 (12.8–14.1)	0.0712	0.0631 (0.0261–0.0867)
Absorption half-life	T_{abs}	min	19.8 [a] 11.2 [b]	20.2 (9.65–45.1) [a] 11.3 (6.20–18.1) [b]	1.10 [a] 0.983 [b]	1.01 (0.627–1.35) [a] 0.969 (0.518–1.34) [b]
Reabsorption half-life from intestine	T_{reabs}	min	65.4 [a] 20.8 [b]	65.5 (41.0–89.7) [a] 20.0 (6.37–41.8) [b]	0.334 [a] 0.804 [b]	0.0720 (0.00768–0.600) [a] 0.747 (0.0965–1.27) [b]
Volume of distribution for central comp.	V1	L	40.8	39.8 (22.2–58.6)	0.435	0.417 (0.0313–0.632)
Volume of distribution for peripheral comp.	V2	L	65.4	66.6 (50.2–76.7)	0.131	0.0619 (0.00851–0.309)
Non-renal clearance	CL_{NR}	L/h	8.56	8.59 (7.44–9.77)	0.238	0.224 (0.125–0.310)
Renal clearance	CL_{R}	L/h	0.705	0.710 (0.662–0.753)	0.168	0.166 (0.0111–0.265)
Distribution clearance	CL_{D}	L/h	406	414 (164–1,199)	1.19	1.18 (0.693–2.05)
Disease factor for nonrenal clearance	$F_{CYF, NR}$	-	0.861	0.850 (0.694–1.07)	0.05	fixed
Disease factor for renal clearance	$F_{CYF, R}$	-	1.53	1.53 (1.21–1.78) [c]	0.05	fixed
Disease factor for volume of distribution	$F_{CYF, VSS}$	-	0.916	0.931 (0.739–1.15)	0.05	fixed
Maximum rate of exsorption	CL_{gut}	L/h	66.0	66.0 (fixed)	0	fixed
Plasma conc. associated with half-maximal Vm_{EX}	Km_{EX}	mg/L	1.44	1.50 (0.711–2.50)	0.1	fixed
Norfloxacin						
Formation fraction	fm_{NOR}	-	0.201 [a] 0.174 [b]	0.198 (0.168–0.239) [a] 0.172 (0.162–0.185) [b]	-	-
Pefloxacin-N-oxide						
Formation fraction	fm_{NOX}	-	0.244 [a] 0.178 [b]	0.247 (0.220–0.271) [a] 0.180 (0.167–0.190) [b]	-	-

[a] Parameter estimates for patients with CF.

[b] Parameter estimates for healthy volunteers. When only one line of parameter estimates is reported, the same estimate was used in patients with CF and healthy volunteers.

[c] Significantly different from 1.0 ($p < 0.05$; two-sided test) based on 200 bootstrap replicates.

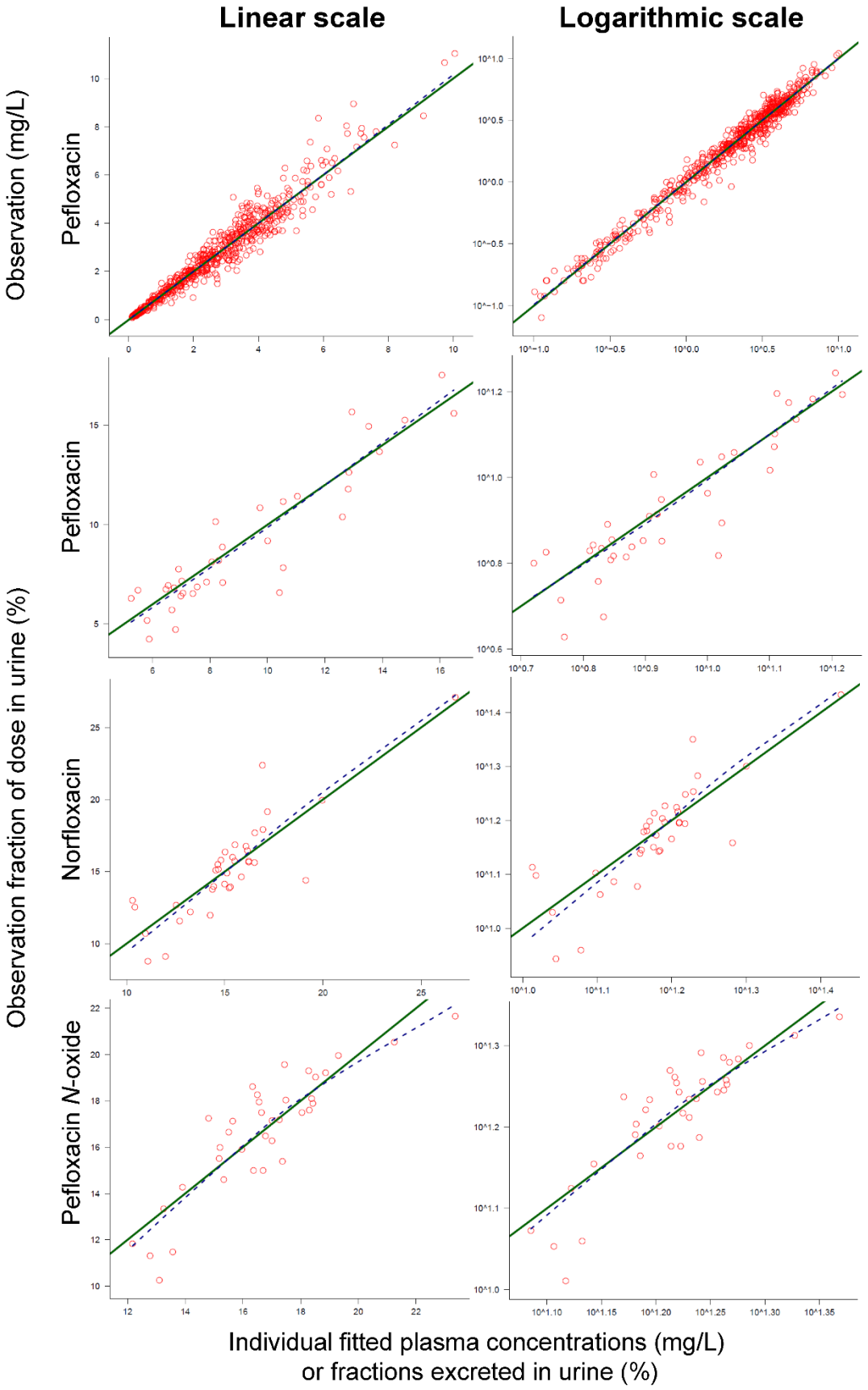

Figure S1. Observed vs. individual fitted plasma concentrations (top) and fractions of dose excreted in urine (rows 2 to 4) on linear (left side) and logarithmic scale (right side). The green line represents the line of identity and the dashed blue line a LOESS smoother.

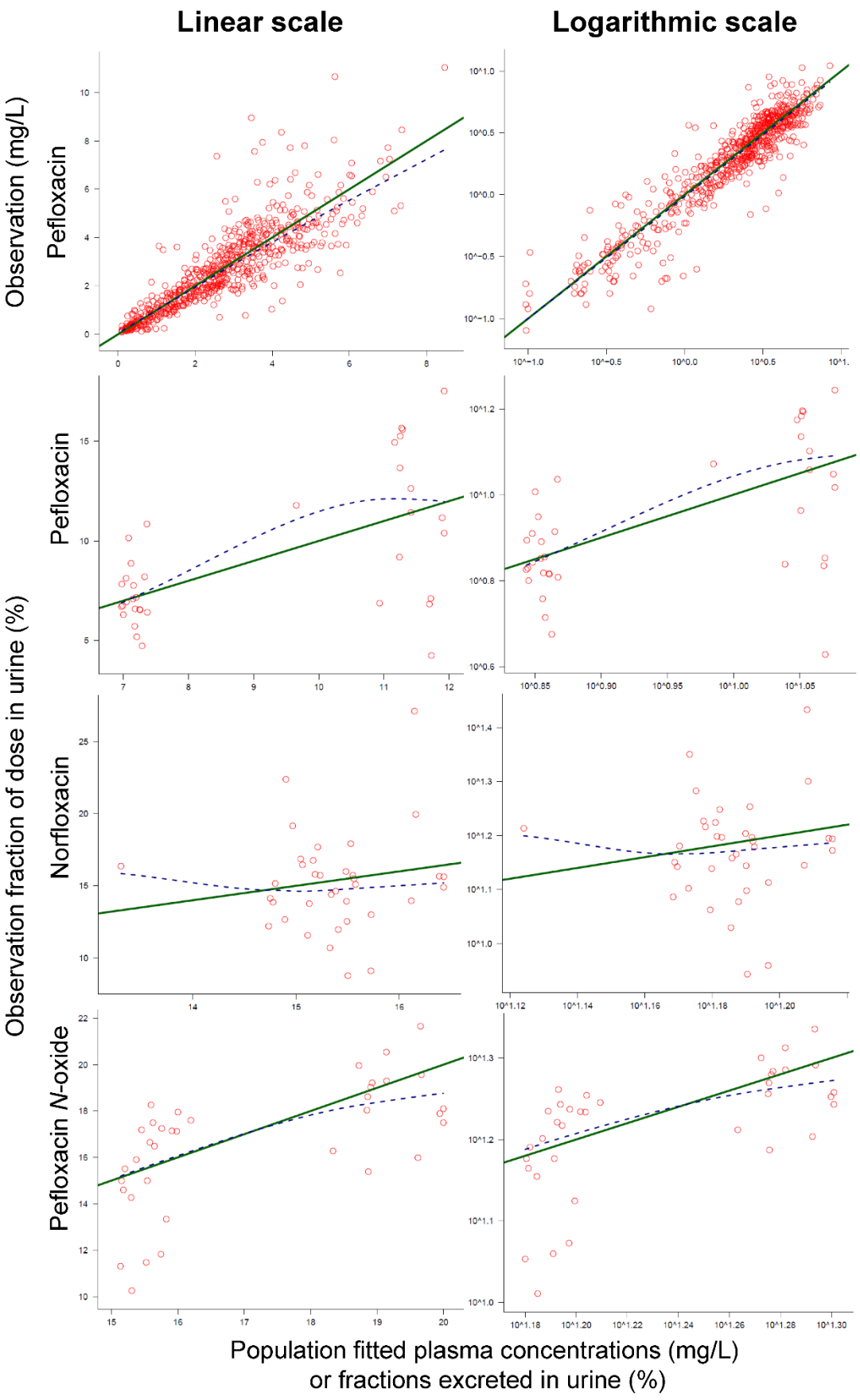

Figure S2. Observed vs. population fitted plasma concentrations (top) and fractions of dose excreted in urine (rows 2 to 4) on linear (left side) and logarithmic scale (right side). The green line represents the line of identity and the dashed blue line a LOESS smoother.

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$PROJECT THIS WILL BE A TERRIFIC PROJECT

$DIFFEQ_DIF

GUT    = X(1)
DC1    = X(2)/V1_COV
DC2    = X(3)/V2_COV
URI    = X(4) ; Amount of pefloxacin         in urine
URINO  = X(5) ; Amount of norfloxacin        in urine
URIDE  = X(6) ; Amount of pefloxacin-N-oxide in urine
GUTEHC = X(7)

TPD = MOD(T,72)

IF (TPD.GT.TLAGH) THEN
   KAT = KA
ELSE
   KAT = 0
ENDIF

CLMM = CLgut_COV*KM / (KM+DC1)

XP(1)  =       - KAT*GUT
XP(2)  =  R(1) + KAT*GUT - CLR_COV*DC1 - CLNR_COV*DC1 - CLMM*DC1 - CLD_COV*DC1 + CLD_COV*DC2 + KAEHC*GUTEHC
XP(3)  =                                                          CLD_COV*DC1 - CLD_COV*DC2

XP(4)  =                   CLR_COV*DC1
XP(5)  =                          FM_NOR*CLNR_COV*DC1
XP(6)  =                          FM_NOX*CLNR_COV*DC1

XP(7)  =                                              + CLMM*DC1                              - KAEHC*GUTEHC

$OUTPUT_GLB

IF (GRP.EQ.1) THEN
 ; Patients with Cystic Fibrosis
   FBIO        = FBIO_CF
   KA          = LOG(2)/(TABS_CF/60)
   KAEHC       = LOG(2)/(TAEHC_CF/60)

   FCYF_CLR    = FCLR
   FCYF_CLNR   = FCLNR
   FCYF_CLEX   = FCLEX
   FCYF_VSS    = FVSS

   TFM_NOR     = TFM_NORCF
   DFM_NOX     = DFM_NOXCF
ELSE
 ; Healthy volunteers
   FBIO        = FBIO_HV
   KA          = LOG(2)/(TABS_HV/60)
   KAEHC       = LOG(2)/(TAEHC_HV/60)

   FCYF_CLR    = 1
   FCYF_CLNR   = 1
   FCYF_CLEX   = 1
   FCYF_VSS    = 1

   TFM_NOR     = TFM_NORHV
   DFM_NOX     = DFM_NOXHV
ENDIF
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Figure S3. code for the final model in SADAPT-TRAN format.

```
BOLUSF(1) = FBIO

FM_NOR     = 1/(1+EXP(-TFM_NOR))

TFM_NORNOX = DFM_NOX + TFM_NOR
FM_NORNOX  = 1/(1+EXP(-TFM_NORNOX))

FM_NOX2    = FM_NORNOX - FM_NOR
FM_NOX     = MAX(0,FM_NOX2) ; to improve robustness of code

TLAGH= TLAG/60

FWTCL  = (FFM/53)**0.75
FWTV   = (FFM/53)

; Elimination clearances
CLR_COV     = FCYF_CLR  * FWTCL * CLR
CLNR_COV    = FCYF_CLNR * FWTCL * CLNR
CLgut_COV   = FCYF_CLEX * FWTCL * CLgut
CLD_COV     =             FWTCL * CLD
V1_COV      = FCYF_VSS  * FWTV  * V1
V2_COV      = FCYF_VSS  * FWTV  * V2

$OUTPUT_ICS

$OUTPUT_EQN

IF (X(1).LT.0) X(1) = 0
IF (X(2).LT.0) X(2) = 0
IF (X(3).LT.0) X(3) = 0
IF (X(4).LT.0) X(4) = 0
IF (X(5).LT.0) X(5) = 0
IF (X(6).LT.0) X(6) = 0
IF (X(7).LT.0) X(7) = 0

C1   = X(2)/V1_COV ; Serum concentrations of pefloxacin (mg/L)

Y(1) = C1

Y(2) = 100*X(4)/400  ; fraction of dose excreted in urine as unchanged pefloxacin
Y(3) = 100*X(5)/400  ; fraction of dose excreted in urine as norfloxacin
Y(4) = 100*X(6)/400  ; fraction of dose excreted in urine as pefloxacin-N-oxide

; Empty the bucket for the cumulative amount excreted into urine (=reset event)
IF (EVID.EQ.5) THEN
   X(1) = 0
   X(2) = 0
   X(3) = 0
   X(4) = 0
   X(5) = 0
   X(6) = 0
   X(7) = 0
ENDIF

$VARMOD_EQN

V(1) = ( SDin + SDsl*Y(1) ) * ( SDin + SDsl*Y(1) )

V(2) = UPin * UPin
V(3) = URin * URin
V(4) = UXin * UXin

$POPMOD_EQN
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Figure S3. code for the final model in SADAPT-TRAN format (**continued**).