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| [**WorldWide Antimalarial Resistance Network**](https://www.wwarn.org/impact-outcomes/publications/population-pharmacokinetic-properties-piperaquine-falciparum-malaria)  [Pharmacometric Scientific Group](https://www.wwarn.org/working-together/scientific-groups)  Version 1. Created 10 April 2019. |
| WWARN is committed to supporting efficient and quality data collection and analysis for antimalarial drug research. As such we are sharing the NONMEM code used for this publication. NONMEM is a computer program, NONlinear Mixed Effects Modeling, used by WWARN’s [Pharmacometric Scientific Group](https://www.wwarn.org/working-together/scientific-groups).  For further information, please contact [info@wwarn.org](mailto:info@wwarn.org) |
| **Please use the following reference:**  WWARN NONMEM **Code 2** file used to develop: [Artemether-lumefantrine dosing for malaria treatment in young children and pregnant women: a pharmacokinetic-pharmacodynamic meta-analysis.](https://www.wwarn.org/impact-outcomes/publications/artemether-lumefantrine-dosing-malaria-treatment-young-children-and)  F. Kloprogge, L. Workman, S. Borrmann, M. Tékété, G. Lefèvre, K. Hamed, P. Piola, J. Ursing, P.E. Kofoed, A. Mårtensson, B. Ngasala, A. Björkman, M. Ashton, S.F. Hietala, F. Aweeka, S. Parikh, L. Mwai, T.M.E. Davis, H. Karunajeewa, S. Salman, F. Checchi, C. Fogg, P.N. Newton, M. Mayxay, P. Deloron, J.F. Faucher, F. Nosten, E.A. Ashley, R. McGready, M. van Vugt, S. Proux, R.N. Price, J. Karbwang, F. Ezzet, R. Bakshi,  K. Stepniewska, N.J. White, P.J. Guerin, K.I. Barnes, J. Tarning.  *PLoS Medicine*. 2018 Jun 12;15(6):e1002579.  Read the full summary of the [Antimalarial – Lumefantrine POP/PK Study Group](https://www.wwarn.org/working-together/study-groups/antimalarial-lumefantrine-poppk-study-group) |
| $INPUT  ID ; Patient ID  TIME ; Time of sample  DV ; Dependent variable (natural logarithm of observed concentrations, nmol/L)  WT ; Body weight (covariate)  EVID ; Event ID record  MDV ; Missing dependent variable (1=missing)  AMT ; Dose amount (μmol)  CMT ; Compartment (1=dose, 2= lumefantrine, 4= desbutyl-lumefantrine)  PREG ; Pregnancy (covariate; 0=non-pregnant, 1=pregnant)  LNPC ; Parasite count (covariate; logarithm of parasite count)  DOSE ; Lumefantrine dosage (covariate; mg/kg)  $DATA  dataset.csv IGNORE=#  $SUBROUTINE  ADVAN5 TRANS1  $MODEL  COMP = (1) ; Dose  COMP = (2) ; Lumefantrine (LUM) central compartment  COMP = (3) ; LUM peripheral compartment  COMP = (4) ; Desbutyl-lumefantrine (DLF) central compartment  COMP = (5) ; DLF peripheral compartment  $PK  ;------------------------------------Dose covariate----------------------------------------------------------------------  D50 = THETA(12) ; Dose (mg/kg) to reach 50% of full saturation effect  DS = 1 - (DOSE/(DOSE+D50) ) ; Dose (mg/kg) covariate relationship  ;------------------------------------------------------------------------------------------------------------------------------------  ;------------------------------------ Pregnancy covariate ----------------------------------------------------------------  PREGNANCY = (1 + THETA(13) \* PREG) ; Linear covariate relationship for pregnancy  ;------------------------------------------------------------------------------------------------------------------------------------  ;------------------------------------Parasite biomass covariate-------------------------------------------------------------  PARASITE = ((LNPC /4.20)\*\*THETA(14)) ; Power covariate relationship for parasite biomass  ;--------------------------------------------------------------------------------------------------------------------------------------  TVCL = THETA(1) \* ((WT/42)\*\*0.75) ; Population LUM clearance  CL = TVCL \* EXP(ETA(1)) ; Individual LUM clearance  TVV2 = THETA(2) \* ((WT/42)\*\*1) ; Population LUM central volume  V2 = TVV2 \* EXP(ETA(2)) ; Individual LUM central volume  TVQ1 = THETA(3) \* ((WT/42)\*\*0.75) ; Population LUM inter-compartment clearance  Q1 = TVQ1 \* EXP(ETA(3)) ; Individual LUM inter-compartment clearance  TVV3 = THETA(4) \* ((WT/42)\*\*1) ; Population LUM peripheral volume  V3 = TVV3 \* EXP(ETA(4)) ; Individual LUM peripheral volume  TVKA = THETA(5) \* PREGNANCY ; Population absorption rate constant  KA = TVKA \* EXP(ETA(5)) ; Individual absorption rate constant  TVF1 = THETA(6) \* DS \* PARASITE ; Population relative bioavailability  BXPAR = THETA(11) ; Box-Cox shape parameter  PHI = EXP(ETA(6)) ; Exponential of IIV  ETATR = (PHI\*\*BXPAR-1)/BXPAR ; Box-Cox tranfomation of IIV  F1 = TVF1 \* EXP(ETATR) ; Individual relative bioavailability  TVV4 = THETA(7) \* ((WT/42)\*\*1) ; Population DLF central volume  V4 = TVV4 \* EXP(ETA(7)) ; Individual DLF central volume  TVCLM = THETA(8) \* ((WT/42)\*\*0.75) ; Population DLF clearance  CLM = TVCLM\* EXP(ETA(8)) ; Individual DLF clearance  TVQ2 = THETA(9) \* ((WT/42)\*\*0.75) ; Population DLF inter-compartment clearance  Q2 = TVQ2\* EXP(ETA(9)) ; Individual DLF inter-compartment clearance  TVV5 = THETA(10) \* ((WT/42)\*\*1) ; Population DLF peripheral volume  V5 = TVV5 \* EXP(ETA(10)) ; Individual DLF peripheral volume  K12 = KA ; Absorption rate constant  K23 = Q1/V2 ; LUM distribution rate constant (COMP 2 --> 3)  K32 = Q1/V3 ; LUM distribution rate constant (COMP 3 --> 2)  K24 = CL/V2 ; LUM elimination rate constant (COMP 2 --> 4)  K45 = Q2/V4 ; DLF distribution rate constant (COMP 4 --> 5)  K54 = Q2/V5 ; DLF distribution rate constant (COMP 5 --> 4)  K40 = CLM/V4 ; DLF elimination rate constant (COMP 4 --> 0)  S2 = V2/1000 ; Scaling for LUM central volume  S4 = V4/1000 ; Scaling for DLF central volume  $ERROR  IF (CMT.EQ.2) CP = A(2) / S2 ; Predicted LUM plasma concentration  IF (CMT.EQ.4) CP = A(4) / S4 ; Predicted DLF plasma concentration  IF(CP.GT.0) IPRED = LOG(CP) ; Natural logarithm of predictions  IF (CMT.EQ.2) W = SQRT(SIGMA(1,1)) ; LUM residual error  IF (CMT.EQ.4) W = SQRT(SIGMA(2,2)) ; DLF residual error  IRES = IPRED – DV ; Individual residual error  IWRES = IRES / W ; Individual weighted residual error  IF (CMT.EQ.2) Y = IPRED + EPS(1) ; LUM additive residual error  IF (CMT.EQ.4) Y = IPRED + EPS(2) ; DLF additive residual error  ;------------------------------------------------------------------------------------------------------------------------------------  $THETA ; Initial estimates of theta  (0, 1.56) ; 1. LUM clearance  (0, 21.2) ; 2. LUM central volume of distribution  (0, 0.381) ; 3. LUM inter-compartment clearance  (0, 53.8) ; 4. LUM peripheral volume of distribution  (0, 0.0409) ; 5. Absoprtion rate constant  (1 FIX) ; 6. Relative bioavailability  (0, 2470) ; 7. DLF central volume of distribution  (0, 78.4) ; 8. DLF clearance  (0, 104) ; 9. DLF inter-compartment clearance  (0, 8650) ; 10. DLF peripheral volume of distribution  (-1, -0.449) ; 11. Box-Cox shape parameter  (3.86 FIX) ; 12. Dose (mg/kg) reaching 50% of full absoption  (-1, 0.513) ; 13. Pregnancy on absoprtion rate constant  (-1, -0.226) ; 14. Parasite biomass on relative bioavailability  $OMEGA ; Initial estimates for omega  (0 FIX) ; 1. LUM IIV clearance  (0.803) ; 2. LUM IIV central volume  (0 FIX) ; 3. LUM IIV inter-compartment clearance  (0 FIX) ; 4. LUM IIV peripheral volume  (0 FIX) ; 5. IIV absorption rate constant  (0.289) ; 6. IIV relative bioavailability  (0.554) ; 7. DLF IIV central volume  (0.140) ; 8. DLF IIV clearance  (0.115) ; 9. DLF IIV inter-compartment clearance  (0.205) ; 10 DLF IIV peripheral volume  $SIGMA ; Initial estimates of sigma  (0.251) ; 1. LUM residual variability  (0.0560) ; 2. DLF residual variability  $ESTIMATION POSTHOC MAXEVAL=9999 METHOD=1 INTER |