Population Pharmacokinetics (PK) of Rucaparib (CO-338) in Patients with Advanced Ovarian Cancer (AOC) or Other Solid Tumors

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BACKGROUND

- Rucaparib is a poly(ADP-ribose) polymerase (PARP) inhibitor approved in the United States as monotherapy for the treatment of patients with deleterious germline and/or somatic *BRCA1* or *BRCA2* mutation associated AOC who have received ≥2 prior chemotherapy regimens[1]
- Here we describe the results of a population PK (PPK) analysis based on data from 3 clinical studies of rucaparib: Study 1014 (A4991014; NCT01009190), Study 10 (CO-338-010; NCT01482715), and ARIEL2 (CO-338-017; NCT01891344)

OBJECTIVES

- To develop a PPK model to describe rucaparib PK and variability, and the covariates influencing rucaparib PK variability

METHODS

- A PPK model was developed based on data pooled from 454 rucaparib-treated patients from 1 completed (Study 1014) and 2 ongoing (Study 10 and ARIEL2) clinical studies (**Table 1**)

Table 1. Summary of Studies Included in the PPK Analysis

Study	Description	Patients[a]	Dosage	PK sampling
Study 1014 (NCT01009190), phase 1	Single-dose PK	30/35[b]	24, 27, or 40 mg as 30-min IV infusion 72, 80, 120, 180, 240, and 360 mg PO	Intensive
Study 10 (NCT01482715), phase 1/2	Part 1 (phase 1): safety, PK, and MTD	56	40–500 mg QD and 240–840 mg BID PO	Intensive and sparse[c]
			40 and 300 mg QD (food effect)	Intensive and sparse[c]
	Part 2A (phase 2): ORR[d]	42	600 mg BID PO	Sparse
	Part 3 (phase 2): steady-state PK; food effect with higher-strength tablets	26	600 mg BID PO 600 mg PO (food effect)	Intensive and sparse[c]
ARIEL2 (NCT01891344), phase 2	Part 1: PFS by HRD subgroup	196	600 mg BID PO	Sparse
	Part 2: ORR by HRD subgroup	104	600 mg BID PO	Sparse

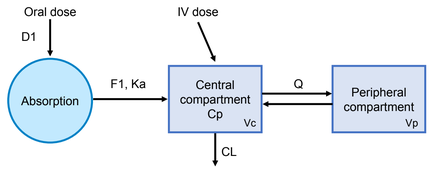
All trials were nonrandomized, open-label studies.
[a]Enrollment cutoff date: Oct 1, 2015 (includes all enrolled patients in Study 1014, Study 10, and ARIEL2 Part 1; enrollment in ARIEL2 Part 2 is ongoing). Visit cutoff dates: Apr 2, 2014 (Study 1014); Nov 30, 2015 (Study 10 Parts 1 and 2A); Dec 10, 2015 (Study 10 Part 3); Feb 29, 2016 (ARIEL2 Parts 1 and 2).
[b]In PPK model development, oral and IV PK data were available for 30 and 9 patients, respectively. Late in model development, additional rucaparib data became available, resulting in a total of 35 patients with both oral and IV data. The PPK model was updated with all available data from the 3 studies.
[c]Intensive PK data was collected following single-dose administration and at steady state; sparse PK data was collected in subsequent cycles.
[d]Per Response Evaluation Criteria In Solid Tumors version 1.1.
BID, twice daily; HRD, homologous recombination deficiency; IV, intravenous; MTD, maximum tolerated dose; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; PO, by mouth; PPK, population pharmacokinetics; QD, once daily.

- The model was developed using first-order conditional estimation with interaction method in NONMEM® (version 7.3; ICON, plc, Dublin, Ireland) and evaluated based on goodness-of-fit metrics[2,3]
- Clinical covariates of interest were tested in a stepwise covariate model or evaluated graphically by post hoc comparison

RESULTS

- Rucaparib PK was well described by a 2-compartment model with sequential 0-order and 1st-order absorption and elimination (**Figure 1**)
- Parameter estimates for the final PPK model are shown in **Table 2**

Figure 1. Rucaparib Structural Model



CL, clearance; Cp, plasma concentration; D1, duration of the 0-order absorption; F1, bioavailability in the central compartment; IV, intravenous; Ka, absorption rate constant; Q, intercompartmental clearance; Vc, volume of central compartment; Vp, volume of peripheral compartment.

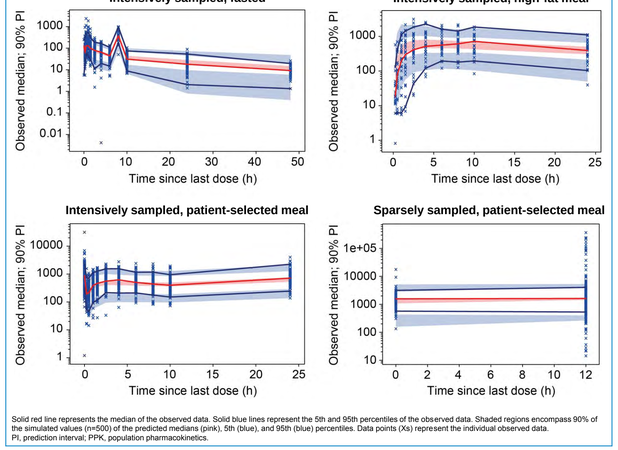
Table 2. Model Parameter Estimates for the Final PPK Model

Parameters		NONMEM estimate	Bootstrap estimate	Bootstrap 95% CI	%CV	Shrinkage
PK parameters	CL, L/h	10.26	10.36	8.573, 12.82	48.8	8.84
	Vc, L	16.92	16.98	13.73, 20.33	–	–
	Q, L/h	17.44	17.9	14.55, 22.96	–	–
	Vp, L	165.9	164.7	132.5, 199.7	–	–
	Ka, h^{-1}	0.07175	0.0732	0.05712, 0.0891	63.5	5.21
	D1, h	0.6188	0.6195	0.4771, 0.812	111	11.8
	LF1	-0.5234	-0.5175	-0.828, -0.1276	–	–
	F1	0.3720	0.3734	0.3041, 0.4681	–	–
Residual errors	ResErr(Prop), all patients	0.3821	0.3772	0.3573, 0.3991	–	–
	ResErr(Add), patients with intensive PK	0.8314	0.8364	0.5435, 3.082	–	–
	ResErr(Add), patients with sparse PK only	378.9	377.2	269.1, 458	–	–
Covariates	F1, dose ≤480 mg	-0.3802	-0.3768	-0.7392, -0.09048	–	–
	F1, fasted, dose >480 mg	-0.2017	-0.2686	-0.7004, 0.1833	–	–
	F1, high-fat, dose >480 mg	0.5903	0.5518	0.05534, 1.086	–	–
	Ka, fasted	0.4009	0.4501	0.1151, 1.072	–	–
	Ka, dose	-0.3249	-0.3012	-0.4082, -0.1776	–	–
	CL, albumin	0.7202	0.7226	0.2873, 1.159	–	–
	CL, CLCR	0.3130	0.3213	0.1969, 0.4463	–	–
IIV	D1, patients with intensive PK only	1.241	1.192	0.9131, 1.608	–	–
	Ka, patients with intensive PK only	0.4035	0.3975	0.2809, 0.5237	–	–
	CL, all patients	0.2386	0.2332	0.1692, 0.3357	–	–

CI, confidence interval; CL, clearance; CLCR, creatinine clearance; CV, coefficient of variation; D1, duration of the 0-order absorption; F1, absolute bioavailability; IIV, interindividual variability; LF1, logit of bioavailability; Ka, absorption rate constant; Vc, volume of central compartment; Q, intercompartmental clearance; PK, pharmacokinetics; PPK, population pharmacokinetics; ResErr(Add), additive residual error; ResErr(Prop), proportional residual error; Vp, volume of peripheral compartment.

- When stratified by sampling intensity and meal status, the final PPK model predictions were generally consistent with the observed data (**Figure 2**)

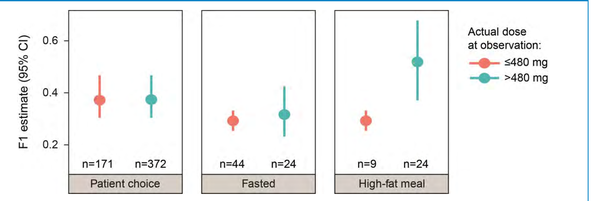
Figure 2. Prediction-Corrected Visual Predictive Check for the Final PPK Model, Stratified by Sampling Intensity and Meal Status



Solid red line represents the median of the observed data. Solid blue lines represent the 5th and 95th percentiles of the observed data. Shaded regions encompass 90% of the simulated values (n=500) of the predicted medians (pink), 5th (blue), and 95th (blue) percentiles. Data points (Xs) represent the individual observed data.
PI, prediction interval; PPK, population pharmacokinetics.

- No apparent food effect was observed at ≤480 mg; at 600 mg, the oral bioavailability was 32.7% and 51.7% under fasted condition and with a high-fat meal, respectively (**Figure 3**)

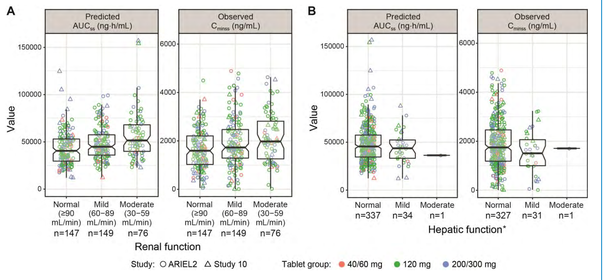
Figure 3. Effect of Dose and Food on F1 in the Final PPK Model



Food effect was only tested at 40 mg QD, 300 mg QD, and 600 mg BID doses; patients may have PK data with different doses and/or different meals.
BID, twice daily; CI, confidence interval (from the nonparametric bootstrap analysis); F1, absolute bioavailability; PK, pharmacokinetics; PPK, population pharmacokinetics; QD, once daily.

- For patients who received rucaparib 600 mg twice daily (BID), mean rucaparib exposure largely overlapped when stratified by renal impairment (normal, mild, or moderate; **Figure 4A**) or hepatic impairment (normal, mild, or moderate; **Figure 4B**)
  - The model-predicted steady-state area under the concentration-time curve (AUC_{ss}) was approximately 15% and 33% higher for patients with mild and moderate renal impairment, respectively, than that for patients with normal renal function
  - The model-predicted AUC_{ss} and observed minimum concentration (C_{min}) were comparable between patients with normal and mildly impaired hepatic function

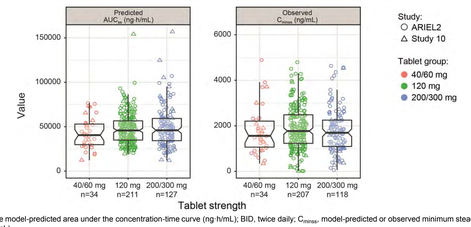
Figure 4. Model-Predicted and Observed Steady-State Exposures at 600 mg BID Stratified by (A) Renal Function Category and (B) Hepatic Function Category



*Categories of hepatic function are calculated from the National Cancer Institute's Organ Dysfunction Working Group criteria based on an assumed bilirubin ULN of 1.2 mg/dL and aspartate aminotransferase ULN of 40 U/L.
AUC_{ss}, steady-state model-predicted area under the concentration-time curve (ng·h/mL); BID, twice daily; C_{minss}, model-predicted or observed minimum steady-state concentration (ng/mL); ULN, upper limit of normal.

- Tablet strength did not affect PK as assessed by observed C_{min} or post hoc estimates of AUC_{ss} following rucaparib 600 mg BID (**Figure 5**)

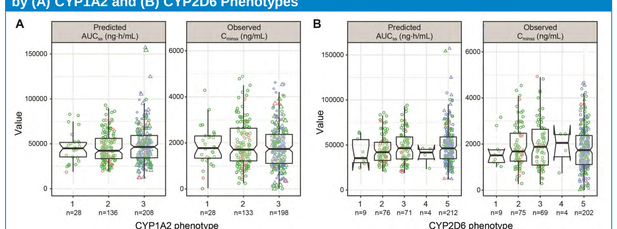
Figure 5. Model-Predicted and Observed Steady-State Exposures at 600 mg BID Stratified by Tablet Strength



AUC_{ss}, steady-state model-predicted area under the concentration-time curve (ng·h/mL); BID, twice daily; C_{minss}, model-predicted or observed minimum steady-state concentration (ng/mL).

- Phenotypes of cytochrome P450 (CYP) 1A2 (normal metabolizers and hyperinducers) and CYP2D6 (poor, normal, intermediate, and ultra-rapid metabolizers) did not affect rucaparib PK at 600 mg BID (**Figure 6**)

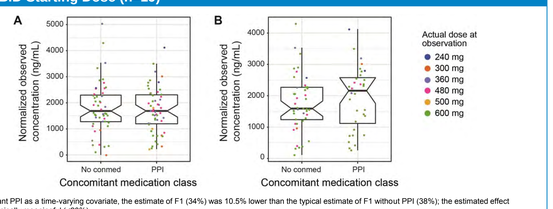
Figure 6. Model-Predicted and Observed Steady-State Exposures at 600 mg BID Stratified by (A) CYP1A2 and (B) CYP2D6 Phenotypes



AUC_{ss}, steady-state model-predicted area under the concentration-time curve (ng·h/mL); BID, twice daily; C_{minss}, model-predicted or observed minimum steady-state concentration (ng/mL); CYP, cytochrome P450.

- In an analysis of concomitant medications as time-varying covariates in patients from all starting dose groups, median dose-normalized, steady-state trough concentrations were comparable with or without a proton-pump inhibitor (PPI) (**Figure 7**)
- Strong CYP1A2 and CYP2D6 inhibitors were taken concomitantly by too few patients (≤3) to accurately examine the drug-drug interaction for these as time-varying covariates[4]

Figure 7. Normalized Observed Steady-State Trough Concentrations with and Without Concomitant PPI (A) in Patients at All Starting Doses (n=22) and (B) in Patients at the 600 mg BID Starting Dose (n=19)



With concomitant PPI as a time-varying covariate, the estimate of F1 (34%) was 10.5% lower than the typical estimate of F1 without PPI (38%); the estimated effect was unlikely clinically meaningful (<20%).
Note: Figures include patients with steady-state trough PK data both with and without PPIs. Observations are dose-normalized to 600 mg based on the actual dose. All doses were taken with a patient-selected meal.
BID, twice daily; F1, absolute bioavailability; PK, pharmacokinetics; PPI, proton-pump inhibitor.

DISCUSSION AND CONCLUSIONS

- The sequential 0-order and 1st-order absorption adequately described the PK data
- A moderate food effect on rucaparib PK at the 600 mg dose was observed; because the effect was not considered clinically significant, rucaparib can be taken with or without food
- Despite the numerical increases in rucaparib exposure with renal impairment, no dose adjustment is recommended for patients with mild (creatinine clearance [CLCR] 60–89 mL/min) to moderate (CLCR 30–59 mL/min) renal impairment
- No apparent PK difference was observed between patients with normal or mildly impaired hepatic function per National Cancer Institute guidelines
- The 200/300 mg strength tablets showed comparable PK with lower-strength tablets, and PK data support pooling of clinical efficacy data of all tablet strengths
- Phenotypes of CYP1A2 and CYP2D6 did not show a significant impact on rucaparib PK
- Concomitant PPIs showed no clinically meaningful effect on rucaparib PK

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