Cancer Chemother Pharmacol (2016) 77:89–98
DOI 10.1007/s00280-015-2891-8

ORIGINAL ARTICLE

# Population pharmacokinetic modeling of idelalisib, a novel PI3Kδ inhibitor, in healthy subjects and patients with hematologic malignancies

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Received: 13 October 2015 / Accepted: 19 October 2015 / Published online: 8 December 2015


**Abstract**
*Purpose* Idelalisib is a potent PI3Kδ inhibitor that was recently approved for treating hematologic malignancies. The objective of this analysis was to develop a population pharmacokinetic model for idelalisib and its inactive metabolite GS-563117 and to evaluate the impact of covariates on idelalisib/GS-563117 PK.
*Methods* Data from 10 phase I or II studies in healthy volunteers or patients with hematologic malignancies ($n = 736$) were analyzed using NONMEM. Stepwise forward addition followed by backward elimination was implemented in the covariate (age, gender, race, body weight, baseline CLcr, AST, ALT, disease status, and type of cancer) model building process. Various model assessment methods were used to evaluate the models.
*Results* Idelalisib plasma PK was best described by a two-compartment model with first-order absorption, first-order elimination from the central compartment, and a lag time. A nonlinear relationship between dose and relative bioavailability was included in the final model. Two statistically significant covariates were identified and incorporated into the final model: health status (healthy vs. patient) on CL/F and Q/F and body weight on CL/F. Despite being a statistically significant covariate, the effect of body weight on idelalisib exposures was weak, as evidenced by minor changes of steady-state exposure ($C_{trough}$: 16 %; AUC and $C_{max}$: 10 %) for a patient with extreme body weight (5th and 95th percentile) relative to the typical patient, and not considered to be clinically relevant.
*Conclusions* PopPK models were developed to adequately describe the plasma concentrations of idelalisib and GS-563117. There were no covariate that had a clinically meaningful impact on idelalisib or GS-563117 exposure.

**Keywords** Idelalisib · PI3Kδ · Population pharmacokinetics · Covariates

## Introduction

Phosphatidylinositol 3-kinases (PI3Ks) are enzymes that regulate several important cellular functions [1]. Activation of PI3K generates phospholipid second messengers at the cell membrane that recruit and activate multiple intracellular enzymes that are regulators of cell proliferation, survival, and motility. PI3K signaling is mediated by four catalytic isoforms of the p110 subunit of the enzyme—$\alpha$, $\beta$, $\gamma$, and $\delta$ [1, 2]. PI3K$\delta$ is critical for multiple signaling pathways that are hyperactive in B cell malignancies [3]. Inhibition of PI3K$\delta$ modulates B cell receptor (BCR) signaling as well as signaling through cytokine and chemokine receptors and integrins. These signaling pathways act via downstream enzymes (most importantly the serine/threonine protein kinase, Akt) to regulate proliferation, apoptosis, motility, homing, and retention of malignant B cells in lymphoid tissues and bone marrow compartments [1, 4].

**Electronic supplementary material** The online version of this article (doi:10.1007/s00280-015-2891-8) contains supplementary material, which is available to authorized users.

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Idelalisib (IDELA, formerly CAL-101; supplement Fig. 1) is a PI3Kδ inhibitor and is highly selective competitive inhibitor of adenosine-5′-triphosphate binding to the catalytic subunit of PI3Kδ [5]. In lymphoid cell lines derived from B cell malignancies and primary tumor samples from patients, idelalisib blocked PI3Kδ-AKT signaling and resulted in inhibition of proliferation and in induction of apoptosis [3, 5, 6]. Recently, idelalisib was approved for the treatment of relapsed chronic lymphocytic leukemia (CLL) in combination with rituximab, relapsed follicular B cell non-Hodgkin lymphoma (FL), and relapsed small lymphocytic lymphoma (SLL). Clinical efficacy has been demonstrated using idelalisib as monotherapy for the treatment of previously treated indolent non-Hodgkin's lymphoma (iNHL) where the response rate was 57 % (71 out of 125 patients) and the median duration response was 12.5 months [7]. Additionally, in a randomized placebo-controlled phase III study, patients with relapsed chronic lymphocytic leukemia (CLL) received idelalisib as a combination therapy with rituximab had improved overall response (81 % vs. 13 %) and overall survival at 12 months (92 % vs. 80 %) compared to patients received rituximab alone [8].

The object of this analysis was to develop population PK models to characterize the concentration–time course of idelalisib and its inactive metabolite, GS-563117, in plasma following oral administration of idelalisib to healthy subjects or patients with hematologic malignancies. Significant covariates that influence the PK of idelalisib and GS-563117 were also identified and evaluated during the model building process. The model was further used to evaluate the effect of various factors on idelalisib and GS-563117 exposures to support the dosing and labeling of idelalisib for treating subjects with hematologic cancers.

## Materials and methods

### Study population, PK sampling, and bioanalysis

Plasma idelalisib concentration data from subjects enrolled in 10 phase I to II idelalisib clinical trials (five healthy volunteer trials and five patient trials; supplement Table 1) were included in the PopPK analysis. In these studies, subjects received idelalisib as either single dose or multiple doses (once a day or twice a day) at dose ranging from 17 to 400 mg (healthy volunteer 17, 50, 100, 150, 200, and 400 mg; patient 50, 100, 150, 200, 300, and 350 mg). Idelalisib given as 150 mg oral dose twice a day was indicated as the clinical dose for treating hematologic cancers (CLL, FL, and SLL), and five studies contain such dosing regimens. Eight out of these studies contained intensive sampling schedules.

The plasma samples of idelalisib were analyzed using a validated liquid chromatography-mass spectrometry/mass spectrometry (LC/MS/MS) method with a lower limit of quantitation (LLOQ) of 1 ng/mL.

### Model development and evaluation

PopPK analysis was performed using the nonlinear mixed effects modeling approach. This approach estimates the typical value of parameters and their variances. Model parameter estimation and model evaluation were implemented with NONMEM 7, version 7.1.2 (ICON Development Solutions; Ellicott City, Maryland, USA) [9] with Intel(R) Fortran Compiler (version 10.1.021), PerlSpeaksNONMEM (PsN) version 3.2.12 (Uppsala University, Sweden) [10, 11] and S-PLUS 6.2 (TIBCO Software Inc). PopPK estimation was performed using the first-order conditional estimation (FOCE) method in NONMEM. Log-transformed idelalisib and GS-563117 concentration data were used in the PopPK analysis.

Based on graphical evaluation of idelalisib plasma concentration–time profiles and the previous PK analysis, an initial structural model was selected and then tested with various modifications. The goodness of fit of the models was evaluated. Symmetry of the individual parameters around the estimated median parameter was assessed graphically. Model diagnostics provided directions for further model modifications and/or refinements. The best structural PopPK model (final base model) was selected after comparison of various structural models.

Inter-individual variability (IIV) was modeled for all PK parameters as follows:

$$\theta_i = e^{(\theta_T + \eta_i)}$$

where $\theta_i$ is the parameter for the $i$th subject, $\theta_T$ is natural logarithm of the typical value of the parameter in the population, and $\eta_i$ (ETA) is a random inter-individual effect with mean 0 and variance $\omega^2$.

Residual variability was modeled as follows:

$$\ln\left(y_{ij}\right) = \ln\left(\hat{y}_{ij}\right) + \varepsilon_{ij}$$

where $y_{ij}$ and $\hat{y}_{ij}$ represent the $j$th observed and predicted concentration, respectively, for the $i$th subject; $\varepsilon_{ij}$ is the residual error for the $i$th subject and $j$th concentration, which are independent and normally distributed with mean zero and variance $\sigma^2$.

Covariates were then tested for their impact on the model parameters from the final base model. The following covariates were examined for their influence on the PK parameters: baseline age, body weight, gender, and race (Caucasian vs. non-Caucasian), type of cancer (CLL, iNHL, and other), type of background therapies, baseline

serum creatinine clearance (CrCL), baseline serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST), and disease status (healthy volunteer [HV] vs. patient).

Relationships of PK parameters to continuous covariates were modeled as follows. This equation provides log normalization of continuous covariates when the PK parameters are estimated in log domain.

$$\theta_i = \exp\left(\theta_T + k_{\text{cov}} \cdot \ln\left(\frac{\text{Cov}_i}{\text{Cov}_{\text{pop}}}\right) + \eta_i\right)$$

Relationships to categorical covariates were modeled as follows:

$$\theta_i = \exp(\theta_T + k_{\text{cov}} \cdot X_i + \eta_i)$$

where $\theta_i$ is the individual model parameter for the $i$th subject; $\theta_T$ is natural logarithm of the typical value of the parameter in the population; $\text{Cov}_i$ is the individual value of a continuous covariate for the $i$th subject; $\text{Cov}_{\text{pop}}$ is the population median value of a continuous covariate for the typical population; $X_i$ is the individual categorical covariate indicator, where a value of zero represents the population with the covariate of the most frequent category, and other integer values represents other categories; $k_{\text{cov}}$ is the coefficient describing the strength of the covariate effect; and $\eta_i$ is a random inter-individual effect with mean zero and variance $\omega^2$.

A step-wise forward addition and backward deletion model selection strategy was used, and linear as well as nonlinear relationships between the explanatory covariates and model parameters were evaluated. Model selection was done on the basis of a log-likelihood ratio test at an acceptance $p$ value of 0.01 (forward addition) or 0.001 (backward elimination). For nonsignificant covariates, the difference in −2 times the log of the likelihood (−2LL) between a full and reduced model was assumed to have a Chi-square asymptotic distribution with degrees of freedom equal to the difference in number of parameters between the two models. The final PopPK model only contained covariates that met the pre-defined statistical criteria.

Convergence of NONMEM was assessed on the basis of: (1) acceptable goodness-of-fit plots; (2) number of significant digits ≥3 for all parameters (also a criterion for successful termination); (3) successful covariance step; and (4) convergence with different initial estimates. The following model diagnostics were used to evaluate the final PopPK model: goodness-of-fit diagnostics, visual predictive check (VPC) plots [12], numerical predictive check (NPC) [13], and bootstrap assessments [14].

### Assessment of the impact of covariates on idelalisib exposures

Simulation analysis was performed to examine the influence of statistically significant covariates on idelalisib/GS-563117 PK parameters based on the final model. The effect of extreme values (5th and 95th percentiles) of each statistically significant covariate on affected idelalisib PK parameters was evaluated against clinically relevant patient populations.

In addition, the impact of extreme covariates (5th and 95th percentiles) on idelalisib steady-state exposures was also evaluated to show the isolated influence of each covariate on the steady-state exposure of idelalisib after repeated doses of 150 mg BID. The steady-state area under the plasma concentration versus time curve (AUC), the maximum concentration of idelalisib ($C_{\text{max}}$), and the trough concentration ($C_{\text{trough}}$) were computed for each of the scenarios based on the final PopPK model.

## Results

### PopPK analysis datasets

The PopPK dataset contained a total of 7870 data points from 738 subjects. Because outlier data points could bias the correlation between PK parameters and covariates in the PopPK analysis, individual data points were investigated and considered for omission if conditional weighted residual—|CWRES| > 6 after development of the base PopPK model, before covariate analyses. Based on this criterion, 28 idelalisib plasma concentrations were excluded from the PopPK dataset. As a result, the final PopPK data included 7842 idelalisib plasma concentration measurements from 736 subjects (638 patients and 98 healthy volunteers) and was used to derive the final PopPK model. Because GS-563117 plasma concentrations were only measured in six clinical studies (two healthy volunteer studies and four patient studies) out of 10 total trials, the final PopPK data for GS-563117 contained 2148 samples from 279 subjects.

### Model development and covariate analysis

The structural PopPK model that best described the idelalisib data was a two-compartment model with first-order absorption, first-order elimination from the central compartment, and a lag time, as illustrated in supplement Fig. 2. The PK model was parameterized with clearance (CL/F), central volume ($V_c/F$), distributional clearance ($Q/F$), peripheral volume ($V_p/F$), absorption rate constant

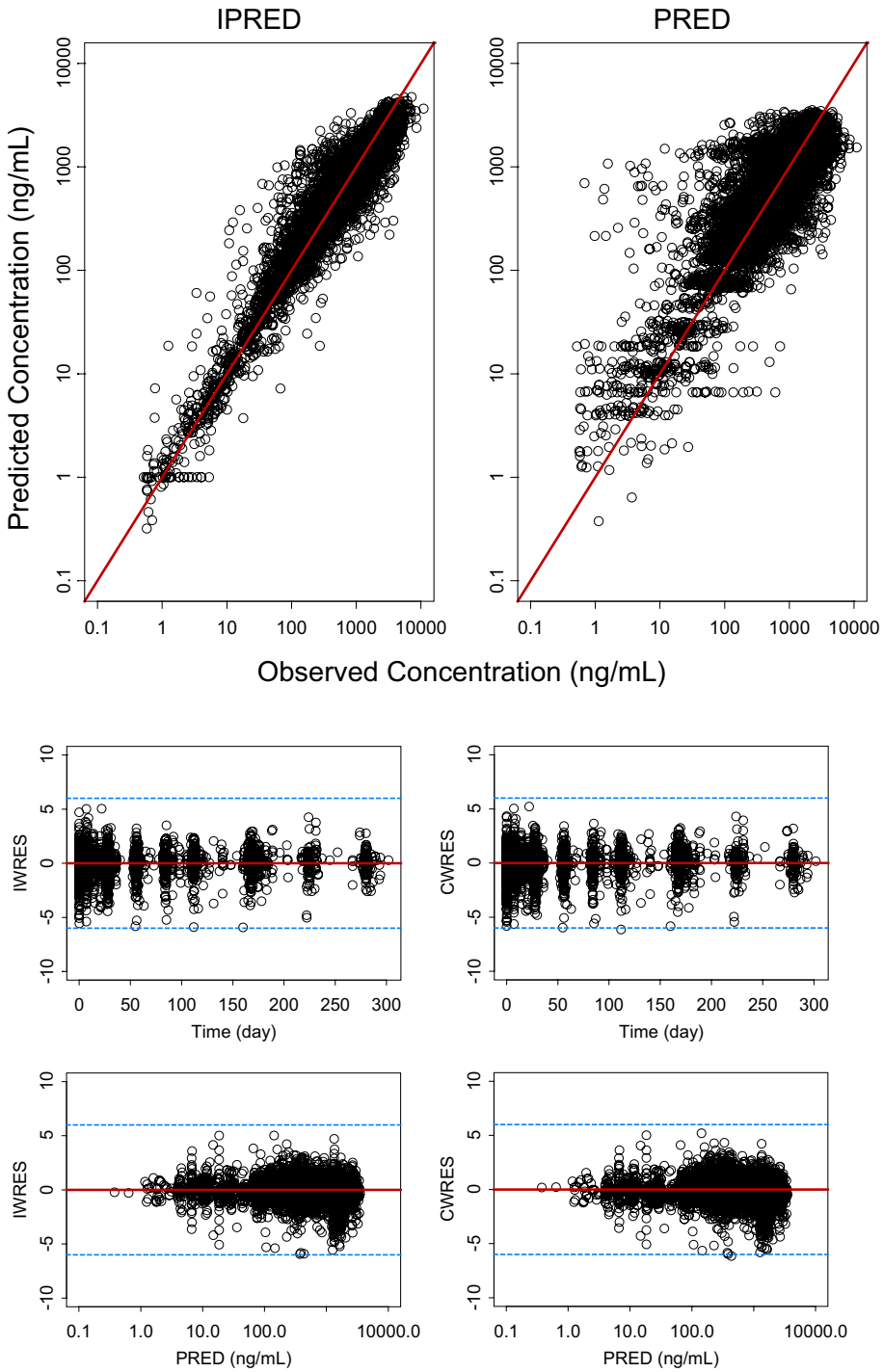


**Fig. 1** Model diagnostic plots for idelalisib. **a** Predicted versus observed goodness-of-fit plots for the final PopPK model. **b** Residual goodness-of-fit plots for the final PopPK model

($k_a$), and relative bioavailability (F1). In addition, a non-diagonal Ω matrix was implemented to estimate correlation between random effects between clearance and volume parameters (CL/F vs. $V_c/F$ and $Q/F$ vs. $V_p/F$).

Based on the graphical analysis, idelalisib concentrations appeared to increase in a less than dose proportional manner. Therefore, a nonlinear relationship between dose and relative bioavailability ($F_1$) was added and defined as the function:

$$F_1 = \exp\left(\theta_7 \cdot \log\left(\frac{\text{dose}}{150}\right)\right),$$

where $\theta_7$ is defined as a negative value, allowing $F_1$ to decrease as the dose increases and $F_1$ is 1 at 150 mg.

**Table 1** Idelalisib final PopPK parameters

| Idelalisib parameter | Parameter description | Population estimate | Bootstrap final model median (2.5th, 97.5th percentiles) |
|---|---|---|---|
| | Apparent oral clearance, CL/*F* (L/h) | | |
| $Exp(\theta_1)$ | Patient | 14.88 | 14.90 (14.38, 15.55) |
| $Exp(\theta_8)$ | HV | 19.69 | 19.68 (18.43, 21.25) |
| $\theta_{10}$ | Influence of body weight on CL/*F* | 0.245 | 0.244 (0.141, 0.293) |
| $Exp(\theta_2)$ | Apparent central volume, $V_c/F$ (L) | 22.65 | 22.65 (20.52, 24.80) |
| | Apparent inter-compartmental clearance, Q/F (L/h) | | |
| $Exp(\theta_3)$ | Patient | 11.82 | 11.81 (10.47, 12.99) |
| $Exp(\theta_9)$ | HV | 7.846 | 7.855 (7.024, 9.002) |
| $Exp(\theta_4)$ | Apparent peripheral volume, $V_p/F$ (L) | 72.97 | 72.90 (66.16, 77.83) |
| $Exp(\theta_5)$ | Absorption rate constant, $k_a$ (1/h) | 0.482 | 0.482 (0.463, 0.518) |
| $Exp(\theta_6)$ | Lag time (h) | 0.247 | 0.247 (0.245, 0.248) |
| $\theta_7$ | Influence of dose on bioavailability ($F_1$) | −0.262 | −0.262 (−0.317, −0.226) |
| Inter-individual variability (%) | CL/*F* | 38.21 | 38.22 (35.54, 41.06) |
| | $V_c/F$ | 85.15 | 85.40 (83.05, 101.3) |
| | $Q/F$ | 38.86 | 39.06 (38.84, 56.59) |
| | $V_p/F$ | 73.35 | 70.36 (56.18, 77.13) |
| | $k_a$ | 38.34 | 37.77 (15.60, 38.34) |
| | Lag time | 45.50 | 45.51 (40.33, 52.37) |
| $\omega^2_{CL,Vc}$ | Covariance between CL/F and $V_c/F$ | 0.112 | 0.112 (0.058, 0.166) |
| $\omega^2_{Q,Vp}$ | Covariance between Q/F and $V_p/F$ | 0.231 | 0.228 (0.183, 0.348) |
| $\sigma$ | Residual error (%) | 53.48 | 53.46 (50.77, 55.58) |

The effects of baseline demographic covariates (age, body weight, gender, race), cancer- and treatment-history-related covariates (disease status, cancer type, background treatment), hepatic function-related covariates (ALT, AST), and renal function-related covariates (CrCL) on each of the idelalisib PK parameters were assessed based on individual Bayesian post hoc PK parameter estimates generated from the base PopPK model. The covariates showing significant ($p < 0.01$) trends with PK parameters in this screening step were evaluated in the covariate model building and included: baseline age, body weight, gender, CrCL, and disease status on CL/F; baseline body weight, gender, and rituximab usage on $V_c/F$; baseline age, body weight, disease status, and rituximab usage on Q/F; baseline age and disease status on $V_p/F$, disease status on $k_a$.

Following covariate model development, the final PopPK model was established and included the following parameter-covariate relations:

$$CL_i = \exp\left(\theta_1 \cdot (\text{patient}) + \theta_8 \cdot (\text{HV}) + \theta_{10} \cdot \log\left(\frac{\text{weight}}{75}\right) + \eta_{CL}\right)$$

$$Q_i = \exp\left(\theta_3 \cdot (\text{patient}) + \theta_9 \cdot (\text{HV}) + \eta_Q\right)$$

$$F_1 = \exp\left(\theta_7 \cdot \log\left(\frac{\text{dose}}{150}\right)\right)$$

The PK parameter estimates from the final PopPK model for idelalisib are presented in Table 1. The estimated idelalisib CL/F for a typical patient and HV (body weight of 75 kg) was 14.88 and 19.69 L/h, respectively. The estimated $V_c/F$ was 22.65 L. The inter-individual variability (IIV) was 38.21 % for CL/F and 85.15 % for $V_c/F$. The estimated $Q/F$ was 11.82 L/h for a patient and 7.846 L/h for a healthy volunteer, and $V_p/F$ was 72.97 L. The population terminal elimination half-live for a typical patient as calculated from the final PopPK model parameters was 8.2 h. The median values and ranges of individual Bayesian post hoc CL/*F* and $V_c/F$ estimates for 736 patients were 15.55 (minimum to maximum 3.28–63.85) L/h and 21.1 (minimum to maximum 6.05–767.8) L, respectively. The median and 2.5–97.5 percentile range of terminal elimination half-live, calculated from individual Bayesian post hoc PK parameter estimates, was 8.09 h (4.32–16.81 h). Intra-individual variability in plasma idelalisib concentrations expressed as a coefficient of variation was 53.48 %.

Median values of PopPK parameter estimates from bootstrapping were similar to the parameter estimates of the analysis dataset with reasonable 95 % CIs, indicating that the final PopPK model parameters were accurately estimated.

GS-563117 PK was adequately described by a two-compartment model with first-order absorption, first-order elimination from the central compartment, and a lag time. A nonlinear relationship between dose and relative bioavailability ($F_1$) was added during model building process, consistent with idelalisib PK model.

The final PopPK model includes the following parameter-covariate relations:

$$\mathrm{CL}_i = \exp(\theta_1 + \theta_8 \cdot (\mathrm{HV}) + \eta_{\mathrm{CL}})$$

$$F_1 = \exp\left(\theta_7 \cdot \log\left(\frac{\mathrm{dose}}{150}\right)\right)$$

The PK parameter estimates from the final PopPK model for GS-563117 are presented in Table 2. The estimated GS-563117 CL/F for a typical cancer patient and HV was 4.39 and 6.69 L/h, respectively. The estimated $V_c/F$ was 7.54 L. The IIV was 49.5 % for CL/$F$ and 54.2 % for $V_c/F$. The estimated $Q/F$ was 1.278 L/h and $V_p/F$ was 16.12 L. The population terminal elimination half-life for a typical patient as calculated from the final PopPK model parameters was 11.58 h. The median values and ranges of individual Bayesian post hoc CL/$F$ and $V_c/F$ estimates for 279 subjects were 4.44 (minimum to maximum 0.855–42.66) L/h and 7.24 (minimum to maximum 3.04–21.64) L, respectively. The median and 2.5–97.5 percentile range of terminal elimination half-live, calculated from individual Bayesian post hoc PK parameter estimates, was 11.60 h (9.75–15.09 h). Intra-individual variability in plasma GS-563117 concentrations expressed as a coefficient of variation was 34.8 %.

Median values of PopPK parameter estimates from bootstrapping were similar to the parameter estimates of the analysis dataset with reasonable 95 % CIs, indicating that the final PopPK model parameters were accurately estimated.

## Model evaluation

The general goodness-of-fit plots of the final idelalisib PopPK model are shown in Fig. 1. A good agreement between the predicted concentrations and the observed concentrations was observed. No apparent bias was observed in the residual plots over time and across predicted concentration.

The VPC stratified by study and dose level evaluated the ability of the model to reproduce the distribution of the data. VPC simulations of 17–400 mg of idelalisib administered single dose or QD or BID were performed as a validation of the final PopPK model. A total of 1000 replicates of the trials were simulated using the observed covariates for each individual, the final PopPK model parameter estimates, the estimated subject specific random effects, and the residual error. The VPC plots (supplement Figures 5-7) showed that the final idelalisib PopPK model adequately predicted the central tendency and variability of the plasma idelalisib concentrations in cancer patients across all studies for dose regimens of 50–350 mg BID and 150–300 mg QD.

NPC simulations of idelalisib administered as a single dose, QD or BID were performed to evaluate the final PopPK model. A total of 1000 replicates of the trials were simulated using the observed covariates for each individual, the final PopPK model parameter estimates, the estimated subject specific random effects, and the residual error. NPC results are presented in supplement Table 2. Overall, the NPC results suggested that the model adequately described central tendency and variability of idelalisib PK concentrations. Additional model evaluations showed that GS-563117 final PopPK model was adequately developed with sufficient robustness.

## Impact of covariate on idelalisib exposures

The parameter–covariate relationships that were included in the final idelalisib PopPK model are presented in Fig. 2. Collectively, these plots indicated that the covariate model accurately described the relationship between individual PK parameter estimates and patient covariates. Although baseline body weight was identified as statistically significant in the PopPK analysis, the impact across the range on idelalisib CL/F was low: CL/F at extreme low (5 %) and high (95 %) body weight was within the window of 92–110 % relative to CL/F value at typical body weight of 75 kg.

Further analysis suggested that the magnitude of the effect of all statistically significant covariates on idelalisib steady-state exposure was low. Compared to a typical patient with median exposures, the exposures (AUC, $C_{\mathrm{max}}$, and $C_{\mathrm{trough}}$) of a patient with covariate values (5th and 95th percentile) varied as much as ~18, ~10, and ~31 %, respectively (Fig. 3). Given the low variability caused by covariates relative to the range in the population, all covariates are not expected to have clinically meaningful impacts on idelalisib exposure. The current dose regimen of 150 mg BID without further correction is considered appropriate.

The impact of body weight on the idelalisib PK was further assessed by categorizing patients into three categories based on their quartile (<25th, 25th–75th, and >75th). Idelalisib exposure was also simulated using the Bayesian post hoc PK parameters for idelalisib 150 mg BID. This simulation took into account potential correlations among covariates and the potential confounding effects of multiple covariates on PK parameters. The impact of body weight on idelalisib exposure is presented in supplement Table 3. Patients with lower body weight have slightly higher steady-state exposures ($p$ = 0.0036, <0.01, and 0.391 for AUC, $C_{\mathrm{max}}$, and

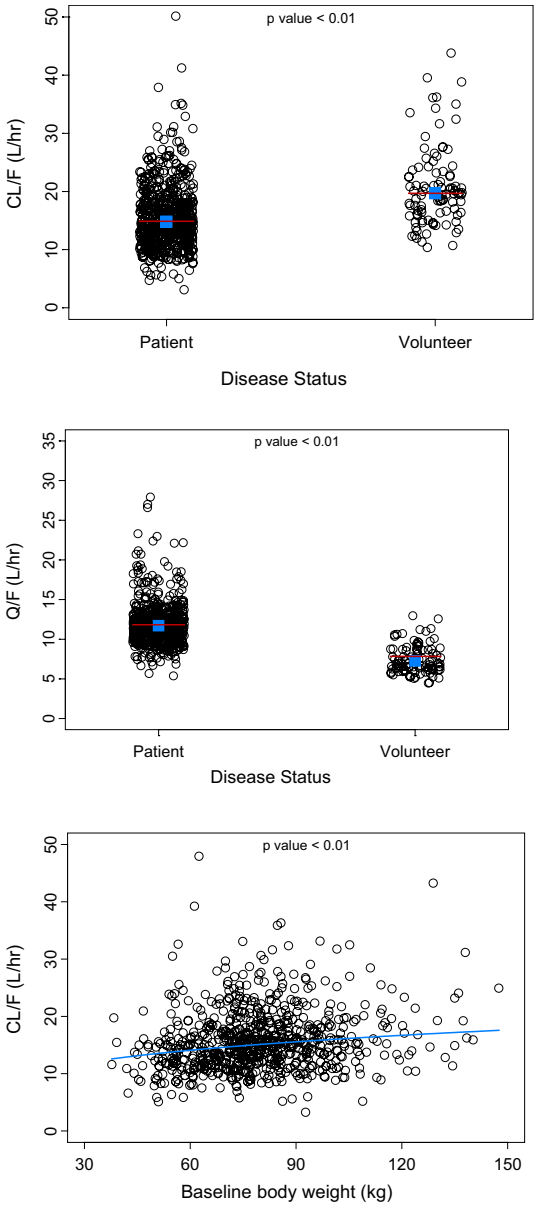


**Fig. 2** Covariate influence on idelalisib PK parameters. **a** Individual predicted CL/F of patient versus healthy volunteer. **b** Individual predicted Q/F of patient versus healthy volunteer. **c** Individual predicted CL/F over the observed range of body weight

$C_{trough}$, respectively, ANOVA). Based on this result, no dose adjustment appears necessary in the heavier patients.

The impact of other covariates such as age, gender, race, type of cancer, background therapy (rituximab or not) was also evaluated and presented in supplement Table 3. Overall, the effect of these covariates on idelalisib steady-state exposures was minor and not considered to be clinically meaningful.

The only significant covariate included in the final GS-563117 PopPK model was disease status (healthy vs. patients). As such, for a cancer patient, there was no significant covariate identified based on PopPK analysis. Further assessment on GS-563117 exposures based on post hoc predictions (supplement Table 4) also showed that body weight age, gender, race, type of cancer, background therapy (rituximab or not) had minor impacts on GS-563117 exposure and these impacts were not considered clinically meaningful.

## Discussion

The PK data of idelalisib in cancer patients and healthy subjects from 10 phase I or II idelalisib clinical trials were well described by a two-compartment model with first-order absorption, first-order elimination from the central compartment, and a lag time. Idelalisib concentrations appeared to increase in a less than dose proportional manner. Addition of a nonlinear relationship between dose and relative bioavailability significantly improved the model fitting. The typical idelalisib oral clearance (CL/F) was 14.88 L/h for a theoretical patient with body weight of 75 kg. The CL/F value in healthy volunteers was approximately 32 % faster than that in cancer patients. The typical elimination half-life was 8.2 h for idelalisib. The central volume of distribution of idelalisib was 22.6 L. The peripheral volume of distribution of idelalisib was also relatively small (72.97 L). The half-life estimates were in line with the observed data which showed minimal accumulation of idelalisib with a BID regimen. A relatively small IIV was estimated for idelalisib CL/F from the base PopPK model without covariates (38.2 %) and was further reduced in the final PopPK model after incorporating covariate effects (36.6 %). Of note, a relatively large inter-subject variability on volume parameters was observed. Given the lack of exposure–response relationship over a wide range of idelalisib exposures (~tenfold) in the pivotal trial for treating iNHL, the impact of the variability on these parameters is likely not clinically meaningful [15].

The final PopPK model for idelalisib was extensively evaluated based on multiple methods. Goodness-of-fit criteria and model evaluation methods revealed that the final PopPK model was adequate to describe the observed data without systematic bias. Internal model evaluations such as VPC and NPC provided evidence that both the fixed and random effect components of the final PopPK model were reflective of the observed data. Bootstrap resampling techniques showed that the model was numerically stable with precise parameter estimation.

Baseline body weight and disease status were identified as statistically significant covariates for idelalisib clearance. Patients with greater body weight had a slightly higher CL/F. Further simulation analysis results suggested these statistically significant covariates were unlikely to

**Table 2** GS-563117 final PopPK parameters

| GS-563117 parameter | Parameter description | Population estimate | Bootstrap final model median (2.5th, 97.5th percentiles) |
|---|---|---|---|
| $Exp(\theta_1)$ | Apparent oral clearance, CL/$F$ (L/h, cancer patient) | 4.393 | 4.402 (4.072, 4.713) |
| $\theta_8$ | Influence of disease status on CL/$F$ | 0.421 | 0.421 (0.261, 0.553) |
| $Exp(\theta_2)$ | Apparent central volume, $V_c/F$ (L) | 7.538 | 7.506 (6.527, 8.779) |
| $Exp(\theta_3)$ | Apparent inter-compartmental clearance, $Q/F$ (L/h, cancer patient) | 1.278 | 1.277 (1.189, 1.329) |
| $Exp(\theta_4)$ | Apparent peripheral volume, $V_p/F$ (L) | 16.12 | 16.01 (12.90, 18.37) |
| $Exp(\theta_5)$ | Absorption rate constant, $k_a$ (1/h) | 0.081 | 0.081 (0.074, 0.092) |
| $Exp(\theta_6)$ | Lag time (h) | 0.480 | 0.480 (0.467, 0.500) |
| $\theta_7$ | Influence of dose on bioavailability (F1) | −0.499 | −0.499 (−0.619, −0.347) |
| Inter-individual variability (%) | CL/$F$ | 49.50 | 50.73 (49.10, 60.90) |
| | $V_c/F$ | 54.22 | 54.30 (52.84, 72.85) |
| | $Q/F$ | 31.40 | 31.37 (17.98, 32.19) |
| | $V_p/F$ | 39.37 | 39.44 (22.13, 44.91) |
| | $k_a$ | 56.92 | 56.77 (37.76, 57.05) |
| | Lag time | 48.68 | 48.70 (46.84, 54.67) |
| $\omega^2_{CL,\ Vc}$ | Covariance between CL/$F$ and $V_c/F$ | 0.087 | 0.088 (0.020, 0.148) |
| $\omega^2_{Q,\ Vp}$ | Covariance between $Q/F$ and $V_p/F$ | 0.059 | 0.059 (0.009, 0.087) |
| $\sigma$ | Residual error (%) | 34.79 | 34.70 (31.78, 36.96) |

have a clinically meaningful impact on idelalisib exposure. The current regimen of 150 mg BID is appropriate, and no further dose adjustment is recommended. Compared to a typical patient with median exposures, the exposures (AUC, $C_{max}$, and $C_{trough}$) of a patient with covariate values (5th and 95th percentile) changed as much as ~18, ~10, and ~31 %, respectively. Overall, the moderate covariate effects suggest that further dose adjustment based on any of the statistically significant covariates are unlikely to have a clinically meaningful reduction in inter-individual PK variability of idelalisib. Given the IIV in idelalisib PK parameters is low, inclusion of any additional covariate is not likely to have any clinically meaningful impact.

Based on PopPK covariate analysis and comparison of expected idelalisib exposure simulated from post hoc PK parameters, it was found that no dose adjustment appears to be necessary for different gender, elderly population, and non-Caucasian patients. Patients with or without rituximab treatment also had similar idelalisib PK.

Based on the covariate assessment of the impact of serum creatinine clearance on idelalisib PK parameters and the comparison of expected idelalisib exposure simulated from post hoc PK parameters of patients with different renal functions, mild or moderate impaired renal function appeared to have no effect on idelalisib exposure. Although data were limited for patients with severe renal impairment and end-stage renal disease since the assessment was limited to only 1.11 % patients ($n = 8$) with severe renal impairment, based on a phase I study that evaluated idelalisib PK in subject with severe renal impairment versus matched healthy control subjects, the observed changes in idelalisib exposure in subjects with severe renal impairment were relatively minimal (27, 27, and 5 % for $AUC_{last}$, $AUC_{inf}$, and $C_{max}$, respectively) and not considered to be clinically meaningful [16]. Overall, these results are consistent with the findings that only a small portion of drug (<15 %) is eliminated through kidney based on the mass balance study of idelalisib [17].

Patients with significantly impaired hepatic function were excluded from the clinical studies that were used for PopPK analysis, and as such, Child-Pugh scores were not formally evaluated as a covariate in the population PK analysis. Instead, common markers of drug-induced liver injury (AST and ALT) were individually tested as covariates of idelalisib PK. There was no evidence to suggest that commonly used markers of hepatic function had a clinically meaningful effect on idelalisib exposure, and further dose adjustment based on covariates related to hepatic function is unlikely to lead to a clinically meaningful reduction in IIV of idelalisib PK. In addition, a phase I study evaluating idelalisib PK in moderate or severe hepatic impaired subject versus healthy control subjects showed that there was only moderate change in idelalisib AUC (58–60 %) in hepatic impaired subjects and these changes were not clinically relevant [18].

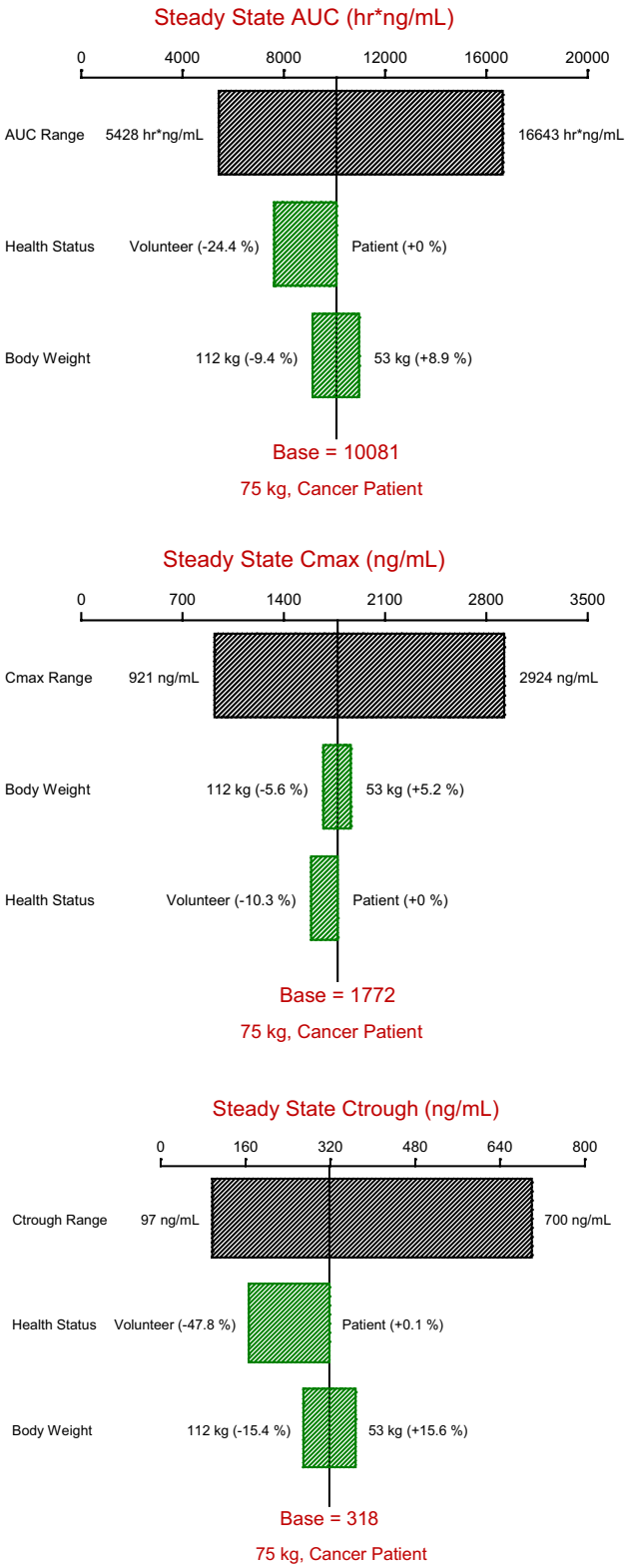


**Fig. 3** Analysis of covariate impact on idelalisib steady-state exposures following 150 mg BID oral administration. Base, as represented by the black vertical line and red values, refers to the predicted steady-state exposure (AUC or $C_{max}$ or $C_{trough}$) of idelalisib in a typical cancer patient with body weight of 75 kg. The black shaded bar shows the 5th to 95th percentile exposure range across the entire population. Each green shaded bar represents the influence of a single covariate on the steady-state exposure after repeated idelalisib dose of 150 mg BID. The upper and lower values for each covariate capture 90 % of the plausible range in the population. The length of each bar describes the potential impact of that particular covariate on idelalisib exposure, with the percentage value in the parentheses at each end representing the percent change of exposure from the base value. **a** Steady-state AUC. **b** Steady-state $C_{max}$. **c** Steady-state $C_{trough}$ ▶

The PK data of GS-563117 following idelalisib administrations were well described by a two-compartment model with first-order absorption, first-order elimination from the central compartment, and a lag time. GS-563117 concentrations appeared to increase in a less than dose proportional manner and addition of a nonlinear relationship between dose and relative bioavailability significantly improved the model fitting. The typical GS-563117 CL/F was 4.39 L/h for a theoretical patient. The CL/F value in healthy volunteers was approximately 52 % faster than that in cancer patients. The typical elimination half-life was 11.58 h for GS-563117. The central volume of distribution of GS-563117 was 7.54 L.

A relatively larger IIV was estimated for GS-563117 CL/F from the base PopPK model without covariates (57.1 %) and was further reduced in the final PopPK model after incorporating covariate effects (49.5 %).

The final PopPK model for GS-563117 was extensively evaluated based on multiple methods. Goodness-of-fit criteria and model evaluation methods revealed that the final PopPK model was adequate to describe the observed data without systematic bias. Internal model evaluations such as VPC and NPC provided evidence that both the fixed and random effect components of the final PopPK model were reflective of the observed data. Bootstrap resampling techniques showed that the model is numerically stable with precise parameter estimation.

Disease status was identified as statistically significant covariate for GS-563117 clearance. Further simulation analysis showed that the magnitude of effect of the disease status on GS-563117 steady-state exposures was modest (<38 %).

Based on PopPK covariate analysis and comparison of expected GS-563117 exposure simulated from post hoc PK parameters of patients with different covariates, it was

found that age, race, gender, baseline creatinine clearance, baseline AST and ALT, type of cancer, co-usage of rituximab have no clinically meaningful impact on GS-563117 PK. No dose adjustment appears to be necessary for these covariates.

## Conclusion

Robust and predictive population PK models were developed to characterize PK of idelalisib and its inactive metabolite, GS-563117. Based on the results of this analysis, idelalisib and GS-563117 in cancer patients were not meaningfully impacted by any covariates included in the analysis. As a result, no dose modification is considered necessary with different covariate values. These population PK models provide a valuable predictive framework that can be used for exposure comparisons of different dosing regimens and covariates, and exposure–response analysis.

**Acknowledgments** The results of this study were presented in part at the 2014 American Conference of Pharmacometric (ACOP) (October 13, 2014, Las Vegas, NV). Financial support for this study was provided by Gilead Sciences, Inc.

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