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A Population Pharmacokinetic Meta-Analysis of Veliparib, a PARP Inhibitor, Across Phase 1/2/3 Trials in Cancer Patients

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Abstract

Veliparib (ABT-888) is a poly(ADP-ribose) polymerase inhibitor in development for the treatment of high-grade ovarian cancer or *BRCA*-mutated breast cancer in combination with carboplatin and paclitaxel. The population pharmacokinetics of veliparib were characterized using combined data from 1470 adult subjects with ovarian cancer, breast cancer, or other solid tumors enrolled in 6 phase 1 studies, 1 phase 2 study, and 2 phase 3 studies of veliparib oral doses of 10 to 400 mg twice daily as monotherapy or in combination with chemotherapy. A 1-compartment model with linear clearance and first-order absorption best characterized veliparib pharmacokinetics. The predicted apparent oral clearance (CL/F) and volume of distribution (V_c/F) were 479 L/day and 152 L, respectively. The significant covariates in the final model included albumin, creatinine clearance, strong inhibitors of cytochrome P450 (CYP) 2D6, and sex on CL/F and albumin, body weight, and sex on V_c/F. Mild and moderate renal impairment increased veliparib median (95%CI) steady-state AUC (AUC_{ss}) by 27.3% (23.7%-30.9%) and 65.4% (56.0%-75.5%), respectively, compared with normal renal function. Male subjects had 16.5% (7.53%-23.9%) lower AUC_{ss} compared with female subjects and coadministration with strong CYP2D6 inhibitors increased AUCss by 13.0% (6.11%-20.8%). Race, age, region, cancer type, or enzyme (CYP3A4, CYP2C19) or transporter (P-glycoprotein, multidrug and toxin extrusion protein 1/2, organic cation transporter 2) inhibiting/inducing comedications were not found to significantly impact veliparib pharmacokinetics. Other than baseline creatinine clearance and hence renal impairment effect on veliparib clearance, no other covariates had a clinically meaningful effect on veliparib exposure warranting dose adjustment.

Keywords

covariates, creatinine clearance, meta-analysis, pharmacokinetics, population pharmacokinetics, veliparib

Veliparib (ABT-888) is an orally bioavailable small-molecule poly(ADP-ribose) polymerase (PARP) inhibitor, which inhibits the repair of deoxyribonucleic acid (DNA) single-strand breaks, inhibits PARylation, and traps PARP enzyme on DNA.[1] In a recent phase 3 study in patients with previously untreated high-grade serous ovarian carcinoma, veliparib in combination with carboplatin and paclitaxel for 6 cycles followed by veliparib maintenance therapy led to significantly longer progression-free survival (PFS) than carboplatin plus paclitaxel induction therapy alone in the entire population.[2] In another double-blind, randomized, controlled phase 3 study in patients with advanced *BRCA*-mutated breast cancer, veliparib treatment in combination with carboplatin/paclitaxel with the option to continue as monotherapy resulted in statistically significant and clinically meaningful improvement in PFS compared with the placebo plus carboplatin/paclitaxel treatment.[3]

Veliparib is a Biopharmaceutical Classification System class 1 compound exhibiting high solubility and permeability. It is absorbed rapidly, with a median T_{max} of about 1.5 hours. Veliparib has previously been shown to display linear pharmacokinetics in the dose range of 10-400 mg and has an elimination half-life of about 6 hours.[4,5] Veliparib is primarily cleared by renal excretion. The mean urinary recovery of unchanged veliparib was 73%, and the total urinary recovery of veliparib (as parent compound and M8 metabolite) was 90%.[6] Veliparib also undergoes liver metabolism

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mediated primarily by CYP2D6 and, to a lesser extent, by CYP2C19 and CYP3A4.[7] Veliparib has one major metabolite in human plasma, M8, a lactam derivative of the parent drug whose plasma AUC is about 20% that of the parent compound.[6] The cellular PARP-inhibitory activity of M8 was 15-fold lower than veliparib and was not expected to contribute significantly to the pharmacological activity of veliparib.

Reports on population pharmacokinetic analysis of veliparib have been published previously.[8-12] The current analysis includes the most comprehensive data (including the largest number of subjects [n = 1470] and more covariates) from the phase 1 through 3 trials.

The objective of this analysis was to characterize population pharmacokinetics following administration of veliparib to determine the relationship between various intrinsic and extrinsic factors and the pharmacokinetic parameters of veliparib that might explain intersubject variability in exposure following veliparib administration.

Methods

Analysis Population and Data

All studies were conducted in accordance with Good Clinical Practice and under the ethical principles established by the Declaration of Helsinki. The study protocols were approved by the institutional review boards of the individual study sites, and all study subjects gave written informed consent prior to enrollment.

The population pharmacokinetic analysis was performed using pharmacokinetic data obtained from 9 clinical studies of veliparib. Veliparib oral doses of 10 to 400 mg twice daily were administered as monotherapy or in combination with chemotherapy in adult subjects with ovarian cancer, breast cancer, or other solid tumors (Table 1).

All pharmacokinetic data from enrolled subjects who received at least 1 dose of veliparib and had at least 1 concentration measurement were included in the pharmacokinetic data set. All observed plasma concentrations below the lowest limit of quantitation (LLOQ) were set to LLOQ/2 and included in the analysis (M5 method).[13]

An outlier identification and exclusion rule was applied to avoid bias in the population and individual pharmacokinetic parameter estimates because of possible inaccurate dosing or sample collection times. Because of the variability in the absorption phase, the method was only applied for data with time since last dose of more than 2.5 hours (longest mean T_{max} observed).[14] A linear analysis of variance (ANOVA) was performed using the natural logarithm of veliparib plasma concentrations as response variable (using the lm function from the stats package in R 3.5.2) at the binned time since last dose and dose at 2.5, 3, 5, 8, 11, 15, 20, 45, 100, and 168 hours. The upper and lower limits were defined as the exponent of the mean predicted natural logarithm of concentrations +2.33 times and −2.33 times the estimated standard deviation of the random errors, respectively, based on the ANOVA model, to exclude only 1% of normally distributed observations. All concentrations greater or less than the computed upper and lower limits, respectively, were excluded from the primary analysis. Sensitivity analysis including all concentrations classified as outliers was also performed.

Sample Collection and Quantification

Pharmacokinetic sampling was performed in each study as shown in Table 1. Blood samples were collected by venipuncture or indwelling catheter into potassium ethylenediaminetetraacetic acid tubes and stored on ice prior to centrifugation. Plasma concentrations of veliparib were determined using a validated online solid-phase extraction followed by liquid chromatography with tandem mass spectrometric detection.[15] In 1 phase 1 study, veliparib concentrations were determined by simple protein precipitation extraction method and liquid chromatography with tandem mass spectrometric detection. The LLOQ of the veliparib assay was approximately 1 ng/mL (range, 1.0-1.13 ng/mL) in each study. The coefficient of variation ranged from 2% to 16.7%; the mean bias ranged from −9.5% to 11.6%.

Population Pharmacokinetic Methodology

A nonlinear mixed-effects modeling approach was used to analyze the observed veliparib plasma concentration-time profiles using NONMEM (version 7.4.3; ICON Development Solutions, Ellicott City, Maryland). The pharmacokinetic models were fitted to the data using the first-order conditional estimation method with η-ε interaction.

Base Model. The base model was parameterized in terms of apparent oral clearance (CL/F), apparent volume of distribution of the central compartment (V_c/F), and first-order absorption rate constant (k_a). The effect of a meal prior to the dose (fasting vs fed vs unknown [reference]) was included on k_a in the base model based on the effect of food on the absorption characteristics as determined from a phase 1 study.[14] In the development of the base model, 1-compartment models with and without lag time were evaluated. Between-subject variability (BSV) in pharmacokinetic parameters was modeled using a multivariate log-normal distribution. Residual variability was evaluated using a combined (additive and proportional) error model.

Covariate Model. Once the structural model was identified, potential covariates were included in the model to evaluate the impact of patient demographics

Table 1. Studies Included in the Veliparib Population PK Meta-Analysis

Study/NCT #	Study Description	Safety Data Set[a]/PK Data Set, n	Tumor Type	Veliparib Doses	Veliparib PK Sampling
1/00526617	Phase 1 multiple-dose, dose-escalation, open-label study; veliparib with temozolomide	42/42	Metastatic melanoma and nonhematologic malignancies	10, 20, 30, 40, 60, 80 mg BID	Cycle 1 day 3 and cycle 1 day 7 prior to dose and 0.5, 1, 1.5, 2, 4, and 6 hours after morning veliparib dose.
2/01063816	Phase 1 open-label, multiple-dose, dose-escalation study; veliparib with carboplatin and gemcitabine	75/74	Advanced solid tumors	30, 60, 80, 140, 210, 250, 310 mg BID	Dose-escalation cohort—cycle 2 day 1 prior to dose and 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after morning veliparib dose. Expanded safety cohort—cycle 1 day—1 and day 1 prior to dose and 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after morning veliparib dose.
3/01199224	Phase 1 open-label, 2-stage, single-dose, randomized, 4-period crossover study; veliparib monotherapy	27/27	Solid tumors	40-mg single dose	Day 1 of each period prior to dosing and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours after veliparib dosing.
4/02009631	Phase 1 single-dose, double-blind, placebo-controlled, randomized, 3-period, 6-sequence crossover study; veliparib monotherapy	47/47	Relapsed or refractory solid tumors	200, 400 mg single dose	Day 1 of each period prior to dosing and 0.5, 1, 2, 3, and 10 hours after veliparib dosing.
5/01506609	Phase 2 randomized, partially blinded study; veliparib with temozolomide or carboplatin and paclitaxel	294/183	Breast cancer	40, 120 mg BID	Cycle 1 day 1 at 0.5, 1, 2, and 3 hours after morning veliparib dose and cycle 1 day 3 prior to dose and 0.5, 1, 2, and 3 hours after morning veliparib dose.
6/02163694	Phase 3 randomized, double-blind study; veliparib with carboplatin and paclitaxel	507/333	Breast cancer	120 mg BID	Cycle 1 day 1 prior to dose and 1 and 3 hours after morning dose of veliparib. Cycle 2 day 1 prior to morning veliparib dose.
7/02470585	Phase 3 randomized, placebo-controlled, double-blind, stratified study; veliparib with carboplatin and paclitaxel	1124/739	Ovarian, fallopian tube, and primary peritoneal cancer	150, 300 mg BID	Cycle 1 day 1 prior to dose and 1, 2, and 3 hours after morning dose of veliparib. Cycles 2, 3, and 4 day 1 prior to morning veliparib dose.
8/02210663	Phase 1 open-label, dose-escalation study; veliparib monotherapy	16/16	Japanese subjects with advanced solid tumors	200, 300, 400 mg BID	Cycle 1 day 1 prior to dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours after morning veliparib dose.
9/02483104	Phase 1 open-label, dose-escalation study; veliparib with carboplatin and paclitaxel	9/9	Japanese subjects with ovarian cancer	100, 150 mg BID	Cycle 1 day 1 prior to dose and 1, 2, 2.5, 3, 4, 6, 8, and 24 hours after morning veliparib dose.

BID, twice-daily dosing; NCT, national clinical trial.

[a] Subjects who received study drug (veliparib or placebo).

Table 2. List of Covariates Evaluated in the Population PK Model

Covariate	Parameter	Reference Value
Body weight (kg)	CL/F, V_c/F	70 kg
Sex (male vs female)	CL/F, V_c/F	Female
Race (black vs other)	CL/F, V_c/F	Other
Age (years)	CL/F, V_c/F	Population median[b]
Region (Japan vs other)	CL/F, V_c/F	Other
Cancer type (breast vs ovarian vs other)	CL/F, V_c/F	Other
AST (U/L)	CL/F	Population median
ALT (U/L)	CL/F	Population median
Total bilirubin (mg/dL)	CL/F	Population median
Albumin (g/L)	CL/F, V_c/F	Population median
CrCL (mL/min)[a]	CL/F	120 mL/min
Lean body weight (kg)	V_c/F	Population median
Comedications (inhibitors of MATE1/2K, inhibitors of P-gp, inhibitors of OCT2, strong inhibitors of CYP2D6, strong inhibitors of CYP3A4, strong inhibitors of CYP2C19, strong inducers of CYP3A4, strong inducers of CYP2C19)	F, CL/F, V_c/F	No concomitant use

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CL/F, apparent oral clearance; CrCL, creatinine clearance; CYP, cytochrome P450; F, relative bioavailability; MATE1, multidrug and toxin extrusion protein 1; OCT2, organic cation transporter 2; P-gp, P-glycoprotein; V_c/F, apparent volume of distribution of the central compartment.

[a] CrCL (based on Cockcroft-Gault formula[19]) was tested both unrestricted and capped at 120 mL/min in the first step, and the more significant improvement was taken forward.[10]

[b] Median was calculated from all subjects included in the population PK analysis (Table 3).

and baseline characteristics on veliparib pharmacokinetics. The covariates evaluated are shown in Table 2. Continuous covariates were included in the model using power functions scaled by a reference value (Table 2) of each covariate in the data set using the following equation:

$$\mathrm{TVP} = \theta \times \left(\frac{\mathrm{COV}}{\mathrm{Reference\ \ value}}\right)^{\theta_{cont}}$$

where TVP is the typical value of the population PK parameter, θ is the pharmacokinetic parameter estimate at the reference value of the covariate (COV), and θ_{cont} is the power exponent for the covariate effect. Categorical covariates were tested with a multiplicative model to obtain the fractional difference of pharmacokinetic parameters between the tested categorical groups using the following equation:

$$\mathrm{TVP} = \theta \times (1 + \mathrm{I_{cat}} \times \theta_{\mathrm{cat}})$$

where TVP is the typical value of the population pharmacokinetic parameter when $\mathrm{I_{cat}}$ is 0 (binary categorical covariate), and θ_{cat} is the proportional change in TVP when $\mathrm{I_{cat}}$ is 1. Significance of the covariates was determined based on a stepwise forward-inclusion and backward-elimination covariate model-building procedure. Forward inclusion and backward elimination steps were conducted at significance levels of $\alpha = 0.01$ and $\alpha = 0.001$, respectively, using the likelihood ratio test.

The developed models were evaluated via goodness-of-fit plots, prediction-corrected visual predictive checks (pcVPCs), and bootstrap analyses. Goodness-of-fit plots included population-predicted versus -observed concentrations, individual predicted versus observed concentrations, conditional weighted residuals (CWRES) versus population-predicted concentrations, CWRES versus time, and CWRES versus time since last dose. Histograms and quantile-quantile plots of intersubject random effects (ETAs) and CWRES were examined to assess the underlying normal distribution, and shrinkage in ETAs was also evaluated. The pcVPCs with 500 simulated replicates of the pharmacokinetic data set were generated to evaluate the adequacy of the final model. Bootstrap evaluation was performed with 1000 replicated data sets to evaluate the stability and performance of the final model. For each bootstrap replicate, model parameters were estimated, and the resulting values from all replicates were used to estimate medians and confidence intervals. Bootstrap statistics were based on replicates that converged successfully. Model parameters based on the original data set were then compared against the bootstrap results.

Results

A total of 9160 veliparib plasma concentrations (9262 including outliers) collected from 1470 subjects following administration of veliparib doses ranging from 10 to 400 mg twice daily were included in the population pharmacokinetic model. About 2.9% of concentration records were below the LLOQ. Given the small fraction of concentrations below the limit of quantitation, the M5 imputation method was used by imputing concentrations below the LLOQ with LLOQ/2. Only a small fraction of concentrations (1.1%) were identified as outliers and excluded from the analysis. A summary of demographic and other intrinsic factors for subjects included in the analysis is presented in Table 3. The median age of the population pharmacokinetic data set was 55 years (range, 22-86 years), with a median body weight of 66 kg (range, 36-182 kg). The patient population was predominantly female (97%) and white (75%).

Population Pharmacokinetic Model

A 1-compartment model with linear clearance and first-order absorption best described the data. The effect of

Table 3. Patient Demographics and Baseline Factors in Veliparib Population PK Data Set

		Study 1 (n = 42)	Study 2 (n = 74)	Study 3 (n = 27)	Study 4 (n = 47)	Study 5 (n = 183)	Study 6 (n = 333)	Study 7 (n = 739)	Study 8 (n = 16)	Study 9 (n = 9)	All Subjects (n = 1470)
Age (years)	Mean (SD)	55.8 (12.7)	52.9 (10.5)	57.0 (14.4)	57.0 (10.9)	45.9 (10.3)	46.8 (10.8)	60.9 (10.3)	60.1 (11.3)	54.6 (17.2)	55.1 (12.5)
	Median	57	52	56	58	45	47	62	59	62	55
	Min-Max	33-79	28-80	29-79	34-80	22-70	24-82	22-86	43-83	27-72	22-86
Lean body weight (kg)	Mean (SD)	49.9 (12.0)	44.1 (8.35)	45.9 (9.45)	45.7 (10.2)	43.2 (7.4)	42.7 (6.23)	41.2 (6.77)	37.3 (5.24)	32.5 (3.37)	42.3 (7.43)
	Median	47.6	42.8	42.0	41.9	42.1	42.0	40.4	35.5	32.4	41.3
	Min-Max	31.3-79.2	29.4-74.6	33.6-68.9	34.6-84.7	29.4-82.2	30.7-69.3	26.1-68.6	30.1-46.5	27.9-38.5	26.1-84.7
Body weight (kg)	Mean (SD)	77.6 (19.1)	70.7 (16.2)	70.7 (11.2)	74.3 (19.3)	71.4 (17.2)	70.4 (16.4)	68.4 (18.5)	59.0 (12.0)	48.0 (6.4)	69.6 (17.8)
	Median	76.0	68.5	68.0	68.6	68.0	67.7	64.0	53.6	49.0	66.0
	Min-Max	48.0-127	43.0-120	52.0-91.0	52.0-133	43.0-158	43.2-146	35.7-182	44.9-86.4	40.4-60.7	35.7-182
Sex	Male, n (%)	15 (36%)	9 (12%)	6 (22%)	7 (15%)	4 (2%)	4 (1%)	–	–	–	45 (3%)
	Female, n (%)	27 (64%)	65 (88%)	21 (78%)	40 (85%)	179 (98%)	329 (99%)	739 (100%)	16 (100%)	9 (100%)	1425 (97%)
Race	White, n (%)	40 (95%)	58 (78%)	21 (78%)	38 (81%)	157 (86%)	260 (78%)	533 (72%)			1107 (75%)
	Black, n (%)	–	2 (3%)	–	1 (2%)	12 (7%)	14 (4%)	27 (4%)			56 (4%)
	Asian, n (%)	1 (2%)	4 (5%)	–	1 (2%)	1 (1%)	24 (7%)	121 (16%)	16 (100%)	9 (100%)	177 (12%)
	Other, n (%)	1 (2%)	10 (14%)	6 (22%)	7 (15%)	13 (7%)	35 (11%)	58 (8%)			130 (9%)
ALT (U/L)	Mean (SD)	29.6 (20.0)	33.6 (23.9)	28.9 (33.4)	26.3 (17.2)	32.0 (32.2)	28.0 (25.9)	21.8 (14.7)	16.3 (7.13)	14.4 (6.86)	25.5 (21.8)
	Median	22	27	20	25	22	20	18	15	12	19
	Min-Max	10-104	11-150	8-184	4-96	8-240	6-254	4-168	8-33	7-30	4-254
AST (U/L)	Mean (SD)	41.1 (39.4)	29.0 (15.1)	28.6 (20.9)	24.1 (17.3)	34.8 (25.9)	29.3 (23.9)	23.3 (11.4)	21.0 (6.20)	18.3 (8.25)	27.0 (19.3)
	Median	29	25	25	21	26	24	20	20	16	22
	Min-Max	16-220	13-88	11-122	3-109	11-159	9-252	8-103	12-37	11-37	3-252
Albumin (g/L)	Mean (SD)	39.6 (5.20)	42.7 (3.72)	39.1 (4.14)	37.8 (4.28)	43.2 (4.30)	41.1 (4.04)	37.8 (4.99)	42.8 (4.12)	37.5 (2.62)	39.6 (5.05)
	Median	40	43	39	38	44	42	38	41	37	40
	Min-Max	27-49	30-50	31-48	26-45	27-52	27-51	20-50	38-52	34-42	20-52
Total bilirubin (mg/dL)	Mean (SD)	0.46 (0.29)	0.24 (0.11)	0.54 (0.19)	0.38 (0.19)	0.39 (0.22)	0.44 (0.21)	0.39 (0.17)	0.56 (0.22)	0.45 (0.17)	0.40 (0.20)
	Median	0.40	0.20	0.50	0.33	0.35	0.41	0.38	0.55	0.40	0.37
	Min-Max	0.20-1.50	0.10-0.60	0.30-1.20	0.12-1.10	0.12-1.80	0.11-1.51	0.10-1.40	0.30-1.00	0.30-0.80	0.10-1.80
Hepatic function	Normal	22 (52%)	56 (76%)	20 (74%)	38 (81%)	116 (63%)	238 (71%)	602 (81%)	15 (94%)	8 (89%)	1115 (76%)
	Mild impairment	20 (48%)	18 (24%)	7 (26%)	9 (19%)	67 (37%)	95 (29%)	137 (19%)	1 (6%)	1 (11%)	355 (24%)
Creatinine clearance (mL/min)	Mean (SD)	101 (32.3)	97.0 (32.7)	101 (36.0)	96.0 (36.0)	118 (35.1)	115 (34.4)	93.1 (33.1)	84.1 (31.0)	96.2 (46.3)	102 (35.4)
	Median	103	97.7	101	86.9	113	109	88.1	88.4	75.0	96.5
	Min-Max	33.9-166	37.7-186	38.2-188	45.2-203	53.5-220	50.4-257	28.2-289	39.2-130	48.8-186	28.2-289
Renal function	Normal	27 (64%)	44 (59%)	17 (63%)	21 (45%)	144 (79%)	251 (75%)	349 (47%)	8 (50%)	3 (33%)	864 (59%)
	Mild impairment	10 (24%)	18 (24%)	7 (26%)	20 (43%)	34 (19%)	76 (23%)	296 (40%)	3 (19%)	4 (44%)	468 (32%)
	Moderate impairment	5 (12%)	12 (16%)	3 (11%)	6 (13%)	5 (3%)	6 (2%)	93 (13%)	5 (31%)	2 (22 %)	137 (9 %)
	Severe impairment	–	–	–	–	–	–	1 (0%)	–	–	1 (0%)
Cancer type	Breast cancer	5 (12%)	11 (15%)	10 (37%)	8 (17%)	183 (100%)	333 (100%)	–	1 (6%)	–	551 (38%)
	Ovarian cancer	10 (24%)	49 (66%)	4 (15%)	25 (53%)	–	–	739 (100%)	14 (88%)	9 (100%)	850 (58%)
	Other	27 (64%)	14 (19%)	13 (48%)	14 (30%)	–	–	–	1 (6%)	–	69 (5%)
Region	Japan	–	–	–	–	–	–	52 (7%)	16 (100%)	9 (100%)	77 (5%)
	Other	42 (100%)	74 (100%)	27 (100%)	47 (100%)	183 (100%)	333 (100%)	687 (93%)	–	–	1393 (95%)
Strong CYP2D6 inhibitors[a]	No	42 (100%)	69 (93%)	27 (100%)	45 (96%)	179 (98%)	327 (98%)	687 (93%)	15 (94%)	9 (100%)	1400 (95%)
	Yes	–	5 (7%)	–	2 (4%)	4 (2%)	6 (2%)	52 (7%)	1 (6%)	–	70 (5%)
Strong CYP3A inhibitors[a]	No	42 (100%)	73 (99%)	27 (100%)	47 (100%)	183 (100%)	333 (100%)	729 (99%)	16 (100%)	9 (100%)	1459 (99%)
	Yes	–	1 (1%)	–	–	–	–	10 (1%)	–	–	11 (1%)
Strong CYP3A inducers[a]	No	41 (98%)	74 (100%)	27 (100%)	46 (98%)	183 (100%)	332 (100%)	736 (100%)	16 (100%)	9 (100%)	1464 (100%)
	Yes	1 (2%)	–	–	1 (2%)	–	1 (0%)	3 (0%)	–	–	6 (0%)
Strong CYP2C19 inhibitors[a]	No	42 (100%)	70 (95%)	27 (100%)	47 (100%)	183 (100%)	332 (100%)	711 (96%)	16 (100%)	9 (100%)	1437 (98%)
	Yes	–	4 (5%)	–	–	–	1 (0%)	28 (4%)	–	–	33 (2%)
Strong CYP2C19 inducers[a]	No	41 (98%)	74 (100%)	27 (100%)	47 (100%)	183 (100%)	333 (100%)	739 (100%)	16 (100%)	9 (100%)	1469 (100%)
	Yes	1 (2%)	–	–	–	–	–	–	–	–	1 (0%)
P-gp inhibitors[a]	No	42 (100%)	73 (99%)	24 (89%)	47 (100%)	183 (100%)	333 (100%)	718 (97%)	16 (100%)	9 (100%)	1445 (98%)
	Yes	–	1 (1%)	3 (11%)	–	–	–	21 (3%)	–	–	25 (2%)
MATE1/MATE2K inhibitors[a]	No	41 (98%)	71 (96%)	27 (100%)	46 (98%)	178 (97%)	316 (95%)	667 (90%)	15 (94%)	9 (100%)	1370 (93%)
	Yes	1 (2%)	3 (4%)	–	1 (2%)	5 (3%)	17 (5%)	72 (10%)	1 (6%)	–	100 (7%)

(*Continued*)

Table 3. Continued

		Study 1 (n = 42)	Study 2 (n = 74)	Study 3 (n = 27)	Study 4 (n = 47)	Study 5 (n = 183)	Study 6 (n = 333)	Study 7 (n = 739)	Study 8 (n = 16)	Study 9 (n = 9)	All Subjects (n = 1470)
OCT2 inhibitors[a]	No	41 (98%)	71 (96%)	27 (100%)	46 (98%)	178 (97%)	316 (95%)	667 (90%)	15 (94%)	9 (100%)	1370 (93%)
	Yes	1 (2%)	3 (4%)	–	1 (2%)	5 (3%)	17 (5%)	72 (10%)	1 (6%)	–	100 (7%)
Meal prior to dose[b]	Fasting	–	–	27 (52%)	–	–	–	–	–	–	27 (2%)
	Fed	–	–	25 (48%)	47 (100%)	–	–	–	–	–	72 (5%)
	Unknown	42 (100%)	74 (100%)	–	–	183 (100%)	333 (100%)	739 (100%)	16 (100%)	9 (100%)	1396 (93%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CYP, cytochrome P450; MATE1, multidrug and toxin extrusion protein 1; MATE2K, multidrug and toxin extrusion protein 2K; Max, maximum; Min, minimum; OCT2, organic anion transporter 2; P-gp, P-glycoprotein

[a] Stated "yes" if at least 1 observation occurred during comedication.

[b] Study 3 followed a crossover food-effect evaluation design; therefore, subjects may have been counted in both fasting and fed states.

a meal prior to the dose (fasting vs fed vs unknown [reference]) was included on the rate of absorption based on the known effect of food on the absorption characteristics in a phase 1 study.[14]

To account for differences in the accuracy of dosing and sampling time recordings, separate proportional error terms for phase 1 versus phase 2 and 3 studies were considered, but it did not significantly reduce the objective function value (OFV). A BSV term on k_a was also tested, but it was not included in further model development because of the lack of visible improvement in the model fit and the difficulty in identifying the individual parameters in sparsely sampled subjects. Finally, different error terms (proportional as well as additive) for the absorption phase (before T_{max} at 2.5 hours)[14] and elimination phase improved the OFV by 1128 points and also lead to improved capture of the overall variability in the pcVPC and thus were included in the model. A model with lag time in absorption did not improve the OFV. A graphical inspection of the data did not support a second compartment.

Significant Covariates

The covariate forward-inclusion and backward-elimination process resulted in the addition of creatinine clearance (CrCL, capped at 120 mL/min), strong inhibitors of CYP2D6, albumin, and sex on CL/F and body weight, and albumin and sex on V_c/F for the full model. All covariates included in the full model were found to be significant in the backward-elimination process and remained in the final model. Overall, by adding the covariates, the BSV was reduced by 25% and 32% for CL/F and V_c/F, respectively. Parameter estimates from the final model are presented in Table 4. All parameters were estimated with good precision. The typical valuse of CL/F, V_c/F, and k_a from the final model were presented as follows:

$$CL/F = 479 \cdot \left(\frac{\min(CrCL,120)}{120}\right)^{0.513} \cdot \left(\frac{ALB}{40}\right)^{0.427} \cdot 1.20^{\text{Male}} \cdot 0.885^{\text{CYP2D6}} \ \frac{L}{day}$$

$$V_c/F = 152 \cdot \left(\frac{WTKG}{70}\right)^{0.505} \cdot \left(\frac{ALB}{40}\right)^{0.260} \cdot 1.25^{\text{Male}} L$$

$$k_a = 59.4 \cdot 1.11^{\text{Fasting}} \cdot 0.356^{\text{Fed}} \ \frac{1}{day}$$

where WTKG is body weight (kg), ALB is albumin (g/L), and CYP2D6 is strong CYP2D6 inhibitor comedication. For categorical covariates, the indicator function used was 1 if subject was in the respective category and 0 elsewise.

Model Qualification

The goodness-of-fit plots for the final model depicted in Figure 1a,b show a good agreement between observed and model-predicted veliparib plasma concentrations, indicating that the 1-compartment model adequately described most of the observed veliparib concentrations. The plots of CWRES versus population-predicted concentrations (Figure 1c,d) or time since last dose indicated that the model is unbiased.

Prediction-corrected visual predictive checks[16] showed good agreement between simulated and observed concentrations with respect to both overall trend and variability, as shown in Figure 2. The small discrepancies in the absorption phase may be partly attributed to variability in the phase 1 studies that cannot be captured by the model because the estimation of additional individual parameters was not supported by the phase 2 and 3 data. The estimated pharmacokinetic parameter values based on the original data set were in good agreement with the medians of the parameter values estimated from the bootstrap (Table 4). The bootstrap analysis confirmed the robustness of the parameter estimates.

Impact of Significant Covariates on Veliparib Exposure

The impact of the covariates on the exposure (area under the plasma concentration-time curve at steady-state [AUC_{ss}], computed as dose divided by clearance) compared with a reference subject (female, no concomitant strong CYP2D6 inhibitors, CrCL $\geq$ 120 mL/min, albumin = 40 g/L) is shown in Figure 3. Mild (CrCL = 75 mL/min) and moderate (CrCL = 45 mL/min) renal impairment are predicted to result in a median increased veliparib AUC_{ss}, of 27.3% (95%CI,

Table 4. Final Parameter Estimates for Veliparib Population Pharmacokinetic Final Model

	Population Analysis	Bootstrap Analysis[a]	
Parameter	Estimate (%RSE)	Median	95%CI
CL/F (L/day)	479 (1.35)	479	466-490
V_c/F (L)	152 (1.10)	152	148-155
k_a (1/day)	59.4 (2.61)	59.4	50.5-77.4
Fed on k_a	0.356 (3.93)	0.350	0.257-0.447
Fasting on k_a	1.11 (4.05)	1.10	0.726-1.55
Albumin on CL/F	0.427 (14.6)	0.426	0.290-0.565
Creatinine clearance on CL/F	0.513 (5.98)	0.513	0.453-0.571
Strong inhibitors of CYP2D6 on CL/F	0.885 (3.29)	0.887	0.817-0.953
Albumin on V_c/F	0.260 (23.9)	0.259	0.104-0.417
Male on V_c/F	1.25 (5.44)	1.25	1.14-1.38
Body weight on V_c/F	0.505 (6.79)	0.506	0.430-0.585
Male on CL/F	1.20 (4.95)	1.20	1.09-1.32
Parameter (BSV)	Estimate (%CV)[b]		
BSV on CL/F	0.085 (29.8)	0.084	0.0753-0.0943
BSV on V_c/F	0.064 (25.7)	0.062	0.0463-0.0818
Parameter (RUV)	Estimate (%RSE)		
Additive error in absorption phase (μg/mL)	0.004 (4.78)	0.003	0.00137-0.00595
Proportional error in absorption phase	0.208 (2.95)	0.209	0.193-0.226
Additive error in elimination phase (μg/mL)	2.96×10^{-7} (36.0)	2.95×10^{-7}	2.71×10^{-7} to 3.32×10^{-7}
Proportional error in elimination phase	0.078 (1.44)	0.078	0.0691-0.0863

BSV, between-subject variability; CI, confidence interval; CL/F, apparent oral clearance; CV, coefficient of variation; CYP, cytochrome P450; k_a, first order absorption rate constant; RSE, relative standard error; V_c/F, apparent volume of distribution of the central compartment.

[a] All runs converged successfully.

[b] %CV is calculated as sqrt(exp[OMEGA(i,i)] − 1) × 100 from the NONMEM output.

23.7%-30.9%) and 65.4% (95%CI, 56.0%-75.5%), respectively, compared with subjects with reference renal function (CrCL ≥ 120 mL/min). Male subjects were predicted to have 16.5% (7.53%-23.9%) lower AUC_{ss} compared with female subjects. Concomitant administration of strong CYP2D6 inhibitors was associated with a 13.0% (6.11%-20.8%) increase in AUC_{ss}. An increase or decrease in albumin of 5 g/L from the population median of 40 g/L was associated with a median decrease of 4.91% (95%CI, 3.53%-6.26%) or a median increase of 5.87% (95%CI, 4.16%-7.60%) in steady-state exposure (AUC_{ss}), respectively.

Discussion

The population pharmacokinetics of veliparib were characterized in subjects with ovarian cancer, breast cancer, or other solid tumors. Previously reported veliparib population pharmacokinetic analyses included data primarily from phase 1 studies with 30-90 subjects[8,10,11] or from a combination of phase 1 and phase 2 studies with up to 425 subjects.[9,12] Current analysis involved the largest data set yet, with data from 1470 subjects obtained from a combination of 6 phase 1, 1 phase 2, and 2 phase 3 studies. The final model was a 1-compartment model with first-order absorption and first-order elimination. Although food effect was not identified as a significant covariate consistent with lack of significant food effect on veliparib pharmacokinetics, effect of food was included on the rate of absorption to best capture the delayed absorption in the presence of food in a small fraction of phase 1 patients in whom food effect was evaluated with extensive sampling in the absorption phase.[14]

An outlier identification and exclusion rule as described above was applied to the data during the postabsorption phase to avoid bias in the population and individual pharmacokinetic parameter estimates because of possible inaccurate dosing or sample collection times and resulted in less than 1.1% of data excluded from the analysis. A sensitivity analysis conducted with inclusion of the outliers resulted in the population estimates of the pharmacokinetic parameter estimates that were in close agreement with those estimated after exclusion of outliers. The goodness-of-fit plots and pcVPC plots were generally acceptable. Although the trough concentrations were captured well, small discrepancies in the absorption phase were

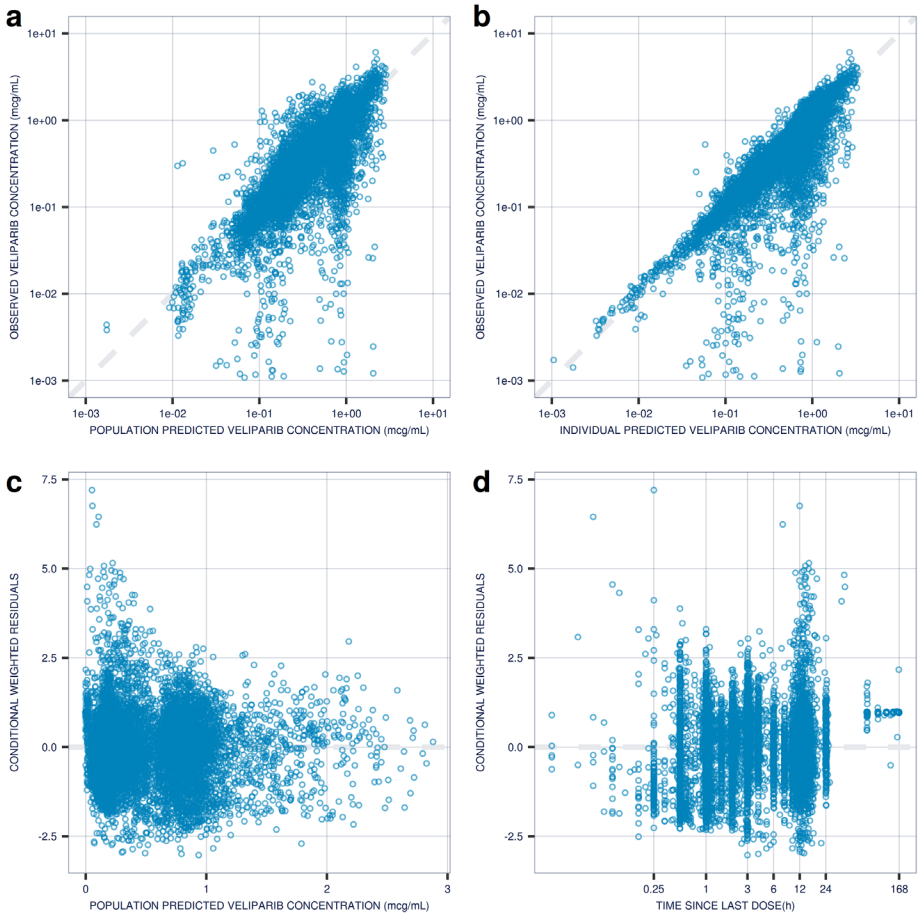

Figure 1. Goodness-of-fit plots for the veliparib final population pharmacokinetic model.

observed, which may be partly attributed to variability in the phase 1 studies (fasted vs. fed) that could not be captured by the model because the sparse pharmacokinetic data from phase 2 and 3 studies did not support estimation of additional pharmacokinetic parameters. The outlier detection and removal procedure further stabilized the model. The estimate of shrinkage for BSV on CL/F was small (13%), whereas that for V_c/F was slightly larger (28%). This is consistent with the majority of the data in the population pharmacokinetic data set being from phase 2 or 3 studies with sparse sampling and little data available in the absorption phase. Thus, the model was well suited for use in an exposure-response analysis that uses steady-state AUCs and average concentrations, whereas model-derived C_{max} must be used with caution.

Veliparib is primarily metabolized by CYP450 (CYP) 2D6 and, to a lesser extent, by CYP3A4 and CYP2C19 enzymes.[7] Veliparib is also a substrate of P-glycoprotein (P-gp), organic cation transporter 2 (OCT2), and multidrug and toxin extrusion protein 1/2K (MATE1/2K) transporters.[17] In addition to the patient demographics and baseline characteristics

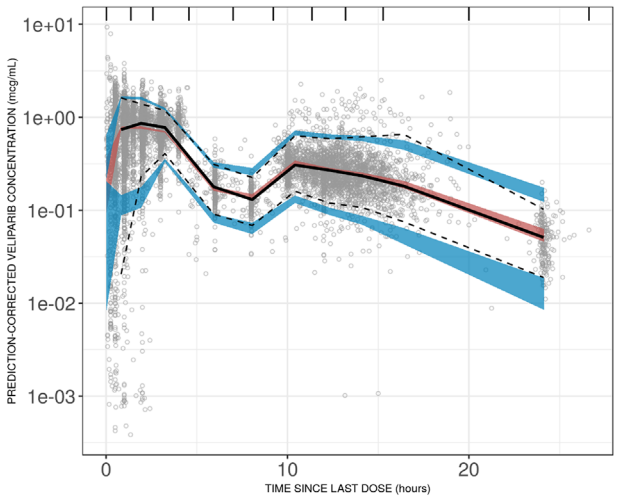

Figure 2. Prediction-corrected visual predictive check for veliparib final population pharmacokinetic model. The gray circles denote the observed concentrations. The shaded blue areas represent the 90% prediction interval of the 5th and 95th percentiles of simulated concentrations, the red areas represent the 90% prediction interval of the 50th percentile of simulated concentrations, the solid black line represents the median of observed concentrations, and the dashed black lines represent the 5th and 95th percentiles of the observed concentrations.

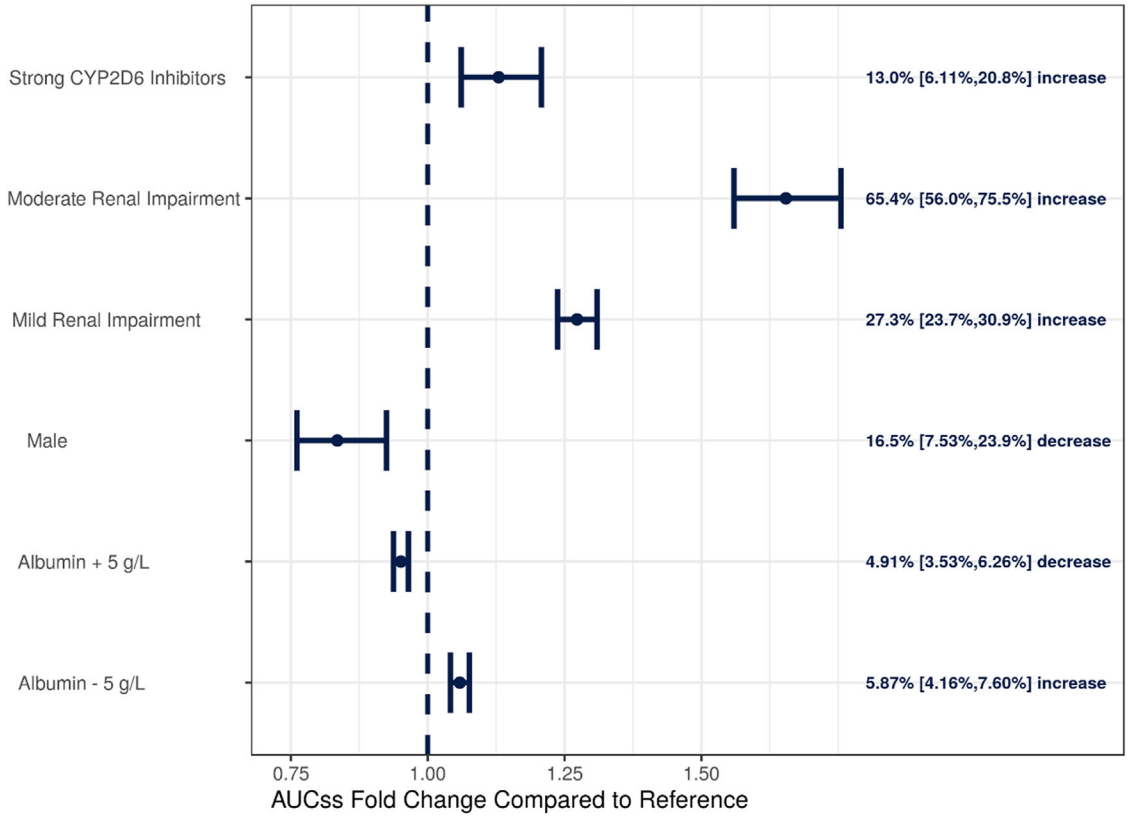

Figure 3. Model-predicted covariate effects on veliparib steady-state AUC compared with a reference subject. Note: reference for sex was female, for CrCL ≥ 120 mL/min, CYP2D6 inhibitors other than strong, and for the other covariates the population median. Moderate and severe impairment meant CrCL of 75 and 45 mL/min, respectively. Covariate effects are shown as median % AUC_{ss} fold increase/decrease with corresponding 95%CI.

(including renal and hepatic function markers), concomitant medications including strong inhibitors of CYP2D6, strong inhibitors and inducers of CYP3A4 and CYP2C19, and inhibitors of transporters MATE1/2K, P-gp, and OCT2 were evaluated as covariates on veliparib pharmacokinetic parameters. This is the first report of evaluation of the effect of enzyme inhibitors/inducers and transporter inhibitors on veliparib pharmacokinetics in a population pharmacokinetic analysis.

Consistent with the previous reports,[8-12] creatinine clearance and body weight were found to be significant covariates of systemic clearance (CL/F) and V_c/F, respectively. It is also consistent with renal clearance being the predominant route of elimination for veliparib.[6] Mild (CrCL = 75 mL/min) and moderate (CrCL = 45 mL/min) renal impairment are predicted to increase veliparib steady-state AUC (AUC_{ss}) by 25% and 65%, respectively, compared with subjects with reference renal function (CrCL ≥ 120 mL/min). A wide range of CrCL values (28.2 to 289 mL/min) was observed in the data set with 9.4% of subjects below 60 mL/min (138 subjects) and 1.6% (23 subjects) below 45 mL/min, thus providing reasonable confidence in the estimated effect of renal impairment. However, additional risk-benefit analyses are required to inform dose adjustment in subjects with renal impairment.

Body weight was shown to have an impact on V_c/F. For a 10-kg change in body weight (in the range of 35.7 to 182 kg), the apparent volume of distribution changed only by about 7% and was considered not clinically relevant. Furthermore, body weight did not affect the model-predicted veliparib AUC_{ss}. In addition, albumin, strong CYP2D6 inhibitors, and sex were identified as statistically significant covariates on CL/F and albumin and sex on V_c/F. An increase or decrease in albumin of 5 g/L from the population median of 40 g/L was associated with a median < 5% decrease or < 6% increase in AUC_{ss}, respectively. Male subjects were predicted to have about 17% lower AUC_{ss} compared with female subjects. Concomitant administration of strong CYP2D6 inhibitors was associated with a 13% increase in AUC_{ss} and is consistent with metabolism playing a minor role in veliparib clearance. These effects, although statistically significant, were not considered clinically relevant changes in veliparib exposure and thus do not warrant any adjustment of veliparib dose.

Race, age, region, cancer type, and concomitant use of strong inhibitors of CYP3A4 and CYP2C19, strong

inducers of CYP2C19 and CYP3A4, and inhibitors of transporters (P-gp, [MATE]1/2, OCT2) were not found to significantly impact veliparib pharmacokinetic parameters. Lack of effect of region or ethnicity on veliparib pharmacokinetics was consistent with results from a phase 1 study of veliparib monotherapy in Japanese subjects that showed comparable veliparib pharmacokinetics between Japanese and Western subjects.[18]

In summary, the robustness of the model, size of the data set and range of covariates suggest that the analysis adequately characterized the population pharmacokinetics of veliparib in the cancer population.

Conclusions

The pharmacokinetics of veliparib were extensively characterized in patients with ovarian cancer, breast cancer, and other solid tumors and evaluated the influence of patient demographics and baseline characteristics on veliparib disposition using a large data set across phase 1/2/3 trials. Other than creatine clearance, no covariates had a clinically relevant effect on veliparib exposure. Dose adjustments of veliparib based on body weight, age, sex, race, ethnicity, tumor type, coadministration of enzyme inhibitors/inducers or transporter inhibitors, and liver dysfunction are not warranted.

Conflicts of Interest

AbbVie contributed to the study design, research, interpretation of the data and to the writing, review, and approval of the article. All authors are current or former AbbVie employees and may hold AbbVie stock or options. The authors have indicated that they have no other conflicts of interest with regard to the content of this article. Medical writing support was provided by Therese Stickler, a freelance writer under contract with AbbVie.

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Data-Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal and statistical analysis plan (SAP) and execution of a data-sharing agreement (DSA). Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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