**Supplemental Material**

Supplemental Table 1. Summary of clinical trials included in the PopPK analysis

| **Study** | **Enrolled** | **N\*** | **Population** | **Treatment** |
| --- | --- | --- | --- | --- |
| 101-01  Phase I | 64 | 48 | HV | GS-1101 single dose: 17, 50, 125, 250, 400 mg  GS-1101 multiple dose (7 days): 50, 100, 200 mg BID |
| 101-02  Phase I | 191 | 189 | Hematologic  Malignancies | GS-1101 x 28 days: 50, 100, 150, 200, 350 mg BID; 150, 300 mg QD  GS-1101 x 21 days/7 days off: 150 mg BIDa |
| 101-04  Phase I | 41 | 39 | Allergic rhinitis | GS-1101 100 mg BID over 7 days |
| 101-05  Phase I | 12 | 12 | HV | GS-1101 400 mg single dose  GS-1101 10 μg + 100 nCi [14C]GS-1101 single dose |
| 101-06  Phase I | 15 | 15 | HV | GS-1101 100 mg single dose |
| 101-07  Phase I | 226c | 197 | Relapsed or refractory  iNHL or CLL | GS-1101: 100 or 150 mg BID PO continuouslya given in combination with:   * Rituximab: 375 mg/m2 IV weekly x 8 weeks * Bendamustine: 70 or 90 mg/m2 IV Days 1 and 2 every 4 weeks x 24 weeks * Rituximab-Bendamustine: Rituximab 375 mg/m2 IV every 4 weeks x 24 weeks, and Bendamustine 70 or 90 mg/m2 Days 1 and 2 every 4 weeks x 24 or 48 weeks * Ofatumumab: 300 mg IV Day 1 or 2, then 1000 mg * weekly for Weeks 2-8, followed by 1000 mg every 4 weeks for 4 doses during Weeks 9-12 * Fludarabine: 40 mg/m2 PO Days 1-5 every 4 weeks x 24 weeks * Everolimus: 10 mg PO Days 1-28 of every 4-week cycle |
| 101-08  Phase II | 64c | 64 | Untreated CLL or SLL | GS-1101: 100 or 150 mg BID PO x 48 weeks  Rituximab: 375 mg/m2 IV weekly x 8 weeks |
| 101-09  Phase II | 125 | 124 | iNHL refractory to both rituximab and alkylating agents | GS-1101 150 mg BID continuouslyb |
| 101-11  Phase II | 25 | 25 | Relapsed or refractory HL | GS-1101 150 mg BID continuouslyb |
| 339-0101  Phase I | 24c | 23 | HV | GS-9973 (day 1-4): 200 or 600 mg BID PO under fed condition  GS-1101 (day 15-18): 100 or 150 mg BID PO under fed condition  GS-1101+GS9973 (day 29-32) under fed condition   * Cohort 1: GS-9973 200 mg, GS-1101 100 mg * Cohort 2: GS-9973 600 mg, GS-1101 100 mg * Cohort 3: GS-9973 600 mg, GS-1101 150 mg |
| BID=twice daily; CLL= chronic lymphocytic leukemia; HL = Hodgkin lymphoma, iNHL = indolent non-Hodgkin Lymphoma; HV=healthy volunteer; IV= intravenous; PO = orally; QD=once daily; SLL=small lymphocytic lymphoma  a Administered until earliest occurrence of disease progression, intolerable toxicity, or completion of 12 cycles of therapy.  b Administered until earliest occurrence of disease progression, intolerable toxicity, or no clinical benefit in the opinion of the investigator.  c Only data from the GS-1101 dose group were included  \* Number of subjects included in the PopPK model dataset | | | | |

**Supplemental Material**

Supplemental Table 2. Summary of numeric predictive check

|  |  |
| --- | --- |
| Range | Observation (%) |
| Above 95th %ile | 4.2 |
| Above 75th %ile | 19.8 |
| Above 50th %ile | 45.1 |
| Below 50th %ile | 54.9 |
| Below 25th %ile | 23.9 |
| Below 5th %ile | 3.3 |

**Supplemental Material**

Supplemental Table 3. Impact of Covariates on Idelalisib Exposures in Cancer Patients

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Body Weight (kg) | | |
| <68 | 68-90 | >90 |
| No. of patients (%) | 159 (26.54) | 276 (46.08) | 164 (27.38) |
| AUC (hr\*ng/mL)\* | 11567 (6332, 18281) | 10232 (5730, 16685) | 10267 (5595, 16005) |
| Cmax (ng/mL)\* | 2175 (1077, 3488) | 1853 (903, 2881) | 1758 (909, 2726) |
| Ctrough (ng/mL)\* | 390 (138, 776) | 345 (100, 696) | 368 (121, 711) |
| Characteristics | Age (year) | | |
| <65 | 65-75 | >75 |
| No. of patients (%) | 212 (35.39) | 258 (43.07) | 129 (21.54) |
| AUC (hr\*ng/mL)\* | 10392 (5663,17527) | 10413 (5841,16647) | 11298 (6188,17226) |
| Cmax (ng/mL)\* | 1861 (862, 2871) | 1910 (999, 2975) | 2003 (953, 3462) |
| Ctrough (ng/mL)\* | 357 (115, 731) | 349 (104, 702) | 403 (163, 773) |
| Characteristics | Race | | |
| Caucasian | Non-Caucasian |  |
| No. of patients (%) | 520 (86.81) | 79 (13.19) |  |
| AUC (hr\*ng/mL)\* | 10575 (5877, 16807) | 10737 (5114, 17919) |  |
| Cmax (ng/mL)\* | 1905 (918, 2953) | 1960 (1158, 3038) |  |
| Ctrough (ng/mL)\* | 363 (117, 710) | 364 (97, 746) |  |
| Characteristics | Gender | | |
| Male | Female |  |
| No. of patients (%) | 404 (67.45) | 195 (32.55) |  |
| AUC (hr\*ng/mL)\* | 10292 (5595, 16340) | 11226 (6270, 18109) |  |
| Cmax (ng/mL)\* | 1819 (899, 2858) | 2107 (1092, 3420) |  |
| Ctrough (ng/mL)\* | 356 (101, 717) | 379 (142, 736) |  |
| Characteristics | Cancer Type | | |
| CLL | iNHL | Other |
| No. of patients (%) | 212 (35.39) | 258 (43.07) | 129 (21.54) |
| AUC (hr\*ng/mL)\* | 10392 (5663,17527) | 10413 (5841,16647) | 11298 (6188,17226) |
| Cmax (ng/mL)\* | 1861 (862, 2871) | 1910 (999, 2975) | 2003 (953, 3462) |
| Ctrough (ng/mL)\* | 357 (115, 731) | 349 (104, 702) | 403 (163, 773) |
| Characteristics | Rituximab Usage | | |
| No | Yes |  |
| No. of patients (%) | 486 (81.14) | 113 (18.86) |  |
| AUC (hr\*ng/mL)\* | 10683 (5774, 17175) | 10220 (5887, 16359) |  |
| Cmax (ng/mL)\* | 1947 (939, 3069) | 1764 (867, 2669) |  |
| Ctrough (ng/mL)\* | 365 (116, 717) | 355 (118, 737) |  |

**Supplemental Material**

Supplemental Table 4. Impact of Covariates on GS-563117 Exposures in Cancer Patients

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Body Weight (kg) | | |
| <65 | 65-88 | >88 |
| No. of patients (%) | 58 (23.2) | 121 (48.4) | 71 (28.4) |
| AUC (hr\*ng/mL)\* | 50372 (18277, 99425) | 35721 (14475, 65003) | 35362 (18748, 63112) |
| Cmax (ng/mL)\* | 5011 (2109, 9571) | 3604 (1655, 6589) | 3564 (1824, 6507) |
| Ctrough (ng/mL)\* | 3260 (928, 6676) | 2264 (703, 4256) | 2245 (1126, 4257) |
| Characteristics | Age (year) | | |
| <65 | 65-75 | >75 |
| No. of patients (%) | 105 (42.0) | 107 (42.8) | 38 (15.2) |
| AUC (hr\*ng/mL)\* | 40473 (16969, 72935) | 35564 (14165, 67877) | 44723 (18221, 95704) |
| Cmax (ng/mL)\* | 4088 (1882, 7365) | 3597 (1665, 6560) | 4358 (1791, 8950) |
| Ctrough (ng/mL)\* | 2565 (943, 4557) | 2245 (616, 4369) | 2968 (1129, 6384) |
| Characteristics | Race | | |
| Caucasian | Non-Caucasian |  |
| No. of patients (%) | 225 (90) | 25 (10) |  |
| AUC (hr\*ng/mL)\* | 38746 (16961, 72951) | 41466 (13525, 90968) |  |
| Cmax (ng/mL)\* | 3902 (1811, 7221) | 4067 (1577, 8897) |  |
| Ctrough (ng/mL)\* | 2463 (899, 4642) | 2731 (556, 5985) |  |
| Characteristics | Gender | | |
| Male | Female |  |
| No. of patients (%) | 160 (64) | 90 (36) |  |
| AUC (hr\*ng/mL)\* | 38123 (16710, 74792) | 40610 (16931, 72178) |  |
| Cmax (ng/mL)\* | 3796 (1729, 7592) | 4137 (1935, 7174) |  |
| Ctrough (ng/mL)\* | 2458 (913, 4681) | 2546 (749, 4848) |  |
| Characteristics | Cancer Type | | |
| CLL | iNHL | Other |
| No. of patients (%) | 71 (28.4) | 137 (54.8) | 42 (16.8) |
| AUC (hr\*ng/mL)\* | 33684 (13447, 65608) | 39307 (17108, 72397) | 47093 (20604, 78556) |
| Cmax (ng/mL)\* | 3348 (1516, 6540) | 3970 (1956, 7209) | 4719 (2138, 8163) |
| Ctrough (ng/mL)\* | 2194 (554, 4293) | 2479 (947, 4649) | 3022 (1153, 5201) |
| Characteristics | Rituximab Usage | | |
| No | Yes |  |
| No. of patients (%) | 186 (74.4) | 64 (25.6) |  |
| AUC (hr\*ng/mL)\* | 41298 (17537, 74115) | 32393 (13428, 63900) |  |
| Cmax (ng/mL)\* | 4139 (1912, 7545) | 3280 (1493, 6362) |  |
| Ctrough (ng/mL)\* | 2642 (952, 5047) | 2046 (512, 4242) |  |

**Supplemental Material**

Supplement Figure 1. Idelalisib chemical structure

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**Supplemental Material**

Supplement Figure 2. Idelalisib structural PopPK model



**Supplemental Material**

Supplement Figure 3. GS-563117 predicted versus observed goodness-of-fit plots



**Supplemental Material**

Supplement Figure 4. GS-563117 residual goodness-of-fit plots



**Supplemental Material**

Supplement Figure 5. VPC of idelalisib plasma concentration-time profiles for single dose of idelalisib stratified by treatment group



**Supplemental Material**

Supplement Figure 6. VPC of idelalisib plasma concentration-time profiles for once daily of idelalisib stratified by treatment group



**Supplemental Material**

Supplement Figure 7. VPC of idelalisib plasma concentration-time profiles for twice daily of idelalisib stratified by treatment group



**Supplemental Material**

Control Stream of Final Idelalisib Model

;##############################################################################

;Project Name: GS-1101 PopPK

;Project ID: pop PK analysis NONMEM VII

;Kineticist: Christine Yuying Gao

;Model Description:

; 2-COMP LINEAR MODEL, LNCN w additive ERR

;##############################################################################

$PROB Population PK Analysis for GS-1101

$INPUT C ID STUDY SUJID SID DROP HOUR TIME NTIME AMT ADDL II EVID CONC MDV DROP DROP TSLD DV AGE SEXF RACE PAT DIS WT BMI BSA CLCR FORM BACKTX DROP FAST DOSE REGIM DROP AST ALT ROWC

$DATA pkinput1101.csv

IGNORE=C

$SUBROUTINE ADVAN4 TRANS4

$PK

; covariate relationship

; PAT: 1=patient; 2=heathy subject

CLT=THETA(1)

IF (PAT.EQ.2) CLT=THETA(8)

QT=THETA(3)

IF (PAT.EQ.2) QT=THETA(9)

FWT=WT

IF (ID.EQ.161) FWT=75

IF (ID.EQ.211) FWT=75

IF (ID.EQ.421) FWT=75

IF (ID.EQ.434) FWT=75

IF (ID.EQ.480) FWT=75

SWT=THETA(10)\*LOG(FWT/75)

; PK parameters

CL=EXP(CLT+SWT+ETA(1))

V2=EXP(THETA(2)+ETA(2))

Q=EXP(QT+ETA(3))

V3=EXP(THETA(4)+ETA(4))

KA=EXP(THETA(5)+ETA(5))

ALAG1=EXP(THETA(6)+ETA(6))

F1=EXP(THETA(7)\*LOG(DOSE/150))

K=CL/V2

K23=Q/V2

K32=Q/V3

S2=V2/1000

$ERROR

IPRED=F

IF(F.GT.0) THEN

IPRED=LOG(F)

ELSE

IPRED=0

ENDIF

Y=IPRED+EPS(1)

IRES=DV-IPRED

$THETA

(1,2.7,4) ; CL (L/hr)

(1,3.12,4) ; V2 (L)

(1,2.46,4) ; Q (L/hr)

(3,4.21,6) ; V3 (L)

(-3,-.733,-.1) ; KA (1/hr)

(-3,-1.4,-.1) ; LAG (hr)

(-.5,-.262,-.1) ; DOSE ON F1

(2,2.98,4)

(1,2.06,3)

(0,.249,1)

$OMEGA BLOCK(2)

.146

.114 .72

$OMEGA BLOCK(2)

.15

.234 .55

$OMEGA .147 .206

$SIGMA .283

$EST METHOD=1 INTER POSTHOC MAXEVAL=9999 NOABORT PRINT=20 NSIG=3 SIGL=9

$COV MATRIX=R UNCONDITIONAL

$TABLE ROWC STUDY DOSE REGIM SUJID SID ID TIME NTIME TSLD CONC IPRED IRES CWRES

AGE SEXF RACE PAT DIS WT BMI BSA CLCR FORM BACKTX FAST

AST ALT CL V2 Q V3 KA ALAG1 F1 ETA1 ETA2 ETA3 ETA4 ETA5 ETA5 ETA6

NOPRINT ONEHEADER FILE=RES52

Control Stream of Final GS-563117 PopPK Model

;##############################################################################

;Project Name: GS-563117 PopPK

;Project ID: pop PK analysis NONMEM VII

;Kineticist: Christine Yuying Gao

;Model Description:

; 2-COMP LINEAR MODEL, LNCN w additive ERR

;##############################################################################

$PROB Population PK Analysis for GS-563117

$INPUT C ID STUDY SUJID SID DROP HOUR TIME NTIME AMT ADDL II EVID CONC MDV DROP DROP TSLD DV

AGE SEXF RACE PAT DIS WT BMI BSA CLCR FORM BACKTX DROP FAST DOSE REGIM BLOQ AST ALT ROWC

$DATA pkinput563117.csv

IGNORE=C

$SUBROUTINE ADVAN4 TRANS4

$PK

; covariate relationship

; PAT: 1=patient; 2=heathy subject

SPAT=THETA(8)\*(PAT-1)

; pk parameters

CL=EXP(THETA(1)+SPAT+ETA(1))

V2=EXP(THETA(2)+ETA(2))

Q=EXP(THETA(3)+ETA(3))

V3=EXP(THETA(4)+ETA(4))

KA=EXP(THETA(5)+ETA(5))

ALAG1=EXP(THETA(6)+ETA(6))

F1=EXP(THETA(7)\*LOG(DOSE/150))

K=CL/V2

K23=Q/V2

K32=Q/V3

S2=V2/1000

$ERROR

IPRED=F

IF(F.GT.0) THEN

IPRED=LOG(F)

ELSE

IPRED=0

ENDIF

Y=IPRED+EPS(1)

IRES=DV-IPRED

$THETA

(-1,1.52,5) ;CL (L/hr)

(.1,1.99,6) ;V2 (L)

(.1,.352,5) ;Q (L/hr)

(.1,2.84,6) ;V3 (L)

(-5,-2.53,1) ;KA (1/hr)

(-5,-.754,1) ;LAG (hr)

(-1,-.443,1) ;DOSE ON F1

(0,.413,1)

$OMEGA BLOCK(2) .25 .09 .156

$OMEGA BLOCK(2) .1 .0482 .134

$OMEGA .55 .143

$SIGMA .122

$EST METHOD=1 INTER POSTHOC MAXEVAL=9999 NOABORT PRINT=20 NSIG=3 SIGL=9

$COV MATRIX=R UNCONDITIONAL

$TABLE ROWC STUDY DOSE REGIM SUJID SID ID TIME NTIME TSLD CONC IPRED IRES CWRES

AGE SEXF RACE PAT DIS WT BMI BSA CLCR FORM BACKTX BLOQ FAST

AST ALT CL V2 Q V3 KA ALAG1 F1 ETA1 ETA2 ETA3 ETA4 ETA5 ETA6

NOPRINT ONEHEADER FILE=RES25