[PROB]

Perjeta_valid.cpp

Perjeta population simulation

Source: run20d.lst

Time unit: day

Volume units: L

Validated: Yes

[PKMODEL] // option to use analytical solution for 1- and 2- cpt models

cmt = "CENT PERIPH", depot = FALSE

[PARAM] @annotated // list model parameters and covariates

TVCL : 0.235   : Clearance (L/day), theta 1

TVV1 : 3.11   : Volume of central compartment (L), theta 2

TVQ   : 0.534   : Intercompartmental clearance (L/day), theta 3

TVV2 : 2.46   : Volume of peripheral compartment (L), theta 4

LBWCL : 0.516   : Effect of LBW on CL, theta 5

LBWV1 : 0.747   : Effect of LBW on V1, theta 6

ALBCL : -1.06   : Effect of ALBU on CL, theta 7

LBWV2 : 0.83   : Effect of LBW on V2, theta 8

LBW   : 48   : Typical individual value of LBW

ALBU : 3.9   : Typical individual value of ALBU

[OMEGA] @annotated @block // describe between-subject variability

ETA_CL : 0.116   : ETA on CL

ETA_V1 : 0.0239   0.0342   : ETA on V1

ETA_V2 : -0.0416   0.0179   0.211 : ETA on V2

[SIGMA] @annotated // describe residual error

ADD : 0.0328 : Additive Error (log scale)

```
[MAIN] // NONMEM equivalent: $PK

// effect of covariates on parameters
double CLCOV = pow((LBW/48), LBWCL) * pow((ALBU/3.9), ALBCL);
double V1COV = pow((LBW/48), LBWV1);
double V2COV = pow((LBW/48), LBWV2);

// PK parameters
double CL    = TVCL * CLCOV * exp(ETA_CL);
double V1    = TVV1 * V1COV * exp(ETA_V1);
double Q     = TVQ;
double V2    = TVV2 * V2COV * exp(ETA_V2);

[TABLE] // NONMEM equivalent: $ERROR
double val = CENT/V1;
double IPRED = 0;
double IPREDnormal = 0;

if (val > 0) IPRED = log(val);
if (val > 0) IPREDnormal = exp(IPRED);

double DV = IPRED + ADD;
double DVnormal = exp(DV);

[CAPTURE] @annotated
IPREDnormal : Concentration without residual variability (normal scale)
DVnormal    : Concentration with residual variability (normal scale)
IPRED : Concentration without residual variability (log scale)
DV    : Concentration with residual variability (log scale)
```

[PROB]

Perjeta.ind.cpp

Perjeta individual simulation

Source: Perjeta_valid.cpp

Time unit: day

Volume units: L

[PKMODEL] // option to use analytical solution for 1- and 2- cpt models

cmt = "CENT PERIPH", depot = FALSE

[PARAM] @annotated // list model parameters and covariates

CLind : 0.235 : Clearance (L/day), theta 1

V1ind : 3.11 : Volume of central compartment (L), theta 2

Qind : 0.534 : Intercompartmental clearance (L/day), theta 3

V2ind : 2.46 : Volume of peripheral compartment (L), theta 4

//[OMEGA] @annotated @block // describe between-subject variability

[SIGMA] @annotated // describe residual error

ADD : 0.0328 : Additive Error (log scale)

[MAIN] // NONMEM equivalent: $PK

// PK parameters

double CL = CLind;

double V1 = V1ind;

double Q = Qind;

double V2 = V2ind;

[TABLE] // NONMEM equivalent: $ERROR

double val = CENT/V1;

```
double IPRED = 0;
double IPREDnormal = 0;

if (val > 0) IPRED = log(val);
if (val > 0) IPREDnormal = exp(IPRED);

double DV = IPRED + ADD;
double DVnormal = exp(DV);

[CAPTURE] @annotated
IPREDnormal : Concentration without residual variability (normal scale)
DVnormal    : Concentration with residual variability (normal scale)
IPRED : Concentration without residual variability (log scale)
DV    : Concentration with residual variability (log scale)
```

[PROB]

Perjeta.sensitivity.cpp

Perjeta sensitivity analysis

Source: Perjeta_valid.cpp

Time unit: day

Volume units: L

[PKMODEL] // option to use analytical solution for 1- and 2- cpt models

cmt = "CENT PERIPH", depot = FALSE

[PARAM] @annotated // list model parameters and covariates

TVCL : 0.235 : Clearance (L/day), theta 1

TVV1 : 3.11 : Volume of central compartment (L), theta 2

TVQ : 0.534 : Intercompartmental clearance (L/day), theta 3

TVV2 : 2.46 : Volume of peripheral compartment (L), theta 4

PARA : 1 : 1 for TVCL, 2 for TVV1, 3 for TVQ, 4 for TVV2

RANK : 1 : rank the parameter values (1 is lowest)

LBWCL : 0.516 : Effect of LBW on CL, theta 5

LBWV1 : 0.747 : Effect of LBW on V1, theta 6

ALBCL : -1.06 : Effect of ALBU on CL, theta 7

LBWV2 : 0.83 : Effect of LBW on V2, theta 8

LBW : 48 : Typical individual value of LBW

ALBU : 3.9 : Typical individual value of ALBU

[OMEGA] @annotated @block // describe between-subject variability

ETA_CL : 0.116 : ETA on CL

ETA_V1 : 0.0239 0.0342 : ETA on V1

ETA_V2 : -0.0416 0.0179 0.211 : ETA on V2

```
[SIGMA] @annotated // describe residual error
ADD : 0.0328 : Additive Error (log scale)

[MAIN] // NONMEM equivalent: $PK

// effect of covariates on parameters
double CLCOV = pow((LBW/48), LBWCL) * pow((ALBU/3.9), ALBCL);
double V1COV = pow((LBW/48), LBWV1);
double V2COV = pow((LBW/48), LBWV2);

// PK parameters
double CL    = TVCL * CLCOV * exp(ETA_CL);
double V1    = TVV1 * V1COV * exp(ETA_V1);
double Q     = TVQ;
double V2    = TVV2 * V2COV * exp(ETA_V2);

[TABLE] // NONMEM equivalent: $ERROR
double val = CENT/V1;
double IPRED = 0;
double IPREDnormal = 0;

if (val > 0) IPRED = log(val);
if (val > 0) IPREDnormal = exp(IPRED);

double DV = IPRED + ADD;
double DVnormal = exp(DV);

[CAPTURE] @annotated
IPREDnormal : Concentration without residual variability (normal scale)
DVnormal    : Concentration with residual variability (normal scale)
IPRED : Concentration without residual variability (log scale)
DV    : Concentration with residual variability (log scale)
```

[PROB]

Pola.ind.cpp

Pola individual simulation

Source: PKcase_Polatuzumab.valid.cpp (provided in the model library)

Time unit: hr

Volume units: L

[CMT] @annotated

CENT : central compartment for acMMAE

PERI : peripheral compartment for acMMAE

CMMAE : central compartment for MMAE

CMMAE2: peripheral compartment for MMAE

[PARAM] @annotated

covBBCC:19: Baseline B cell count 10^6/L (median)

covCOMBO:1:

covSEXN:1:

covRRFN:1:

covRACEN:1: 0 Not Asian, 1 Asian

covBHPTGRPN: 1: Baseline Hepatic Function Group 1 'Normal'; 2 'MILD1'; 3 'MILD2'; 4 'MODERATE'; 5 'SEVERE'; 9999 'missing'.

covBECOG:1: Baseline ECOG

covBTMBD:3031: Baseline tumor size

covBALBUM:39: Baseline Albumin

covBWT:77.9: Baseline Weight

PKETA1 : 0.1: random effect 1

PKETA2 : 0.1: random effect 2

PKETA3 : 0.1: random effect 3

PKETA4 : 0.1: random effect 4

PKETA5 : 0.1: random effect 5

PKETA6 : 0.1: random effect 6

PKETA7: 0.1: random effect 7

PKETA8 :0.1: random effect 8

PKETA9 : 0.1: random effect 9

PKETA10 : 0.1: random effect 10

PKETA11 :0.1: random effect 11

TVKDES :0.0046: 1~KDES

TVCLT:0.0062 : 2~CLT

TVCLINF:0.0344 : 3~CLINF

TVV1:3.14 : 4~V1

TVV2: 3.96: 5~V2

TVQ:0.014 : 6~Q

TVVMAX:0.0204 : 7~VMAX

TVKM:0.604 : 8~KM

TVCLIMAX: 0.223: 9~CLinf decrease EMAX

T50_Mon :3.51:10~CLinf T50 (month)

TVGAM :2.27 :11~CLing GAM

TVVMMAE: 83.3 :12~VMMAE

TVCLMMAE :1.91:13~CLMMAE

TVQMMAE :36.5:14~QMMAE

TVV2MMAE: 202 :15~V2MMAE

TVVMAXMM :0.0305:16~VMAXMMAE

TVKSS :0.584:17~KSS

TVFRAC1 :3.71:18~FRAC1

TVFRAC2 :2.70:19~FRAC2

ALPH_H :0.167:20~alpha

TVFREMAX: 0.138:21~FREMAX

WTCLF: 0.735:22~WT to CLinf

WTVQ: 0.501 :23~WT to V1 V2 Q

SEXV1: 1.2:24~SEX on V1

ASIV1: 0.93 :25~ASIAN on V1

NAIVV1: 1.2 :26~NAIVE on V1

SEXCLINF: 1.1:27~SEX on CLinf

ALBCLINF:-0.247 :28~ALBUM to CLinf

RTXCLINF: 0.843:29~RTX GA101 to CLinf

BCECLINF:0.0210 :30~power BCEL1 to CLinf

TMBCLINF: 0.052 :31~TMBD to CLinf

NAIVKDES: 3.36:32~NAIVE to KDES

RTXKDES:0.936 :33~RTX GA101 to KDES

NAIVECLT: 3.53:34~NAIVE to CLT

BTMBCLT:1152 :35~BTMBD50 to CLT

BBCC_CUT:120:36~BBCC cutoff

BCELCLT: 0.589:37~BCEL to CLT power

BWTFRAC0:-0.468 :38~BWT to FRAC0

SEXFRAC0: 0.918:39~SEX to FRAC0

NAIFRAC0:0.760 :40~NAIVE to FRAC0

RTXFRAC0:0.714 :41~RTX/OB to FRAC0

HEPFRAC0:1.18 :42~HEPA to FRAC0

ECOFRAC0: 0.904:43~ECOG0 to FRAC0

ALBFRAC0: -0.613:44~ALBUM to FRAC0

[OMEGA]

EERR1: 0.052 :10~IIV_ERR1

EERR2: 0.038 0.043 :11~IIV_ERR2

[SIGMA] @annotated

PROP1: 0.0254 : ~Err_PROP

PROP2: 0.0726 : ~Err_PROP

[MAIN]

double BCEL = 1;

```
if (covBBCC > BBCC_CUT) BCEL=covBBCC/BBCC_CUT;

double BCEL1 = 1;

if (covBBCC > 1) BCEL1=covBBCC;


double RTX = 0;

if (covCOMBO==1) RTX = 1;

double GA101 = 0;

if (covCOMBO==2) GA101 = 1;


double SEX = covSEXN-1;


double NAIVE = 0;

if (covRRFN==0) NAIVE=1;


double ASIAN = 0;

if (covRACEN==1) ASIAN = 1;


double HEPA = 0;

if ((covBHPTGRPN>1.5) & (covBHPTGRPN!=9999)) HEPA = 1;


double ECOG0 = 0;

if (covBECOG==0) ECOG0 = 1;

double ECOG2 = 0;

if (covBECOG==2) ECOG2 =1;


double COVV1    = pow(SEXV1,SEX)*pow(ASIV1,ASIAN)*pow(NAIVV1,NAIVE);

double COVCLINF =
pow(SEXCLINF,SEX)*pow((covBALBUM/35),ALBCLINF)*pow(RTXCLINF,(RTX+GA101))*pow(BCEL1,BCECLINF)*(1+TMBCLI
NF*(covBTMBD/5000-1));

double COVKDES  = pow(NAIVKDES,NAIVE)*pow(RTXKDES,(RTX+GA101));

double COVCLT   = pow(NAIVECLT,NAIVE)*covBTMBD/(BTMBCLT+covBTMBD)*pow(BCEL,BCELCLT);


double KDES  = TVKDES*COVKDES;
```

```
double CLT   = TVCLT*COVCLT*exp(PKETA1) ;

double CLINF = TVCLINF*pow((covBWT/75),WTCLF)*COVCLINF*exp(PKETA2);

double V1    = TVV1*pow((covBWT/75),WTVQ)*COVV1*exp(PKETA3);

double V2    = TVV2*pow((covBWT/75),WTVQ)*exp(PKETA4);

double Q     = TVQ*pow((covBWT/75),WTVQ)*exp(PKETA5);

double VMAX  = TVVMAX*exp(PKETA6);

double KM    = TVKM;

double CLINFEMAX= TVCLIMAX;

double T50      = T50_Mon*24*30;

double GAM      = TVGAM;

double T50GAM   = pow(T50,GAM);


//double S1 = V1;

double K12   = Q/V1;

double K21   = Q/V2;


double COVMMAE1= pow((covBWT/75),
BWTFRAC0)*pow(SEXFRAC0,SEX)*pow(NAIFRAC0,NAIVE)*pow(RTXFRAC0,(RTX+GA101))*pow(HEPFRAC0,HEPA);

double COVMMAE = COVMMAE1*pow(ECOFRAC0,ECOG0)*pow((covBALBUM/35),ALBFRAC0) ;


double FRAC0  = COVMMAE*exp(PKETA7) ;

double VMMAE  = TVVMMAE ;

double CLMMAE = TVCLMMAE*exp(PKETA8);

double QMMAE  = TVQMMAE;

double V2MMAE = TVV2MMAE*exp(PKETA9);

double VMAXMMAE = TVVMAXMM ;

double KSS      = TVKSS;

double FRAC1    = TVFRAC1 ;

double FRAC2    = TVFRAC2 ;

double ALPH     = ALPH_H/24/30;

double FREMAX   = TVFREMAX;

double K34    = QMMAE/VMMAE;

double K43    = QMMAE/V2MMAE;
```

```
double K30    = CLMMAE/VMMAE;


[ODE]

double FRAC     = FRAC0*(1+FREMAX*exp(-ALPH*SOLVERTIME));

double TGAM = 0;

if (SOLVERTIME > 0) TGAM = pow(SOLVERTIME,GAM);

double CL=CLT*exp(-KDES*SOLVERTIME)+CLINF*(1+CLINFEMAX*T50GAM/(T50GAM+TGAM));

double K10   = CL/V1;

double KINPUT = FRAC*(FRAC1*CLT*exp(-
KDES*SOLVERTIME)/V1+CLINF*(1+CLINFEMAX*T50GAM/(T50GAM+TGAM))/V1+FRAC2*VMAX/(KM+CENT/V1));


dxdt_CENT= K21*PERI-K12*CENT-K10*CENT-VMAX*CENT/(KM+CENT/V1);

dxdt_PERI=-K21*PERI+K12*CENT;

dxdt_CMMAE= KINPUT*CENT-K30*CMMAE - K34*CMMAE + K43*CMMAE2 -
VMAXMMAE*CMMAE/(KSS+CMMAE/VMMAE);

dxdt_CMMAE2=K34*CMMAE - K43*CMMAE2;


[TABLE]

double ACMMAE = CENT/V1;

double MMAE   = CMMAE/VMMAE;


double TY=ACMMAE; // Ab Conjugated

double TY6=MMAE; // For Type==6, MMAE


double DV_acMMAE=TY*(1+PROP1*exp(PKETA10));

double DV_MMAE=TY6*(1+PROP2*exp(PKETA11)) ; // For Type==6


[CAPTURE] @annotated

ACMMAE: Concentration without residual variability for acMMAE

MMAE: Concentration without residual variability for MMAE

DV_acMMAE: Concentration with residual variability for acMMAE

DV_MMAE : Concentration with residual variability for MMAE
```