CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206162Orig1s000

<u>CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)</u>

206162 Clinical Pharmacology Review

NDA	206162
Submission Date:	3rd February 2014
Brand Name:	Lynparza ^{TM}
Generic Name:	Olaparib
Formulation:	50 mg Capsules
OCP DCP5 Reviewer:	Elimika Pfuma, PharmD, PhD
PBPK Reviewer	Ping Zhao, PhD
OCP Team Leader and PBPK Secondary Reviewer:	Qi Liu, PhD
Pharmacometrics Reviewer:	Hongshan Li, PhD
Pharmacometrics Team Leader:	Liang Zhao, PhD
OCP Division:	Division of Clinical Pharmacology V
OND Division:	Division of Oncology Products1
Applicant:	AstraZeneca
Submission Type; Code:	0000/1
Proposed Dosing regimen:	400 mg (eight 50 mg capsules) taken twice daily
Proposed Indication:	Monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

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1   EXECUTIVE SUMMARY

Olaparib is a PARP (poly ADP ribose polymerase) inhibitor proposed as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The applicant proposes an oral dosing regimen of 400 mg (eight 50 mg capsules) taken twice daily (BID).

To support the accelerated approval of olaparib, the applicant submitted data from 205 patients with deleterious or suspected deleterious germline BRCA mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The patients are from one pivotal Trial D0810C00042 (Trial 42) and five supportive trials. Trial 42 was a phase 2 non-randomized trial of monotherapy olaparib in patients with advanced gBRCA mutated tumors and only a subset of the patients [N=137] that had ovarian cancer will be considered in the current NDA application. Treatment with olaparib in the 137 patients in Trial 42 resulted in an overall response rate (ORR) of 34% (95% CI: 26, 42) and a median duration of response (DOR) of 7.9 months (95% CI: 5.6, 9.6).

The safety database for the proposed indication includes 223 patients (only 205 of these 223 patients were evaluable for efficacy) from Trial 42 and the five supportive trials. Additional safety data from Trial 19, a randomized study in the maintenance setting for patients with gBRCA mutated ovarian cancer (N= 96), are also added to the labeling.

The MTD of olaparib was identified as 400 mg BID in phase 1. The applicant observed a numerical advantage, which was not statistically significant, in the ORR and progression-free survival (PFS) for the 400 mg capsule BID dose compared to 100 mg and 200 mg capsule BID doses in two phase 2 trials (Trials 9 and 12) when used as maintenance therapy. Pharmacometrics analysis found no apparent exposure-response relationship for PFS following olaparib capsule doses of 200 and 400 mg BID. However, an exposure response relationship was identified for anemia in the dose range of the 100 – 400 mg BID. The risk of anemia increased with increase in steady-state concentration of olaparib.

Pharmacokinetic (PK) samples were not collected in pivotal Trial 42. Single and multiple dose pharmacokinetic data are available from 13 phase 1 and 2 trials, including evaluation of food effect, mass balance, impact of renal impairment (preliminary data), and drug interaction potential for olaparib. The mean half-life is 12 hours at the 400 mg dose with an accumulation ratio of 1.4 with twice daily dosing. A high-fat meal did not increase the exposure of olaparib significantly; therefore olaparib can be dosed without regard to food. The results from the oral mass balance trial suggest that metabolism is an important elimination pathway for olaparib, but the contribution of the renal route cannot be ruled out. Dedicated hepatic and renal impairment trials are currently ongoing. In the dedicated renal impairment trial, the AUC and Cmax of olaparib increased by 1.5- and 1. 2-fold, respectively, when olaparib was dosed in patients with mild renal impairment (CLcr = 50 - 80 mL/min; N=14) compared to those with normal renal function (CLcr > 80 mL/min; N=8). No dose adjustment to the starting dose is required in patients with CLcr of 50 to 80 mL/min, but patients should be monitored closely for toxicity.

Data are not available in patients with CLcr < 50 mL/min, patients on dialysis, or patients with baseline serum bilirubin > 1.5 X ULN.

Olaparib is primarily metabolized by CYP3A. Itraconazole (strong CYP3A inhibitor) increased the AUC of olaparib by 2.7-fold and PBPK modeling predicted that fluconazole (moderate CYP3A inhibitor) would likely increase olaparib AUC by 2-fold. Therefore, a dose reduction to 150 mg BID is recommended for concomitant use of a strong CYP3A inhibitor and a dose reduction to 200 mg BID is recommended for concomitant use of a moderate CYP3A inhibitor. Rifampin (strong CYP3A inducer) decreased the AUC of olaparib by 87% and PBPK modeling predicted that efavirenz (moderate CYP3A inducer) would likely decrease olaparib AUC by half. Increasing the dose could be impractical given the number of capsules to be administered. Therefore, we recommend that concomitant use of a strong or moderate CYP3A inducer should be avoided. If a moderate CYP3A inducer must be co-administered, be aware that it may result in reduced efficacy.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology (Division of Clinical Pharmacology V and Division of Pharmacometrics) has reviewed the information contained in NDA 206162. This NDA is acceptable from a clinical pharmacology perspective. The adequacy or inadequacy of specific drug information is provided below:

Decision	Sufficiently Supported?	Recommendations and Comments
Evidence of Effectiveness	☒ Yes ☐ No ☐ NA	Pivotal and supportive trials
Proposed dose for general population	☒ Yes ☐ No ☐ NA	The proposed dose appears sufficiently efficacious and safe in the proposed patient population with the current capsule formulation. Please refer to the clinical reviews for safety and efficacy.
Proposed dose adjustment in specific patients or patients with co-medications	☒ Yes ☐ No ☐ NA	Labeling Recommendations: 1. A dose reduction to 200 mg BID is recommended for concomitant use of a moderate CYP3A inhibitor and a reduction to 150 mg BID is recommended for concomitant use of a strong CYP3A inhibitor. PMR studies: 1. Submit the final study report for the ongoing trial evaluating the effect of mild and moderate hepatic impairment on olaparib exposure. 2. Submit the final study report for the trial evaluating the effect of mild and moderate renal impairment on olaparib exposure.
Pivotal bioequivalence studies	☐ Yes ☐ No ☒ NA	A formal bioequivalence trial was not performed. The to-be-marketed formulation is the same and will be manufactured in the same site as that used in Trial 42 and the supportive efficacy trials. Trial 2 and 9 that contribute 29 patients to the efficacy analyses used both capsules manufactured at this site and a previous site.
Labeling	☒ Yes ☐ No ☐ NA	

1.2   POST MARKETING REQUIREMENTS

1. Submit the final report for trial D0816C00005 entitled, "An Open-label, Non-randomized, Multicenter, Comparative, Phase I Study to Determine the Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumors and Normal Hepatic Function or Mild or Moderate Hepatic Impairment."
2. Submit the final report for trial D0816C00006 entitled, "An Open-label, Non-randomized, Multicenter, Comparative, and Phase I Study of the Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumors and Normal Renal Function or Renal Impairment."

1.3   SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Olaparib is a PARP (poly ADP ribose polymerase) inhibitor proposed as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The applicant proposes an oral dosing regimen of 400 mg (eight 50 mg capsules) taken twice daily (BID).

Single and multiple dose pharmacokinetic (PK) data are available from 13 phase 1 and 2 trials, including evaluation of food effect, mass balance, impact of renal impairment (preliminary data), and drug interaction potential for olaparib.

Olaparib exposure increases with dose in the range evaluated (up to 600 mg). Limited data suggest that the systemic exposure (AUC) of olaparib increases less than proportionally with dose over the dose range of 100 to 400 mg, but the PK data were variable across trials. A high-fat meal did not increase the exposure of olaparib significantly; therefore olaparib can be dosed without regard to food. The mean half-life is 12 hours at the 400 mg dose. The results from the oral mass balance trial suggest that metabolism is an important elimination pathway for olaparib, but the contribution of the renal route cannot be ruled out. Dedicated hepatic and renal impairment trials are currently ongoing. In the dedicated renal impairment trial, the AUC and Cmax of olaparib increased by 1.5- and 1. 2-fold, respectively, when olaparib was dosed in patients with mild renal impairment (CLcr = 50 - 80 mL/min; N=14) compared to those with normal renal function (CLcr > 80 mL/min; N=8). No dose adjustment to the starting dose is required in patients with CLcr of 50 to 80 mL/min, but patients should be monitored closely for toxicity. Data are not available in patients with CLcr < 50 mL/min, patients on dialysis, or patients with baseline serum bilirubin > 1.5 X ULN.

Olaparib is primarily metabolized by CYP3A. Itraconazole (strong CYP3A inhibitor) increased the AUC of olaparib 2.7-fold and PBPK modeling predicted that fluconazole (moderate CYP3A inhibitor) would likely increase olaparib AUC by 2-fold. Therefore, a dose reduction to 150 mg BID is recommended for concomitant use of a strong CYP3A inhibitor and a dose reduction to 200 mg BID is recommended for concomitant use of a moderate CYP3A inhibitor. Rifampin (strong CYP3A inducer) decreased the AUC of olaparib by 83% and PBPK modeling predicted

that efavirenz (moderate CYP3A inducer) would likely decrease olaparib AUC by half. Increasing the dose could be impractical given the number of capsules to be administered. Therefore, we recommend that concomitant use of a strong or moderate CYP3A inducer should be avoided. If a moderate CYP3A inducer must be co-administered, be aware that it may result in reduced efficacy.

The MTD of olaparib was identified as 400 mg BID in phase 1 for the capsule formulation. The applicant observed a numerical advantage, which was not statistically significant, in the ORR and progression-free survival (PFS) for the 400 mg BID dose compared to the 100 mg BID dose and the 200 mg BID dose in two phase 2 trials (Trials 9 and 12) when used as maintenance therapy. Further analysis by the pharmacometrics reviewer found no apparent exposure-response relationship for the PFS following olaparib doses of 200 and 400 mg BID doses. However, an exposure response relationship was identified for anemia in the dose range of 100 – 400 mg BID.

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2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Olaparib is planned to be available as 50 mg hard capsules for oral administration.

Figure 1: Structural Formula of Olaparib
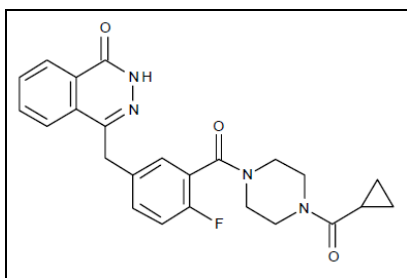
Established names: Olaparib
Stereochemistry: Achiral
Molecular Weight: 434.46
Molecular Formula: $C_{24}H_{23}FN_4O_3$
Partition coefficient (log D): 1.49 (pH=7.4)
Dissociation Constant (pKa): -1.16 and 12.07
Chemical Name: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)-one
Melting Point Range: 206°C
Solubility: 0.1 mg/mL in aqueous media. Poorly soluble and pH independent.
Physical State: Crystalline (b) (4)
Solid State Form: (b) (4)

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Olaparib is a PARP (poly ADP ribose polymerase) inhibitor proposed as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

PARPs are a family of enzymes involved in base excision repair of single-strand breaks in DNA. BRCA 1 and 2 proteins are important in the repair of damaged DNA through the homologous recombination (HR) pathway. Evidence suggests that inhibition of PARP1 in BRCA-deficient cells would lead to an increase of DNA lesions that would not be effectively repaired, resulting in apoptosis (synthetic lethality).

2.1.3   What are the proposed dosage(s) and route(s) of administration?

The applicant proposes an oral dosing regimen of 400 mg (eight 50 mg capsules) taken twice daily (BID).

2.2   GENERAL CLINICAL PHARMACOLOGY

2.2.1   What are the design features of the clinical pharmacology and clinical trials used to support dosing or claims?

To support the approval of olaparib, the applicant is relying on data from 205 patients with deleterious or suspected deleterious germline BRCA mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The majority of the data are provided by 137 patients in Trial D0810C00042 (Trial 42). Trial 42 was a phase 2, open-label, non-randomized, non-comparative, multicenter trial to assess the efficacy and safety of olaparib given orally twice daily in patients with advanced cancers who have a confirmed genetic BRCA1 and/or BRCA2 mutation (the subset of the patients with ovarian cancer will be considered in the current NDA application). The sponsor has submitted data from five additional trials as supportive evidence of the activity of olaparib 400 mg BID monotherapy in this setting:

Trial D0810C00002: Phase 1, dose escalation and expansion trial in patients with advanced solid tumors

Trial D0810C00009: Phase 2 efficacy and safety trial in gBRCA mutated ovarian cancer

Trial D0810C00012: Phase 2 gBRCA ovarian monotherapy dose finding trial

Trial D0810C00020: Phase 2 relapsed ovarian and breast cancer trial

Trial D0810C00024: Phase 1 trial to determine relative bioavailability of the tablet formulation

The safety database includes 223 patients with gBRCA mutated ovarian cancer that received monotherapy olaparib from the aforementioned trials. Additional safety data from patients with gBRCA mutated ovarian cancer in a randomized Trial 19 (N= 96) are also added to the labeling. Trial 19 was a randomized, double blind, multi-center trial evaluating maintenance olaparib in platinum sensitive high grade serous ovarian cancer patients who had received 2 or more previous platinum-containing regimens. Trial 19 was the planned pivotal trial for the maintenance indication proposed when this original NDA was submitted. A major amendment to the NDA was submitted for consideration of the currently proposed indication after the Oncologic Drugs Advisory Committee (ODAC) voted 11: 2 against approval in the maintenance setting before the results of the planned confirmatory SOLO-2 trial.

Single and multiple dose pharmacokinetic (PK) data are available for 8 phase 1 and 2 trials shown in **Table 1**

Table 1: Overview of Clinical Pharmacology Related Trials Submitted in the NDA

Trial Number	Trial Description	Treatment Regimen
D0810C00001 (Trial 1)	Phase 1, single and multiple dose escalation, safety and tolerability trial in Japanese patients (N=12)	100, 200 and 400 mg as single dose; 100, 200 and 400 mg BID
D0810C00002 (Trial 2)	Phase 1, single and multiple dose escalation, safety and tolerability assessment followed by biological evaluation of olaparib in patients with advanced solid tumors (N= 46 in dose escalation and N=52 in expansion)	10, 20, 40, 60, 80, 100, 200, 400 and 600 mg single dose; 10, 20, 40 and 80 mg QD; 60, 100, 200, 400 and 600 mg BID; 200 mg BID (PD assessment)
D0810C00007 (Trial 7)	Phase 1 pharmacodynamics concentration - response trial in intermediate/high-risk breast cancer (N=60)	10, 30, 100, 200 and 400 mg BID
D0810C00008 (Trial 8)	Phase 2 efficacy and safety trial in gBRCA mutated breast cancer (N=54)	100 and 400 mg BID
D0810C00009 (Trial 9)	Phase 2 efficacy and safety trial in gBRCA mutated ovarian cancer (N=57)	100 and 400 mg BID
D0810C00010 (Trial 10)	Absorption, distribution, metabolism and excretion trial in patients with advanced solid tumors (N=6)	100 mg single dose of $[^{14}C]$-olaparib
D0810C00012 (Trial 12)	Phase 2 efficacy and safety of olaparib vs. PLD in gBRCA ovarian cancer (N=96)	Olaparib 200 and 400 mg BID vs. doxorubicin 50 mg/m^2
D0810C00024 (Trial 24)	Phase 1 study to determine relative bioavailability of the tablet formulation	50, 100 or 400 mg capsule as single dose; 400 mg BID (expansion cohort)

In addition, preliminary study reports were submitted with PK data for the trials shown in **Table 2**.

Table 2: Overview of Additional Clinical Pharmacology Related Trials Submitted

Trial Number	Trial Description
D081AC00001	Phase 1 trial to determine the effect of food on the pharmacokinetics of olaparib following single 400 mg doses of the capsule formulation in patients with advanced solid tumors.
D0816C00004	Phase 1 trial to determine the effect of food on the pharmacokinetics of olaparib and to provide data on the effect of olaparib on QT Interval following oral dosing of a tablet formulation in patients with advanced solid tumors.
D0816C00006	Phase I trial to determine of the pharmacokinetics, safety and tolerability of olaparib following a single oral 300 mg tablet dose to patients with advanced solid tumors and normal renal function or renal impairment (preliminary data)
D0816C00007	Phase 1 trial to assess the effect of itraconazole (a CYP3A inhibitor) on the pharmacokinetics of olaparib following oral dosing of a tablet formulation, and to provide data on the effect of olaparib on QT.
D0816C00008	Phase 1 trial to assess the effect of rifampicin, a CYP inducer, on the pharmacokinetics of olaparib following oral dosing of a tablet formulation in patients with advanced solid tumors.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical trials?

The primary endpoint used is overall response rate (ORR), which is an appropriate endpoint in this advanced setting in patients that have received at least 3 lines of prior chemotherapy.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Plasma samples from clinical trials were assessed for the parent drug (olaparib). Olaparib is the active moiety. Olaparib accounted for 70% of the total radioactivity in plasma in the ADME trial.

2.2.4 Exposure-Response

No exposure response analysis has been conducted for the proposed indication in the treatment of patients with gBRCA associated platinum-sensitive ovarian cancer who have received more than 3 prior chemotherapy regimens because no olaparib plasma concentration samples were collected in Trial D0810C00042. Exposure response analyses were performed for trials in which PK data were available. Refer to **Appendix 3.2** for more details.

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and PD marker?

No exposure- efficacy relationship was identified at the 200 and 400 mg BID olaparib dose. No plasma concentration samples were collected in Trial 42.

No exposure-PFS relationship was identified in 60 patients treated with olaparib 200 or 400 mg BID (capsule) in Trial D0810C00012 which was performed in patients with advanced BRCA1- or BRCA2 associated ovarian cancer (**Figure 2**). Dose-response analysis performed for the same patients in Trial D0810C00012 suggested that the 400 mg capsule BID olaparib dose demonstrated a numerically higher median PFS than that of the 200 mg capsule BID dose, although the two survival curves intersected 3 times (**Figure 3**).

Additional exposure-PFS analyses were performed for 58 patients with BRCA mutated ovarian cancer treated with olaparib 100 mg BID or 400 mg BID (capsule) in Trial D0810C00009. Although the median PFS in Q2 was longer than Q1, it was confounded by covariates. More BRCA2 mutation patients and less prior chemotherapies were found in Q2 than Q1 and the sample size was too small for a reasonable conclusion (**Figure 4**).

Figure 2: Kaplan Meier Plot of PFS by Olaparib Exposure Quantile and Balance Check between the Two Quantiles on Major Covariate for Study 12.

Number of Patients		
	Q1	Q2
200 mg BID	22	8
400 mg BID	8	22
BRCA1m	24	26
BRCA2m	6	4

Dataset: pk3eff.xpt. N=30 for Q1 and N=30 for Q2. There were 32 patients received olaparib treatment and collected PK data in each of the 200 mg BID and 400 mg BID arms. However, only 31 patients in 200 mg arm and 30 patients in 400 mg arm contributed concentration data to the NONMEM dataset (q2ii-pk-pool-05march2014.csv); and only 30 patients in 200 mg arm and 30 patients in 400 mg arm contributed data to exposure-efficacy dataset (pk3eff.xpt).
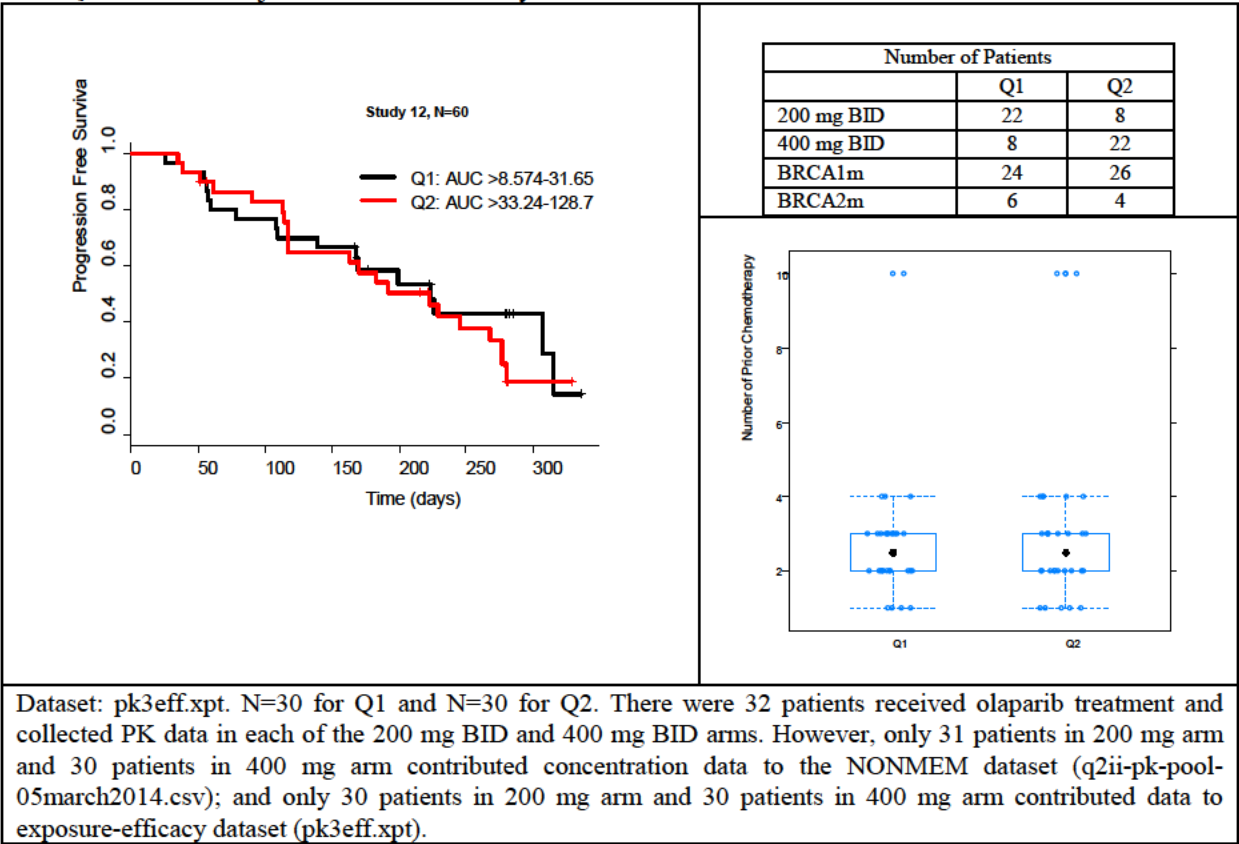
Figure 3: Kaplan Meier Plot of Disease Progression Free Period by Olaparib Dose for Study 12.

Dataset: pk3eff.xpt. N=30 for Dose1 and N=30 for Dose2. There were 32 patients received olaparib treatment and collected PK data in each of the 200 mg BID and 400 mg BID arms. However, only 31 patients in 200 mg arm and 30 patients in 400 mg arm contributed concentration data to the NONMEM dataset (q2ii-pk-pool-05march2014.csv); and only 30 patients in 200 mg arm and 30 patients in 400 mg arm contributed data to exposure-efficacy dataset (pk3eff.xpt).
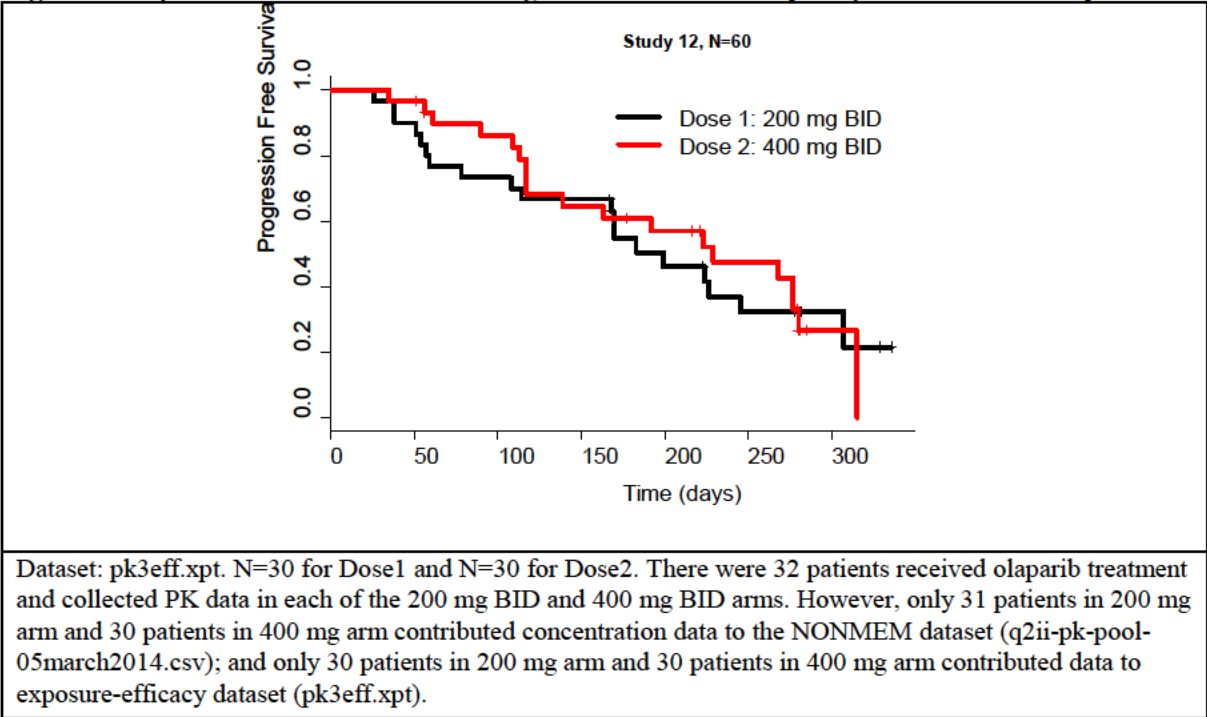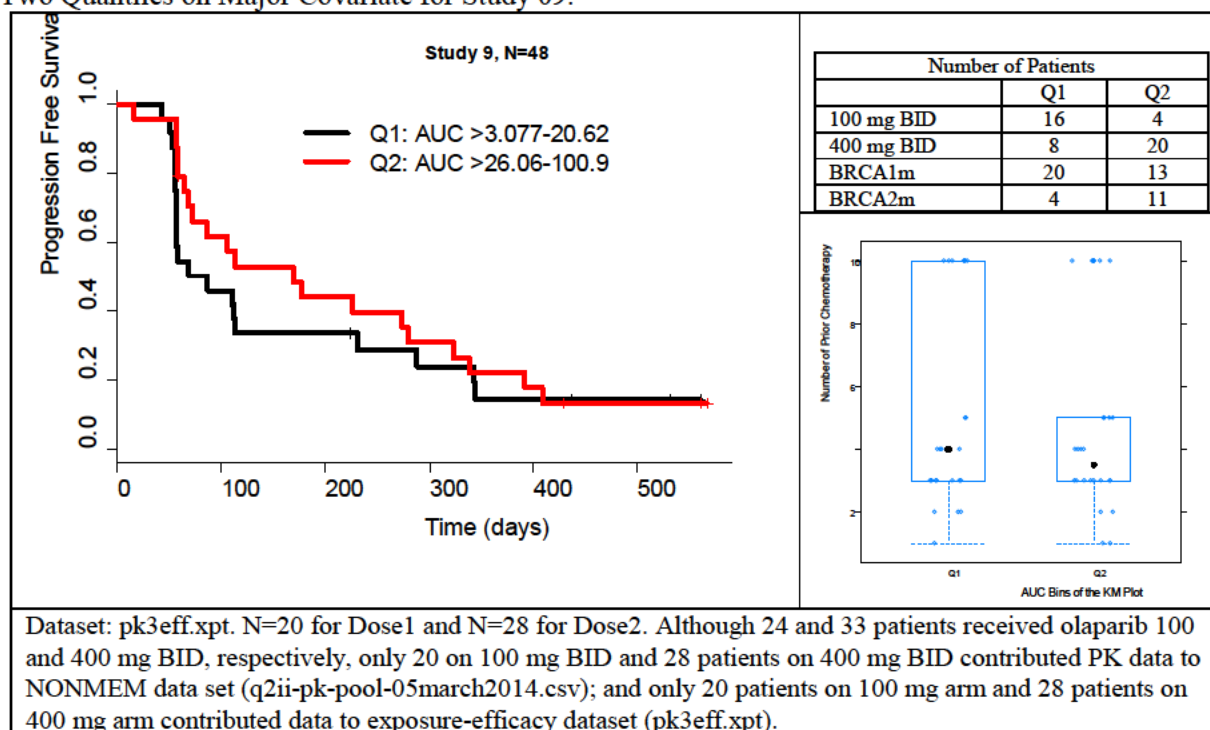
Figure 4: Kaplan Meier Plot of PFS by Olaparib Exposure Quantile and Balance Check between the Two Quantiles on Major Covariate for Study 09.

Number of Patients		
	Q1	Q2
100 mg BID	16	4
400 mg BID	8	20
BRCA1m	20	13
BRCA2m	4	11

Dataset: pk3eff.xpt. N=20 for Dose1 and N=28 for Dose2. Although 24 and 33 patients received olaparib 100 and 400 mg BID, respectively, only 20 on 100 mg BID and 28 patients on 400 mg BID contributed PK data to NONMEM data set (q2ii-pk-pool-05march2014.csv); and only 20 patients on 100 mg arm and 28 patients on 400 mg arm contributed data to exposure-efficacy dataset (pk3eff.xpt).

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

An exposure response relationship was observed for anemia. Exposure-response analyses for safety were performed using data from Trials 2, 8, 9, 12 and 24 for anemia, thrombocytopenia, neutropenia, lymphopenia and fatigue. The olaparib steady-state observed Cmin and predicted (popPK) Cmax (400 mg BID capsule) both showed an exposure-response relationship for anemia (**Figure 5**). The proposed olaparib 400 mg capsule BID dose is predicted to result in an average anemia rate of about 40% for the relationship observed using data from the 5 trials. Accordingly, the rate of ≥ Grade 2 anemia observed in the randomized Trial 19 was 38% for the 400 mg BID dose using the capsule formulation. This exposure-response relationship for anemia was also observed when analysis on data from Trial 24 for the tablet formulation was performed (**Figure 7**). In addition, an exposure-response relationship was observed for ≥ Grade 3 fatigue.

Figure 5: Exposure-Anemia Relationship Based on Pooled Data of Trials 02, 08, 09, and 12

Source: pk3safe.xpt
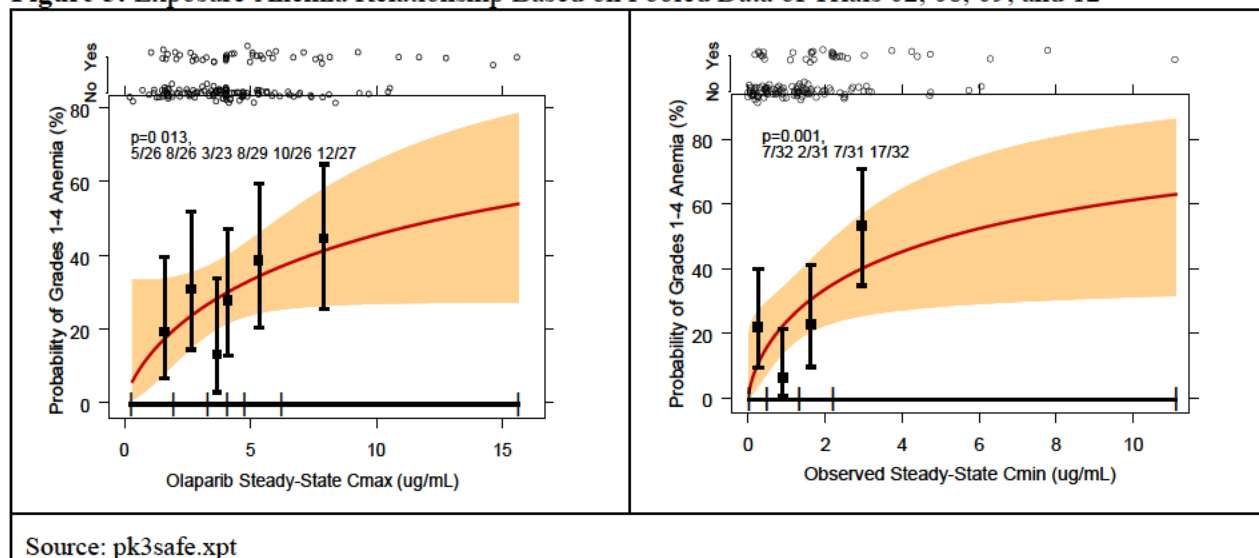
2.2.4.3 Does this drug prolong the QT or QTc interval?

No QT signal was detected in the clinical trials. The sponsor performed QT evaluation in Trials D0816C00004 (food effect trial) and D0816C00007 (CYP3A4 inhibitor trial). The QT/IRT concluded that no large change (i.e., > 20 msec) in the QTc interval was detected at therapeutic drug exposures. The studies did not include positive control (moxifloxacin) arms.

2.2.4.4 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The applicant has proposed an oral dosing regimen of 400 mg twice daily. This proposed dose has activity and appears to be safe with the current capsule formulation. It is possible that the safety and tolerability profile of the tablet at the 300 mg dose being used by the applicant in the proposed confirmatory trial(s) will not be similar to the current profile. The mean steady-state exposure of the tablet at the 300 mg dose BID is 1.5 fold that of the capsule formulation at the MTD of 400 mg BID. Refer to Section **2.2.4.2 and 2.2.4.6** and **Appendix 3.1** for further details.

The following were considered by the applicant for the dose selection for the capsule formulation:

❖ The IC_{50} values for the inhibition of various members of the PARP family by olaparib determined against isolated enzymes were 5 nM for PARP-1, 1 nM for PARP-2, 4 nM for PARP- and 1500 nM for tankyrase 1. In in vitro cell lines, enhanced olaparib sensitivity was observed in cell lines with known BRCA mutations (IC_{50} < 0.2 μM) or in some with low expression of homologous recombination repair (HRR) genes/proteins (BRCA and non-BRCA). In a BRCA2 breast cancer mouse model (HBCx-10), tumor volume reduction was only observed at doses that sustained exposures above the IC_{50} for >13 hours and IC_{90} for > 6 hours. The applicant reports that their mechanistic modeling suggested that

significant increases in single-strand breaks and clinical activity are related to doses that can achieve unbound steady-state exposures above IC_{90} for PARP inhibition. Mean steady-state PK unbound trough concentrations at doses of 200 and 400 mg BID exceed the applicant reported IC_{90}. The steady state unbound exposures for 100 mg BID or 400 mg daily (using single dose data) are below the IC_{90}. The sponsor uses these data to support the use of a dose of $\geq$ 200 mg BID.

Figure 6: Olaparib IC_{50} Values in Various Cancer Cell lines
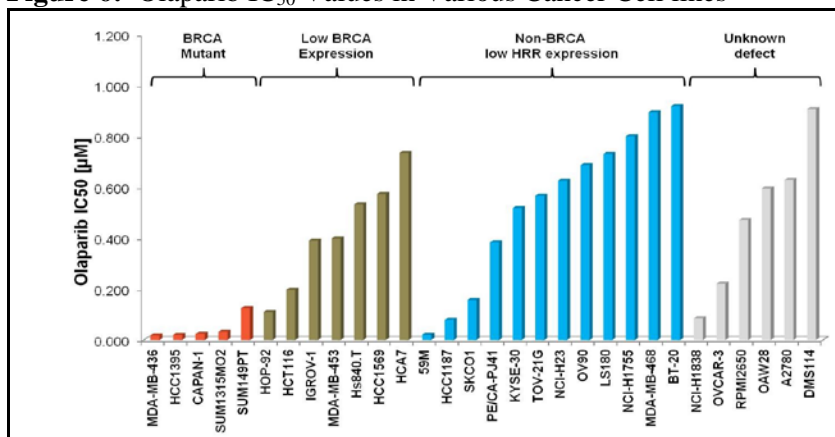
Source: Sponsor's Figure 4 in the nonclinical pharmacology written summary

❖ The dose of 400 mg BID was identified as the MTD in the Phase 1 Trial D0810C00002.
❖ In the phase 2 Trial D0810C00009 in which patients with gBRCA mutated advanced ovarian cancer were treated with olaparib, the overall response rate (ORR) was observed to be numerically higher in the 400 mg BID dose group compared to the 100 mg BID dose. The sponsor reports an ORR of 35.5% (11/31) at the 400 mg dose and 13.6% (3/22) at the 100 mg dose.
❖ In the phase 2 Trial D0810C00012, patients were randomized 1:1:1 (N=97) to receive olaparib 200 and olaparib 400 mg BID versus doxorubicin 50 mg/m^2. Neither olaparib regimens were statistically different from doxorubicin. The applicant observed a numerical advantage of the 400 mg BID regimen compared to the 200 mg BID regimen with a median PFS of 8.8 months (95%CI: 5.4, 9.2) versus 6.5 months (95%CI: 5.5, 10.1) and an ORR of 31% versus 25%. Of note, the 400 mg dose was not statistically different from the 200 mg dose.
❖ Of the 223 gBRCA-mutated patients who received 3 or more prior lines of chemotherapy (population being considered in current trial) at the 400 mg BID dose, adverse events led to dose interruption in 40% of patients, dose reduction in 4%, and discontinuation in 7%. The median exposure to olaparib in these patients was 168 days (5.5 months).
❖ Patients in the randomized Trial D0810C00019 were treated at the dose of 400 mg BID.
  • In the overall trial population, 97% (132/136) of patients in the olaparib group and 93% (119/128) of patients in the placebo group reported AEs. The olaparib group had more Grade $\geq$ 3 adverse events compared to placebo (40.4% versus 21.9%).
  • Adverse events led to dose interruptions in 30% (41/136) of patients on olaparib and 8.6% (11/128) of patients on placebo, dose reductions in 22.8% (31/136) of patients on olaparib and 3.9% (5/128) of patients on placebo and discontinuation in 5.1%

(7/136) of the olaparib group and 1.6% (2/128) of placebo group. The median durations of interruption due to AEs were 8 days (range: 1 to 33 days) in the olaparib group and 4.5 days (range: 0 to 27 days) in the placebo group.

- The mean dose adherence was reported to be lower in the olaparib group (84%) compared with the placebo group (96.2%).
- The median treatment duration was longer in the olaparib arm compared to placebo (263.5 days versus 141 days). The median duration of therapy at the starting dose was 170 days for olaparib and 132.5 days for placebo.

The applicant's current PD, efficacy and safety data support the use of olaparib 400 mg BID for the proposed indication.

2.2.4.5 Do the exposure response relationships for efficacy and safety support the proposed dose adjustments for safety events?

Yes. In the proposed labeling, the applicant recommends a dose reduction to 200 mg BID and to 100 mg BID if further dose reduction is needed. This is consistent with the dose reduction plan used in the clinical trials.

Of the 223 gBRCA-mutated patients who received 3 or more prior lines of chemotherapy (population being considered in current trial), adverse events led to dose interruption in 40% of patients, dose reduction in 4%, and discontinuation in 7%.The median exposure to olaparib in these patients was 168 days (5.5 months).

2.2.4.6 Do the exposure response relationships for efficacy and safety support the dose for the confirmatory SOLO-2 trial?

No. A tablet formulation is being used in ongoing and future trials including the confirmatory trials for this NDA application, while the current NDA is for a capsule formulation. The tablet formulation was introduced because the capsule formulation requires the use of 16 capsules daily to achieve the dose of 400 mg BID. One of the ongoing trials that may be used as a confirmatory trial is SOLO-2. SOLO-2 is using the tablet formulation at a dose of 300 mg BID.

The steady-state exposure for the tablet formulation at 300 mg BID was approximately 1.5 times that of the capsule at 400 mg BID in the relative bioavailability data from Trial 24 (**Table 3**). Therefore, the exposure will likely be higher in patients in the confirmatory trial compared to the trials performed with 400 mg BID that were used to support the current NDA. Therefore, it is possible that the safety and tolerability profile of the tablet at the 300 mg dose being used by the applicant in the proposed confirmatory trial(s) will not be similar to the current profile.

Table 3: Comparison of Steady-State AUC, Cmax and Cmin in Group 6 of Study 24

	300 mg Tablet BID	400 mg Capsule BID	Tablet/Capsule Ratio
	Mean (CV%)		
Day 1	**N=18**	**N=18**	
C_{max} (µg/ml)	10.4 (40)	5.73 (40)	1.8
AUC_{0-12} (µg·h/ml)	55.2 (57)	28.8 (67)	1.9
Day 29	**N=17**	**N=17**	
$C_{max,ss}$ (µg /ml)	9.37 (47)	6.36 (34)	1.5
$AUC_{0-12,ss}$ (ug·h/ml)	58.4 (44)	41.5 (63)	1.4
$C_{min,ss}$ (µg /ml)	1.84 (67)	1.04 (137)	1.8
Day 57	**N=15**	**N=-14**	
$C_{max,ss}$ (µg /ml)	9.15 (20)	6.16 (33)	1.5
$AUC_{0-12,ss}$ (ug·h/ml)	54.0 (32)	39.6 (60)	1.4
$C_{min,ss}$ (µg /ml)	1.41 (93)	0.93 (133)	1.5
Source: Adapted from Table 55 on Page 149 of CSR of Study D0810C00024 [6].			

This concern is supported by the exposure-response relationship for anemia for both the tablet and capsule formulations in the Trial 24 (**Figure 7**). Of note, 400 mg BID was the MTD for the capsule formulation. The sponsor selected the 300 mg BID dose because their initial assessment of data in Trial 24 suggested that the 200 mg BID tablet dose was numerically inferior to the 400 mg BID capsule dose in terms of percentage change in tumor size at Weeks 8 and 16 (14.7 % difference in means with 95% [CI]: -15.4%, 44.9%; p=0.320). They reported that the 300 mg BID tablet dose appeared to be numerically inferior to the 400 mg BID capsule in terms of percentage change in tumor size at Weeks 8 and 16 in the overall population, but had similar activity in a set of ovarian cancer patients only. The 400 mg BID tablet dose was observed to be numerically superior to the 400 mg BID capsule dose in percentage change in tumor size. No differences were statistically significant. However, Grade 3 or higher anemia was reported in 22% at the 300 mg tablet dose level and 400 mg capsule dose level and 29% at the 400 mg tablet dose level) of patients. Therefore, the 400 mg tablet dose was not pursued.

Figure 7: Exposure-Anemia Relationship for Capsule and Tablet Data of Studies 24 Respectively Shown in the Two Lower Panels and for Pooled Data of the Two Formulations of Studies 24 Shown the Two Upper Panels.

Source: pk3safe.xpt for capsule data of Study 24, and pk3saf24.xpt for tablet data of Study 24
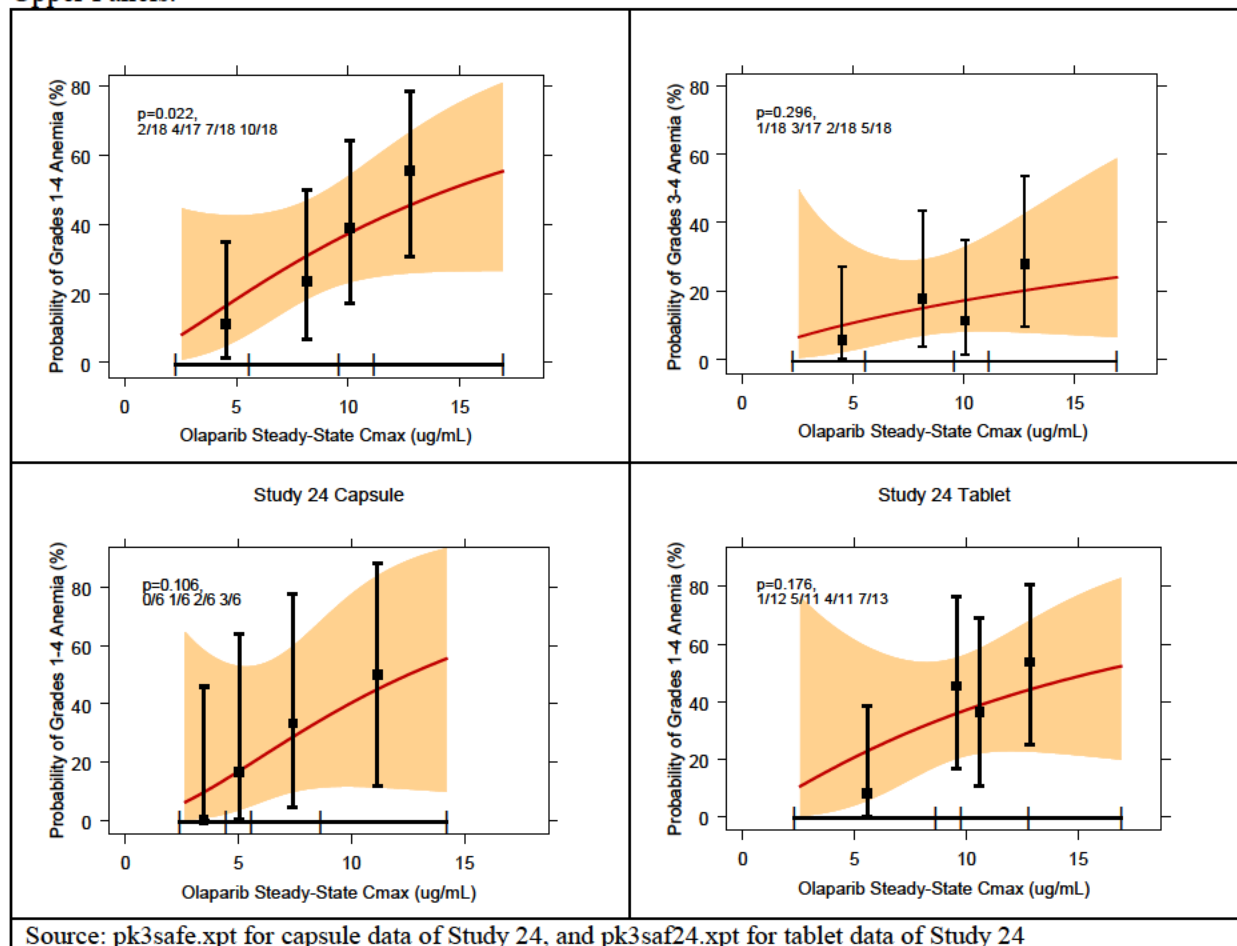
2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose and multiple dose PK parameters?

<u>Single dose PK</u>

Intensive PK sampling was done in two phase 1 trials (Trial D0810C00002 performed in Western countries and Trial D0810C00001 performed in Japanese patients) and in the ongoing Trial D0810C00024.

Single dose PK parameters (non-compartmental analysis) of olaparib were evaluated in Trial D0810C00002 (**Table 4**). The single doses of 10 - 600 mg (10, 20, 40 and 80 mg QD and 60, 100, 200, 400 and 600 mg BID) were evaluated in patients with gBRCA mutated solid tumors. The median Tmax across dose levels was 1- 3 hours and the mean terminal $t_{1/2}$ was 5 – 7 hours ($t_{1/2}$ calculated only for dose levels that used QD). The PK data suggest nonlinearity; however high variability was observed in the PK. Of note, conclusion on non-linearity was not consistent among trials (Refer to **Section 2.2.5.8**).

Table 4: Summary of (Mean ± SD (CV %)) Olaparib Pharmacokinetic Parameters after Single Dose Olaparib in Patients with Cancer in Trial D0810C00002

Dose (mg)	N	Cmax (µg/mL)	Tmax (hr)[a]	AUC$_{0-10}$ (µg*hr/mL)	AUC$_{0-24}$ (µg*hr/mL)	T$_{1/2}$ (hr)	Cl/F (L/hr)	V/F (L)
10	3	0.4 ± 0.1 (30)	2.0 (0.5 – 2.0)	1.3 ± 0.5 (37)	1.5 ± 0.6 (40)	6.7 ± 0.3	7.0 ± 2.4	67 ± 26
20	3	1.2 ± 0.6 (54)	1.5 (1.0 – 1.5)	4.0 ± 1.9 (47)	5.1 ± 2.4 (46)	6.1 ± 0.5	4.2 ± 1.6	38 ± 16
40	5	2.0 ± 0.5 (23)	1.5 (1.0 – 4.0)	10 ± 2.2 (22)	14 ± 4.2 (31)	6.1 ± 0.5	3.0 ± 0.9	26 ± 6.7
60	4	2.7 ± 0.9 (33)	2.3 (0.5 – 3.0)	9.5 ± 2.1 (22)	NC	NC	NC	NC
80	3	3.5 ± 0.7 (20)	1.5 (1.5 – 1.5)	14 ± 6.1 (43)	18 ± 10 (55)	5.5 ± 0.3	5.1 ± 2.4	40 ± 17
100	9	3.6 ± 1.6 (45)	1.0 (1.0 – 3)	19 ± 13 (66)	NC	NC	NC	NC
200	32	5.3 ± 2.9 (55)	1.5 (1.0 – 4.0)	26 ± 17 (64)	NC	NC	NC	NC
400	8	6.2 ± 1.2 (19)	1.75 (1.5 – 8.0)	33 ± 11 (35)	NC	NC	NC	NC
600	5	11 ± 3.5 (32)	3.0 (2.0 – 4.0)	67 ± 26 (39)	NC	NC	NC	NC

[a] reported as median

Figure 8: PK Profiles for Cycle 1 Day 1 after Single Dose Olaparib 10 – 600 mg
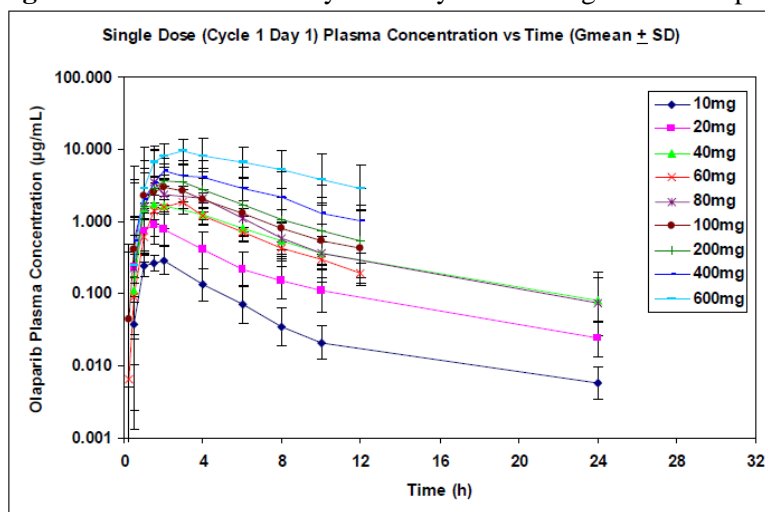
Source: Sponsor's Figure 9 in D0810C00002 study report

Doses of 100, 200 and 400 mg BID were evaluated in D0810C00001 in Japanese patients. A single dose was given on Day 1 and BID dosing was started 48 hours after. The median Tmax was 1- 2.4 hours (*similar range to that observed in Trial D0810C00002*). However, the exposure observed in this trial appears 25 – 51% lower than that observed in Trial D0810C00002. The sponsor argues that this is due to the high variability in PK observed with a small number of patients (N=3) at each dose.

Table 5: Summary of (Mean ± SD (CV %)) Olaparib Pharmacokinetic Parameters after Single Dose Olaparib in Japanese Patients with Cancer in Trial 1

Dose	100 mg	200 mg	400 mg
N	3	3	6
Cmax (μg/mL)	2.3 ± 0.9 (39)	3.5 ± 0.7 (19)	4.9 ± 0.7 (15)
Tmax (hr)[a]	1.0 (0.5 – 1.4)	2.1 (1.5 – 3)	2.4 (1.6– 4.2)
AUC_{0-12} (μg*hr/mL)	11 ± 5.3 (48)	16 ± 3.3 (21)	28 ± 7.3 (26)
AUC(μg*hr/mL)	17 ± 12(69)	21 ± 6.6 (32)	39 ± 12 (30)
$T_{1/2}$ (hr)	7.8 ± 6.5	6.9 ± 3.8	11 ± 5.3
Cl/F (L/hr)	9.3 ± 7.8	10 ± 3.4	12 ± 4.9
V/F (L)	59 ± 17	75 ± 9.9	112 ± 37

Trial D0810C00024 is a relative bioavailability trial with PK data available for the capsule formulation at the 50, 100 and 400 mg doses. As observed in Trial D0810C00001, the half-life appeared longer at the higher doses (PK Profile shown in **Figure 9**).

Table 6: Summary of (GeoMean (CV %)) Olaparib Pharmacokinetic Parameters after Single Dose Olaparib in Trial 24

Parameter	Statistic	50 mg	100 mg	400 mg
Cmax (μg/mL)	Gmean (CV)	1.8 (26)	2.9 (23)	5.7 (47)
Tmax (hr)	Median (Range)	1.5 (1.0 - 3.0)	1.3 (1.0 - 2.0)	1.3 (1.0 - 8.0)
AUC_{0-t} (μg*hr/mL)	Gmean (CV)	9.9 (43)	17 (33)	54.7 (79)
AUC (μg*hr/mL)	Gmean (CV)	10 (45)	17 (32)	58 (78)
Half-life (h)	Amean (SD)	7.9 ± 1.7	8.4 ± 2.9	12 ± 4.8
CL/F (L/h)	Amean (SD)	5.4 ± 2.4	6.2 ± 2.1	8.6 ± 7.1
V/F (L)	Amean (SD)	61 ± 31	81 ± 50	167 ± 196

Figure 9: Concentration-Time Profile following Single Oral Doses of 50, 100 and 400 mg of the Capsule Formulation in Trial D0810C00024
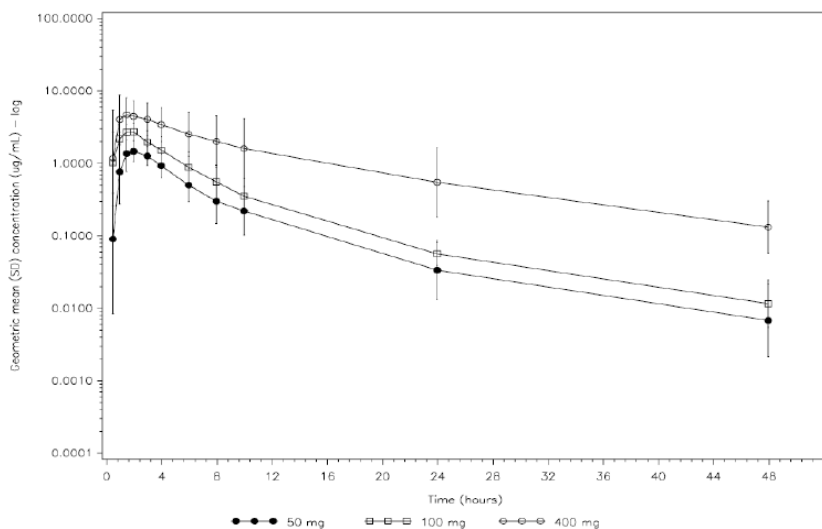
Source: Figure 12 in the Sponsor's Study Report for Trial D0810C00024

Multiple Dose PK

Multiple dose PK parameters of olaparib were also evaluated in Trial D0810C00002 at Day 14. The median Tmax was 1 - 3 hours in the 10 - 600 mg dose range and the mean half-life was 8.1 – 9.5 hours at doses of 10 – 80 mg QD. No significant accumulation was observed with a mean accumulation ratio of 1 - 1.6 for the once daily regimen and 1.4 – 1.5 for the twice daily regimen.

Table 7: Summary of (Mean ± SD (CV %)) Olaparib Pharmacokinetic Parameters on Day 14 in Patients with Cancer in Trial D0810C00002

Dose (mg)	N	Cmax (µg/mL)	Tmax (hr)[a]	AUC_{0-tau} (µg*hr/mL)	$T_{1/2}$ (hr)	Cl/F (L/hr)
10	3	0.5 ± 0.2 (45)	1.0 (0.5 – 2.0)	1.7 ± 0.7 (38)	8.3, 12[b]	5.4 ± 1.8
20	2[b]	1.7	NC (1.0 – 1.0)	5.5	9.3,12[b]	NC
40	4	1.8 ± 0.1 (7)	1.8 (1.0 – 4.0)	9.3 ± 1.7 (18)	9.5 ± 1.7	3.1 ± 0.7
60	3	2.1 ± 0.3 (12)	3.0 (1.0 – 6.0)	12 ± 5.5 (48)	NC	5.7± 2.5
80	3	4.9 ± 0.7 (14)	1.5 (1.0 – 2.0)	20 ± 5.6 (29)	8.1 ± 0.7	3.4 ± 1.3
100	8	3.8 ± 1.2 (32)	1.5 (1.0 – 4.0)	18 ± 6.6 (37)[c]	NC	5.4 ± 2.4
200	29	6.8 ± 3.8 (56)	1.5 (1.0 – 6.0)	35 ± 26 (74)[d]	NC	8.1 ± 6.3[d]
400	6	7.9 ± 2.0 (26)	2.0 (1.5 – 3.0)	44 ± 17 (38)	NC	9.4 ± 3.4
600	5	12 ± 4.5 (37)	1.5 (1.0 – 3.0)	82 ± 28 (35)[e]	NC	7.3 ± 3.1

[a] median ; [b] SD not calculated as N=2 due to missing data on 3rd patient; [c] N=7; [d] N=26; [e] N=3

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Olaparib has not been evaluated in healthy volunteers.

2.2.5.3   What are the characteristics of drug absorption?

The median Tmax of olaparib is approximately 1 - 3 hours. Preliminary assessment showed that a high-fat meal did not affect olaparib Cmax, but increased olaparib AUC by 20% and delayed Tmax from 1.7 to 4 hours (**Tables 19 and 20**).

Olaparib is a substrate of the efflux transporter P-gp, in vitro. The absolute bioavailability of olaparib has not been evaluated but is likely highly variable. The applicant attributes potential non-linearity with the capsule formulation to the absorption of the drug.

2.2.5.4   What are the characteristics of drug distribution?

Plasma Protein Binding:

Olaparib had mean plasma protein binding of 89% (91% at 10, 100 and 1000 ng/mL and 82% at 10 000 ng/mL) in human plasma. Protein binding was assessed using equilibrium dialysis over 4 hours in Study # KPJ019. The protein binding in human plasma was higher than that observed in nonclinical species (70% in mice, 73% in rat, and 59% in dog). The protein binding appears to decrease at higher concentrations of olaparib. As a Cmax of > 7000 ng/mL can be achieved at the proposed dose of 400 mg BID the protein binding could be as low as 82%. The effect of varied levels of proteins has not been evaluated. Ex vivo protein binding from patients treated with olaparib has not been evaluated. In addition, the extent olaparib binds to human serum albumin

and/or α1-acid glycoprotein has not been evaluated. Protein binding will be evaluated in the organ impairment trials.

Blood to Plasma Ratio: In vitro, the whole blood to plasma ratio for olaparib was approximately 0.6 - 0.8 at concentrations of 100 and 1000 ng/mL incubated for 120 minutes (Study KPJ019). Olaparib was stable in blood and plasma and the blood and plasma ratio was constant for the 120 minute duration. In the human mass balance trial, the mean whole blood to plasma ratio for total radioactivity was approximately 0.6 - 0.7.

Tissue Distribution:

The estimated single dose V/F was 167 ± 196 L (the mean was 88 L when 1of the 6 patients is excluded) for the capsule at the 400 mg dose in Trial D0810C00024. The mean V/F was estimated as 73.4 L in the ADME trial. An absolute bioavailability study has not been performed.

The sponsor measured tumor concentrations in tumor biopsies collected from breast cancer patients scheduled for elective surgery in Trial D0810C00007. The sponsor reports tumor concentrations of 63 - 1830 ng/g (146 - 4217 nM when assume the density of the tissue = 1.0) in the patients dosed at 400 mg BID. The timing of the biopsy after dose and how many doses the patients had received at the time of biopsy are not specified. The sponsor concluded that the concentrations observed in the tumors were above the tumor concentration of 100 nM that in vitro experiments determined was needed for maximal PARP inhibition.

Transporter Proteins: Olaparib is a substrate of P-gp, but is not a substrate of BCRP. Refer to **Section 2.4.2.4**

2.2.5.5   Does the mass balance trial suggest renal or hepatic as the major route of elimination?

Olaparib is the major moiety in plasma (65% of radioactivity). Metabolism is an important elimination pathway for olaparib, but renal contribution cannot be ruled out. About 41.8% (6% unchanged) and 44.1% (15% unchanged) were found in feces and urine, respectively when a total of 85.8% of radioactivity was recovered.

In the mass balance trial # D0810C00010, six patients with advanced solid tumors received a single oral 100 mg dose of [^{14}C]-olaparib. The single dose was given as one radiolabeled 50 mg [^{14}C]-olaparib capsule (120 µCi; 4.44 MBq) and one 50 mg non-radiolabelled olaparib capsule. The dose was given in the morning and patients were required to fast from midnight the previous night until 4 hours after the single dose. The formulation was a (b) (4) (b) (4) capsule.

Patients in the trial were required to have adequate renal and hepatic function. Strong CYP3A inhibitors and inducers and drugs known to affect renal function were not permitted during the trial. Concentrations of olaparib were measured in plasma, urine and feces and total radioactivity (^{14}C) was measured in plasma, whole blood, urine and feces. The blood to plasma ratio and metabolic profile were determined. Blood samples for determination of olaparib concentrations

in plasma and total radioactivity in blood and plasma were collected up to 168 hours post-dose. Blood samples for metabolite profiling were collected up to 48 hours post-dose. Urine samples were collected pre-dose, in the 0-6, 6-12, 12-24 post-dose intervals, daily for 6 day and then weekly for 3 weeks. Fecal samples were collected in 24-hour intervals for 7 days and weekly for another 3 weeks.

Plasma and urine concentrations were analyzed using a validated LC-MS/MS method discussed in **Section 2.6.4**. Liquid scintillation was used for assessment of radioactivity in blood, plasma, urine and feces. One of the patients (0003) was wrongly dosed and received only the 50 mg capsule with radioactivity. Therefore, the mean plasma PK data are derived from only 5 patients, but the mean urine and fecal radioactivity data include all 6 patients.

Blood and Plasma:

The observed olaparib Tmax of 1.5 – 2 hours was consistent with that observed in the trials with PK discussed in Section **2.2.5**. The terminal half-life was between 2.4 and 4.7 hours in 4 of the 5 patients that received the full dose, but one patient (#7) had an estimated half-life of 149 hours (*the baseline bilirubin, AST/ALT and SrCr for patient 7 were within similar range as the other patients*). The volume of distribution was not extensive with mean V/F estimated as 73.4 L for olaparib. The major moiety in plasma was olaparib and the mean ratio of olaparib in plasma to radioactivity in plasma of 0.65 (range of 0.49 – 0.77 at time-points up to 16 hours post-dose). The mean blood to plasma ratio for the total radioactivity was about 0.6 (range of 0.48 - 0.73).

Table 8: Mean (SD) Pharmacokinetic Parameters of Olaparib in Plasma and Total Radioactivity in Blood and Plasma Following a Single Oral Administration of 50 mg ^{14}C-Olaparib and 50 mg Olaparib

	N	Olaparib (Plasma)	Total Radioactivity (Plasma)	Total Radioactivity (Blood)
Cmax ng/mL (ng.eq/g for ^{14}C)	5	3984 ± 2379	4410 ± 2274	3210 ± 1700
AUC$_{0-t}$ ng.hr/mL (ng.eq*hr/g for ^{14}C)	5	29277 ± 34303)	36105 ± 34857	22232 ± 16682
AUC$_{0-\infty}$ ng.hr/mL	5	31333 ± 38198	NR	NR
^{a}Tmax (hr)	5	2.0 (1.5-2)	1.6 (1 - 2)	1.6 (1 - 2)
T$_{1/2}$ (hr)	5	^{c}32.6 ± 65.2	^{b}25, 25	^{b}5.5, 3
CL/F (L/h)	5	6.8 ± 4.9	NR	NR
V/F (L)	5	73.4 ± 81.5	NR	NR

^{a} Median (range); ^{b}N=2; ^{c}mean T1/2 is 3.4 hours if exclude 1 patient with half-life 149 hours

Urine and feces:

Two patients had little or no fecal samples for up to 96 hours. Radioactivity was observed up to Day 21 in the feces of these 2 patients, but the percent of dose excreted after 168 hours was not calculated because samples were only collected for 24 hour intervals weekly for the 3 weeks following.

If these 2 patients are excluded, the mean total recovery of radioactivity at 168 hours was 97.2% of which 55.5% was in the feces and 41.7% was in the urine. If all six patients are considered a

mean of 85.8% was recovered, with 41.8% in the feces and 44.1% in the urine. Approximately 15% of the dose was excreted in urine as unchanged olaparib. The estimated renal clearance was slightly higher than the rate of renal filtration which the applicant states implies a likelihood of a small contribution of active secretion into the urine.

Table 9: Individual (N=7) and Mean (SD) Cumulative Excretion of Total Radioactivity Over 168 Hours in Urine and Feces Following Single Oral Administration of 140 mg ^{14}C-Olaparib

	1	2	3	5	6	7	Mean ± SD[a]
^{14}C Urine (U)	49.68	49.19	45.87	35.27	35.85	48.48	**44.06 ± 6.71 (41.68 ± 7.23)**
^{14}C Feces (F)	54.97	11.67	49.49	59.37	58.26	16.92	**41.78 ± 21.63 (55.52 ± 4.43)**
^{14}C U+F	104.65	60.86	95.36	94.64	94.11	65.40	**85.84 ± 18.07 (97.19 ± 5.00)**
Olaparib in U	20.55	12.20	12.86	12.52	12.99	20.35	**15.25± 4.04 (14.73 ± 3.89)**

[a] Mean and standard deviation in brackets excludes patients 2 and 7; Results expressed as percentage of dose recovered over the 168 h collection period

The results from this trial suggest that metabolism is an important elimination pathway for olaparib, but renal contribution cannot be ruled out. Both the effects of renal and hepatic impairment are being evaluated in dedicated organ impairment trials. Refer to **Section 2.3.2** for discussion of the effect of renal and hepatic impairment on olaparib.

2.2.5.6   What are the characteristics of drug metabolism?

Olaparib is primarily metabolized by CYP3A. In the mass balance trial # D0810C00010, the main circulating moiety in blood and plasma was olaparib (65%). Olaparib accounted for 15% (10 - 19%) of radioactivity in urine suggesting it is extensively metabolized with a total of 37 metabolites identified in the urine.

<u>Metabolic Profiling and Identification</u>

Metabolite profiling (report KMX032) of plasma in the mass balance trial D0810C00010 showed that olaparib was the main circulating moiety accounting for about 65% (56 – 84%) of total radioactivity. Three metabolites each accounted for approximately 10% of the radioactivity (M12 at 9.3%, M15 at 10.3% and M18 at 13.7%). However, the pharmacological activity of the metabolites has not been assessed. The M12 is identified as a ring-opened hydroxyl-cyclopropyl moiety, M15 as a mono-oxygenated metabolite and M18 as a dehydrogenated piperazine. Dehydrogenation and oxidation are identified as the major metabolic pathways. These 3 metabolites were also identified in male rat plasma. Three of the metabolites (M8, M10 and M36) detected in humans were not detected in rats, but they each accounted for <1% of dose.

About 44% (35 - 49%) of radioactivity was recovered in urine with 86% (61 – 105%) total recovery in urine and feces. Olaparib accounted for 15% (10 - 19%) of the radiochemical dose in the urine suggesting it is extensively metabolized with a total of 37 metabolites identified. Of the 18 metabolites in the urine that were quantifiable, M15 accounted for approximately 6% of the dose and the remaining components each represented <2%.

About 42% (12 - 59%) of radioactivity was recovered in feces. Twenty moieties were identified in the feces. Olaparib accounted for 0.6 - 14% of radioactivity and M15 accounted for 5% of radioactivity.

Figure 10: Proposed Metabolic Pathways for Olaparib in Patients based on Trial # D0810C00010

(b) (4)

The three metabolites at about 10% each in plasma (M12, M15 and M18) are marked with a box.
Source: Part of Applicants Figure 2 in summary-clin-pharm.pdf with minor metabolites M2, M4b, M8 and M28 missing

2.2.5.7   What are the characteristics of drug excretion?

Elimination: Olaparib is extensively metabolized and excreted both through the feces (42%) and urine (44%) as unchanged drug (15% in urine and 6% in feces) and many metabolites (38 moieties identified in urine and 20 moieties identified in feces). Please refer to **Section 2.3.2.6 and 2.3.2.7** for discussion of hepatic and renal impairment.

Clearance: The mean apparent Vd is estimated as 73 L and Cl/F as 6.8 L/h in the mass balance trial. The estimated single dose V/F was 167 ± 196 L (the mean was 88 L when 1of the 6 patients is excluded) for the capsule at the 400 mg dose in Trial D0810C00024. The population PK model was not deemed suitable for use for parameter estimation (Refer to **Appendix 3.2**).

Half-life: The mean elimination half-life of olaparib was reported as 12 hours for the 400 mg dose in Trial 24. The mean half-life was 5 – 8 hours at lower doses. The sponsor believes that

nonlinearity explains the differences in half-life with doses. However, it is not clear if variability and sampling times can also account for these differences.

2.2.5.8   Based on PK parameters, what is the degree of linearity or non-linearity?

Dose-proportionality cannot be concluded based on available PK data. The sponsor had reported that the exposure of olaparib PK appeared to increase in a less than dose proportional manner above the 100 mg dose. The non-linearity was assumed to be due to nonlinearity in the absorption of the drug. However, the conclusion of non-linearity was not consistent among trials. Although, the sponsor's population PK model that included all trials was used to conclude non-linearity, the sponsor was asked to report dose-proportionality analyses in each trial.

The sponsor's conclusion was as follows: There was some evidence to support dose proportionality seen in Studies D0810C00001, D0810C00002 and D0810C00007, but only limited evidence was seen from Studies D0810C00001, D0810C00002, D0810C00009 and D0810C00012.

The variability in the PK likely introduced difficulty in the assessment of dose proportionality. We cannot at this time make a conclusion about dose-proportionality in the PK with the administration of olaparib capsules. The sponsor reported dose proportionality for the tablet formulation in Trial 24. This tablet data will be reviewed as part of the supplemental NDA application for the tablet formulation from the confirmatory SOLO-2 trial if submitted.

Table 10: Summary of Sponsor's Dose Proportionality Analysis Results

Trial	N	Dose Regimen	Dose Levels (mg)	Parameter	Slope Parameter
D0810C00001	12	Single (BID)	100, 200, 400	AUC0-12 (ug.h/mL)	0.7 (0.4,1.0)
				AUC (ug.h/mL)	0.7 (0.3, 1.2)
				Cmax (ug/mL)	0.6 (0.4, 0.8)
	11	Multiple (BID)	100, 200, 400	AUC0-12 (ug.h/mL)	0.3 (-0.3, 0.9)
				Cmax (ug/mL)	0.3 (-0.1, 0.7)
D0810C00002	14	Single (QD)	10, 20, 40, 80	AUC0-10 (ug.h/mL)	1.2 (0.9, 1.4)
				AUC (ug.h/mL)	1.2 (0.9, 1.5)
				Cmax (ug/mL)	1.1 (0.8, 1.3)
	54	Single (BID)	60, 100, 200, 400, 600	AUC0-12 (ug.h/mL)	0.7 (0.4, 0.9)
	58			Cmax (ug/mL)	0.6 (0.4, 0.7)
	12	Multiple (QD)	10, 20, 40, 80	AUC0-12 (ug.h/mL)	1.2 (1.0, 1.4))
				Cmax (ug/mL)	1.0 (0.8, 1.2)
				Cmin (ug/mL)	1.4 (0.9, 1.9)
	46	Multiple (BID)	60, 100, 200, 400, 600	AUC0-12 (ug.h/mL)	0.7 (0.5, 1.0)
	51			Cmax (ug/mL)	0.7 (0.5, 1.3)
	46			Cmin (ug/mL)	0.9 (0.5, 1.3)
D0810C00007	60	Multiple (BID)	10,30, 100, 200, 400	AUC0-12 (ug.h/mL)	0.9 (0.8, 1.0)
				Cmax (ug/mL)	0.8 (0.7, 0.9)
				Cmin (ug/mL)	1.0 (0.9, 1.2)
D0810C00009	42	Multiple (BID)	100, 400	AUC0-12 (ug.h/mL)	0.4 (0.1, 0.7)
				Cmax (ug/mL)	0.3 (0.1, 0.5)
				Cmin (ug/mL)	0.4 (0.0, 0.8)
D0810C00012	58	Multiple (BID)	200, 400	AUC0-12 (ug.h/mL)	0.6 (0.3, 1.0)
				Cmax (ug/mL)	0.6 (0.3, 0.8)
				Cmin (ug/mL)	0.7 (0.2, 1.2)

2.2.5.9   How do the PK parameters change with time following chronic dosing?

Mean accumulation ratios of < 2 were observed at steady-state compared to single dose exposures. The estimated clearance appears to be the same after a single dose as with multiple doses. The PK variability was high for both single and multiple dose PK (see **Tables 4 and 7**).

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

High PK variability was observed for both the single (CV of up to 65%) and multiple dose (CV of up to 74%). The population PK model was not deemed appropriate to describe the variability. Olaparib has not been assessed in healthy volunteers.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, race, weight, height, _____ (b) (4) and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

In the mass balance trial, olaparib is extensively metabolized and excreted both through the feces (42%) and urine (44%) as unchanged drug (15% in urine and 6% in feces) and many metabolites (38 moieties identified in urine and 20 moieties identified in feces). _____ (b) (4)
_____ . The data from the dedicated trials evaluating the effect of renal and hepatic impairment on the PK of olaparib will be available in the post-marketing setting.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

The population PK model submitted by the sponsor was not deemed adequate by the pharmacometrics reviewer and was not used to evaluate the effect of covariates on PK. In addition, the high variability in PK in part due to the inconsistency in the formulation introduced difficulty in assessing the effect of covariates on PK. Therefore, we cannot comment on the effect of age, body weight, gender and race on the PK of olaparib. Observed steady-state Cmin values were used to evaluate the effect of renal impairment on PK as discussed in **Section 2.3.2.2**.

2.3.2.1 Pediatric patients

Safety and effectiveness of olaparib have not been established in pediatric patients.

2.3.2.2 Race

The majority of the patients in the supportive trials and Trial 42 were Caucasian (93%). Due to

the limitations in the population PK model and the limited number of individuals of non-Caucasian races, the effect of race on PK has not been established.

2.3.2.3 Renal impairment

(b) (4)

. The recommendation is acceptable.

A renal impairment trial D0816C00006 is currently ongoing and final data from the trial will only be available in the post marketing setting. The trial is evaluating a single 300 mg tablet dose of olaparib in patients with normal renal function (CLcr > 80 mL/min), mild renal impairment (50- 80 mL/min) and moderate renal impairment (30 – 50 ml/min). Preliminary PK data are available in patients with mild renal impairment in this dedicated trial.

The preliminary data showed a 1.2 fold higher Cmax and 1.5 fold higher AUC (based on geometric mean) with a 26% decrease in apparent clearance observed in patients with mild renal impairment (N=14) compared to those with normal renal function (N=8). Protein binding data were not submitted in this preliminary report. This data support that dose adjustment is not needed in patients with mild renal impairment. A PMR will be issued for the submission of the final study report of this ongoing trial.

Table 11: Mean ± SD of Olaparib PK Parameters when a Single 300 mg Tablet Dose of Olaparib is Administered in Patients with Normal Renal Function (CLcr >80 mL/min) and in Mild Renal Impairment (CLcr of 50 – 80 mL/min)

Parameter	Normal (N=8)	Mild RI (N=14)
Cmax (µg/mL)	7.4 ± 2.5(33.3)	9.4 ± 3.9 (41.1)
Tmax (hr)^a	2.0 (1.0 – 3.0)	1.8 (1.0 – 3.0)
AUC$_{0-t}$ (µg*hr/mL)	48.1 ± 23.8 (49.4)	80.1 ± 50.4 (63.0)
AUC$_{0-\infty}$ (µg*hr/mL)	48.6 ± 23.8 (49.4)	80.6 ± 50.8 (63.1)
T$_{1/2}$ (hr)	23.9± 9.8 (41.2)	16.7± 7.8 (46.5)
Cl/F (L/hr)	7.8 ± 4.2 (54.3)	5.8 ± 4.2 (72.1)
V/F (L)	289.1 ± 201.9 (69.8)	135.0 ± 106.9 (79.2)

2.3.2.4 Hepatic impairment

A hepatic impairment trial is ongoing and data from the trial will only be available after approval. A PMR will be issued for the study report of this ongoing trial.

Inclusion criteria regarding hepatic function for all olaparib clinical trials required baseline serum bilirubin <1.5 X ULN and AST/ALT ≤2.5 x ULN (≤5 x ULN in the presence of liver metastases) for enrollment into trials. (b) (4)

. This appears to be a reasonable approach until data will be available from the dedicated trial.

2.3.2.5 Pregnancy and lactation

The safety and effectiveness of olaparib have not been established in pregnancy and in lactating

women.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Olaparib is a CYP3A substrate. Preliminary data from dedicated trials with a strong CYP3A inhibitor and inducer show that CYP3A inhibitors and inducers have an effect on olaparib exposures. Refer to **Section 2.4.2.2** for details. The effects of extrinsic factors such as herbal products, diet, smoking and alcohol use on the dose-exposure and/or dose-response for olaparib were not assessed in a formal study.

2.4.1.1 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

(b) (4)

However, a dose adjustment can be recommended for both strong and moderate CYP3A inhibitors using data from a dedicated drug interaction trial and PBPK modeling.
A dose reduction to 150 mg BID for the capsule formulation when olaparib is concomitantly dosed with a strong CYP3A inhibitor and a dose reduction to 200 mg BID when a moderate CYP3A inhibitor is concomitantly dosed with olaparib are likely to result in exposures observed when olaparib 400 mg BID is dosed alone.

(b) (4)

as a dose adjustment cannot be recommended for the mean AUC decrease of 87% and the mean Cmax decrease of 71% observed when olaparib was dosed with rifampin (N=22). Increasing the dose could be impractical given the number of capsules to be administered. In addition, doses higher than 1000 mg have not been used clinically and absorption could potentially plateau at a certain dose with no increase in plasma exposure observed with increasing doses. Refer to see **Section 2.4.2.2** for details.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes, olaparib is a CYP3A substrate and in vitro studies suggest that it is primarily metabolized by CYP3A. It is not expected to be an inhibitor of any major CYP enzymes at the 400 mg BID clinical dose. However, it may have the potential to induce CYP2B6.

2.4.2.2 Is the drug a substrate of CYP enzymes?

Yes, olaparib is a CYP3A substrate. Enzymes involved in the metabolism of olaparib were determined in Studies KMX009 and KMX041. Three metabolites (MF1, MF2 and MF3) were identified when ^{14}C olaparib (20 µM) was incubated in human liver microsomes in Study KMX009. The formation of all 3 metabolites was inhibited by ketoconazole, suggesting that CYP3A plays a role in the formation of the 3 metabolites. Three main peaks were identified in Study KMX041: M11a/b (a monooxygenated, dehydrogenated piperazine metabolite and a monooxygenated, fluorophenol metabolite), M15/M16 (a fluorophenol metabolite, and an N, N-desethyl piperazine metabolite) and M18/M39 (a dehydrogenated piperazine metabolite and a monooxygenated metabolite). CYP3A/5 were identified as the major isoforms responsible for the formation of the metabolites in the 3 peaks. CYP3A expressing cDNA metabolized olaparib to the 3 identified metabolites. CYP2A6 and CYP1A1 also formed the 3 metabolites but to a lesser extent.

Effect of CYP3A Inhibitors

Strong CYP3A Inhibitors

PK data are available from Trial D0816C00007, "A non-randomized, open-label, sequential, three-part, phase 1 study to assess the effect of itraconazole (a CYP3A inhibitor) on the pharmacokinetics of olaparib following oral dosing of a tablet formulation, and to provide data on the effect of olaparib on QT interval following oral dosing of a tablet formulation to patients with advanced solid tumors". This section of the review only covers the drug interaction portion of the trial which is Part A of this 3 part trial.

Part A was a non-randomized, open-label, 2-treatment period sequential design. Each patient received a single 100 mg dose of olaparib tablets alone in the fasted state (overnight fast pre-dose and 4 hours post-dose). The patients received itraconazole 200 mg daily starting on Day 5. Patients received a second single dose of olaparib on Day 9 concomitantly with the itraconazole dose. Itraconazole dosing was continued until the day of collection of the final olaparib pharmacokinetic sample. PK sampling was up to 72 hours post-dose.

A 2.7 fold increase in mean AUC and a 1.4 fold increase in Cmax were observed when a single 100 mg dose was given with multiple doses of itraconazole compared to when given alone. The mean terminal half-life did not change and the median Tmax increased from 1 to 1.5 hours when olaparib was dosed with itraconazole compared to without (**Table 12**).

Figure 11: Mean Plasma Concentration-Time Profiles for Olaparib following a Single 100 mg Olaparib (Tablet) Dose With or Without Co-administered Itraconazole 200 mg Once Daily
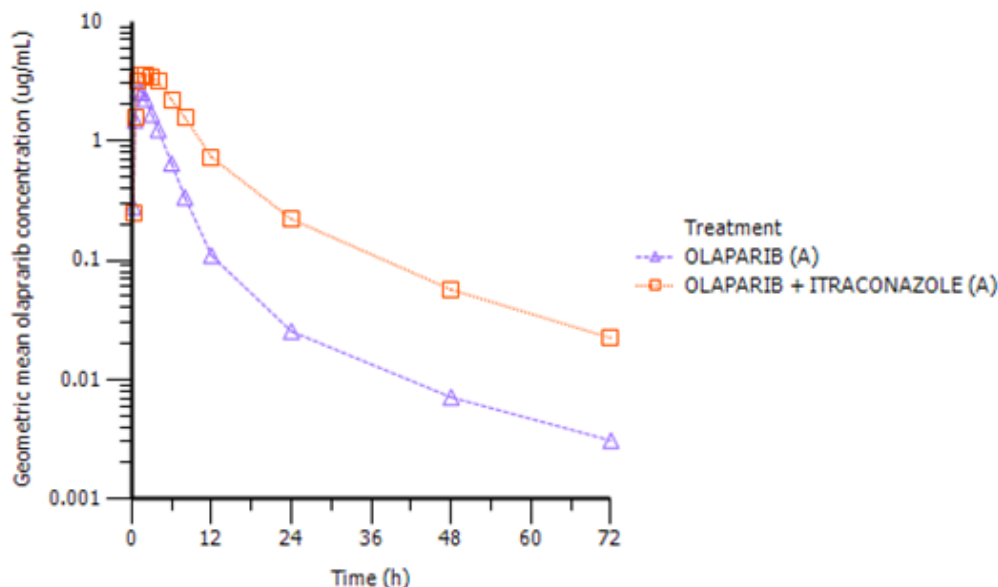
Source: Figures 1 from Page 6 in study-report –d0816c00007-interim-report-of-pk-data.pdf

Table 12: Mean±SD (CV %) of Olaparib PK Parameters When Single-dose Olaparib is Administered Alone or in Combination with Itraconazole

Parameter	N	Olaparib	N	Olaparib + Itraconazole	GMR (90% CI)
Cmax (µg/mL)	56	3.3 ± 1.7 (51.1)	53	4.5 ± 1.6 (36.2)	**1.4 (1.3 – 2.1)**
Tmax (hr)[a]	56	1.0 (0.5 – 8.3)	55	1.5 (0.5 – 12.0)	
AUC_{0-t} (µg*hr/mL)	52	19.5 ± 16.5 (84.8)	52	47.8± 33.6 (70.2)	**2.7 (2.4 – 3.0)**
$AUC_{0-\infty}$ (µg*hr/mL)	53	19.1 ± 16.7 (87.7)	49	49.4 ± 37.1 (75.1)	**2.7 (2.4 – 2.9)**
$T_{1/2}$ (hr)	53	15.0± 8.2 (54.9)	49	15.6± 6.4 (41.4)	
Cl/F (L/hr)	53	8.2 ± 4.6 (56.5)	49	3.1 ± 2.1 (68.9)	
V/F (L)	53	191.8 ± 172.4 (89.9)	49	75.1 ± 81.3 (108.2)	

TR- Treatment Ratio (i.e Cmax in olaparib alone/ Cmax in olaparib + itraconazole).Geometric mean ratio and 90% CI not calculated for this preliminary data and is planned in final study report.

As the mean AUC increases about 2.7 fold with the use of the strong CYP3A inhibitors, a dose of 148 mg BID would be predicted to result in exposures in the range of 400 mg BID used alone if linear PK of olaparib were assumed. Therefore, we recommend a dose of 150 mg BID.

Moderate CYP3A Inhibitors

A dedicated trial has not been performed to assess the effect of moderate and weak inhibitors of CYP3A. The applicant was asked to submit a physiological based pharmacokinetic (PBPK) model to predict the effects of moderate and weak inhibitors. Dr. Ping Zhao evaluated the adequacy of the sponsor's olaparib PBPK model to predict the DDI potential (*Details in Appendix 3.3*).

The sponsor's PBPK modeling of olaparib can be summarized in three parts:

(A). Model building: Results of in vitro experiments and physicochemical properties, and in vivo PK studies were used to describe absorption, distribution, metabolism, and excretion (ADME) characteristics in the model.

(B). Model verification: Clinical drug-drug interaction studies with strong CYP3A inhibitor or inducer (itraconazole and rifampin) were used to verify olaparib PBPK model.

(C). Model applications: The sponsor conducted simulations to predict the following:
1. 300 mg single dose olaparib tablet in the presence of a moderate CYP3A inhibitor, fluconazole.
2. 300 mg single dose olaparib tablet in the presence of a moderate CYP3A inducer, efavirenz.

The model predicted a 2.8 fold increase in AUC and a 1.2 fold increase in Cmax with the use of itraconazole. These predicted results for the inhibitor were similar to the 2.7 fold increase in AUC and the 1.4 fold increase in Cmax observed in Trial D0816C00007. The PBPK model was then used to predict the drug interaction with a moderate CYP3A inhibitor, fluconazole. The model predicted a 2 fold increase in AUC and no significant increase in Cmax (14% increase) with the use of fluconazole. The prediction was performed for a single 300 mg dose of olaparib as the tablet formulation given on Day 5 dosed with fluconazole 200 mg daily for 7 days.

The prediction suggests that an olaparib capsule dose of 200 mg BID can be used with moderate CYP3A inhibitors to have exposures in a similar range as 400 mg BID used alone. The prediction was not performed for weak inhibitors but the increase, if any, would likely be less than 2 fold. Considering the high variability in PK of olaparib it is unlikely an adjustment would be needed when olaparib is used in combination with a weak inhibitor.

(b) (4)

. However, a dose adjustment can be recommended for strong inhibitors based on data from the itraconazole dedicated drug interaction trial and PBPK modeling for moderate CYP3A inhibitors. As discussed above, we would recommend a dose of 150 mg BID when the capsule formulation is used with a strong CYP3A inhibitor and 200 mg BID when used with a moderate CYP3A inhibitor. No dose adjustments are recommended when olaparib capsules are used concomitantly with weak CYP3A inhibitors.

Effect of CYP3A Inducers

Strong CYP3A Inducers

PK data are available from Trial D0816C00008 entitled, "A non-randomized, open-label, sequential, multicenter, two-part, phase 1 study to assess the effect of rifampicin, a known CYP inducer, on the pharmacokinetics of olaparib following oral dosing of the tablet formulation to patients with advanced solid tumors". The effect of rifampin on the PK of olaparib was assessed in Part A and patients are allowed continued access to the drug in Part B.

In Part A of the trial, 22 patients received a single 300 mg dose of olaparib on Day 1 taken after an overnight fast. Daily rifampicin 600 mg was given on Days 5 - 17. A second single 300 mg dose of olaparib was given on Day 14 taken together with rifampin after an overnight fast. PK samples for olaparib were collected up to 72 hours post-dose after each single dose of olaparib. PK samples for rifampin and plasma samples for concentrations of 4β-hydroxy cholesterol (*show induction of enzyme*) were collected 2 hours post-dose on Days 5, 9, 14 and 17.

The mean $AUC_{0-\infty}$ decreased by 87% (ratio of 0.13 [90% CI: 0.11, 0.16]) and the mean Cmax decreased by 71% (ratio of 0.29 [90% CI: 0.24, 0.33]) when olaparib was dosed with rifampin (**Table 13**). ⟨   ⟩ ⟨   ⟩. This is a reasonable approach as a dose adjustment cannot be recommended. Increasing the dose could be impractical given the number of capsules to be administered. In addition, doses higher than 600 mg have not been used clinically and absorption could potentially plateau at a certain dose with no increase in plasma exposure observed with increasing doses.

Figure 12: Mean Plasma Concentration-Time Profiles for Olaparib following a Single 300 mg Olaparib (Tablet) Dose With or Without Co-administered Rifampin 600 mg Once Daily
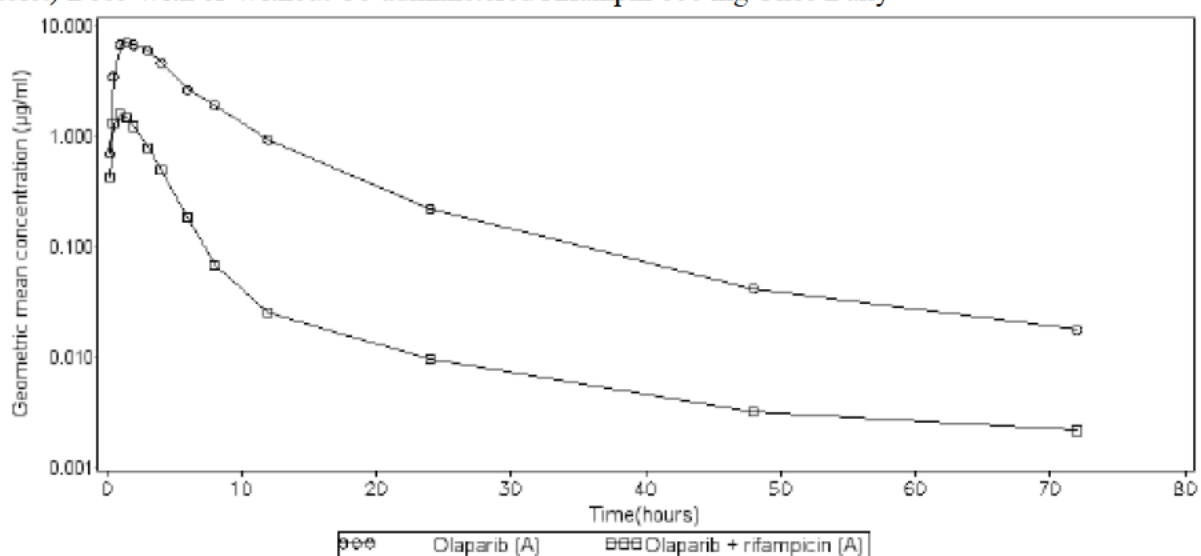
Source: Figures 2 from Page 53 in study-report –d0816c00008 .pdf

Table 13: Mean±SD (CV%) of Olaparib PK Parameters When Single Dose Olaparib is Administered Alone or in Combination with Rifampin

Parameter	N	Olaparib	N	Olaparib + Rifampin	GM T/R (90%CI))
Cmax (µg/mL)	22	8.3 ± 1.9 (22.9)	18	2.5 ± 1.2 (48.9)	0.29 (0.24, 0.33)
Tmax (hr)[a]	22	1.5 (0.6 - 3.1)	18	0.8 (0.3 – 6.0)	
AUC_{0-t} (µg*hr/mL)	22	65.6 ± 48.4 (73.7)	18	7.1 ± 3.6 (50.5)	0.12 (0.10, 0.15)
$AUC_{0-\infty}$ (µg*hr/mL)	21	67.6 ± 52.7 (78)	17	7.4 ± 3.4 (45.6)	0.13 (0.11, 0.16)
$T_{1/2}$ (hr)	21	13.0 ± 4.2 (32.0)	17	15.8 ± 9.6 (60.4)	
Cl/F (L/hr)	21	6.4 ± 3.5 (54.6)	17	48.3 ± 21.0 (43.5)	
V/F (L)	21	112.1 ± 59.8 (53.4)	17	1076 ± 868.8 (80.7)	

TR- Treatment Ratio (i.e Cmax in olaparib alone/ Cmax in olaparib +rifampin). Geometric mean ratio and 90% CI not calculated for this preliminary data and is planned in final study report.

Moderate CYP3A Inducers

A dedicated trial has not been performed to assess the effect of moderate and weak inducers of CYP3A. The PBPK model reviewed by Dr. Ping Zhao was also used to simulate the effect of the moderate CYP3A inducer, efavirenz. The PBPK model under predicted the interaction with the strong CYP3A inducer. The model predicted an AUC ratio of 0.33 (observed of 0.13) and Cmax ratio of 0.61 (observed 0.29) for use with rifampin 600 mg QD. The current SimCYP rifampin model tends to under predict the interaction when used as is.

The sponsor created 2 models for efavirenz and the FDA reviewer used another efavirenz model submitted by another sponsor. The AUC was predicted to decrease 49 – 61% with efavirenz (AUC ratio of 0.39 and 0.47 by the current sponsor methods and 0.51 by the older method) compared to olaparib taken alone. The Cmax was predicted to decrease 22 – 31% with efavirenz (Cmax ratio of 0.69 and 0.75 by the current sponsor methods and 0.78 older method) compared to olaparib taken alone. As stated for strong CYP3A inducers, increasing the number of capsules from 8 a day to 16 a day may be needed to match the olaparib AUC in the absence of a moderate CYP3A inducer, which appears impractical. In addition, doses above 600 mg have not been evaluated and absorption above that dose is not known. We recommend language stating that the concomitant use of a moderate CYP3A inducer with olaparib should be avoided, but if used, it may result in reduced efficacy. If the tablet formulation is introduced at a later date, a consideration for dose adjustment may be made.

2.4.2.3   Is the drug an inhibitor and/or an inducer of CYP enzymes?

Based on in vitro studies, olaparib is unlikely to inhibit any major CYPs. In vitro, it did not induce CYP1A2, CYP2C9, CYP2C19 and CYP3A, but showed some induction of CYP2B6.

As a CYP inhibitor:

The potential for olaparib (0.1 – 100 µM) to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A in human liver microsomes was evaluated in Study KMX001. The IC_{50} values were not estimated for the CYP enzymes because limited inhibition was observed (up to 10% inhibition for all enzymes evaluated other than CYP3A at olaparib concentrations of 0.1 – 100 µM. Up to 30% inhibition of CYP3A activity was observed at 30 µM and 44% at 100 µM when midazolam and testosterone were used as probe substrates) compared to the controls. The IC_{50} values for all the evaluated CYP isozymes were all considered >100 µM and olaparib is likely not an inhibitor at the clinical dose of 400 mg BID (steady-state Cmax of 18µM). Time dependent inhibition was not observed for any of the assessed CYP enzymes. From these results, olaparib is not expected to be an inhibitor of any of the assessed CYP enzymes at clinically used doses.

As a CYP inducer:

The potential for olaparib (0.3 – 30µM) to induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and

CYP3A in human hepatocytes was evaluated in Study KMX002.Olaparib did not induce CYP1A2, CYP2C9, CYP2C19 and CYP3A in the concentration range. Up to 1.5 fold induction of CYP2B6 was observed with 3 µM of olaparib and up to 3.2 fold induction at the olaparib concentration of 30 µM. This represented up to 7% of the positive control induction at 3 µM and up to 40% of the positive control induction at olaparib concentration of 30 µM. It may have the potential to be an inducer of CYP2B6 considering the steady Cmax of up to 8 µg/mL (18 µM) at the 400 mg dose.

Table 14: In Vitro Induction of CYP2B6

Donor #	Treatment (Conc)	Enzyme Activity (pmol/min/10^6 cells)	Fold Induction	%Positive Control
1	[a]Medium Control	11.6 ± 0.1		
	[b]Solvent Control	23.4 ± 0.8		
	Phenobarbital (1mM)	163 ± 5	14.1	
	Olaparib 0.3 µM	27.4 ± 1.7	1.2	2.6
	Olaparib 3 µM	32.3 ± 3.1	1.4	5.9
	Olaparib 30 µM	74.4 ± 2.3	3.2	33.8
2	[a]Medium Control	10.8 ± 1.1		
	[b]Solvent Control	15.6 ± 0.9		
	Phenobarbital (1mM)	61.1 ± 1.3	5.7	
	Olaparib 0.3 µM	12.8 ± 0.7	0.8	0
	Olaparib 3 µM	14.9 ± 0.2	1	0
	Olaparib 30 µM	29.3 ± 1.4	1.9	27.4
3	[a]Medium Control	7.15 ± 0.31		
	[b]Solvent Control	10.3 ± 0.1		
	Phenobarbital (1mM)	51.4 ± 6.9	7.2	
	Olaparib 0.3 µM	10.9 ± 0.3	1.1	1.4
	Olaparib 3 µM	13.2 ± 1.5	1.3	6.5
	Olaparib 30 µM	27.9 ± 0.7	2.7	39.9

[a] control cells for the positive control phenobarbital
[b] control cells for olaparib

2.4.2.4   Are other metabolic/transporter pathways important?

Olaparib (1 - 10 µM) was found to be a substrate of P-gp and OATs (*sponsor could not identify subtype due to high variability in their in vitro assay*). Olaparib was not found to be a substrate of MRP2 or BCRP. Olaparib was identified as an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K in vitro. Drug interactions involving transporter have not been evaluated in humans.

Olaparib as a substrate of transporters

P-gp and BCRP

Both P-gp and BCRP are expressed in the GI tract, liver and kidney and may play a role in limiting oral bioavailability. MDCKII cells transfected with human P-gp and BCRP were used to evaluate whether olaparib is a substrate of P-gp (MDR1) and BCRP in Study KMX006. Olaparib (1 - 10 µM) was found to be a substrate of P-gp (efflux ratio of 6 - 7.5 for olaparib concentrations of 1 – 10 µM), but not of BCRP.

Other Transporters

Olaparib was not found to be a substrate of MRP2 (efflux ratio of 0.7 – 0.9 for olaparib concentrations of $1 – 10$ µM) in Study KMX020. Data suggests that olaparib is a substrate of organic anion transporters (OATs) but the sponsor was not able to specify which ones due to large variability in the study KMX042.

Olaparib as an inhibitor

P-gp and BCRP

The effect of olaparib on P-gp and BCRP was evaluated in study KMN040 using MDCKII cells transfected with MDR1 or BCRP. The marker substrates [³H]-digoxin (MDR1) and [¹⁴C]-PhIP (BCRP) were measured in the absence and presence of eight concentrations (0.1 - 100 µM) of olaparib. Ketoconazole (MDR1) and Ko143 (BCRP) were used as controls as they are inhibitors of the respective transporters. Olaparib was not found to be an inhibitor of P-gp (99 – 102% of control. In contrast, ketoconazole decreased the efflux ratio to 3% of the control value). It is a BCRP inhibitor, but the IC_{50} was not determined by the sponsor as high variability in the system was observed.

Other Transporters

Olaparib is an inhibitor of OCT1, OCT2, OAT3, MATE1 and MATE2K and OATP1B1, in vitro.

In Studies KMN037 and KMN046, olaparib was found to be an inhibitor of human **OATP1B1** in human embryonic kidney 293 (HEK293) cells with estimated IC_{50} values of 20.3 µM (8.8 µg/ml) and 27.1 µM (11.8 µg/ml) in the respective studies. The I/IC_{50} was > 0.1 (0.9 using a Cmax of 18 µM), but the R value was <1.25 (1.16 considering the fu of 0.18 and Cmax of 18 µM). Therefore, a trial evaluating olaparib as an inhibitor of OATP1B1 will not be required. Olaparib 10 µM inhibited the efflux of calcein (MRP2 substrate) by 25% in MDCKII cells transfected with MRP2. This is in contrast to the 75% inhibition by the positive control, MK571 (75 µM). This will unlikely be a significant interaction at the clinical dose (Study KMX042).

The sponsor evaluated HEK293 cells transfected with individual uptake transporters, OATP1B3, OCT1, OCT2, OAT1 and OAT3 and HEK293 cells transfected with individual efflux transporters, MATE1 and MATE2K in Study 13ASTRUKP7S2. Olaparib was found to inhibit OCT1, OCT2, OAT3, MATE1 and MATE2K (**Table 15**).

Table 15: Inhibition of Efflux and Uptake Transporters Evaluated in Study 13ASTRUKP7S2

Transporter	IC_{50} (μM)	I/IC_{50}
OATP1B3	NC (25% inhibition at 100 μM)	NC
OCT1	37.9	0.5
OCT2	19.9	0.9
OAT1	NC (13.5% inhibition at 100 μM)	NC
OAT3	18.4	1.0
MATE1	5.5	3.3
MATE2K	47.1	0.4

2.4.2.5 Are there any other in vivo drug-drug interaction studies?

No.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Olaparib can likely be classified as a BCS Class 4 drug due to low solubility and permeability characteristics (for more information refer to the ONDQA Quality Review). Olaparib has not received official BCS classification/designation from the BCS Classification Committee within the FDA.

<u>Solubility:</u> Olaparib has poor solubility and can be considered very slightly soluble (VSS) in aqueous media and ranges from slightly soluble (SS) to sparingly soluble (SPS) in organic media evaluated (**Table 16**). The solubility is pH independent.   (b) (4) mg of a substance called lauroyl macrogol-32 glycerides (LMG) is used with 50 mg of the drug product in the capsule formulation.

Table 16: Solubility of Olaparib in a Variety of Solvents

Solvent	Temperature (°C)	Solubility (mg/mL)
pH 4.5 Acetate Buffer	37	0.1
pH 6.8 Phosphate Buffer	37	0.1
0.1 M HCl	37	0.1
Water	37	0.1
Acetonitrile	20	3.1
Ethanol	20	5.5
Methanol	20	10.6
Ethanol: water 75:25	20	19.7

Source: Applicant's Table 1 in drug-substance.pdf

<u>Permeability:</u>

Olaparib is a substrate of P-gp, in vitro. MDCKII cells transfected with either human P-gp or BCRP were used to evaluate whether olaparib is a substrate of P-gp (MDR1) and BCRP in Study KMX006. When the control substrate for P-gp, vinblastine sulfate, was used, the efflux ratio of 20.4 was observed in the MDCKII control cells. The sponsor attributes this to the likelihood of canine MDR1 in the cell line. Therefore, the efflux ratios from the transfected cells were corrected for the baseline in the control group. A similar finding was found for BCRP control cells.

Olaparib was found to be a P-gp substrate, in vitro, with a mean corrected efflux ratio of 6 - 7.5 and an apparent permeability from the apical to the basolateral side of 57.9×10^{-6} cm/s at 10 µM. Ketoconazole inhibited the efflux by $40 - 62\%$, but verapamil did not have an effect on the permeability of olaparib 10 µM in these transfected cells.

Table 17: Permeability of Olaparib in MDCKII MDR1 or BCRP Transfected Cells (N=3)

	MDCKII MDR1 Transfected Cells				
Conc (µM)	Papp (AB) * 10^{-6} cm/sec (Mean ±SD)	Papp (BA) * 10^{-6} cm/sec (Mean ±SD)	Corrected Efflux Ratio (ER)	%Papp with Verapamil	%Papp with Ketoconazole
1	0.28 ± 0.1	40.6 ± 1.7	7.5 ± 0.3	98.9 ± 10.3	59.5 ± 3.5
3	0.53 ± 0.1	42.7 ± 2.6	6.0 ± 0.4	93.6 ± 0.8	38.3 ± 2.5
10	0.58 ± 0.1	39.4 ± 1.4	6.0 ± 0.2	98.8 ± 3.0	43.3 ± `1.9
	MDCKII BCRP Transfected Cells				
Conc (µM)	Papp (AB) * 10^{-6} cm/sec (Mean ±SD)	Papp (BA) * 10^{-6} cm/sec (Mean ±SD)	Corrected Efflux Ratio (ER)		
1	2.65 ± 0.3	29.1 ± 1.0	0.57 ± 0.02		
3	2.23 ± 0.7	28.2 ± 1.6	0.95 ± 0.05		
10	2.90 ± 2.3	26.4 ± 1.9	0.79 ± 0.06		

2.5.2 What is the composition of the to-be-marketed formulation?

The planned commercial drug product is formulated as an immediate release 50 mg capsule. It is composed of 50 mg olaparib (active ingredient) with lauroyl macrogol-32 glycerides (LMG) as a [REDACTED] (b) (4) in a hard capsule shell.

2.5.3 What moieties should be assessed in bioequivalence trials?

The parent compound olaparib should be assessed in bioequivalence trials and has been the moiety assessed in clinical trials with available PK data. In the mass balance trial D0810C00010, olaparib was the main circulating moiety (65%) and three metabolites each accounted for approximately 10% (Refer to **Section 2.2.5.5**).

2.5.4 Is the to-be-marketed formulation the same as the clinical trial formulation and if not, is there bioequivalence data to support the to-be marketed formulation?

The to-be-marketed (TBM) 50 mg capsule formulation is the clinical trial formulation used in Trial 42. No PK data are available from the pivotal trial 42. PK differences were suspected based on different sites of manufacturing as PK differences were observed between some of the earlier trials with PK data (Refer to **Section 2.2.5.1**).Trials D0810C00001, D0810C00002, D0810C00008, D0810C00009, D0810C00012 and D0810C00024 were included in Population PK analyses, intensive PK data were available from Trials D0810C00001 and D0810C00002 (**Table 18**).

Table 18: Manufacturing Site by Trial Number for Trials Used for Efficacy Data and PK Data

Formulation/ Manufacturing Site	Trial
50 mg olaparib capsule/ Patheon	Trials D0810C00019, * D0810C00002, * D0810C00008, *D0810C00009, D0810C00012, D0810C00020, D0810C00024, D0810C00042
50 mg olaparib capsule/ (b) (4)	Trials D0810C00001, * D0810C00002, D0810C00007, * D0810C00008, * D0810C00009,
^{14}C olaparib (b) (4) capsules/ (b) (4) 50 mg olaparib (b) (4) capsules/ (b) (4)	Trial D0810C00010

* batches from 2 manufacturers used in trial

2.5.4   What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Data submitted for Trial D081AC00001 showed that a high-fat meal did not have a significant effect on the AUC or Cmax of olaparib, although it delayed the mean Tmax from 1.7 hours to 4 hours. The CV% was high both when olaparib was taken fasted or with meals.

Trial D081AC00001 was a 2 part trial in patients with advanced solid tumors. Part A was used to determine the effect of food on the PK of olaparib and Part B was the continued access part of the trial (within 14 days of Part A). Patients in Part A were randomized sequentially to 1 of 6 treatment sequences (N=31 evaluable). Each patient received a 400 mg oral dose (Eight 50 mg capsules) in each of 3 treatment periods (fasted, high-fat meal, standard meal) in a crossover manner. A washout period of 5 – 14 days was used between doses.

Patients in all treatment periods fasted from at least 10 hours prior to the dose to 4 hours post-dose (except for standardized meal in the fed periods). A high-fat meal was defined according to the FDA guidance as 800 to 1000 kcal, with approximately 150, 250 and 500 to 600 kcal from protein, carbohydrate and fat, respectively. A standard meal was defined as less than 25% fat, with the total calorie content no more than 50% of that of the high fat meal (i.e., no more than 400 to 500 kcal). The standardized meals given in all patients were the same. A patient was still considered evaluable if he/she consumed at least 75% of the meal within 45 minutes. PK samples were collected in each period up to 72 hours after olaparib dosing.

Patients included in this trial had adequate renal and hepatic organ function. In Part A, CYP3A inhibitors were not permitted within a week of dosing and CYP3A inducers were not permitted. A total of 30, 29 and 27 patients were evaluable for PK in the fasted, standard fed and high fat

fed arms, respectively. Olaparib was undetectable in pre-dose samples in Visit 2 but was detectable in some samples in visit 3 in the range of 0.59 – 110 ng/mL (<2% of mean Cmax). The sponsor's statistical analysis showed no period or sequence effect.

The Tmax was delayed from 1.7 hours under fasted conditions to 4 hours with either meal condition. The mean half-life ranged from 12 – 18 hours with a trend towards a longer half-life when taken under fasted conditions versus with food (*the reason for that is unclear*). No significant increases in exposure were observed with an AUC increase of 20% with high-fat and standard fat meals. The PK parameters are summarized in **Tables 19 and 20**.

Table 19: PK Parameters (Mean ± SD) of Olaparib after Single 400 mg Doses Given Fasted, with a Standard meal and with a High Fat Meal in Trial D081AC00001

Group	Fasted (N=30) Mean± SD (CV%)	Standard Fed (N=29) Mean± SD (CV%)	High-fat Fed (N=27) Mean± SD (CV%)
[a]Tmax (h)	1.7 (0.9 – 4.1)	4.0 (1.0 – 8.0)	4.0 (2.0 – 8.0)
Cmax (µg/mL)	6.9 ± 2.9 (43)	7.6 ± 3.4 (44)	6.6 ± 3.0 (46)
AUC_{0-t} (µg.h/mL)	76 ± 69 (91)	93 ± 95 (102)	77 ± 55 (71)
AUC (µg h/mL	80 ± 74 (92)	93 ± 91 (98)	78 ± 56 (72)
$T_{1/2}$ (h)	18 ± 7.0 (38)	15 ± 6.0 (38)	12 ± 4.5 (37)
Cl/F (L/h)	7.9 ± 4.4 (56)	7.0 ± 4.5 (64)	7.1 ± 4.0 (56)
V/F (L)	210 ± 145 (69)	156 ± 125 (80)	130 ± 109 (84)

[a]median(range)

Table 20: Geometric Mean (CV%) and Geometric Mean Ratios of Olaparib after Single 400 mg Doses Given Fasted (Reference), with a Standard meal and with a High Fat Meal in Trial D081AC00001

Group	Cmax GM (CV %)	Cmax GM LSM Ratio (90% CI)	AUC GM (CV %)	AUC GM LSM Ratio (90% CI)
Fasted (Ref)	6.3 (41)	NA	61 (78)	NA
Standard Fed	7.0 (46)	1.1 (1.0 - 1.2)	70 (80)	1.2 (1.1 - 1.3)
High-fat Fed	6.1 (45)	1.0 (0.9 - 1.1)	65 (64)	1.2 (1.1 - 1.3)

LSM = Least square mean; GM = Geometric Mean; Ref = Reference

Figure 13: Cmax and AUC based on Meal (Fasted, Standard Fat Meal and High Fat Meal)
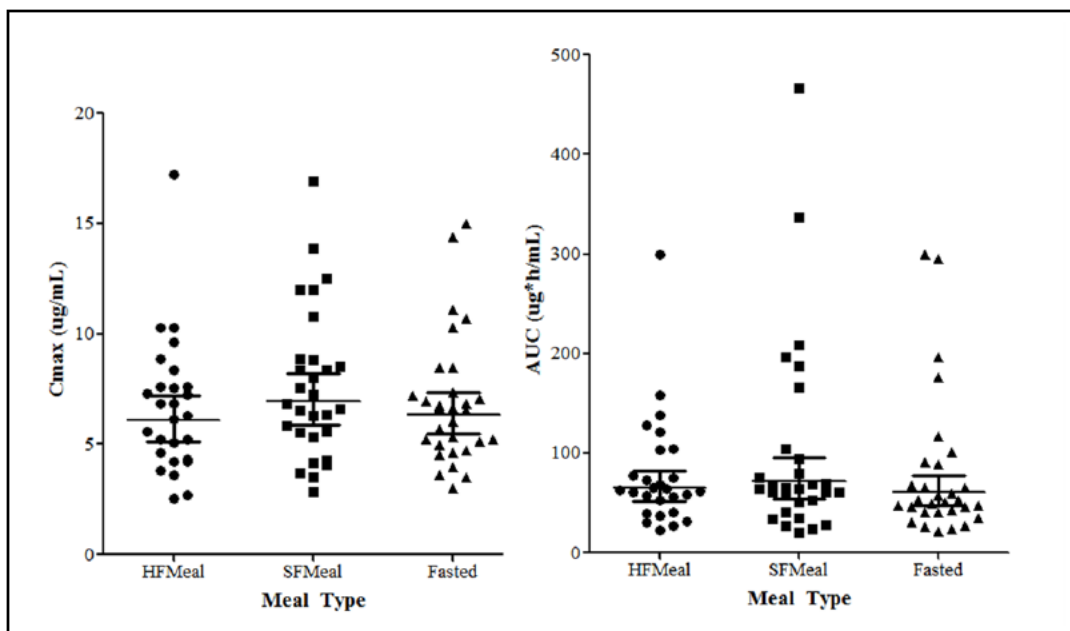
Although, olaparib was dosed at least 1 hour before or 2 hours after a meal in the pivotal trial, we recommend that olaparib be dosed without regards to food as the effect of food on exposure appears minimal. The delay in Tmax will likely not have a large impact for this chronic therapy. The recommendation will likely assist in patient convenience for this twice daily regimen. Although we do not have any data to support that the GI tolerability of olaparib will improve if it is taken with food; food has been used to alleviate GI adverse events for other drugs. In the 223 patients in the safety database with gBRCA-mutated ovarian cancer who received 3 or more prior lines of chemotherapy, 64% had nausea, 43% had vomiting, 31% had diarrhea, 20% had dyspepsia and 7% had upper abdominal pain.

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

The ONDQA Biopharmaceutics reviewer concluded that the dissolution method is acceptable and has recommended changes to the acceptance criteria. Refer to the ONDQA Biopharmaceutics review for more details.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured appropriately in the clinical pharmacology and biopharmaceutics studies?

Yes. All the submitted clinical pharmacology related studies analyzed samples for olaparib. In the mass balance trial # D0810C00010, the main circulating moiety in blood and plasma was olaparib (65%). Three main circulating metabolites were identified accounting for about 10% of the radioactivity each (Refer to **Section 2.2.5.5**). These metabolites were not evaluated in other trials as they were considered minor. The pharmacological activity of the 3 circulating metabolites is not known, but they were all identified in the plasma of rats.

2.6.2 Which metabolites have been selected for analysis and why?

The sponsor does not plan to analyze any of the metabolites. Please refer to **Section 2.6.1**.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total concentration of olaparib in plasma was measured in the clinical trials. Olaparib has mean plasma protein binding of 89%. It had concentration dependent binding with 91% binding observed at concentrations of 10 - 1000 ng/mL (10, 100 and 1000 ng/mL) and 82% at 10 000 ng/mL (protein binding was not assessed at concentrations between 1000 and 10000). As a Cmax of up to 7000 ng/mL can be achieved at the proposed dose of 400 mg BID, the protein binding could be as low as 82%. The effect of varied levels of proteins was not evaluated and protein binding would need to be evaluated in the hepatic impairment trial.

2.6.4   What bioanalytical methods are used to assess concentrations?

Olaparib was measured using LC/MS/MS methods that were developed and validated by
^{(b) (4)}. Validation reports were submitted and QC reports were summarized for the use of the
method in each trial.

Table 21: Summary of LC/MS/MS Methods Used in Trials with PK Data Submitted

Method	Matrix	Trial	Linear Range	Validation Report #
HB-05-033	Plasma	D0810C00002 D0810C00024	0.5 - 500 ng/mL	D2281KPV012
HB-06-065 (*revised from* *HB-05-033*)	Plasma	D0810C00001 D0810C00002 D0810C00024	20 - 20 000 ng/mL	D2281KPV012
HFL100509-1	Plasma	D0810C00007 D0810C00008 D0810C00009 D0810C00010 D0810C00012	20 – 20 000 ng/mL	D2281KPV010
HFL100509-2	Urine	D0810C00007 D0810C00010	20 – 20 000 ng/mL	D2281KPV011
HFL100730-1	Tumor	D0810C00007	40 – 20 000 ng/g	D2281KPV015

*Used more than 1 method in trial

2.6.5   What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The LC/MS/MS methods developed are discussed in **Section 2.6.4**. The concentration ranges, correlation coefficients and inter-assay precision and accuracy for the analytes are summarized for each method (**Table 22**).

The mean Cmax values for the 400 mg dose is up to 7000 ng/mL. The mean Cmax in the inhibitor study was only 4500 ng/mL as a lower dose of 100 mg (tablet) was used. Therefore, the methods with a calibration range of 10 – 20 000 ng/mL were sufficient for analysis in the trials submitted.

Table 22: LC/MS/MS Analytical Methods for Olaparib

Method Name	HB-05-033	HB-06-065	HFL100509-1	HFL100509-2	HFL100730-1
Matrix	Lithium (Li)Heparin Plasma	Li Heparin Plasma	Li Heparin Plasma	Urine	Tumor (xenograft)
Calibration Range	0.5 - 500 ng/mL	20 - 20 000 ng/mL	20 - 20 000 ng/mL	20 - 20 000 ng/mL	40 – 20 000 ng/g
Regression (least-square)	1/x weighting	1/x weighting	$1/x^2$ weighting	$1/x^2$ weighting	
Inter-run Accuracy (%)	92 – 98.9	95 – 100.4		89.5 – 106.8	91.5 – 95.9
Inter-run Precision (CV %)	≤ 7.6		≤ 9	≤ 16.4	≤ 7.9
Intra-run Accuracy (%)	96 - 106	94.8 - 105		94.5 – 112.8	95 – 103.3
Intra-run Precision (CV %)	≤ 6.3	≤13.7	≤ 4.9	≤ 8.8	≤ 9.4
Extraction Efficiency (%)	89.6			80 - 107	
Dilution Integrity	5X dilution	5X		10 X	10 X
Selectivity (interference <20% of LLOQ)	4 out of 6 batches	13 out of 16 batches		6 out of 6	
Stability in Li Heparin Plasma	> 12 months at -20 °C, 24 hours at room temp, 4 freeze-thaw cycles	> 12 months at -20 °C, 24 hours at room temp, 4 freeze-thaw cycles		4 hours at room temp, 6 months at -20 °C, 3 freeze-thaw cycles	4 hours at room temp, , 18 months at -70 °C, 3 freeze-thaw cycles
Processed Sample Stability	3 days at 4 °C	3 days at 4 °C		7 days at 4 °C	48 hours at 4 °C
Stability in Stock Solution (methanol)	1 mg/mL for 24 weeks and 2mg/mL for 7 weeks at 4 °C	1 mg/mL for 24 weeks and 2mg/mL for 7 weeks at 4 °C			
Stability in Working Spiked Solution (methanol)	1 mg/mL for 24 weeks and 2mg/mL for 7 weeks at 4 °C	1 mg/mL for 24 weeks and 2mg/mL for 7 weeks at 4 °C			

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

3.2 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

NDA Number	206162
Drug Name	Olaparib
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Pharmacometrics Team Leader	Liang Zhao, Ph.D.
Sponsor	AstraZeneca

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SUMMARY OF FINDINGS

Olaparib is proposed as the [REDACTED] (b) (4) [REDACTED]. No pharmacokinetics data were collected in the registrational Study d0810c00042 (Study 42) for the new indication. Therefore, no exposure-response (ER) analysis was conducted for safety or efficacy for the new indication.

The reviewer's analysis identified no apparent exposure-efficacy relationship following 400 mg olaparib capsule BID as a maintenance therapy for adult patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline BRCA (gBRCA) mutation. When used as a maintenance therapy, it appeared to have an exposure-anemia correlation for both capsule and tablet formulations.

Based on population pharmacokinetics (PK) analysis, moderate and mild renal impairment patients appeared to have similar olaparib clearance to patients with normal renal function. However, the covariate screening results including for renal impairment might not be reliable given the high variability in PK exposure introduced from other sources such as product variability across manufacture sites and lots. Of note, there is a dedicated PK study (D0816C00006) in renal impairment subjects ongoing, and the result of that study will finally determine if a dose adjustment is needed or not for the renal impairment patients.

1.1   KEY REVIEW QUESTIONS

The purpose of this review is to address the following key questions:

1.1.1   Was there an exposure-response relationship in terms efficacy or safety of olaparib 400 mg capsule BID as the therapy for the newly proposed indication?

For the proposed indication (olaparib 400 mg capsule BID as a [REDACTED] (b) (4) [REDACTED]), no E-R analysis has been conducted due to lack of PK data in Study 42.

1.1.2   Was there an exposure-efficacy relationship for olaparib 400 mg capsule BID as a maintenance therapy for adult patients with platinum-sensitive relapsed ovarian cancer with germline BRCA (gBRCA) mutation?

The reviewer's analysis identified no apparent exposure-efficacy relationship following 400 mg olaparib capsule BID as a maintenance therapy for adult patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline BRCA (gBRCA) mutation. Platinum-sensitive relapsed (PSR) ovarian cancer is defined clinically as a relapse free period of ≥6 months following a response to the last dose of platinum treatment.
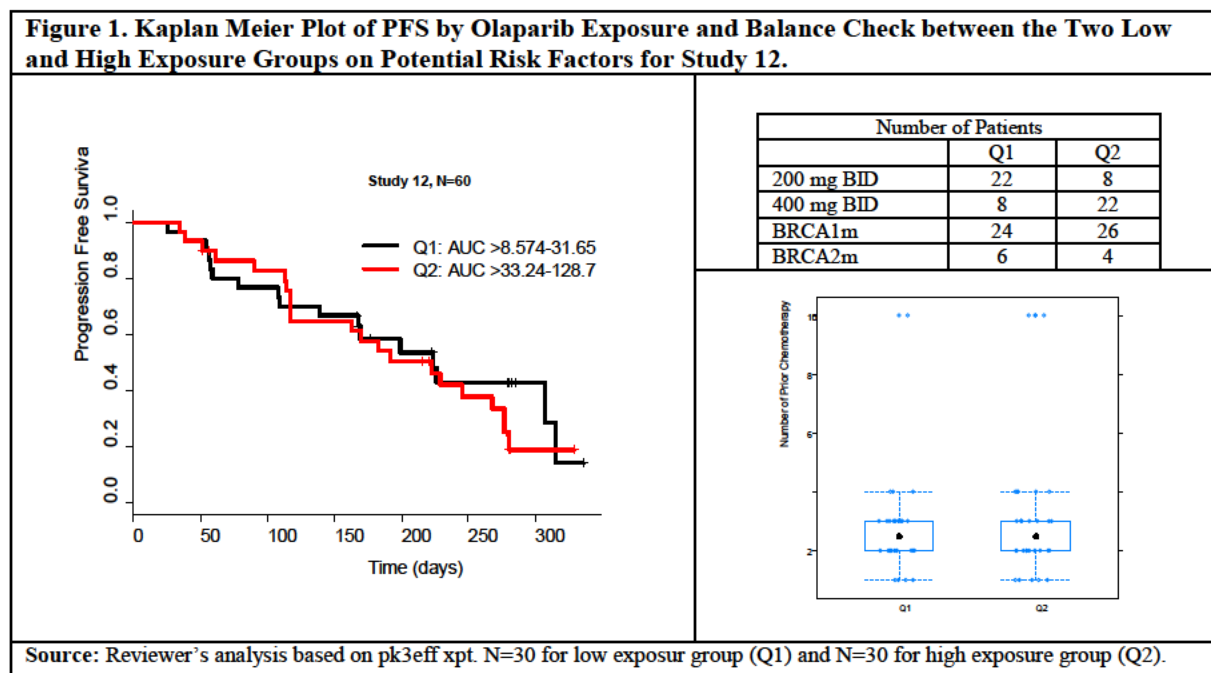
An olaparib regimen of 400 mg capsule BID as maintenance treatment of adult patients with platinum-sensitive relapsed ovarian cancer with germline *BRCA* mutation) was tested in Study d0810c00019 (Study 19), where progression free survival time (PFS) was the primary efficacy endpoint. Study 19 compared the efficacy and safety between placebo and 400 mg olaparib capsule BID, with no pharmacokinetics (PK) data collected that allowed an E-R analysis[1]. Alternatively, exposure-efficacy relationship of olaparib, in BRCA1- or BRCA2-associated

ovarian cancer patients, was evaluated based on data from D0810C00012 (Study 12) due to the following reasons [1-2]:
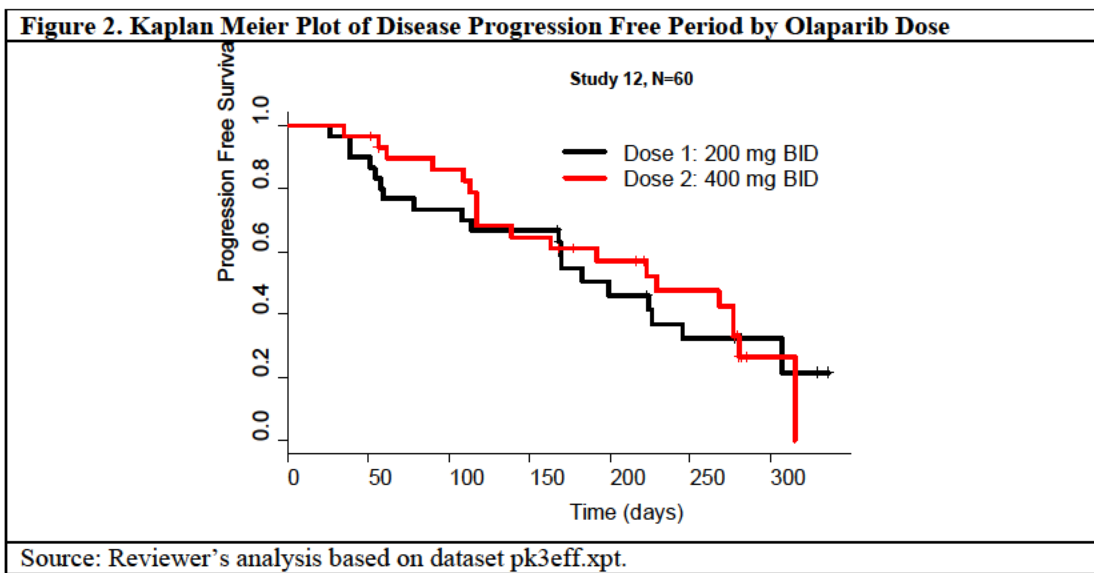
- Similar patient population was studied in Studies 12 and 19. Both studies had PFS as the primary efficacy endpoint.
- Three identical batches of olaparib capsule product were used in the two studies.
- With PK information available, data from Study 12 allows a reasonable exposure-efficacy assessment. In addition, the efficacy and safety data for two dose levels, 200 mg olaparib capsule BID (N=32) and 400 mg olaparib capsule BID (N=32), were available from Study 12.

Of the 64 patients on the two olaparib doses of Study 12, 30 patients of each dose were included in the exposure-efficacy dataset. These 60 patients were divided into low and high exposure groups, referred to as Q1 and Q2 respectively, by $AUCss\_\tau$ estimated from the population PK analysis. The survival analysis by $AUCss\_\tau$ quantile showed that:
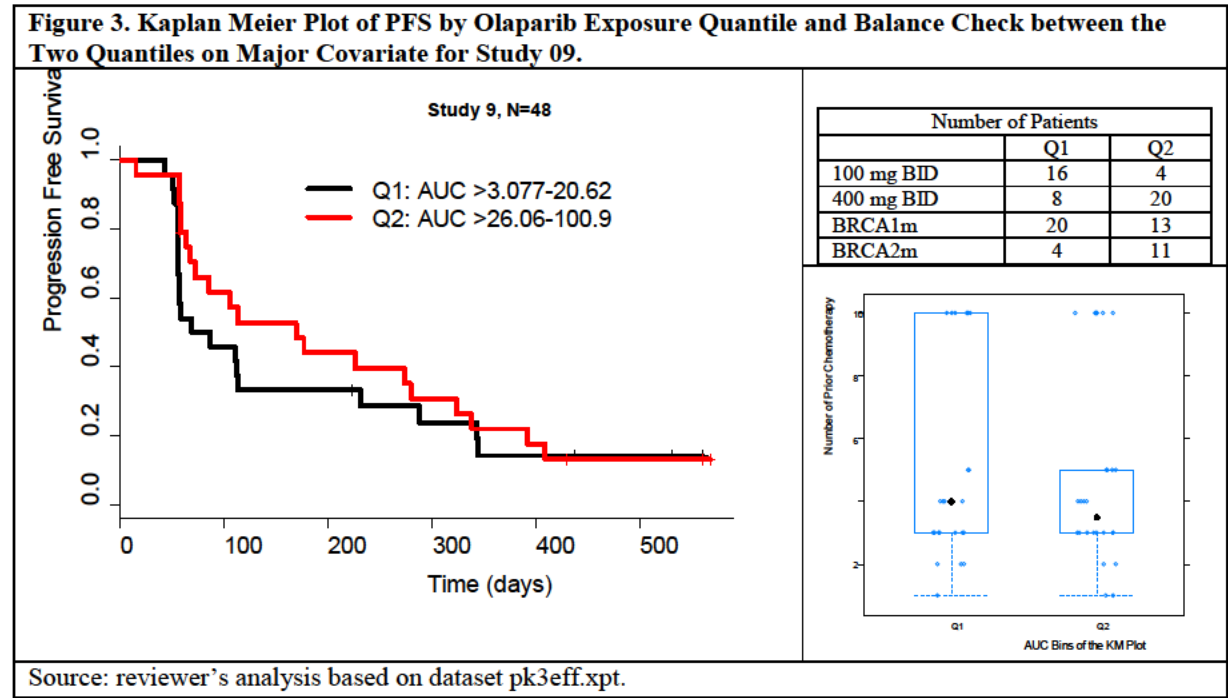
- No exposure-PFS relationship in the 60 patients on 200 or 400 mg capsule BID dose.
  - The Kaplan Meier plots of the two exposure groups approximate to each other over the time course as shown in the left panel of **Figure 1**.
- Potential risk factors were reasonably balanced between the two exposure groups.
  - BRCA mutation types were evenly distributed between the two exposure groups.
  - Prior chemotherapy numbers were well balanced between the two exposure groups.
  - 27% (8/30) patients of the high exposure group were from the 200 mg arm, and 27% (8/30) patients of the low exposure group were from the 400 mg arm.

Figure 1. Kaplan Meier Plot of PFS by Olaparib Exposure and Balance Check between the Two Low and High Exposure Groups on Potential Risk Factors for Study 12.

Number of Patients		
	Q1	Q2
200 mg BID	22	8
400 mg BID	8	22
BRCA1m	24	26
BRCA2m	6	4

Source: Reviewer's analysis based on pk3eff xpt. N=30 for low exposur group (Q1) and N=30 for high exposure group (Q2).

Dose-response analysis for the same dataset by dose showed that 400 mg BID only demonstrated numerically higher median PFS than 200 mg BID (**Figure 2**) (229 days for 400 mg vs 199 days for 200 mg, p-Value=0.8698 for log-Rank test and p=0.5138 for Wilcoxon test).

Figure 2. Kaplan Meier Plot of Disease Progression Free Period by Olaparib Dose

Study 12, N=60

Dose 1: 200 mg BID
Dose 2: 400 mg BID

Source: Reviewer's analysis based on dataset pk3eff.xpt.

D0810C00009 (Study 09), with two treatment arms of the 100 mg and 400 BID olaparib capsule[3], is another study similar to Study 19 in terms of patient population and design. In this study, PFS was collected as the secondary efficacy endpoint. As show in **Figure 3**, median PFS for Q2 was observed to be longer than PFS for Q1. However, caveat should be given to make any conclusion since more BRCA2 mutation patients and less prior chemotherapies were found in Q2 than Q1, and therefore it was in favor of Q2 for a longer median PFS. In addition, the sample size was too small for any definite conclusion regarding exposure-PFS relationship.

Figure 3. Kaplan Meier Plot of PFS by Olaparib Exposure Quantile and Balance Check between the Two Quantiles on Major Covariate for Study 09.

Study 9, N=48

Q1: AUC >3.077-20.62
Q2: AUC >26.06-100.9

Number of Patients		
	Q1	Q2
100 mg BID	16	4
400 mg BID	8	20
BRCA1m	20	13
BRCA2m	4	11

Source: reviewer's analysis based on dataset pk3eff.xpt.

In brief, there appeared no apparent olaparib exposure-PFS relationship for the BID 400 mg olaparib capsule regimen as a maintenance therapy.

1.1.3 Was there an exposure-safety relationship for 400 mg capsule BID as a maintenance therapy for adult patients with platinum-sensitive relapsed ovarian cancer with gBRCA mutation?

There appeared to have a positive exposure-anemia relationship, which can raise safety concerns for the BID 400 mg olaparib capsule regimen as a maintenance therapy.

No pharmacokinetics (PK) data were available for conducting an exposure-safety analysis for Study 19 [1]. Alternatively, the exposure-safety analyses for myelodysplastic syndrome (MDS) related signals such as anemia were conducted based on safety dataset pk3safe.xpt. This dataset was assembled by the sponsor based on observed adverse event data of Study 02 [4], 08 [5], 09 [3], 12 [2] and 24 [6] and exposure data derived from the population PK analysis [7]. For the pooled data of Studies 02 [4], 08 [5], 09 [3], 12 [2], the occurrence probabilities of anemia were found to be correlated to olaparib steady-state C_{max} estimated from population PK analysis (left panel of **Figure 4**). This relationship was confirmed by using observed olaparib steady-state C_{min} as the exposure metrics (right panel of **Figure 4**). Exposure-anemia relationship is also observed in Study 24 [6] regardless of formulation type (**Figure 5**). The anemia rate is less than 50% for the 4th quartile (the highest exposure group) as shown in the 3 panels of **Figure 5**; and the Grade 3-4 anemia rate is 26% as shown in the upper right panel of **Figure 5**.

Similar to anemia, Grade 3-5 fatigue also showed strong exposure-response correlation (results not shown).

In brief, there appeared to be an exposure-anemia relationship, which may highlight a potential MDS risk following olaporib treatment as a maintenance therapy.

Figure 4. Exposure-Anemia Relationship Based on Pooled Data of Studies 02, 08, 09, and 12.

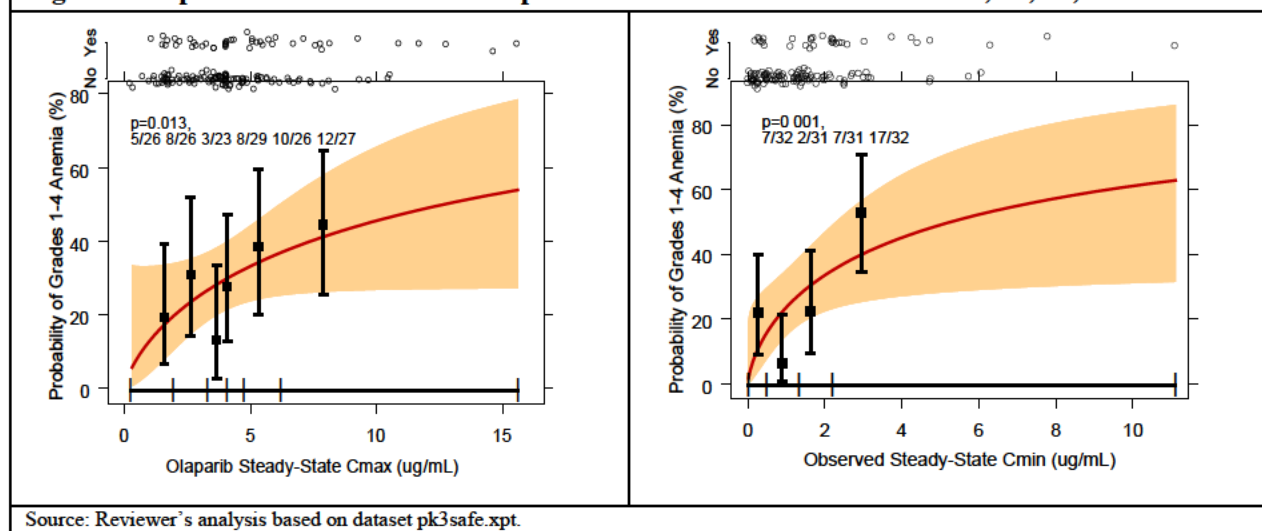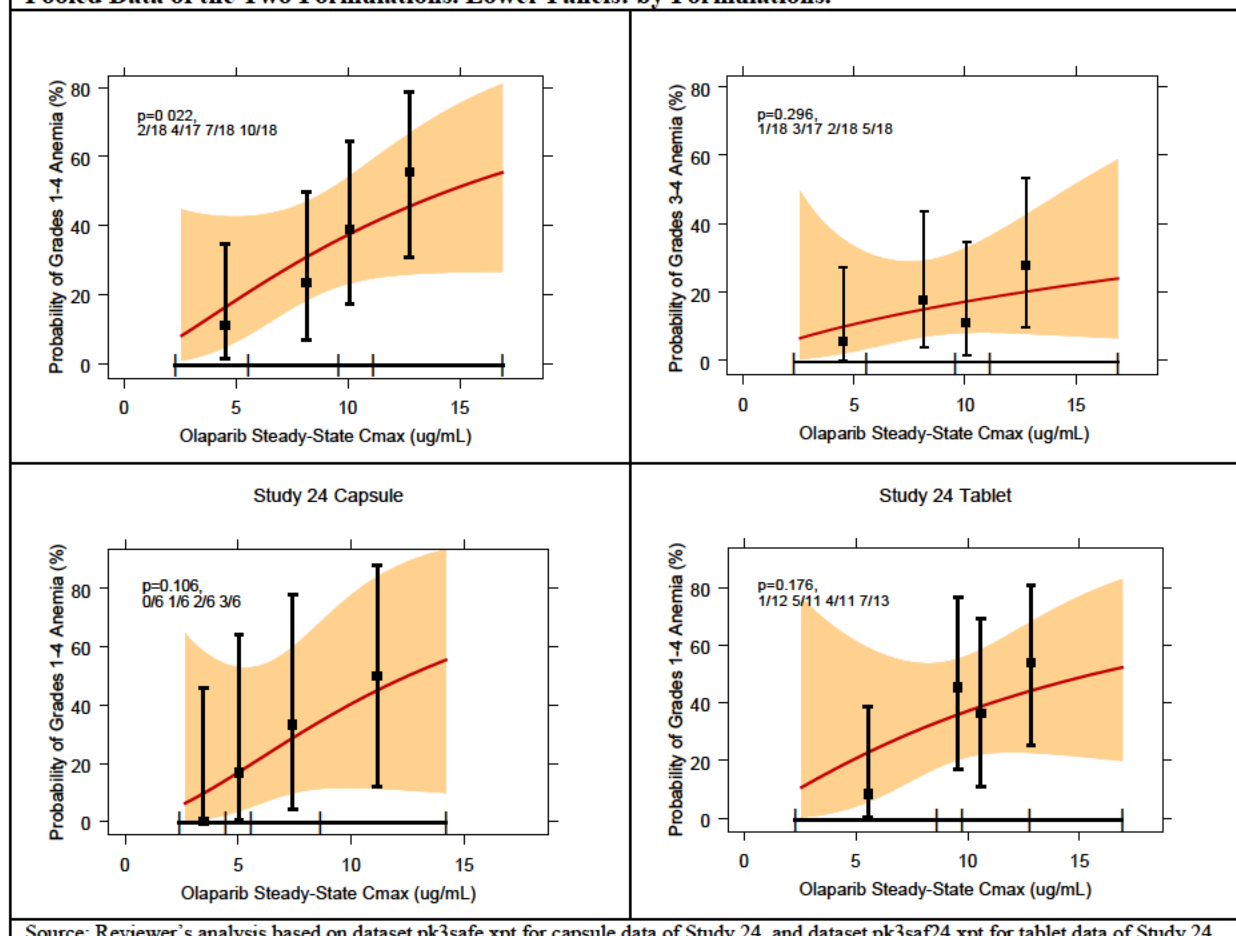Source: Reviewer's analysis based on dataset pk3safe.xpt.

Figure 5. Exposure-Anemia Relationship Based on Capsule and Tablet Data of Studies 24, Top Panels: Pooled Data of the Two Formulations. Lower Panels: by Formulations.

Source: Reviewer's analysis based on dataset pk3safe.xpt for capsule data of Study 24, and dataset pk3saf24.xpt for tablet data of Study 24.

1.1.4 Is olaporib 300 mg tablet BID associated with higher safety risk?

Yes. Based on Study 24, the exposure metrics (C_{max} and AUC_{0-12} on Day 1; $C_{max,ss}$, $AUC_{0-12,ss}$ and $C_{min,ss}$ on Days 29 and 57) of 300 mg olaparib tablet is 1.4-1.9 times of 400 mg olaparib capsule, as shown in **Table 1**. The 40-90% higher exposure is corresponding to the higher safety risk of 300 mg tablet than 400 mg capsule, as shown in **Table 2** for anemia and **Table 3** for fatigue.

In brief, the exposure of BID 300 mg olaparib tablet exceeded the exposure of olaparib MTD (BID 400 mg capsule, as established in Study 02) by 40-90%. This may be associated with higher safety risk.

Table 1. Comparison of Exposure Metrics between 300 mg Tablet and 400 mg Capsule of Study 24

	Mean of 300 mg Tablet	Mean of 400 mg Capsule	Tablet/Capsule Ratio
Day 1			
C_{max} (µg/ml)	10.4	5.73	1.8
AUC_{0-12} (µg·h/ml)	55.2	28.8	1.9
Day 29			
$C_{max,ss}$ (µg/ml)	9.37	6.36	1.5
$AUC_{0-12,ss}$ (ug·h/ml)	58.4	41.5	1.4
$C_{min,ss}$ (µg/ml)	1.84	1.04	1.8
Day 57			
$C_{max,ss}$ (µg/ml)	9.15	6.16	1.5
$AUC_{0-12,ss}$ (ug·h/ml)	54	39.6	1.4
$C_{min,ss}$ (µg/ml)	1.41	0.93	1.5
Source: Table 55 in Page 149 of CSR of Study D0810C00024 [6].			

Table 2. Anemia rate of dose escalation phase of the CSEP (Group 6) for anemia in Study 24

	300 mg bid Tablet	400 mg bid Capsule
All Patients	33.3% (6/18)	0 (0/18)
Ovarian Patients	30.8% (4/13)	0 (0/13)
Source: Tables 29 and 30 in Page 113 of the CSR for D0810C00024 [6].		

Table 3. Fatigue occurrence rate of dose escalation phase of the CSEP (Group 6) for fatigue in Study 24

	300 mg bid Tablet	400 mg bid Capsule
All Patients	38.9% (7/18)	22.2% (4/18)
Ovarian Patients	46.2% (6/13)	15.4% (2/13)
Source: Tables 29 and 30 in Page 113 of the CSR for D0810C00024 [6].		

1.1.5 Is there any relationship between renal function and olaparib clearance that suggests dose adjustment?

Creatinine clearance (CRCL) ranged from 32 to 310 mL/min in the patients of the population PK dataset. There appeared to be no correlation between CRCL and apparent olaparib clearance, as shown in **Figure 6**. The PK data in **Figure 6** included patients with mild (n=120) to moderate (n=40) renal impairment, and patients with normal renal function (n=132). Although this result suggested no dose adjustment for the patients with mild to moderate renal impairment, caveat should be given due to high PK variability introduced from other sources. There is a dedicated PK study in renal impairment subjects ongoing, and the result of that study will finally determine if a dose adjustment is needed or not for renal impairment patients.

Overall, there appeared to be no exposure-PFS relationship in the patients on the 200 or 400 mg olaparib capsule BID dose when used as a maintenance therapy, while there appeared to be an exposure-anemia correlation. Since the BID 300 mg olaparib tablet resulted in a 40-90% higher

exposure than that of the BID 400 mg olaparib capsule, it may potentially lead to some safety risks.

Figure 6. Creatinine Clearance Has No Correlation with Olaparib Clearance.
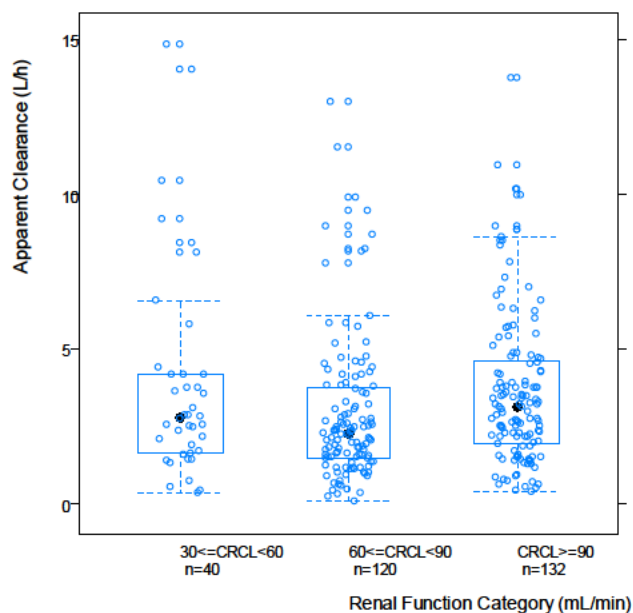
Source: NONMEM dataset (pk1pool.xpt) for CRCL values and NONMEM output file (FINAL.PAR) for CL.

1.2   RECOMMENDATIONS

None. No PK data were collected in pivotal Study 42 that can allow pharmacometrics review to be conducted for the proposed indication. However, the reviewer's analysis suggested a positive exposure-anemia relationship, which may lead to MDS risk at a higher PK exposure.

1.3   LABEL STATEMENTS

Refer to Section 3.1 of Clinical Pharmacology Review for details.

2   PERTINENT REGULATORY BACKGROUND

Olaparib is an oral potent inhibitor of polyadenosine 5'diphosphoribose polymerase (PARP), which exploits deficiencies in DNA repair mechanisms (ie, *BRCA* mutation), to preferentially kill cancer cells. Mutations in the *BRCA* genes are prevalent in high-grade serous ovarian cancer.

- Originally, AstraZeneca seeks accelerated approval for olaparib (400 mg bid capsule formulation) in the following indication (with orphan drug designation approved for ovarian cancer): Olaparib was proposed as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline *BRCA* (*gBRCA*) mutation as detected by an FDA-

approved test, who are in response (complete response or partial response) to platinum-based chemotherapy. The goals of maintenance therapy are to start treatment when the disease burden has been reduced and chemotherapy has been completed, to further delay the return of disease, maintain patients in a well state as long as possible, and reduce the physical and psychological anxiety patients experience waiting for recurrence after completion of the chemotherapy cycles.

Primary data supporting the originally proposed indication was from Study D0810C00019 (Study 19, the pivotal phase II platinum sensitive relapsed ovarian maintenance study), a positive randomized study in 265 patients with platinum sensitive relapsed serous ovarian cancer, unselected for *BRCA* mutation status. However, on June 25th 2014, the FDA's Oncologic Drugs Advisory Committee (ODAC) voted 11-2 against the accelerated approval of the PARP inhibitor olaparib as a maintenance therapy for women with platinum-sensitive relapsed ovarian cancer with germline BRCA mutations. By voting no, the committee recommended waiting for results from the larger phase III SOLO-2 trial, which began enrolling in 2013. The primary endpoint of this study is progression-free survival (PFS) by RECIST criteria. Overall survival (OS) will remain a secondary endpoint, as was the case in earlier phase II trials.

- After the June 25th ODAC meeting, major amendment was submitted to this application proposing olaparib be used   (b) (4)

    This application was largely supported by the single arm study (Study 42) where patients with a variety of tumors were treated with olaparib. As a subgroup of the patient population studied, 193 patients with gBRCAm associated ovarian cancer showed an overall response rate of 31%. A sponsor FDA meeting was held on July 21st 2014 to discuss the study design and the interim result of Study 42.

- The recommended dose of olaparib capsules is 400 mg (eight 50 mg capsules) taken twice daily (bid), equivalent to a total daily dose of 800 mg. It is recommended that treatment be continued until progression of the underlying ovarian cancer.

Over its development course, the key regulatory interactions between Sponsor and the FDA were summarized in **Table 4**.

Table 4. Regulatory Meetings and Correspondence.	
18-Nov-09	End of Phase II meeting to discuss the olaparib development programs for ovarian and breast cancer patients with gBRCA mutations.
22-Nov-11	End of Phase II meeting to discuss the olaparib development programs for high-grade serous ovarian cancer patients was scheduled for 30 November 2011. Cancelled by AstraZeneca after receiving FDA preliminary written feedback
23-Oct-12	Type C meeting to discuss the olaparib development program for patients with gBRCA mutated ovarian cancer. • Study Design for the Phase III PSR maintenance study (D0816C00002) agreed.
19-Mar-13	Breakthrough Therapy Designation Application submitted, for patients with gBRCA mutated ovarian cancer.
15-May-13	FDA informed AstraZeneca that it would be acceptable to base an NDA upon Study D0810C00019 for an accelerated approval.
16-May-13	Breakthrough Therapy Designation denied.

19-Sep-13	FDA provided Pre-NDA pre-meeting comments, including the following: • Clarification of CMC requirements for NDA • Non-clinical package acceptable • DCO and pooling for clinical safety acceptable • Clinical Summary of Efficacy and Safety fulfil ISS and ISE requirements • PMA and NDA should be approved within a reasonable timeframe of each other • Datasets and pooled summary dataset proposal accepted by FDA • Narratives for all patients who died within 28 days of end of treatment should be included in NDA • Proposed table of contents accepted by FDA • FDA would like an orientation session after the NDA has been submitted.
2-Oct-13	Pre-NDA Meeting – Agreements: • Clinical Pharmacology studies (D081AC00001, D0816C00004, D0816C00007 and D0816C00008) interim study reports to be submitted within 120 days of NDA submission, including data on the effect of food on the olaparib capsule, and QT and DDI data in the tablet formulation. • Written narratives would be included in the NDA submission in addition to the electronically-generated narratives
7-Oct-13	Teleconference to confirm contents and delivery of CMC data package prior to NDA submission.
15-Aug-14	Sponsor submitted updated the labeling with a new indication: "Tradename is a PARP (poly ADP ribose polymerase) inhibitor indicated as monotherapy in adult patients with ⟨(b) (4)⟩ deleterious or suspected deleterious germline *BRCA* (g*BRCA*)-mutation (as detected by an FDA-approved test) and who have had three or more prior lines of chemotherapy" vs previous indication: "Tradename is a PARP (poly ADP ribose polymerase) inhibitor indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline *BRCA* (g*BRCA*) mutation as detected by an FDA-approved test who are in response (complete response or partial response) to platinum-based chemotherapy."

Source: Table 6 in Page 37 of Clinical Overview.

In the US, commercial testing for *BRCA* mutations is undertaken by Myriad Genetics Laboratories Inc. AstraZeneca is working with Myriad to deliver a Pre-Market Approval (PMA) for the Integrated BRAC*Analysis*® assay as a companion diagnostic to olaparib. This is being undertaken in accordance with the FDA draft guidance on companion diagnostic development that was issued on 14 July 2011. AstraZeneca and Myriad have conducted a Pre-Submission meeting in March 2013. An Investigational Device Exemption was also submitted 07 May 2013 and granted in full on 23 August 2013 (reference # G130113).

A European Marketing Authorisation Application (MAA) was submitted in September 2013 for olaparib as maintenance treatment of adult patients, with PSR *BRCA* mutated ovarian cancer (including fallopian tube or primary peritoneal), who are in response (complete response or partial response) to platinum-based chemotherapy.

3   RESULTS OF SPONSOR'S ANALYSIS

3.1   SPONSOR'S POPULATION PK AND EXPOSURE-RESPONSE ANALYSIS

Data collected from 6 studies (Studies D0810C00001, D0810C00002, D0810C00008, D0810C00009, D0810C00012 and D0810C00024) were included in this population PK analysis.

The aim of this analysis was to identify sources of PK variability, and to analyze the exposure (C_{min}, C_{max} and AUC) response relationship. Clinical responses included pharmacodynamic (PD) endpoints (CA125 response, tumor response, and tumor size response) and adverse events (stomatitis, nausea and vomiting, dysgeusia, fatigue, dyspepsia, neutrophil, platelets, hemoglobin as categorical variable, cognitive function and diarrhea). Anemia was not assessed in the report.

3.1.1 Data Construction:

A total of 3579 concentration records of 293 subjects were included in the NONMEM dataset.

As shown by **Table 5**, PK data from six Phase I-II studies were pooled for population PK analysis. These six studies were conducted in breast cancer, ovarian cancer, and other solid cancers. Studies used for population PK analysis and their corresponding PK sampling schedules were shown in **Table 6**. Pharmacodynamic sampling schedules were listed in **Table 7**. The following adverse events including the most common adverse events were selected for analysis: nausea and vomiting, stomatitis, dysgeusia, dyspepsia, absolute neutrophil count, platelet, hemoglobin, cognative dysfunction, diarrhea and fatigue.

PK/PD data were extracted from the clinical study databases. The code for generating datasets was validated. Plasma concentrations below the lower quantification limit (i.e≤5 ng/mL) were set to 0.

For patients with missing covariates, missing data were replaced by the median value for the population. The population PK and PK-PD modeling analyses used NONMEM™, version 7.2 (Icon Development Solutions, 6031 University Blvd, Suite 300, Ellicott City, MD 21043 USA). The PK-PD analysis also used R, version 3.0.3 (The R foundation for statistical computing). Graphical representation of data and data manipulation were performed within R.

3.1.2 General Consideration

The selection of structural model and residual error models was based on the goodness-of-fits plots and on the difference in NONMEM objective function (approximately-2xlog likelihood) between hierarchical models (i.e. the likelihood ratio test). This difference is assymetrically $\chi2$ distributed with a degree of freedom equal to the number of additional parameters of the full compared to the reduced model.

Potential covariates were selected by univariate analysis, testing the addition of each covariate on each of the relevant PK or PKPD parameter. A p value of 0.01 was chosen to indicate significance of one addition parameter, i.e. a difference in the objective function >=6.64.

When a set of covariates, identified by the univariate selection, was found to have significant influence based on the likelihood ratio test, all were included into a full model. Backward deletion of these covariates one at a time used the significance level of 0.001, i.e. an increase of the objective function>=10.83. The population models resulted in successful minimization, with at least three significant digits for any parameter, a successful estimation of the covariance, and an absolute value of the last iteration gradients being greater than 0.001 but smaller than 1000.

Confidence intervals of structural parameters did not include zero; absolute value of correlation between two structural parameters were not be greater than 0.95.

The acceptable population models did not lead to trends in the distribution of weighted residuals versus model predictions and versus independent variables. They were not oversensitive to initial

estimates. The predictions versus observations data were evenly distributed around the unit line. Where constraints were applied on parameters, no final estimate was equal to its boundary.

PK model: Linearization methods approximate the hierarchical non-linear model with additive random effects and individual errors using the 1st derivative of the Taylor series expansion.

PKPD model: Estimation in NONMEM was performed using FOCE with interaction for assessment of tumor size change.

Table 5. Summary of clinical studies contributing data to this pooled analysis and their primary clinical objective.

Study 1 D0810C00 001	A Phase I, open-label, dose escalation study to assess the safety and tolerability of AZD2281 following single and multiple oral doses in patients in Japan with advanced solid malignances	The primary objective of this study is to determine the safety and tolerability of AZD2281 in Japanese population
Study 2 D0810C00 002 – (KU36-92)	A Phase I, Pharmacokinetic and Biological Evaluation of a small molecule Inhibitor of poly ADP- Ribose Polymerase-1 (PARP-1) KU-0059436, in Patients with Advanced Tumors.	To determine the safety, tolerability, dose-limiting toxicity PARP inhibitory dose range and maximum tolerated dose of KU-0059436 when administered orally to patients with advanced solid tumors.
Study 8 D0810C000 08- (KU36-44)	A Phase II open-label non- comparative multicenter study to assess the efficacy and safety of KU-0059436 given orally twice daily in patients with advanced BRCA1 or BRCA2 associated breast cancer.	To assess the efficacy of KU-0059436 in terms of objective tumor response rate when administered orally to patients with advanced BRCA1 or BRCA2 associated breast cancer.
Study 9 D0810C0 0009- (KU36-58)	A Phase II open-label non- comparative international multicenter study to assess the efficacy and safety of KU-0059436 given orally twice daily in patients with advanced BRCA1 or BRCA2 associated ovarian cancer.	To assess the efficacy of KU-0059436 in terms of objective tumor response rate when administered orally to patients with advanced BRCa1 or BRCA2 associated ovarian cancer
Study 12 D0810C00 012-	A Phase II open label randomized comparative international multicenter study to assess the safety and efficacy of two different doses of AZD2281 given orally twice daily and verses intravenous liposomal doxorubicin given monthly in patients with advanced BRCA1 or BRCA2 associated Ovarian cancer who have failed previous platinum based chemotherapy	To compare the efficacy of two different dose levels of AZD2281 verses liposomal doxorubicin in patients with advanced BRCA1 or BRCA2 associated ovarian cancer. Assessed with the primary variable of progression free survival.
Study 24 D0810C00 024	A Phase I, randomized, 2 period cross over study to determine the comparative bioavailability of two different oral formulations of AZD2281 in cancer patients with advanced solid tumors.	To determine the comparative bioavailability of the new ▓▓▓▓ (b) (4) (tablet) formulation of AZD2281 compared to the existing ▓▓▓▓ (b) (4) (capsule) formulation.

Source: Page 14 of the population PK report [7].

Table 6. Blood Sampling Schedule for the Population Pharmacokinetics Analysis.	
Study 01	PK samples were taken on single dose period (SDP) Day 1 at pre-dose. This was followed by samples following the first dose at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 (SDP Day1) 24 (SDP Day 2). PK Samples were taken on Day 1 in multiple dose period (MDP) Cycle 1 at pre-morning dose (48 hours post-first dose in SDP). On MDP Cycle 1 Day 15, samples for PK profiling also was taken pre-morning dose and again at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 10 hours (prior to evening dose).
Study 02	At dose levels of 10, 20, 40 and 80mg administered on a once daily basis, blood samples were taken at Cycle 1, Day 1 and 14 at pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 24 hours post last dose. An additional sample at 48 hours post last dose was collected on Cycle 1 Day 14. At dose levels of 60, 100, 200, 400 and 600mg, administered twice daily, blood samples were taken at Cycle 1, Day 1 and 14 at pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours post last dose; and for Cycle 2, Day 1, pre-dose, 1.5, 3, and 6 hours post dose.
Studies 8, 9 & 12	One pre-dose sample was collected on Days 1, 8 and 15. One sample was collected pre-dose on Day 29 and at 0-1.5 hours post dose, at 1.5 –3 hours post dose, at 3 – 6 hours post dose and at 6 – 12 hours post dose.
Study 24	PK samples were collected on Days 1–3. Samples were collected at pre-dose, and then at 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 24 and 48 hours post dose of olaparib. PK samples were collected on Day 29, pre-dose and at 0-1.5 hours post dose, at 1.5 – 3 hours post dose, at 3 – 6 hours post dose and at 6 – 12 hours post dose.
Source: Page 17-18 of the population PK report [7].	

Table 7. Pharmacodynamics Sampling Schedule for the Exposure-Response Analysis.	
CA-125	CA-125 assessments were collected at Day 1 of each cycle, Day 28 of final treatment cycle, and end of study (approximately 30 days after last dose). In study 24 all patients with ovarian cancer supplied plasma samples for CA-125 at screening and at visit 2 and every 8 weeks thereafter prior to receiving AZD2281.
Tumor Size Change	Tumour assessments according to RECIST were performed at baseline (within 28 days before first dose) and at the end of every 2 cycles according to the planned study assessments up to and including the withdrawal visit.
Tumor Response	Response score was reported after every 2 cycles of study drug, and was assigned as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) at each scheduled imaging visit by the investigator.
Source: Page 17-18 of the population PK report [7].	

Table 8. Number of patients in each study included in the Population PK analysis			
	Dose	Number of Patients	% of Patients
Study 1	100, 200, 400	12	4
Study 12	200, 400	61	21
Study 24	100, 400	47	16
Study 8	100, 400	40	14
Study 9	200, 400	48	16
Study 2	10, 20, 40, 60, 80, 100, 200, 400, 600	85	29
Total		293	100
Source: Page 27 of the population PK report [7].			

3.1.3   Population PK Analysis

The structure model is a two-compartment model with consecutive zero- and first-order absorption with a lag time and first-order elimination. The following covariates were tested, one by one, to explain variability in clearance: AGE, SEX, WT, BMI, CRCL, ALB, BILI, AST, ALT, AP. The following covariates were tested to explain variability in volume of distribution: SEX, WT, BMI, ALB. AGE and SEX were tested on the absorption parameters.

The validation of final model had to fulfill all the acceptance criteria defined as:
·   The estimation and covariance step terminate without error messages
·   The 95% confidence intervals of each estimated parameter do not contain their null value
·   The significant digits average 3.0 more
·   All gradients at the last iteration are reasonably small
·   Correlation between model parameters less than 0.95
·   No bias in goodness of fit plots

3.1.4   Population PKPD Analysis

Patients with missing adverse event data were excluded from the analysis and variation between individuals was not accounted for.

For binary data represented as either 1 for response or 0 for no response a logistic model was applied to the data. Analysis was performed in R using the glm function in the stats R-package.

For ordered categorical data, e.g. tumor response data represented as either 0=progression, 1=stable disease, 2=partial response and 3=complete response, a proportional odds logistic regression analysis was performed. Analysis was performed in R. Adverse event data was represented as either 1 = no event, 2=CTC grades 1 and 2, and 3=CTC grades 3, 4 and 5 and was analysis was performed in R using the clm function in the ordinal R-package.

Tumor Size: Analysis used the model as described by (Claret L, Girard P, Hoff M P 2009) which represents the tumor size change as both a growth rate and a drug related inhibition rate.
Progression Free Survival (PFS): was not analyzed.

Table 9. Parameter estimates and C.I. of the Final model						
Symbol	Units	Explanation	Mean	Bias	95% CI	
θ1	h	Duration D1	0.461	0.00266	0.456	0.466
θ2	1/h	Rate const. of absorption, KA	0.20	0.015	0.171	0.229
θ3	L/h	Clearance CL	2.26	0.0307	1.65	2.86
θ4	L	Central volume of distribution, V2	3.75	0.486	2.80	4.70
θ5	L	Peripheral volume of distribution, V3	60.3	11.2	38.3	82.3
θ6	L/h	Inter-compartment Clearance Q	0.868	0.173	0.53	1.21
θ7	h	Absorption lag time	0.209	0.00196	0.205	0.213
θ8		Relative bioavailability (P performance)	0.960	0.0278	0.91	1.01

θ9		Effect of dose on Bioavailability	-0.282	0.0137	-0.309	-0.255
θ10		Effect of weight on V2	-0.902	0.341	-1.57	-0.23
θ11	h	Effect of Sex on D1	-0.150	0.00116	-0.152	-0.148
θ12	1/h	Effect of Sex on Ka	-0.0409	0.014	-0.068	-0.013
ω11	Variance	BSV of Q	1.49	0.437	0.63	2.35
ω22	Variance	BSV of CL	0.586	0.0668	0.455	0.717
ω33	Variance	BSV of V2&V3	0.815	0.149	0.523	1.110
ω44	Variance	BSV of D1	3.07	0.721	1.66	4.48
ω55	Variance	BSV of ALAG	0.092	0.0405	0.01	0.19
ω12	Covariance	BSV CL and Q	0.374	0.11	0.158	0.590
ω13	Covariance	BSV V2&V3 and Q	-0.206	0.161	-0.522	0.110

Source: Page 32-33 of the population PK report [7].

Figure 7. Comparison of bioavailability versus dose split by "Fast/Unknown release profile" (in blue) and "Slower release profile"(in red)

Source: Figure 21 from the Population PK Report [7].
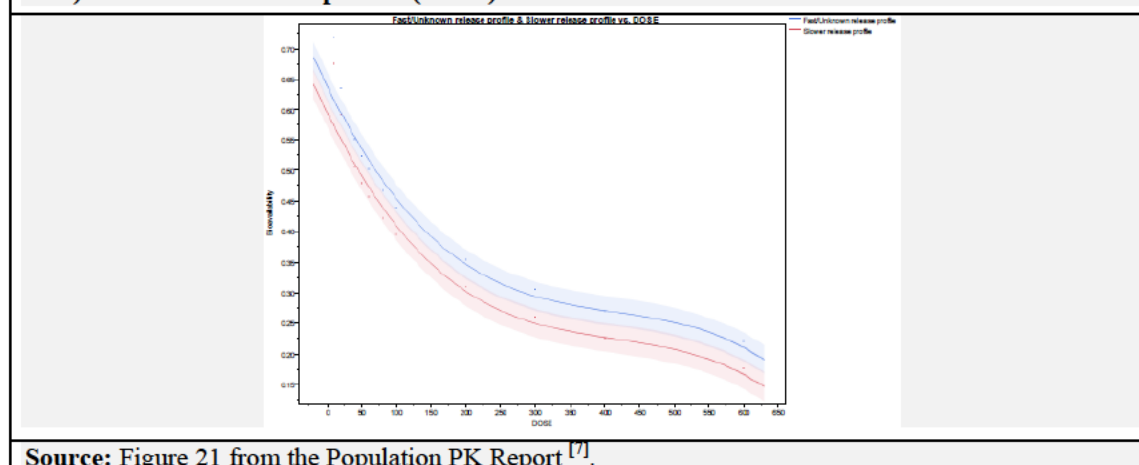
Figure 8. Apparent clearance versus creatinine clearance

Source: Figure 22 from the Population PK Report [7].
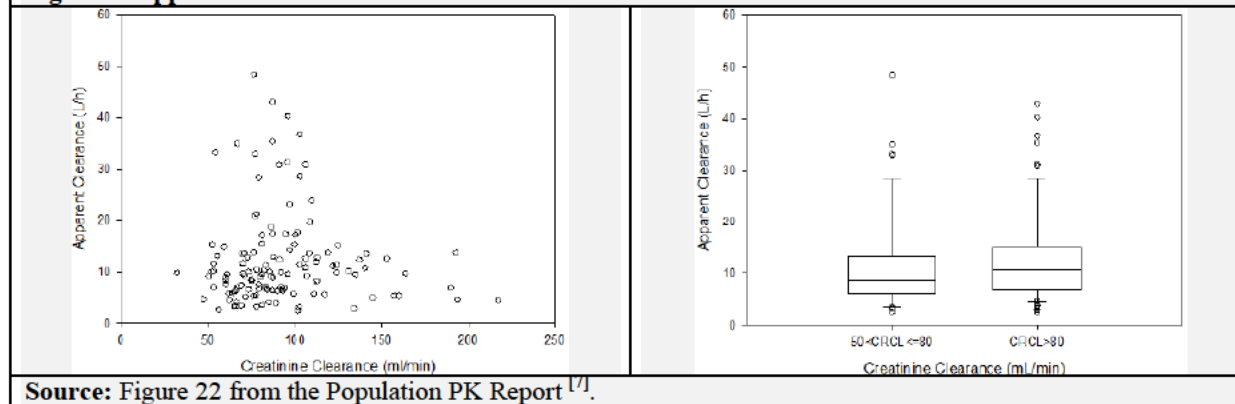
Figure 9. Apparent clearance versus liver function tests

Source: Figure 23 from the Population PK Report [7].
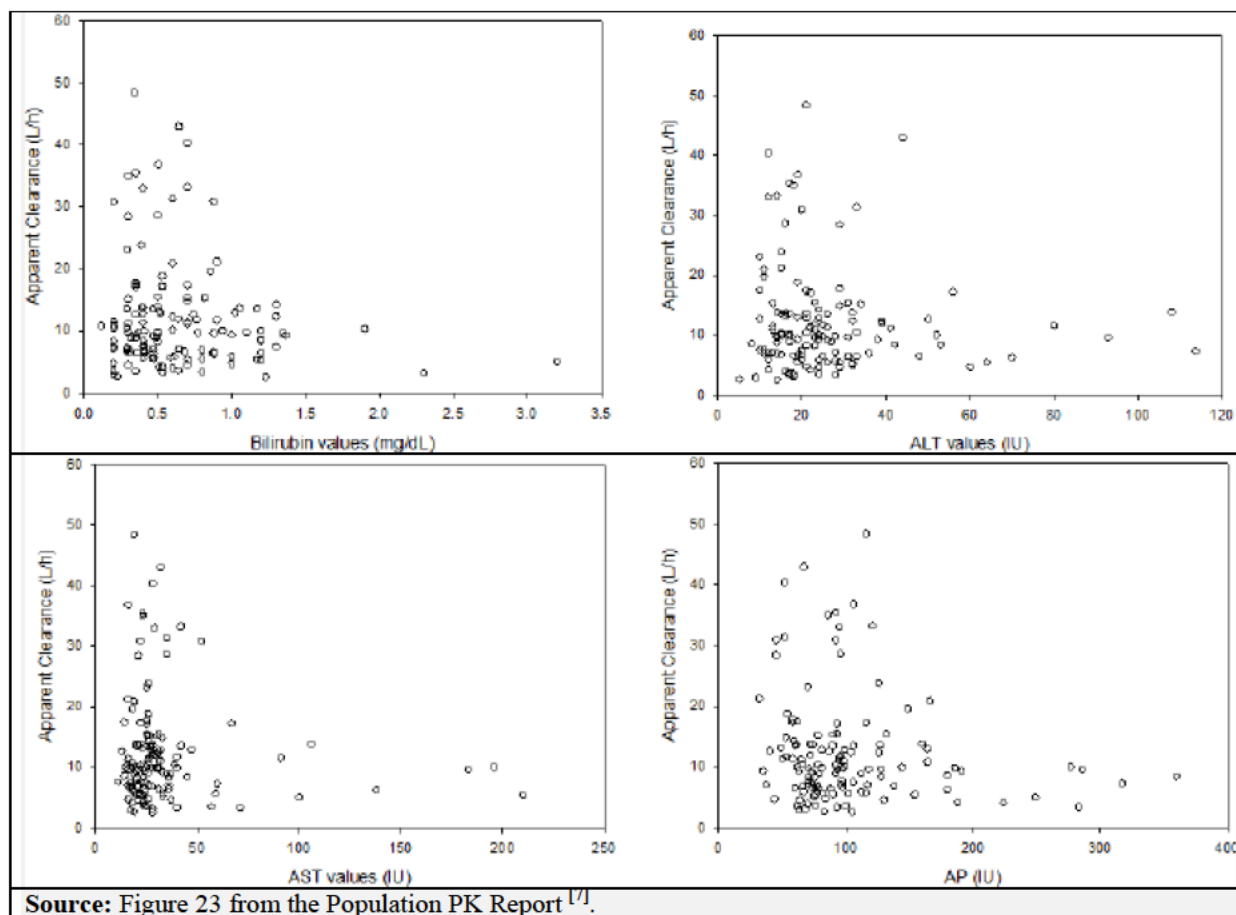
3.1.5 Conclusion

Population PK: the PK of olaparib is described by a two-compartment system with both zero and first order absorption:

- The non-linearity of PK of olaparib was described in F varying with the administered dose. The bioavailability was found to be altered by the dissolution performance of the batch of capsules dosed. For the 400 mg dose the population bioavailability was equal to 0.27 for fast release profile dissolution batches.
- Estimation of PK parameters as CL/F and V/F are similar to those derived with NCA analysis in study 24.
- No clinical impact of covariates on the pharmacokinetics of olaparib.

PKPD for Efficacy: Using individual estimates of steady state exposure (steady state AUC, C_{max} and C_{min}), together with baseline characteristics and the administered dose three markers of response (CA125, tumor response, and tumor size change) were investigated. Dose (log-transformed) was the only significant factors for CA125 response and tumor size change, whereas log dose together with study as categorical was important predictors for tumor response

in the present pooled analysis. Results of the analysis suggested that 400 mg was more effective than 100 or 200 mg with respect to all these parameter changes. Analysis of CA125 suggested a 56% probability of response for 400 mg compared to 31% for 200 mg, while the predicted proportion of patients with partial or complete response was 35 % for 400 mg and 28 % for 200 mg. A 32% reduction of tumor size is predicted for the 400 mg dose after 200 days of treatment compared to 17% and 3% for the 200 and 100mg doses.

PKPD for Safety: There was little evidence to suggest that measures of exposure (AUC, C_{minss} and C_{maxss}) or dose were predictive of nausea and vomiting, absolute neutrophil count, fatigue events, cognitive dysfunction or diarrhea.

Of the measures of exposure, dose was the best predictor of platelet events ($p<0.001$). The model predicted an increase in the probability of the average patient experiencing CTC grade
1 & 2 events with doses of 100 mg, 200 mg and 400 mg: 21.5 %, 27.5 % and 35.8 %, respectively. Similarly, the probability of the average patient experiencing CTC grade 3 or greater events with doses of 100 mg, 200 mg and 400 mg: 1.19%, 2.59 % and 5.20%, respectively.

Although missing the pre-defined threshold, dose was found to be a predictor of dyspepsia events and C_{maxss} was found to be a predictor of hemoglobin events at the 95% significance level. The model predicted a modest increase in the probability of the average patient experiencing dyspepsia with increasing dose: 10.9% at 100 mg, 15.7% at 200 mg and 21.9% at 400 mg. The probability of the average patient experiencing CTC grade 1 & 2 hemoglobin events was predicted to be 58.9 %, 62.7 % and 63.8 % at 100 mg, 200 mg and 400 mg, respectively. The probability of the average patient experiencing CTC grade 3 or greater haemoglobin events was predicted to be 3.96% at 200 mg and 10.4% at 400 mg.

FDA Reviewer's Comments: The sponsor intended to use the population PK model to describe the PK data of multiple studies and generate exposure metrics for exposure-response analysis. Post-hoc individual parameters appeared to be acceptable to characterize individual PK profile and therefore to be used for subsequent exposure-response analysis. However, the covariate screening results might not be reliable given the high variability in PK exposure introduced from other sources as described below.

First, the sponsor used FO method for the population PK analysis, the shrinkage for C_{max}, C_{min} or AUC were not available. Second, olaparib PK is highly variable among studies, for which product variability within and between studies could be important factors. For example, the bioavailability of Study 07, which was only 25-50% of Study 02 for the same doses of 100-400 mg[8],may be largely related to product variability across manufacture sites and lots as compared to other variables such as dose. Third, NONMEM code for bioavailability, $FF1=FORM1+Emax*log_{10}(DOSS)$ (FF1: dissolution related relative bioavailability; FORM1: dissolution related constant; Emax: a dose related coefficient; DOSS: BID dose), in the final model ,may not be supported by data.

Upon FDA information request, the sponsor conducted dose proportionality analysis within each of Studies 01, 02, 07, 09 and 12, and the analysis results showed mixed signals and no definite conclusion was reached. Neither exposure-anemia relationship nor exposure-PFS relationship

was included in the submission. PFS was the primary efficacy endpoint of Study 12 and Study 19.

4   FDA REVIEWER'S ANALYSIS

4.1   OBJECTIVE

The objectives of FDA reviewer's analyses on primary efficacy endpoint (PFS) and major safety (anemia, thrombocytopenia, neutropenia and lymphopenia) data were to evaluate:

- Whether there was an exposure-PFS relationship following 100, 200 and 400 mg olaparib capsule BID.

- Whether there was an exposure-safety relationship.

4.2   METHODS AND SOFTWARE

S-Plus® (TIBCO Spotfire S+ Version 8.1) was used for data organization, graphics, logistic regression and related statistical analyses. R 2.15.1 was used for survival analysis and graphics. Sponsor's population pharmacokinetics analysis was reproduced using NONMEM v7.2.

The logistic regression was used for exposure-safety analyses, where the safety signals included anemia, thrombocytopenia, neutropenia, and lymphopenia.

Exposure-survival analysis and dose-survival analyses was conducted for PFS (the primary efficacy endpoint of Studies 19 and 12).

Patients were grouped by exposure quartiles [9] for relevant exposure-response analyses..

4.3   DATASETS

The datasets for logistic regression analyses and survival analyses were prepared by the sponsor upon the FDA information request.

Dataset "pk3eff.xpt" included efficacy and exposure data for capsule doses of Studies 02, 08, 09, 12 and 24. Dataset "pk3safe.xpt" included major adverse events and exposure data for capsule doses of 5 studies. Additional data information can be found in **Table 6** and **Table 8** for these 5 studies.

Dataset "pk3saf24.xpt" included major adverse events and exposure data for tablet doses of Study 24.

4.4   RESULTS
The results are presented in Sections 1.1.1, 1.1.2 and1.1.3.

4.5   CONCLUSIONS

There appeared to be no apparent exposure-PFS relationship in the patients following the 200 or 400 mg olaparib capsule BID dose, while there appeared to be an exposure-anemia correlation

for both the capsule and tablet formulations. The BID 300 mg olaparib tablet resulted in a 40-90% higher exposure than that of the BID 400 mg olaparib capsule.

5   ANALYSIS DATA AND FILES
Listing of Analyses Codes and Output Files

File Name	Description	Location in \\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews
SASCodeforNONMEM dataset	SAS code for creating NONMEM dataset	Not submitted
Final-mod.txt	Population pharmacokinetic model (Final)	\Olaparib_NDA206162_HL\Pop PK Analysis\From the Sponsor
Final-lst.txt	Output of final population pharmacokinetic model	\Olaparib_NDA206162_HL\Pop PK Analysis\From the Sponsor
q2ii-pk-pool-05march2014.csv	Population pharmacokinetic dataset	\Olaparib_NDA206162_HL\Pop PK Analysis\From the Sponsor
*.ssc	ER analysis	\Olaparib_NDA206162_HL\ER Analysis\Safety
Pk3eff.xpt, pk3safe.xpt, pk3saf24.xpt	Dataset for ER analysis	\Olaparib_NDA206162_HL\Sponsor's Data and Reports\Data

6   REFERENCES

1.   Clinical Study Report of Study D0810C00019, titled "Phase II randomised, double blind, multicentre study to assess the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens", dated 31 July 2013.

2.   Clinical Study Report of Study D0810C00012, titled "A phase II, open-label, randomized, comparative, international multicenter study to compare the safety and efficacy of two different doses of AZD2281 given orally twice daily versus intravenous liposomal doxorubicin given monthly in patients with advanced BRCA1- or BRCA2-associated ovarian cancer who have failed previous platinum-based chemotherapy", dated 13 December 2010.

3.   Clinical Study Report of Study D0810C00009, titled "A phase II, open-label, non-comparative, international, multicenter study to assess the efficacy and safety of KU-0059436 given orally twice daily in patients with advanced BRCA1- or BRCA2-associated ovarian cancer", dated 24 July 2009.

4.   Clinical Study Report of Study D0810C00002, titled "A Phase I, Pharmacokinetic and Biological Evaluation of a Small Molecule Inhibitor of Poly ADP-Ribose Polymerase-1 (PARP-1), KU-0059436, in Patients with Advanced Tumours", dated 1 December 2009.

5.   Clinical Study Report of Study D0810C00008, titled "A Phase II, Open-Label, Non-Comparative, International, Multicentre Study To Assess The Efficacy And Safety Of KU-0059436 Given Orally Twice Daily In Patients With Advanced BRCA1- Or BRCA2-Associated Breast Cancer", dated 1 December 2009.

6.   Clinical Study Report of Study D0810C00024, titled "A phase I, randomised, 2 period cross over study to determine the comparative bioavailability of two different oral

formulations of AZD2281 in cancer patients with advanced solid tumours", dated 23 July 2013.

7. Population Pharmacokinetics Study Report, titled "A Pooled Population analysis of the Pharmacokinetic, efficacy and adverse event data obtained following dosing of olaparib capsule formulation to patients in D0810C00001, D0810C00002, D0810C00008, D0810C00009, D0810C00012 and D0810C00024", dated 09 April 2014.

8. Page 14 of Population PK PD report, titled" Population pharmacokinetic and pharmacodynamic analysis of AZD2281 (KU-0059436) in Study KU-36-92 and Study KU36-13. A pooled analysis", dated 12 October 2008.

9. Hyndman, R. J. and Fan, Y (1996), "Sample Quantiles in Statistical Packages," *The American Statistician,* **50**, 361-364.

3.3   PHYSIOLOGICAL-BASED PHARMACOKINETIC MODELING REVIEW

Physiological-based Pharmacokinetic Modeling Review

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA 206162
Drug Name	Olaparib (AZD2281)
Proposed Indication	Monotherapy in adult patients with ^{(b) (4)} deleterious or suspected deleterious germline BRCA (gBRCA)-mutation (as detected by an FDA-approved test) and who have had three or more prior lines of chemotherapy.
Clinical Division	DOP1
PBPK Consult request	Elimika Pfuma, Pharm.D Ph.D.
Primary PBPK Reviewer	Ping Zhao, PhD
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1. Objectives

The main objectives of this review are to 1) evaluate the adequacy of sponsor's conclusions regarding the ability of a physiologically-based pharmacokinetic (PBPK) model to predict the DDI potential of olaparib as a victim of the CYP3A metabolic pathway and 2) provide a dosing recommendation based on the predicted effect of moderate CYP3A inhibitor or inducer. To support its conclusions the sponsor provided the following PBPK modeling and simulation reports and updates:

1. Simulating the induction of CYP3A4/5 by rifampicin and the effect on the exposure of Olaparib using SimCYP (version 12) based on data from in vitro studies and clinical studies. Study Olaparib SimCYP1 [1]

2. Simulating the inhibition of CYP3A4/5 by itraconazole and the effect on the exposure of Olaparib using SimCYP (version 12) based on data from in vitro studies and clinical studies. Study Olaparib SimCYP2 [2]

3. Overview document: Response to FDA information request regarding PBPK (Email). 24-Jun-2014 [3]

2. Background

2.1. Regulatory history on PBPK submission

Olaparib (AZD2281) is developed as monotherapy in adult patients with ⬜⬜⬜⬜⬜⬜ (b) (4) ⬜⬜⬜⬜⬜⬜⬜⬜ deleterious or suspected deleterious germline BRCA (gBRCA)-mutation (as detected by an FDA-approved test) and who have had three or more prior lines of chemotherapy [4]. The proposed dosing regimen of olaparib is 400 mg orally twice daily (b.i.d.).

A PBPK model of olaparib was developed by the sponsor to predict the effect of strong CYP3A inhibitor itraconazole or inducer rifampin on the exposure of olaparib [1,2]. After initial review of these reports, the FDA reviewers issued two information requests to the sponsor on March 05, 2014 and on June 18, 2014 (01222014IR and 06182014IR. Section 5.2). Sponsor responded to these IRs and an updated model of olaparib and simulations of olaparib PK in the presence and in the absence of various CYP3A modulators were submitted [3,5].

This review evaluates the adequacy of sponsor's olaparib PBPK model to predict the DDI potential, and provides dosing recommendations based on the predicted effect of moderate CYP3A modulators on olaparib PK.

3. Methods

Two versions of a population based PBPK software Simcyp® (Sheffield, UK) [6,7] were used by the sponsor to develop olaparib PBPK model. Initial models were developed in SimCYP Version 12 to prospectively predict the effect of rifampin [1] and itraconazole [2] on olaparib PK. In response to FDA's 06182014IR, sponsor provided an updated PBPK analysis. In this update, the sponsor described the development of an updated olaparib model using SimCYP Version 13.1, which includes a mechanistic absorption model and a full PBPK distribution model. Only the updated model is reviewed in this document. Software's built-in "Healthy volunteer" population and an "Oncology Patient" population [8] were tested. Parameters and their sources for olaparib are summarized in **Appendix Tables A1 and A2**. Unless otherwise stated, all final drug interaction simulations were conducted in "Oncology Patient" populations [8].

Perpetrator models for itraconazole (and its inhibitory metabolite hydroxy-itraconazole, "Sim-Itraconazole.cmp" and "Sim-OH-Itraconazole.cmp"), rifampin ("Sim-Rifampicin.cmp"), and fluconazole ("SV-fluconazole.cmp") from the software's drug model library were directly used. Because the library does not have a model for efavirenz, the sponsor created two efavirenz models in SimCYP Version 13.1 according to literature data [9,10] (**Appendix Table 3**). FDA reviewer used sponsor's efavirenz models and an efavirenz model that FDA previously evaluated to further evaluate the prediction of the effect of efavirenz on the PK of olaparib.

Sponsor's PBPK modeling of olaparib can be summarized in three parts.

(A). Model building: Results of in vitro experiments and physicochemical properties, and in vivo PK studies were used to describe absorption, distribution, metabolism, and excretion (ADME) characteristics in the model (**Appendix Tables 1 and 2**).

(B). Model verification: Clinical drug-drug interaction studies with strong CYP3A inhibitor or inducer (itraconazole and rifampin) [11,12] were used to verify olaparib PBPK model.

(C). Model applications: The sponsor conducted simulations to predict the following:

1. 300 mg single dose olaparib tablet in the presence of a moderate CYP3A inhibitor fluconazole.

2. 300 mg single dose olaparib tablet in the presence of a moderate CYP3A inducer efavirenz. Both efavirenz models were used in this evaluation.

Table 1 summarizes the design of simulations and clinical study for each interacting drug.

Table 1. Designs of simulation and clinical study for evaluating the effect of each interacting drug on the exposure of olaparib

Interacting drugs	Simulation Design	Clinical Study Design [11,12]
Itraconazole	5 trials with 28 subjects each (n=140). Age 23-92 years, 50% females. Dosing: Crossover design Itraconazole 200 mg once daily (q.d.) for 7 days, olaparib 100 mg single dose on day 5 together with itraconazole under fasted state.	Total 59 patients were included in safety analysis dataset (Less with evaluable PK data, see **Table 2**). The median age of the population was 61years with most patients (64.4%) aged between 40 and 65 years. Majority of the patients (71.2%) were female. Dosing: Sequential design Patients received single dose 100 mg olaparib on day 1. Starting day 5, itraconazole 200 mg once daily (q.d.) for 7 days, olaparib 100 mg single dose on day 9 together with itraconazole under fasted state.
Rifampin	20 trials with 8 subjects each (n=160). Age 23-92 years, 50% females. Dosing: Crossover design Rifampin 600 mg q.d. for 13 days, olaparib 300 mg single dose on day 10 together with rifampin under fasted state.	Total 22 patients were included in safety analysis dataset (Less with evaluable PK data, see **Table 3**). The median age of the population was 59 years with 50% patients aged between 40 and 65 years. Majority of the patients (81.8%) were female. Dosing: Sequential design Single dose 300 mg olaparib on day 1. Starting day 5, rifampin 600 mg q.d. for 13 days, olaparib 300 mg single dose on day 14 together with rifampin under fasted state.
Fluconazole	10 trials with 10 subjects each (n=100). Age 23-92 years, 50% females. Dosing: Crossover design Fluconazole 200 mg q.d. for 7 days, olaparib 100 mg single dose on day 5 together with fluconazole under fasted state.	NA
Efavirenz	10 trials with 10 subjects each (n=100). Age 23-92 years, 50% females. Dosing: Crossover design Efavirenz 400 mg q.d. for 13 days, olaparib 300 mg single dose on day 10 together with efavirenz under fasted state.	NA

4. Results

4.1. Can Olaparib PBPK Model Be Used to Predict The Effect of CYP3A Modulation on Olaparib Exposure?

Yes. Two major factors are critical for a substrate PBPK model to predict the effect of CYP inhibition or induction on its PK: quantitative determination of the contribution of the CYP pathway that is modulated by co-medication (e.g., assumption of $f_{m,CYP3A}$ for olaparib), and capability of the model to predict the PK profile under different dosing regimens.

The updated model appears to reasonably describe the observed PK profiles of olaparib, as shown for various dose levels in **Appendix Figure 1**. Sponsor defined $f_{m,CYP3A}$ to be 0.973 based on results in human liver microsomes incubated with CYP inhibitors (**Appendix Table 2**). This is verified using clinical drug-drug interaction data when olaparib was co-administered with itraconazole (a strong CYP3A inhibitor, **Table 2**) and rifampin (a strong CYP3A inducer, **Table 3**). As shown in **Table 2**, PBPK reasonably predicted mean AUC ratio and Cmax ratio by itraconazole. However, the observed and PBPK predicted AUC ratio by inducer rifampin were 0.12 and 0.32, respectively (**Table 3**). The apparent under-estimation of the effect on olaparib clearance (over estimation of exposure) by rifampin may be attributed to inadequacy of library's rifampin PBPK model that has been shown to underestimate its effect on clearance of other CYP3A substrates [15, 16].

Table 2. Comparison of PBPK simulated PK parameters of olaparib in the presence or absence of itraconazole

	PBPK Simulated[a]		Observed[b]	
AUC (µg/ml h)	Geometric Mean	19.35	Geometric Mean (CV%)	14.8 (75.4)
AUC with itraconazole (µg/ml h)	Geometric Mean	53.18	Geometric Mean (CV%)	40.09 (72.1)
AUC ratio	Geometric Mean (95% Confidence Interval)	2.75 (2.68, 2.82)	Geometric Mean (90% Confidence Interval)	2.66 (2.41, 2.93)
Cmax (µg/mL)	Geometric Mean	2.95	Geometric Mean (CV%)	2.99 (48.2)
Cmax with itraconazole (µg/ml h)	Geometric Mean	3.53	Geometric Mean (CV%)	4.24 (37.7)
Cmax ratio	Geometric Mean (95% Confidence Interval)	1.20 (1.18, 1.21)	Geometric Mean (90% Confidence Interval)	1.42 (1.33, 1.52)

[a] *Simulated mean, median, and geometric mean and confidence interval. AUC is AUC $_{0-72hr}$, results can be found in **Appendix Table 4***

[b] *Summarized from Tables 13 (PK) and 14 (exposure ratio) from reference [11]. AUC is AUC from time zero to last measurable time point. (See **Appendix Table 5** for more information including sample size).*

Table 3. Comparison of PBPK simulated PK parameters of olaparib in the presence or absence of rifampin

	PBPK Simulated[a]		Observed[b]	
AUC (µg/ml h)	Geometric Mean	44.79	Geometric Mean (CV%)	54.6 (63.8)
AUC with rifampin (µg/ml h)	Geometric Mean	14.26	Geometric Mean (CV%)	6.19 (60.2)
AUC ratio	Geometric Mean (95% Confidence Interval)	0.32 (0.30, 0.33)	Geometric Mean (90% Confidence Interval)	0.12 (0.10, 0.15)
Cmax (µg/mL)	Geometric Mean	6.73	Geometric Mean (CV%)	8.01 (24.3)
Cmax with rifampin (µg/ml h)	Geometric Mean	3.98	Geometric Mean (CV%)	2.39 (53.4)
Cmax ratio	Geometric Mean (95% Confidence Interval)	0.59 (0.57, 0.61)	Geometric Mean (90% Confidence Interval)	0.29 (0.24, 0.33)

[a] *Simulated mean, median, and geometric mean and confidence interval. AUC is AUC $_{0-72hr}$, results can be found in **Appendix Table 4***

[b] *Summarized from Tables 11 (PK) and 12 (exposure ratio) from reference [12]. AUC is AUC from time zero to last measurable time point. (See **Appendix Table 6** for more information including sample size).*

Olaparib PBPK model was used to predict two untested clinical drug-drug interaction scenarios, and the results are shown in **Table 4**. Simulations show that co-administration with a moderate CYP3A inhibitor fluconazole increased mean AUC and Cmax of olaparib by 126% and 14%, respectively; co-administration with a moderate CYP3A inducer efavirenz decrease mean AUC and Cmax of olaparib by 59% and 31%, respectively. These findings should be considered when drafting labeling for the effect of moderate CYP3A modulators on olaparib exposure.

The sponsor justified the use of a relatively high value (0.973) for $f_{m,CYP3A}$ by stating that it provided the worst-case prediction of the effect of CYP3A modulators. This assumption is considered sufficient based on verification of the model using itraconazole-olaparib and rifampin-olaparib interaction data (**Tables 2 and 3**). Indeed, when sponsor's model was modified by the FDA reviewer using a smaller $f_{m,CYP3A}$ of 0.8 (a value determined from in vitro reaction phenotyping study using recombinant CYPs [4], instead of 0.973 based on human liver microsomes), the model tended to underestimate the effect of itraconazole. The predicted AUC ratio and Cmax ratio were 2.1 and 1.1, respectively, using the model with an f m,CYP3A of 0.8 (FDA analysis using SimCYP Version 13.2); whereas the predicted AUC ratio and Cmax ratio were 2.8 and 1.2 respectively, using sponsor's model with $f_{m,CYP3A}$ of 0.973 (FDA analysis using SimCYP Version 13.2). The effect of rifampin was further underestimated using the alternative model with a lower $f_{m,CYP3A}$, The predicted AUC ratio and Cmax ratio were 0.42 and 0.73, respectively, using the model with an $f_{m,CYP3A}$ of 0.8 (FDA analysis using SimCYP Version 13.2); whereas the predicted AUC ratio and Cmax ratio were 0.37 and 0.67 respectively, using sponsor's model with $f_{m,CYP3A}$ of 0.973 (FDA analysis using SimCYP Version 13.2).

It has to be noted that all simulations were conducted in virtual cancer populations [8] with a male to female ratio of 1:1 (**Table 1**), yet the target population for this NDA is women (patients with ovarian

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cancer). Because the simulations assumed no gender difference in CYP3A metabolism, this simulation design (male to female ratio of 1:1) is acceptable to address the olaparib exposure changes caused by CYP3A modulators.

Table 4. PBPK simulation of the effects of moderate CYP3A modulators on olaparib exposure.

Modulator	Mechanism	Mean AUC ratio	Mean Cmax Ratio
Fluconazole	Moderate CYP3A inhibitor	2.26	1.14
Efavirenz [a]	Moderate CYP3A inducer	0.41	0.69

Simulation followed study design outlined in Table 1. Simulated mean, median, and geometric mean and confidence interval results can be found in Appendix Table 4

[a] *Simulation using efavirenz model based on reference [8]. See **Appendix Table** 7 for additional FDA simulations to confirm the adequacy of efavirenz model used by the sponsor.*

4. Conclusion

Sponsor's PBPK model of olaparib is considered sufficient to predict olaparib PK in patients co-administered with CYP3A modulators. The effect of a moderate inhibitor fluconazole was predicted to increase olaparib exposure by approximately two fold. The effect of a moderate CYP3A inducer efavirenz was predicted to decrease olaparib exposure by approximately half.

5. *Appendices*

5.1. Abbreviations

ADAM, Advanced dissolution, absorption, and metabolism model; ADME, absorption, distribution, metabolism, and excretion; b.i.d., twice daily dosing; B/P, blood to plasma ratio; AUC, area under the concentration-time profile; AUCR, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; B/P, blood to plasma ratio; Cmax, maximal concentration in plasma; CmaxR, the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; CL, clearance; CL_{int}, intrinsic clearance; DDI: drug-drug interaction; F, bioavailability; Fa, fraction absorbed; Fg, fraction that escapes intestinal metabolism; f_{mj}, fraction of total clearance mediated by j CYP isoform or renal elimination; fp, fraction unbound in plasma; $f_{u,mic}$, fraction unbound in microsomes; $f_{u,inc}$, fraction unbound in (hepatocyte) incubation; $f_{u,gut}$, apparent unbound fraction in enterocytes; gBRCA, germline breast cancer susceptibility gene; GI: gastrointestinal; γ, Hill coefficient; IR, immediate release formulation; $I_{nd,max}$, maximal fold induction; $I_{nd,50}$, concentration causing half-maximal fold induction; ka, first order absorption rate constant; K_i, reversible inhibition constant; K_I, inactivation constant, inhibitor concentration resulting in half maximal inactivation; K_m, Michaelis-Menten Constant; k_{inact}, maximal inactivation rate constant; LogP, logarithm of the octanol-water partition coefficient; NA, not applicable; ND, not determined; NDA: new drug application; P_{app}, apparent passive permeability; $P_{eff,man}$, effective passive permeability in man; PBPK: Physiological-based Pharmacokinetic; P-gp: P-glycoprotein; q.d., once daily dosing; Q_{gut}, a hypothetical flow term for the intestine absorption model; Tmax: time at maximal concentration in plasma; T_{LAG}: lag time; V_{max}, maximum reaction velocity; V_{ss}, volume of distribution.

5.2. Information Request

5.2.1. Clinical Pharmacology March 05, 2014 (03052014IR)

We conducted initial review of the PBPK study reports "Olaparib SimCYP1" and "Olaparib SimCYP2". Please submit the updated PBPK reports by addressing the following comments by March 25, 2014.

1.   You should provide justifications, assumptions and references for each input parameter in the Input Parameter Tables.

2.   You should include simulation results for pharmacokinetic studies being used to build/optimize the PBPK model. Specifically, your model should include (a) potential mechanisms responsible for the apparent nonlinear pharmacokinetics between 100 mg and 400 mg olaparib doses, (b) assignment of different elimination pathways given that unchanged olaparib was found in both urine and fecal samples in human mass balance study.

3.   The model should first be independently verified by comparing simulated effect of enzyme inhibitor or inducer on olaparib pharmacokinetics to the interim results of the ongoing drug-interaction studies with itraconazole and rifampin (if applicable). Any modification of the model after verification step should be documented and justified.

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Additional simulations may be requested after we review the updated drug-interaction results and your updated PBPK reports.

5.2.2. Clinical Pharmacology Jun 18, 2014 (06182014IR)

On March 18, 2014, you agreed to submit updated PBPK study reports in late May/early June as part of the Day 120 update. The updated PBPK reports were to address comments provided to you on Mar 12, 2014, including comparison between model prediction and observed data from the ongoing drug interaction studies using strong CYP3A inhibitor itraconazole and strong CYP3A inducer rifampin, and necessary modification of the initial olaparib PBPK model.

1. Based on the observed magnitude of the effect of strong CYP3A modulators on olaparib pharmacokinetics, you should also simulate the following scenarios and find a dose of olaparib in the presence of a moderate CYP3A inhibitor (e.g. 200 mg fluconazole once daily) or a moderate CYP3A inducer (e.g. 400 mg efavirenz once daily) that will match the exposure of 400 mg alone

2. Please explore the effect of dissolution in your olaparib PBPK model to describe potential PK nonlinearity at doses >100 mg.

Please provide the model files used to generate the final PBPK simulations (e.g. drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files. Study report(s) should be provided as PDF files (screenshots can be incorporated if required).

Please submit this information by June 24, 2014

5.3. Appendix Tables and Figures

Appendix Table 1. Physicochemical parameters of olaparib PBPK model (SimCYP Version 13.1, [4])

Model name: "Olaparib enzyme kinetics tablets v6.cmp"

Parameter	Value	Comment
MW (g/mole)	434.5	
LogP	1.55	As Olaparib has a basic pKa of -1.25 and acidic pKa of +12.07 the compound will be almost completely unionised at pH 7.4 so the LogP and LogD values will be almost identical. As such the LogD value of 1.55, which was generated in study BL8475/B, was used.
pKa	Neutral compound	Olaparib is an ampholyte. The pKa values will allow very little ionization of olaparib to occur even at the extremes of physiological pH. It should also be noted that the minimum pKa value accepted by Simcyp is -1. This value is still 2.5 pH units lower than the lowest physiological pH value used in the Simcyp healthy volunteer population (the fasted stomach contents have a pH of 1.5). Consequently it has been decided to model Olaparib as a neutral compound. This has the additional advantage that the models used to predict physiological parameters from physicochemical parameters (e.g. those for volume of distribution, see later) are built on much large data sets than those for ampholytes, so they may be expected to give a better estimate of the true physiological values for olaparib.
B:P (Blood to plasma ratio)	0.7	In study D2281 KPJ019 the mean blood/plasma ratio for olaparib was found to be 0.60 at a concentration of 100 ng/mL and 0.74 at a concentration of 10000 ng/mL. Given the observed Cmax and Cmin values it is considered that 0.7 is an appropriate value to use for the blood/plasma binding value.
fp (fraction unbound in plasma)	0.181	In study D2281 KPJ019 the mean percentage of free fraction of olaparib at concentrations of 10, 100, 1000 and 10000 ng/mL was 8.9%, 8.8%, 9.1% and 18.1% respectively. In study D2281 KPJ043 the mean percentage of free fraction of olaparib at concentrations of 100, 1000 and 10000 ng/mL in plasma pre-^{(b) (4)} dosing was 7.7%, 7.9% and 14.4%, respectively. In study D2281 KPJ043 the mean percentage of free fraction of olaparib at concentrations of 100, 1000 and 10000 ng/mL in plasma post-^{(b) (4)} dosing was 7.4%, 9.1% and 18.1%. In study 8293107 the mean percentage of free fraction of olaparib at concentrations of 10000, 20000 and 40000 ng/mL in plasma was 15.2%, 22.9% and 29.8%. Given the observed Cmax and Cmin values it is considered that 0.181 is an appropriate value to use for the blood/plasma binding value. Reviewer comment: although concentration dependent protein binding may be a reason for nonlinear PK, sponsor decided to use constant fu because concentration dependent fu option in the software does not allow full PBPK distribution model.

Appendix Table 2. Input ADME parameters of olaparib PBPK model (Simcyp software V13.1, [4])

Parameter	Value	Comment

Absorption	Advance Dissolution, absorption, and metabolism (ADAM)	Solid formulation, immediate release (IR) Initial simulations used first order absorption kinetics [1,2]. Sponsor chose ADAM to account for formulation differences and evaluation of potential contribution of intestinal transporters. In initial simulations, permeability of olaparib in a human CaCo-2 cell monolayer assay, and a Q_{gut} 3.505 (L/h) was used.
fu, gut (apparent unbound fraction in enterocytes)	0.2586	The value was assumed to be equal to free fraction in blood (fu in plasma divided by B:P)
Intrinsic solubility (mg/mL)	0.0824	Median value from study BL8474/B
Precipitation Rate Const. (1/h)	2.0	The precipitation rate was set at an arbitrary value 2 h^{-1} (i.e. any super saturated solution will precipitate following a first order process with a 30 minute half-life
Maximum Supersaturation Ratio	100	The value was chosen as the maximum super-saturation ratio to ensure sufficient solubility is seen at all tablet doses.
Dispersion Type	Monodispersed	Default values predicted by the software
Radius (µm)	10.000	Default values predicted by the software
Particle density (g/mL)	1.200	Default values predicted by the software
Diffusion coeff, ionised (10^{-4} cm2/min)	3.968	Default values predicted by the software
Diffusion coeff, micelle (10^{-4} cm2/min) mean	0.780	Default values predicted by the software
Diffusion coeff. (10^{-4} cm²/min)	3.968	Default values predicted by the software
Effective diffusion layer thickness (µm)	10.000	Default values predicted by the software
Bile Micelle mediated solubilization	On	Default values predicted by the software
Bile Micelle Partition: Slope	0.740	Default values predicted by the software
Bile Micelle Partition: Offset	2.290	Default values predicted by the software
Bile Micelle Partition: Ionised Species Correction	2.000	Default values predicted by the software
Effective permeability in man: $P_{eff, man}$ (10^{-4} cm/s)	36.23	via parameter estimation [a]
Distribution	Full PBPK model	Mean apparent steady state volume of distribution (Vss/F) was 73.4 L from mass balance study. The human in vivo oral volume of distribution from studies D0810C00010 and DC0810C0002 suggest that the V/F is between 0.3 and 1 L/kg (assuming a body weight of about 70 kg). Sponsor chose full PBPK mode and the method of predicting tissue:plasma partitioning ratio (Kp) for each organ using methods by Rodgers et al [REF] to allow for future evaluation of potential involvement of drug transporters
Steady state Volume of Distribution: Vss (L/kg)	0.39	By Rodgers et al [ref 13,14]

Kp values	Adipose 0.429 Bone 0.597 Brain 0.615 Gut 0.588 Heart 0.372 Kidney 0.416 Liver 0.474 Lung 0.318 Muscle 0.352 Skin 0.411 Spleen 0.476 Pancreas 0.472	By Rodgers et al [ref 13,14]
Elimination	Enzyme Kinetics module	An apparent plasma clearance (CL/F) of 5.42 L/h was chosen as initial estimate in order to obtain CL/F for a subsequent retrograde calculation of the contribution of liver elimination pathways. The value was which was based on studies D0810C00002 (2.98 to 6.97 L/h following single doses, 3.13 to 9.44 L/h following multiple dosing) and D0810C0010 (4 to 14 L/h). Studies D0810C0010 (Mass Balance study) using capsule formulation show that 15% and 6% of the dosed radioactivity were unchanged olaparib in the urine and feces, and the fraction absorbed (Fa) was estimated to be 0.941. Renal clearance (CL_R) ranged from 0.206 to 1.77 L/h. Study D2281 KMX032 suggested that direct conjugation is not significant in humans. In vitro olaparib is primarily metabolized by CYP3A.
Intrinsic clearance: CL_{int}, CYP3A4 (μL/min/pmol of isoform)	0.0575	A retrograde analysis assumed CL/F of 6.346 L/h [a] to back-calculate intrinsic clearance (CL_{int}) in the liver. The method requires input parameters of CLR, Fg (fraction available after gut metabolism, assumed 1 due to relatively low CL/F), B/P, fu, and fractional metabolism. The sponsor assumed that CYP3A4 and an un-identified pathway in human liver microsomes (HLM) contributed. Fraction metabolized by CYP3A ($f_{m,CYP3A}$) was assumed to be 0.973 according to enzyme inhibition experiments in human liver microsomes ($f_{m,CYP3A}$ calculated to be 0.80 according to supersome experiment).
Additional HLM CL_{int} (μL/min/mg)	0.218	After retrograde analyses, the model was used to simulate olaparib CL/F and CLR in both representative healthy volunteers and cancer patients [8]. Adjustment was made according to the difference between simulated CL/F and observed CL/F in cancer patients to obtain final CLint values (predicted CL/F of 6.18 L/h, fitted CL/F using parameter estimation [a] (119 patients' data) was 6.346 L/h)
Renal clearance CL_R (L/h)	1.096	15% of dose excreted as unchanged olaparib in the urine. Values of CL_R of D0810C0010 was plotted against patients' age and a linear extrapolation was used to calculate CLR for a 25 years old subject to be 1.096 L/h, which was used as input parameter.
Interactions	Not entered	In vitro olaparib only caused time-dependent inhibition of CYP3A in one of the two experiments. Inclusion of time-dependent inhibition parameters in the PBPK model resulted in decreased CL/F after multiple dosing of olaparib, which is inconsistent with clinical pharmacokinetic data.

[a] *Parameter estimation was used to obtain fitted values for $P_{eff,man}$ and CLpo (apparent oral clearance). PK data include (1) those following a single tablet dose of 300 mg under fasted conditions from D0816C00004 and (2) those following single tablet doses or following the first dose of multiple dosing with the tablet formulation from D0810C00024, which was also under fasted conditions [4]. The starting initial estimates for $P_{eff,man}$ and CL_{po} were 2.44×10^{-4} cm/s and 5.14 L/h. Final estimates are included.*

Appendix Table A3. PBPK model input parameter for efavirenz.

Parameter (unit)		Efavirenz Rekic 2010	Efavirenz Siccardi 2012
Mol Weight (g/mol)		315.670	315.700
log P		5.400	4.600
Compound Type		Neutral	Monoprotic Base, pKa 1: 10.20
B/P		0.740	0.740
fp		0.011	0.010
Absorption			
$f_{u,gut}$		1.000	1.000
Apical pH : Basolateral pH		6.5 : 7.4	6.5 : 7.4
Activity		Passive & Active	Passive & Active
Apparent permeability Papp (10^{-6} cm/s)		8.920	2.500
Reference Compound		Propranolol	Propranolol
Reference Papp (10^{-6} cm/s)		21.150	21.150
Predicted hypothetical flow term for the intestine absorption model - Qgut (L/h)		9.174	5.343
Distribution		Minimal PBPK Model	Full PBPK Model
Vss (L/kg)		3.330 (User entered)	2.600 (predicted)
Predicted Kp values		NA	Adipose 0.030 Bone 11.462 Brain 10.549 Gut 8.341 Heart 2.669 Kidney 4.064 Liver 6.629 Lung 1.030 Muscle 4.121 Skin 4.996 Spleen 4.138 Pancreas 6.854
Elimination			
Pathway 1			
fu mic		0.300	0.300
System		Baculovirus	Baculovirus
CYP3A4		Maximum reaction velocity Vmax 0.16 pmol/min/pmol Michaelis Menten Constant Km 23.5 μM	CLint: 0.007 μL/min/pmol
ISEF		0.980	0.980
CYP3A5		Vmax 0.6 pmol/min/pmol Km 19.1 μM	CLint: 0.03 μL/min/pmol
ISEF		0.980	0.980
CYP1A2		Vmax 0.06 pmol/min/pmol Km 8.3 μ M	CLint: 0.07 μL/min/pmol
ISEF		1.170	1.170
CYP2B6		Vmax 3.5 pmol/min/pmol Km 6.4 μM	CLint: 0.55 μL/min/pmol
ISEF		0.980	0.980
CYP2A6		Vmax 1.08 pmol/min/pmol Km 14.7 μM	CLint: 0.08 μL/min/pmol

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Parameter (unit)		Efavirenz Rekic 2010	Efavirenz Siccardi 2012
fu mic		0.300	0.300
System		User	Baculovirus
ISEF			0.980
Pathway 2			
CYP2A6			CL_{int} 0.05 µL/min/pmol
fu mic			1.000
System			Baculovirus
ISEF			0.980
UGT2B7		Vmax 1.5 pmol/min/pmol Km 6.4 µM	CL_{int} 0.05 µL/min/pmol
fu mic		0.300	0.300
CL R (L/h)		0.000	0.000
CYPs and/or UGTs Interaction			
CYP2B6 induction	Maximal induction fold change: $I_{nd,max}$	5.760	6.000
	CV (%)	13.700	30.000
	MIA (pmol/mg microsomal protein)	247.164	294.372
	Concentration causing half-maximal induction: $I_{nd\ C50}$ (µM)	0.820	
	CV (%)	71.900	
	Unbound fraction in (hepatocyte) incubation $f_{u\ inc}$	0.063	
	Hill coefficient γ	1.000	
CYP3A4 Induction	$I_{nd,max}$	6.450	1.500
	CV (%)	18.600	30.000
	MIA (pmol/mg microsomal protein)	1477.693	376.681
	$I_{nd\ C50}$ (µM)	3.930	
	CV (%)	52.500	
	$f_{u\ inc}$	0.063	
	γ	1.000	

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Appendix Table A4. Simulated olaparib exposure values with or without co-administration of CYP3A modulators

Olaparib Parameters	Mean	Median	Geometric mean	95% Confidence Interval	
Itraconazole					
AUC (ng/mL h)	20856.65	20127.05	19351.64	18120.12	20666.85
AUCinh (ng/mL h)	58283.99	54646.90	53175.24	49390.58	57249.92
AUC ratio	2.78	2.74	2.75	2.68	2.82
CMax (ng/mL)	3002.87	2973.81	2953.94	2865.65	3044.95
CMax inh (ng/mL)	3577.97	3548.57	3534.28	3443.46	3627.49
CMax ratio	1.20	1.17	1.20	1.18	1.21
Rifampin					
AUC (ng/mL h)	50859.32	45359.04	44786.77	41355.60	48502.61
AUCinh (ng/mL h)	16938.17	14275.19	14256.84	12995.95	15640.06
AUC ratio	0.33	0.31	0.32	0.30	0.33
CMax (ng/mL)	6947.30	6792.59	6727.50	6464.07	7001.67
CMax inh (ng/mL)	4316.05	4117.58	3979.19	3730.38	4244.58
CMax ratio	0.61	0.59	0.59	0.57	0.61
Fluconazole					
AUC (ng/mL h)	20391.14	20049.28	18855.68	17383.39	20452.66
AUCinh (ng/mL h)	44071.16	43818.99	41972.88	39408.80	44703.78
AUC ratio	2.26	2.17	2.23	2.15	2.30
CMax (ng/mL)	2918.19	2916.42	2856.03	2739.16	2977.87
CMax inh (ng/mL)	3315.60	3334.09	3260.16	3142.32	3382.41
CMax ratio	1.14	1.12	1.14	1.13	1.16
Efavirenz					
AUC (ng/mL h)	56707.73	53585.51	51968.02	47769.32	56535.77
AUCinh (ng/mL h)	22703.07	19802.37	20587.67	18857.86	22476.16
AUC ratio	0.41	0.40	0.40	0.38	0.42
CMax (ng/mL)	7442.72	7467.58	7292.88	7006.97	7590.47
CMax inh (ng/mL)	5161.85	5016.09	4984.24	4725.97	5256.63
CMax ratio	0.69	0.70	0.68	0.66	0.71

Appendix Table A5. Summary of PK parameters of olaparib with/without coadministration of itraconazole (Table 13, reference [11]. AUC, AUC0-inf, AUCt, AUC from zero to last measureable time point)

Parameter	Summary Statistic	Olaparib (N = 57)	Olaparib + Itraconazole (N = 57)
C_{max}, µg/mL	n	56	53
	Geometric mean[a]	2.992	4.236
	GCV (%)[a]	48.2	37.7
	Arithmetic mean	3.329	4.516
	SD	1.700	1.636
	CV (%)	51.1	36.2
	Median	2.965	4.350
	Min	0.980	1.96
	Max	9.04	9.72
t_{max}, hours	n	56	55
	Median	1.03	1.50
	Min	0.48	0.50
	Max	8.25	12.00
AUC, µg.h/mL	n	53	49
	Geometric mean[a]	14.78	40.09
	GCV (%)[a]	75.4	72.1
	Arithmetic mean	19.05	49.4
	SD	16.69	37.08
	CV (%)	87.7	75.1
	Median	13.50	42.59
	Min	4.89	9.73
	Max	86.3	232
$AUC_{(0-t)}$, µg.h/mL	n	52	52
	Geometric mean[a]	15.21	39.52
	GCV (%)[a]	76.0	68.8
	Arithmetic mean	19.52	47.80
	SD	16.54	33.58
	CV (%)	84.8	70.2
	Median	13.92	41.70
	Min	4.87	9.72
	Max	84.6	214
CL/F, L/hour	n	53	49
	Arithmetic mean	8.162	3.054
	SD	4.610	2.104
	CV (%)	56.5	68.9
	Median	7.405	2.348
	Min	1.16	0.431
	Max	20.5	10.3
V_z/F, L	n	53	49
	Arithmetic mean	191.8	75.14
	SD	172.4	81.27
	CV (%)	89.9	108.2
	Median	127.3	47.92
	Min	18.3	12.5
	Max	809	394
$t_{1/2}$, hours	n	53	49
	Arithmetic mean	15.01	15.55
	SD	8.234	6.435
	CV (%)	54.9	41.4
	Median	12.84	13.66
	Min	5.75	7.61
	Max	57.9	42.7

[a] Geometric mean and GCV(%) are calculated using log transformed data.
Derived from: Table 11.2.4.1.1.

Appendix Table A6. Summary of PK parameters of olaparib with/without coadministration of itraconazole (Table 13, reference [11]. AUC, AUC0-inf, AUCt, AUC from zero to last measureable time point)

Parameter	Summary Statistic	Olaparib N=22	Olaparib + rifampicin N=22
C_{max}, µg/mL	n	22	18
	Geometric mean[a]	8.052	2.239
	GCV (%)[a]	24.3	53.4
	Arithmetic mean	8.266	2.509
	SD	1.890	1.227
	CV (%)	22.9	48.9
	Median	8.440	2.315
	Min	4.91	0.753
	Max	12.3	5.50
t_{max}, hours	n	22	18
	Median	1.49	0.78
	Min	0.57	0.27
	Max	3.05	5.95
AUC, µg.h/mL	n	21	17
	Geometric mean[a]	55.20	6.791
	GCV (%)[a]	67.4	46.4
	Arithmetic mean	67.57	7.446
	SD	52.74	3.397
	CV (%)	78.0	45.6
	Median	51.90	7.121
	Min	20.5	3.20
	Max	215	16.7
$AUC_{(0-t)}$, µg.h/mL	n	22	18
	Geometric mean[a]	54.64	6.192
	GCV (%)[a]	63.8	60.2
	Arithmetic mean	65.63	7.057
	SD	48.36	3.564
	CV (%)	73.7	50.5
	Median	51.71	6.802
	Min	20.5	1.51
	Max	202	16.7
CL/F, L/hour	n	21	17
	Arithmetic mean	6.357	48.33
	SD	3.470	21.04
	CV (%)	54.6	43.5
	Median	5.780	42.13
	Min	1.40	17.9
	Max	14.6	93.7
V_z/F, L	n	21	17
	Arithmetic mean	112.1	1076
	SD	59.84	868.8
	CV (%)	53.4	80.7
	Median	111.3	803.2
	Min	35.9	330
	Max	227	3290
$t_{1/2}$, hours	n	21	17
	Arithmetic mean	13.02	15.80
	SD	4.161	9.552
	CV (%)	32.0	60.4
	Median	12.46	12.80
	Min	4.55	3.32
	Max	21.8	40.1

a   Geometric mean and GCV(%) are calculated using log transformed data.
Patient E0582003 did not take full rifampicin dose. In addition, on Day 17 the 2 hour post dose sample was taken late. As a result the rifampicin concentrations for this patient on Day 17 are excluded from all summaries. Patient E5082007 stopped taking rifampicin on Day 16.
AUC area under the plasma concentration-time curve from zero to infinity; AUC_{0-t} area under the plasma concentration-time curve from zero to the last measurable time point; CL/F apparent plasma clearance following oral administration; C_{max} maximum plasma concentration; %CV coefficient of variation; %GCV geometric coefficient of variation; SD standard deviation; $t_{1/2}$ terminal half-life; t_{max} time to reach maximum plasma concentration; V_z/F apparent volume of distribution.
Source: Table 11.2.4.1.

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Appendix Table A7. FDA simulation of the effect of efavirenz on olaparib exposure – the use of different efavirenz models

	Mean	Median	Geometric mean	95% Confidence Interval	
FDA simulation 1 [a]					
AUC (ng/mL h)	60978.34	53529.51	53810.59	48665.08	59500.14
AUCinh (ng/mL h)	23433.22	20605.34	20204.13	18135.30	22508.95
AUC ratio	0.39	0.38	0.38	0.36	0.40
CMax (ng/mL)	7728.51	7578.86	7503.75	7148.83	7876.30
CMax inh (ng/mL)	5377.52	5243.45	5081.83	4746.95	5440.33
CMax ratio	0.69	0.68	0.68	0.65	0.70
FDA simulation 1 [b]					
AUC (ng/mL h)	60978.34	53529.51	53810.59	48665.08	59500.14
AUCinh (ng/mL h)	28088.49	24232.87	24154.83	21641.59	26959.93
AUC ratio	0.47	0.44	0.45	0.42	0.48
CMax (ng/mL)	7728.51	7578.86	7503.75	7148.83	7876.30
CMax inh (ng/mL)	5853.73	5738.47	5547.92	5193.89	5926.08
CMax ratio	0.75	0.76	0.74	0.72	0.76
FDA simulation 3 [c]					
AUC (ng/mL h)	60978.34	53529.51	53810.59	48665.08	59500.14
AUCinh (ng/mL h)	30680.80	28092.86	26755.63	24095.16	29709.86
AUC ratio	0.51	0.51	0.50	0.47	0.52
CMax (ng/mL)	7728.51	7578.86	7503.75	7148.83	7876.30
CMax inh (ng/mL)	6088.46	6053.04	5819.72	5477.44	6183.38
CMax ratio	0.78	0.80	0.78	0.76	0.80

[a] *Simulation using SimCYP Version 13.2. Sponsor's olaparib (Appendix Tables A1 and A2) and efavirenz (Redic model [13], Appendix Table A3) models were used. Study design was based on Table 1.*

[b] *Simulation using SimCYP Version 13.2. Sponsor's olaparib (Appendix Tables A1 and A2) and efavirenz (Siccardi model [14], Appendix Table A3) models were used. Study design was based on Table 1. Modification of efavirenz model was made by the FDA reviewer according to reference [17]. Differences between modified and sponsor's efavirenz models (Siccardi) are:*

enzyme inhibition. Reversible Ki values 115, 15.1, 16, 181, 20.6 μM for CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, respectively

Enzyme induction. $I_{nd\ max}$ 5.7 and 6.5, $I_{nd\ C50}$ 0.800 and 3.93 μM; CV of 71.9% and 52.5% for CYP2B6 and CYP3A4, respectively, a hepatocyte unbound fraction of 0.063 and hill coefficient γ of 1.000 for both CYPs.

[c] *Simulation using SimCYP Version 13.2. Sponsor's olaparib (Appendix Tables A1 and A2) and an efavirenz model developed by another sponsor (FDA in-house database) were used. Study design was based on Table 1. Efavirenz model was also developed according to Redic [13], and key differences include:*

*Compound type: monoprotic base with pKa of 2.09*

*$P_{eff,\ man}$ of 5.844 as an entered value for the prediction of absorption kinetics*

$f_{u,gut}$ was set to small value of 0.0001 to eliminate induction effect in the gut [18]

Full PBPK distribution model using prediction method by reference [19]

Appendix Figure 1. Plots of PBPK simulations of single tablet doses of olaparib to fasted oncology patients overlaid with the data that was used to build the model. Left panels: Normal scale of the y-axis; right panels: log-scale of the y-axis (supporting data submitted with reference [4])

Appendix Figure 1 (Continued)

Appendix Figure 1 (Continued)
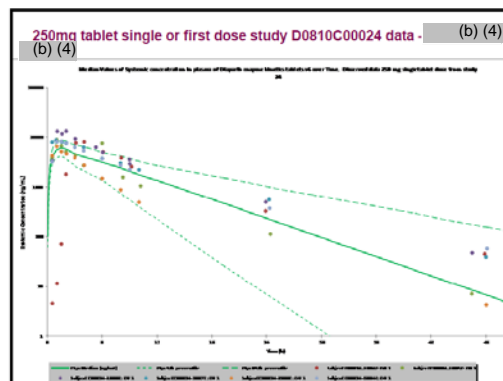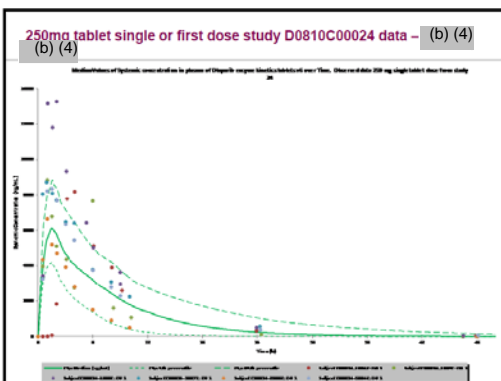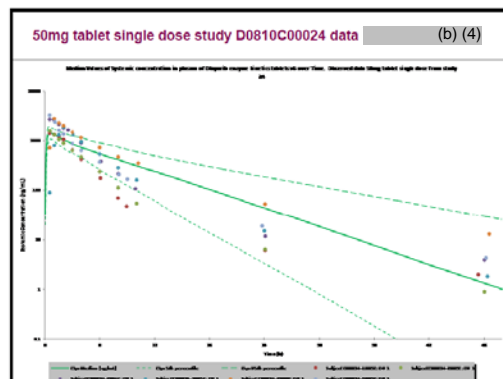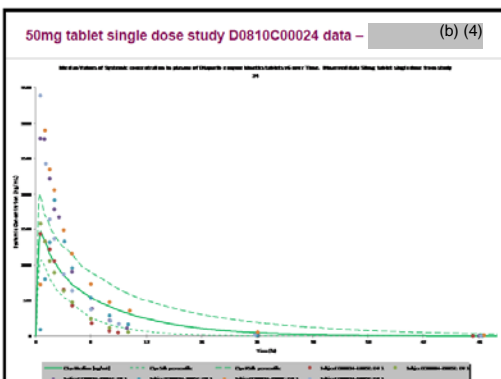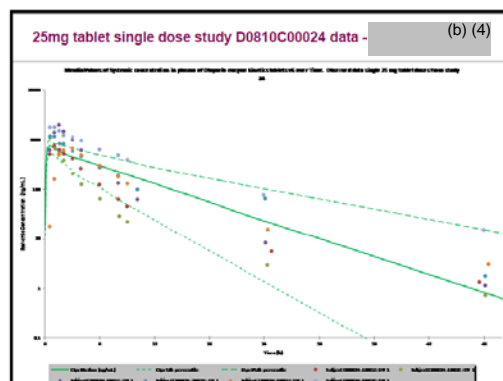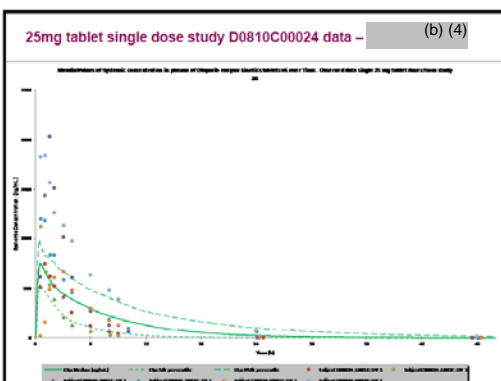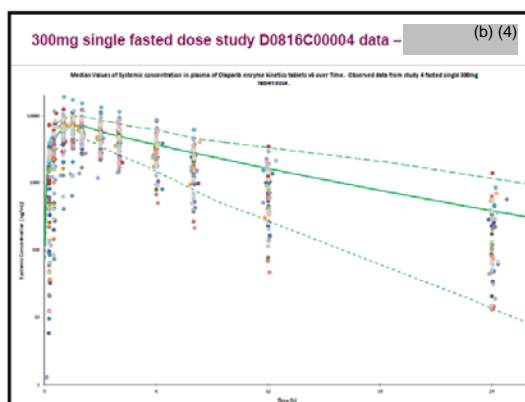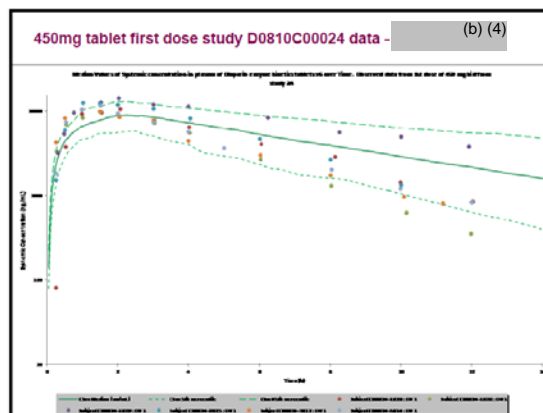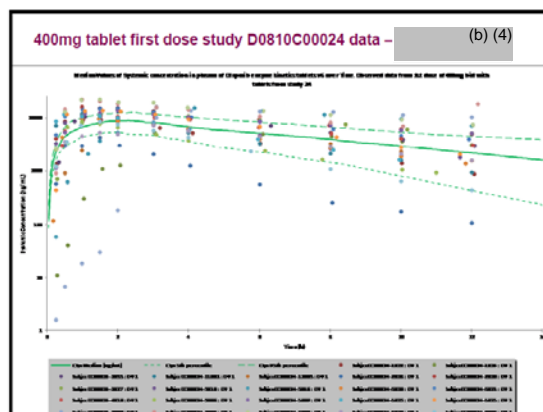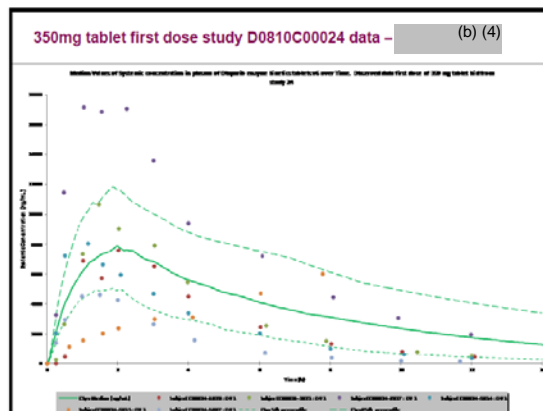
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BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 206162 (**Priority Review**)	**Reviewer:** Okpo Eradiri, PhD	
Division:	DOP1		
Applicant:	AstraZeneca	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Trade Name:	-	**Acting Biopharmaceutics Supervisor:** Paul Seo, PhD	
Generic Name:	Olaparib Capsules, 50 mg	**Date Assigned:**	2/3/2014
Indication	As monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed Ovarian Cancer (including fallopian tube or primary peritoneal) with germline BRCA (gBRCA) mutation as detected by an FDA-approved test who are in response (complete response or partial response) to platinum-based chemotherapy	**Date of Review:**	11/21/2014
Formulation/ Strength	Capsule/ 50 mg; immediate-release	Associated IND: 75-918	
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission Dates		**Date of Informal/Formal Consult**	**Primary Review due in DARRTS**
2/3/2014, 4/21/2014, 5/21/2014, 5/27/2014, 11/21/2014			11/21/2014
Type of Submission:	505 (b)(1) Application (NME)		
Key review points:	- Adequacy of dissolution method - Adequacy of proposed dissolution acceptance criteria		

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I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

The drug substance, olaparib, ⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛ (b) (4) ⬛. The ⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛ (b) (4) of the drug substance that may be relevant in the context of the manufacturing process are ⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛ (b) (4) ⬛⬛⬛⬛. According to the Applicant, all batches of olaparib used to manufacture the capsules for clinical trial were confirmed to be ⬛⬛⬛⬛ (b) (4); the Applicant has not observed ⬛⬛⬛⬛⬛⬛⬛ (b) (4) in long-term, accelerated or stressed storage conditions. Olaparib exhibits very low solubility (0.11-0.13 mg/mL) in aqueous media across the physiologic pH range; as a result, the drug's solubility is pH-independent. The drug also exhibits poor permeability and is therefore classified as a BCS Class 4 drug. The Applicant obtained a slight improvement in solubility of olaparib in 1% Polysorbate 80 (0.17 mg/mL) which is used as the dissolution medium.

The clinical basis for this NDA emanate from results of a Phase II pivotal study (D0810C00019) and three supporting studies (D0810C00012, D0810C00041, and D0810C00042). Later in the review cycle, Study D0810C00042 was designated the pivotal clinical study. Phase III studies are ongoing, and not included in the NDA.

The Biopharmaceutics review will be focused on the evaluation and acceptability of the dissolution method and the proposed dissolution acceptance criteria.

Some of the electronic links associated with biopharmaceutics are as follows:

Specifications Table: \\cdsesub1\evsprod\nda206162\0000\m3\32-body-data\32p-drug-prod\active-capsule-hard-01\32p5-contr-drug-prod\32p51-spec\specifications.pdf

Dissolution Method Development: \\cdsesub1\evsprod\nda206162\0000\m3\32-body-data\32p-drug-prod\active-capsule-hard-01\32p2-pharm-dev\pharmaceutical-development-product.pdf

Dissolution Method Procedure: \\cdsesub1\evsprod\nda206162\0000\m3\32-body-data\32p-drug-prod\active-capsule-hard-01\32p5-contr-drug-prod\32p52-analyt-proc\analyt-dissolution.pdf

Dissolution Method Validation: \\cdsesub1\evsprod\nda206162\0000\m3\32-body-data\32p-drug-prod\active-capsule-hard-01\32p5-contr-drug-prod\32p53-val-analyt-proc\val-dissolution.pdf

Reviewer's Comments:

i. The proposed dissolution method for Olaparib Capsules, 50 mg, is acceptable.
ii. The Applicant's proposal for a 2-point dissolution specification for this immediate release drug product is acceptable. The discriminating ability of the proposed method is evident at the 30-min specification time point.
iii. The dissolution performance of the batches of Olaparib capsules used in pivotal clinical study D0810C00042 was demonstrated to be similar to those used in Study D0810C00019.

iv. In a teleconference with the Applicant on May 21, 2014, it was agreed that the limit of ▢(b) (4) in the dosage form will be set at ≤ ▢(b)(4)%. In this scenario, the conduct of an in-vivo study to investigate the effect of ▢(b) (4) on bioavailability of olaparib in the patient population will not be required.

v. The Applicant has revised the ▢(b) (4) limit in the Specification Table to "NMT ▢(b)(4)%". From a Biopharmaceutics perspective, this limit is acceptable at release and through the life cycle of the drug product. Refer to the CMC's Drug Product review for details.

vi. The biopharmaceutics-related data and discussions on ▢(b) (4) levels in the finished drug product are acceptable to the Biopharmaceutics Review team, provided the CMC team finalizes the product shelf life issues based on ▢(b) (4) levels.

Risk Assessment:

Please refer to the CMC Review.

II) RECOMMENDATION

The ONDQA/Biopharmaceutics team has reviewed NDA 206162 and its amendments submitted on 2/3/2014, 4/21/2014, 5/21/2014, 5/27/2014, 6/6/2014 & 11/21/2014, and find the biopharmaceutics data/information acceptable.

The following dissolution method and acceptance criteria should be implemented for release and stability testing of Olaparib Capsules:

Apparatus/RPM	Medium	Volume	Acceptance Criteria
USP Apparatus 2/ 100 rpm	1% Polysorbate 80 in Water	1000 mL	30 min: NLT (b)(4)% 45 min: Q = (b)(4)%

From the Biopharmaceutics perspective, NDA 206162 for Olaparib Capsules, 50 mg, is recommended for **APPROVAL**.

Okpo Eradiri, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

III) QUESTION-BASED REVIEW: BIOPHARMACEUTICS EVALUATION

A) GENERAL ATTRIBUTES

1   **What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?**

Drug Substance

Olaparib is an NME; its chemical structure is displayed in Figure 1.
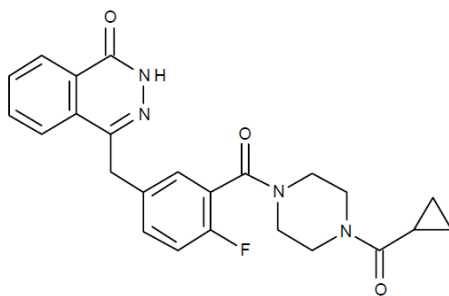
Figure 1: Structural formula of Olaparib (C$_{24}$H$_{23}$FN$_4$O$_3$; M.Wt = 434.46)

Olaparib, an achiral molecule, is a crystalline (b) (4) and is practically insoluble in aqueous media between pH 1 and pH 6.8 (0.1 mg/mL); the drug's solubility is therefore pH-independent. The drug also exhibits poor permeability and is therefore classified as a BCS Class 4 drug. Olaparib is soluble in acetonitrile, ethanol, methanol, and in ethanol/water mixtures (Table 1).

Table 1: Solubility of Olaparib in aqueous and non-aqueous solvents.

Solvent	Temperature (°C)	Solubility (mg/mL)
pH 4.5 Acetate Buffer	37	0.1
pH 6.8 Phosphate Buffer	37	0.1
0.1 M HCl	37	0.1
Water	37	0.1
Acetonitrile	20	3.1
Ethanol	20	5.5
Methanol	20	10.6
Ethanol:water 75:25	20	19.7

The drug substance exists   (b) (4). The (b) (4) of the drug substance that may be relevant in the context of

the manufacturing process are [   ] (b) (4) .
According to the Applicant, all batches of olaparib used to manufacture the capsules for clinical trial were confirmed to be [   ] (b) (4) .

Drug Product

The proposed drug product is a 50 mg, size 0, white opaque hard capsule. The formulation is simply [   ] (b) (4) the API [   ] (b) (4) [   ] (b) (4) lipidic excipient, Lauroyl Macrogol-32-Glycerides, LMG [   ] (b) (4) contained within a hypromellose capsule shell. The composition of the drug product is presented in Table 2.

Table 2: Quantitative composition of Olaparib Capsules, 50 mg.

Components	Quantity (mg per unit)	Function	Standard
Olaparib	50	Active ingredient	AstraZeneca
Lauroyl polyoxyl-32 glycerides[a]			NF
Hypromellose capsule shell[b]			AstraZeneca
Hypromellose			USP
Titanium dioxide			USP
Gellan gum			NF
Potassium acetate			USP
Printing ink for capsule shell			
Shellac			NF
Ferrosoferric oxide			NF
[ ] (b) (4)			USP
Isopropyl alcohol			USP
N-butyl alcohol			NF
Propylene glycol			USP
[ ] (b) (4)			NF
Total	595		

[a] Also known as Lauroyl macrogol-32 glycerides Ph Eur, and referred to throughout the dossier as Lauroyl macrogol-32 glycerides (LMG).
[b] [   ] (b) (4)
[c]
[d]

Interestingly, the [   ] (b) (4) in which the active drug [   ] (b) (4) make up as much as [ ] (b)(4) % of the total capsule weight, indicative of very low drug loading; excluding the weight of the capsule shell, the active drug makes up [   ] (b) (4) % of the [   ] (b) (4) [   ] blend or mixture.

2 Is there any information on BCS classification? What claim did the applicant make based on BCS classification? What data are available to support this claim?

The Applicant classifies olaparib as a BCS 4 compound due to its low solubility in aqueous media and low permeability characteristics compared to propranolol. The solubility and permeability data are summarized in Tables 3 and 4, respectively.

Table 3: Solubility of Olaparib in aqueous media over the physiologic pH range at 37 ˚C.

Media	Solubility (mg/mL)
0.1 M HCl	0.12
pH 4.5 Acetate Buffer	0.13
pH 6.8 Phosphate Buffer	0.11
0.1 M NaOH	1.09
FaSSIF v2	0.12
HIF	0.16

Table 4: Permeability of Olaparib across caco-2 cells; n = 3.

Compound	Apical to Basolateral P_{app} (cm.sec-1 x 10^{-6})	Basolateral to Apical P_{app} (cm.sec-1 x 10^{-6})	Efflux Ratio
10 µM olaparib	3.67 ±0.34	23.70 ±2.84	6.5
260 µM olaparib	7.75 ±0.88	17.75 ±1.19	2.3
700 µM olaparib	8.4 ±0.41	15.06 ±1.42	1.8
Propranolol	19.97 ±2.57	21.48 ±0.33	1.1
Digoxin (efflux marker)	1.34 ±0.03	12.22 ±1.37	9.1

The proposed total daily dose of olaparib, 400 mg, is not soluble in 250 mL of any medium in Table 3; the permeability data also indicate that Pgp-mediated efflux is expected to be sarurated at doses of 40 mg and above.

B.1. DISSOLUTION INFORMATION

3   What is the proposed dissolution method?

The Applicant's proposed dissolution method testing conditions can be summarized as follows:

Apparatus:	USP 2 (Paddle) with sinkers
Medium:	1000 mL 1% v/v Polysorbate 80
Temperature:	37 ± 0.5 ˚C
Rotation speed:	100 ± 2 rpm
Proposed Spec Sampling Time:	45 min
Analysis (HPLC):	(b) (4)

4   What data are provided to support the adequacy of the proposed dissolution method (e.g medium, apparatus selection, etc.)?

(b) (4)

The results of the additional experiments are displayed in Table 5.

(b) (4)

5   What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?

Dissolution Method Validation

The analytical method for the quantitation of olaparib in dissolution samples was validated for accuracy, linearity, specificity, precision, sample stability, and robustness parameters. All validation acceptance criteria were met and the method validation results are acceptable. A summary of the validation experiments can be found at \\cdsesub1\evsprod\nda206162\0000\m3\32-body-data\32p-drug-prod\active-capsule-hard-01\32p5-contr-drug-prod\32p53-val-analyt-proc\val-dissolution.pdf.

6   What data are available to support the discriminating power of the method? Is the proposed dissolution method biorelavant? What data are available to support this claim?

The Applicant investigated the sensitivity of the proposed dissolution method to intentional changes of the following:

- Drug loading

- Olaparib particle size
- (b) (4)

Having established in the dog that the bioavailability of olaparib from the LMG-based capsule formulation is inversely related to drug loading (section 3.2.P.2.2, page 5), the Applicant investigated the sensitivity of the proposed dissolution method to intentional changes in drug loading ((b) (4) %). A rank-order reduction in dissolution rate with increase in drug loading was observed (Figure 2).
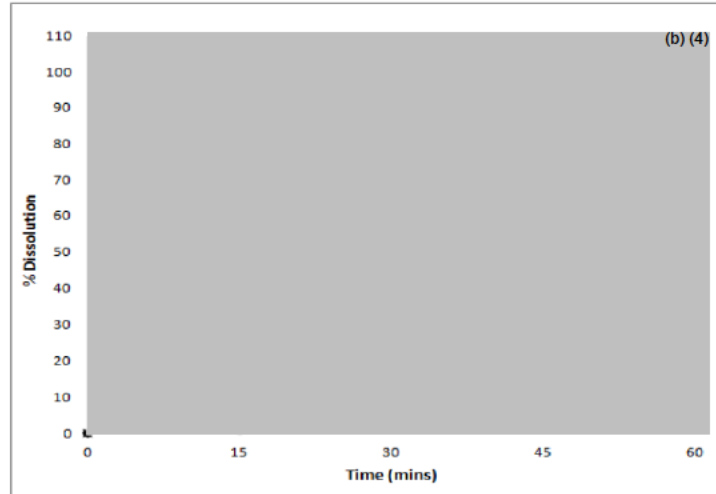

**Figure 2: Effect of drug loading on dissolution rate of Olaparib Capsules, 50 mg
[USP 2, 1000 mL of 1% Polysorbate 80, 100 rpm; n = 6]**

Similar results were obtained using the (b) (4) as the dissolution medium; the Applicant therefore concluded that the Polysorbate 80 dissolution method is biorelevant.
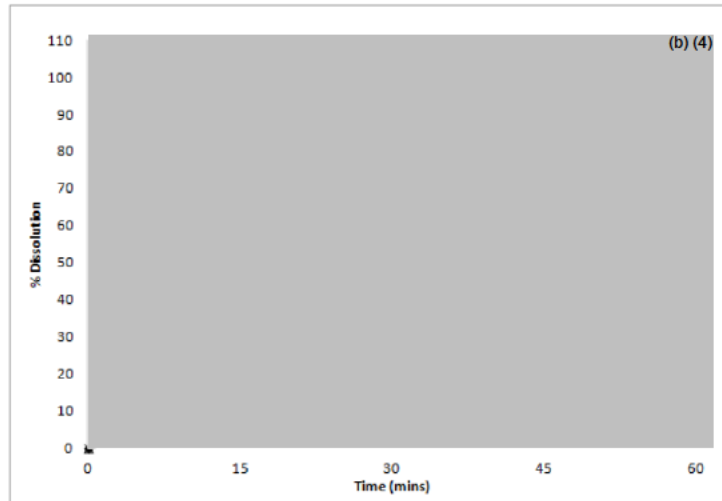
Figure 3: Effect of particle size on dissolution rate of Olaparib Capsules, 50 mg [USP 2, 1000 mL of 1% Polysorbate 80, 100 rpm; n = 6]

Reviewer's Comments

The Applicant has adequately demonstrated the suitability of the dissolution method for batch release and stability testing. The dissolution method's discriminating power to detect changes in drug loading has been demonstrated. The proposed method is (b)(4) *in the drug product; this is no longer a concern since a new* (b)(4) *method has been developed with a proposed acceptance limit of "NMT* (b)(4)*%". The acceptability of the* (b)(4) *will be determined in part by the CMC Reviewer. The relationship between* (b)(4) *and bioavailability of olaparib has been assessed in section 14 of this review..*

7   Is the proposed dissolution method acceptable? If not, what are the deficiencies?

Yes, the dissolution method is acceptable.

B.2. ACCEPTANCE CRITERIA

8   What are the proposed dissolution acceptance criteria for this product?

The Applicant initially proposed Q = (b)(4)% at 45 min as the dissolution acceptance criterion. On receipt of the following dissolution IR comment in the 74-day letter (dated April 3, 2014), the Applicant responded with a proposal for a 2-point specification:

> *The dissolution stability data have been reported at only the proposed specification time point of 45 minutes. Please submit, in Excel format, the complete multi-point dissolution profiles obtained in the stability program for every batch, under all storage conditions and packaging configurations, by April 21, 2014.*

On April 21, 2014, the Applicant provided the requested dissolution data as well as the following proposed 2-point dissolution acceptance criteria:

Proposed Dissolution Acceptance Criterion
30 min: NLT (b)(4)%   45 min: Q = (b)(4)%

The initial (release) dissolution data submitted by the Applicant on 4/21/2014 are plotted in Figure 6.

The Applicant's rationale for two sampling time points is contained in a report entitled "Dissolution performance of clinical batches linked to population PK modelling and proposed 2-point dissolution specification" (\\cdsesub1\evsprod\nda206162\0014\m1\us\responses-quality-position-paper.pdf).

The dissolution profiles of Olaparib Capsules manufactured at the development and commercial sites are displayed in Figure 5. Only drug product batches manufactured at the commercial site were used in the definitive clinical trial (D0810C00042).
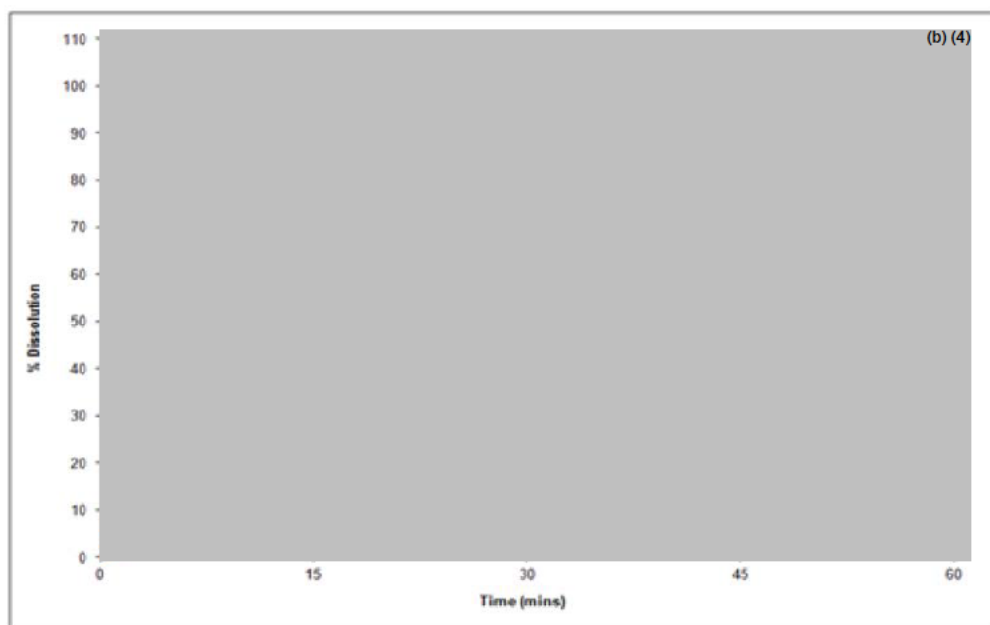
Figure 5: Dissolution profiles of Olaparib Capsules, 50 mg, batches manufactured at development and commercial sites; [USP 2, 1000 mL of 1% Polysorbate 80, 100 rpm]

According to the Applicant, the additional specification time point further ensures consistency of future commercial batches with those used in the pivotal clinical study, D0810C00019.

Reviewer's Comments

This Reviewer agrees with the need for a 2-point dissolution specification for Olaparib Capsules. The dissolution method demonstrates discriminating ability at the additional 30-min specification time point.

9   What data are available to support these criteria?

The Applicant makes reference to data from multipoint dissolution profiles of 7 clinical batches at release and another 23 batches at release and/or under long-term stability storage conditions in support of the proposed dissolution acceptance criterion. Dissolution data for representative clinical and registration stability batches were assessed for adequacy of the proposed acceptance limits. The dissolution data (at release) submitted by the Applicant on 4/21/2014 are plotted in Figure 6.
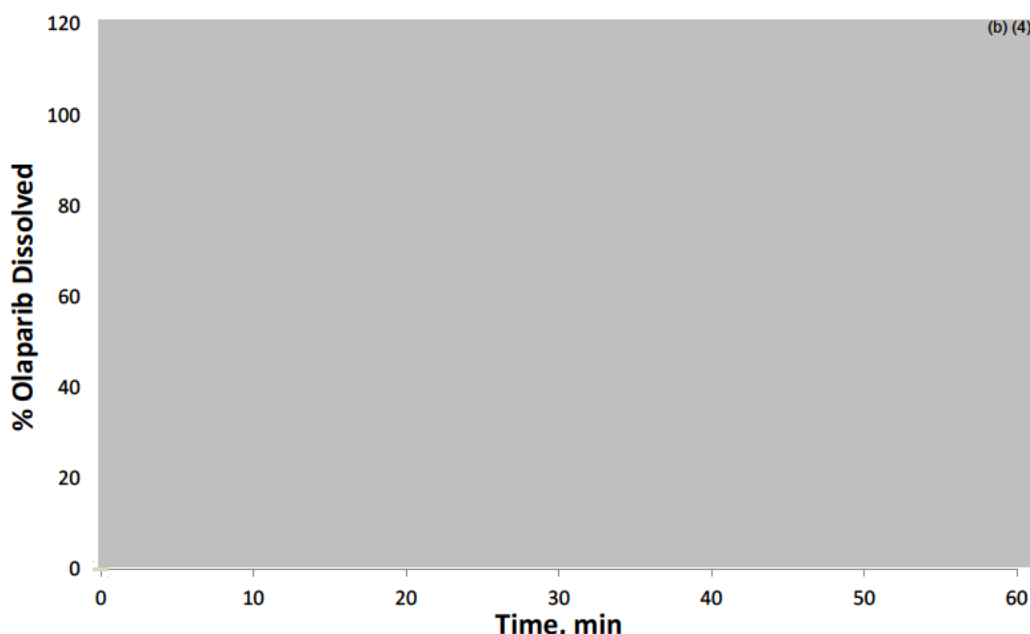
Figure 6: Individual vessel release dissolution profiles of clinical and registration batches of Olaparib Capsules, 50 mg (Batches 3071641R, 3075510R, 3072918R & 3062396R) in Study D0810C00019.

Based on the dissolution profiles in Figure 6, and results of the discriminating experiments, the Applicant's proposed dissolution acceptance criteria, based on mean percent olaparib dissolved values, are acceptable:

30 min: NLT (b)(4) %
45 min: Q = (b)(4) %

10   Are the acceptance criteria satisfactory? If not, what are the recommended criteria? Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches?

Seventeen (17) clinical batches were used in the pivotal Phase II study (# D0810C00019): \\cdsesub1\evsprod\nda206162\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psr-ovarian-cancer\5351-stud-rep-contr\d0810c00019\d0810c00019-study-synopsis.pdf. In order to assess the proposed dissolution acceptance criteria, the following IR comment was sent to the Applicant on May 12, 2014:

> **Dissolution:** *Submit the individual vessel dissolution data with descriptive statistics for each of the 17 batches, at release, used in study D0810C00019 (60227E08, 3075510R, 3070200R, 3071641R, 3072918R, 3065254R,3065255R, 3070199R, 3080106R, 3080721R, 3084949R, 3086689R, 3086691R,3090870R, 3091601R, 3094511R, 3094512R). Provide in tabular form, their respective dates of manufacture and duration*

of use in the Phase II study; include the dissolution test method used in release testing of each batch unless the same proposed regulatory method was used to test all 17 clinical batches. Similar to the stability data submitted earlier, please provide the dissolution data in excel format.

The Applicant responded to the IR on 5/21/204 and 5/27/2014 (\\cdsesub1\evsprod\nda206162\0029\m1\us\responses-quality.pdf). The dissolution data on the 17 clinical batches are summarized in Table 6 and presented graphically in Figure 7.

Table 6: Summary of dissolution data on clinical batches of Olaparib Capsules used in Study D0810C00019.

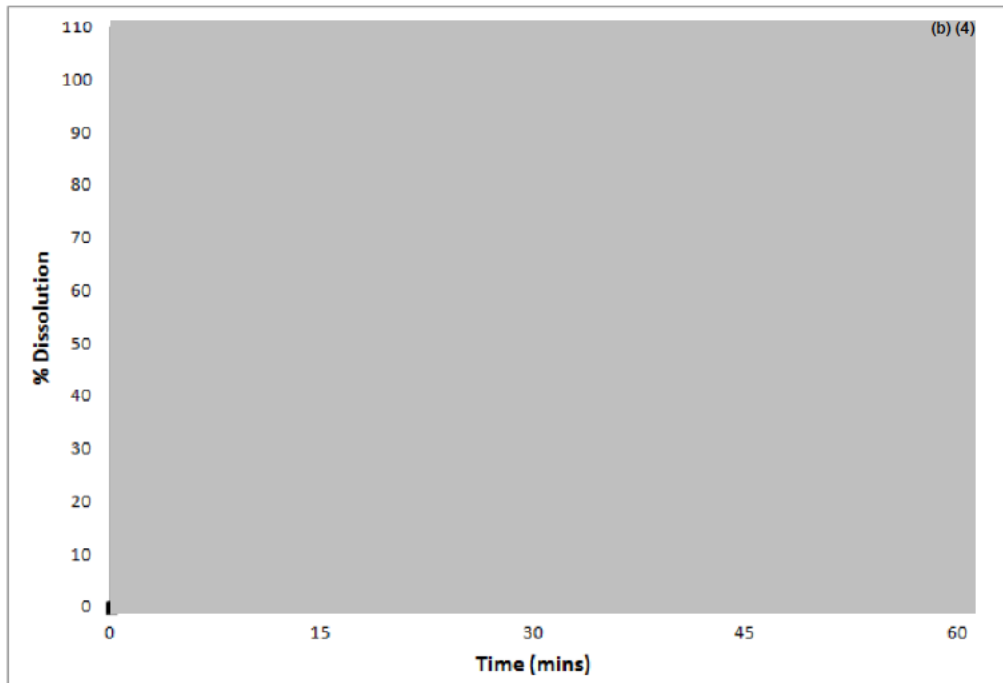| Result	15 minutes	30 minutes	45 minutes	60 minutes
Number of batches	17	17	17	17
Overall mean				(b) (4)
Range of means				
Range of individuals				
SD				

Figure 7: Dissolution profiles of Olaparib Capsule batches used in clinical study D0810C00019

On July 24, 2014, the Applicant filed a major amendment to the NDA that changed the pivotal clinical trial to Study # D0810C00042. This study used a different set of batches

as shown in Table 7. The following IR comments were therefore sent to the Applicant on November 18, 2014:

Provide the following:

- The individual vessel dissolution profile data
- Composite plots of release dissolution profiles of all batches used in clinical study D0810C00042;
- Compare the mean dissolution profiles of these batches to those used in Study D0810C00019 to demonstrate similarity. Present the data graphically and in tabular format;
- The Scatter plots of individual vessel data at 30 min and 45 min for all batches used in Study D0810C00042

Table 7: Batches of Olaparib Capsules used in pivotal Phase II study (#D0810C00042).

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
Olaparib	50 mg ×8 capsules orally twice daily	Patheon on behalf of AstraZeneca	(b) (4)	8525.1/1, 8525.2/1, 8525.3/1, 8525.4/1, 8525.5/1, 8525.6/1, 8525.7/1, 8525.8/1, 8525.9/1, 8525.10/1, 8525.11/1, 8525.12/1, 8525.17/1.

The Applicant responded to the IR by email on 11/21/2014 with a commitment to submit the amendment in DARRTS on 11/25/2014.

Comparison of the mean dissolution data for the two sets of batches used in Studies D0810C00019 and D0810C00042 is presented in Table 8.

Table 8: Comparison of the mean dissolution data for batches of Olaparib Capsules used in Studies D0810C00019 and D0810C00042.

Study number		Time point (minutes)			
		15	30	45	60
D0810C00042	Mean (% dissolved)				(b) (4)
	Standard Deviation				
D0810C00019	Mean (% dissolved)				
	Standard Deviation				

The mean dissolution data for all batches used in the pivotal trial (D0810C00042) are displayed graphically in Figure 8.
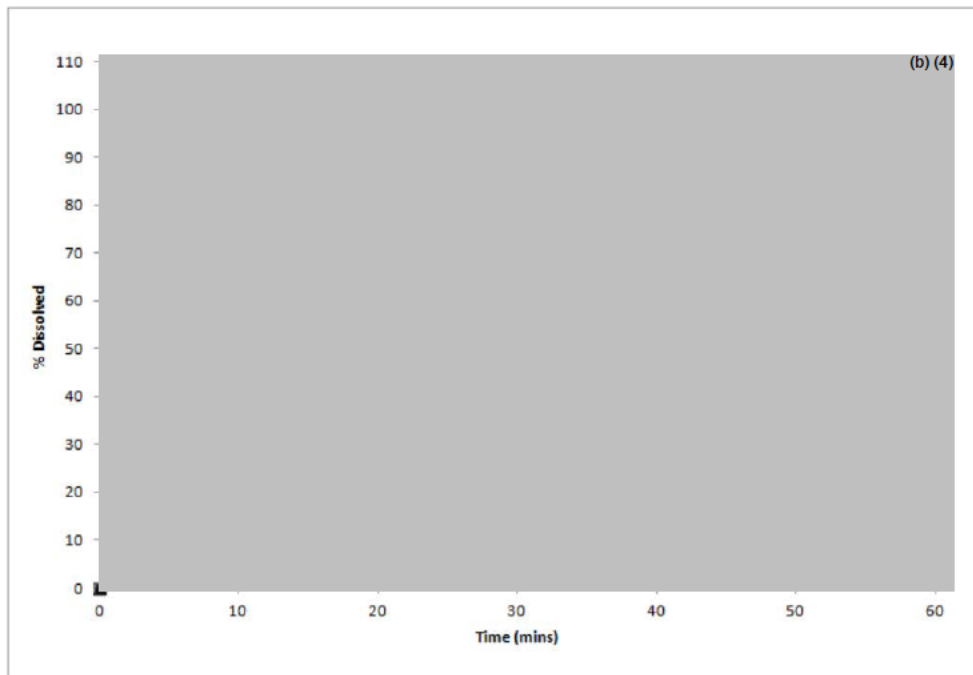
**Figure 8: Dissolution profiles of Olaparib Capsule batches
used in clinical study D0810C00042**

Scatter plots of individual vessel data for the clinical batches (Studies D0810C00042 &
D0810C00042) at the 30 min and 45 min time points are presented in Figures 9 and 10,
respectively.
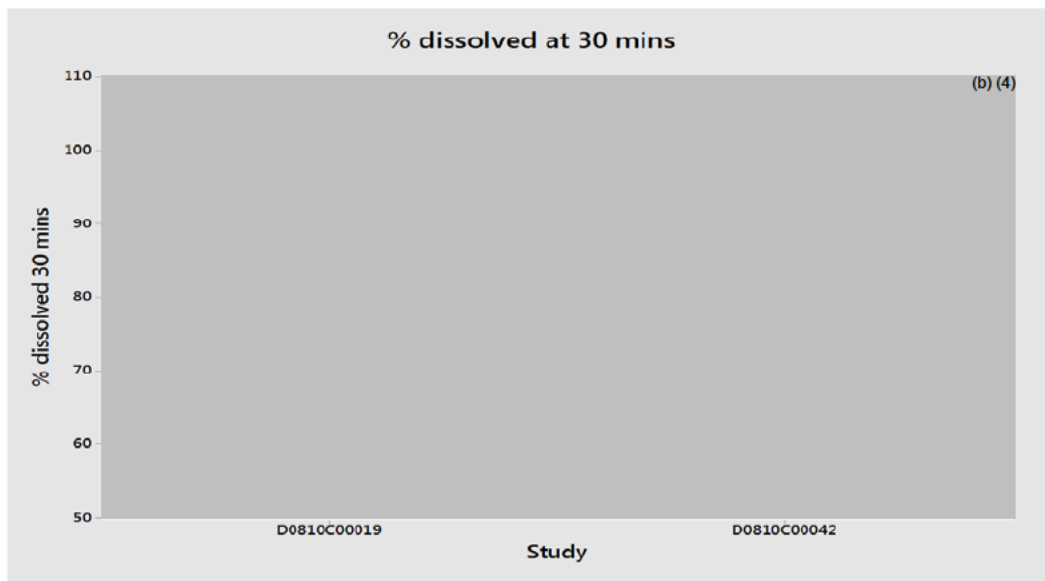
**Figure 9: Scatter plot of individual vessel 30-min dissolution data of Olaparib Capsule
batches used in clinical studies D0810C00019 and D0810C00042.**
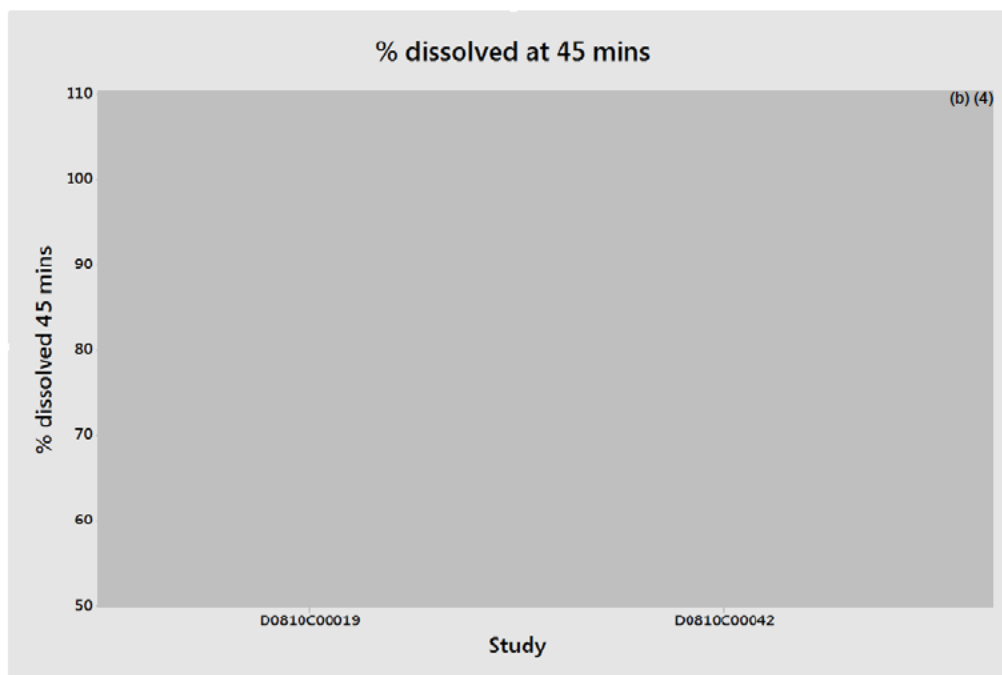
Figure 10: Scatter plot of individual vessel 45-min dissolution data of Olaparib Capsule batches used in clinical studies D0810C00019 and D0810C00042.

Reviewer's Comments

The Applicant has demonstrated similarity in the dissolution profiles of clinical batches of Olaparib Capsules used in clinical studies D0810C00019 and D0810C00042. The justifications of the proposed dissolution specifications based on clinical batches used in study D0810C00019 are therefore applicable to those used in Study D0810C00042.

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES

11   **What are the highlights of the drug product formulation development?**

No rigorous formulation development has been undertaken by the Applicant at this stage of clinical development of the drug product. The manufacturing process involves (b) (4)

12   **Are all the strengths evaluated in the pivotal clinical trials? What data are available to support approval of lower strengths?**

The Applicant is seeking approval for only one dosage strength, 50 mg.

13   **Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?**

The formulation is (b) (4) the API (b) (4) lipidic excipient, Lauroyl Macrogol-32-Glycerides, LMG (b) (4) contained within a hypromellose capsule shell. There are no manufacturing changes to be assessed in the NDA. However, the Applicant moved the manufacturing to a commercial site and compared drug product batches from the two sites through in-vitro dissolution testing (Figure 5) and in an in-vivo dog study. In the dog study, batch 3062396R (manufactured at the commercial site and showing a fast dissolution release profile) was compared to batches BMR/05/158 and BMR/07/429 (manufactured at the development site) which had fast and slower dissolution release profiles, respectively. The Applicant observed differences in systemic exposure between the two sites but concluded that the overlap in olaparib AUC's, observed in Figure 11, indicate that the differences are not significant.
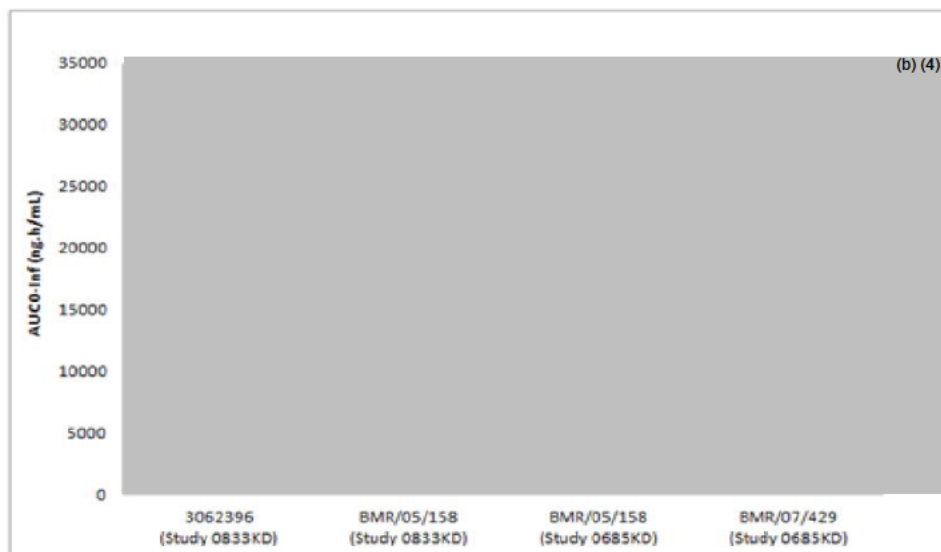
Figure 11: Scatter plot of individual olaparib AUC's in the dog following administration of Olaparib Capsules manufactured at development and commercial sites.

Reviewer's Comments

All of the drug product batches used in the definitive clinical trial were manufactured at the commercial site. Any observed differences in systemic exposure between batches from development and commercial manufacturing sites do not impact the clinical efficacy and safety established in Study D0810C00042. However, the bridging of manufactured batches used in studies D0810C00019 and D0810C00042 are acceptable.

14   What are the bioavailability implications for   (b) (4)   of the drug in the final dosage form? What data support the limit of this   (b) (4)   ?

As previously stated in section 1, olaparib exists   (b) (4)
                              . According to the Applicant, all batches of olaparib used to manufacture the capsules for clinical trial were confirmed to be   (b) (4)   . The solubility of   (b) (4)
                                                        in the finished drug product may therefore reduce bioavailability. Due to this concern, the following IR comments were sent to the Applicant on May 12, 2014:

   Bioavailability:

   a. FDA acknowledges your assurance that additional experimental work will be
      conducted to obtain a comprehensive understanding of   (b) (4)
      in the drug product. However, your assertion that   (b) (4)
      does not affect the bioavailability of your proposed product in humans has not been
      demonstrated. The simulation approach you have taken does not use any clinical
      data and is therefore not acceptable. Conduct an appropriate pharmacokinetic study
      in humans to investigate the effect of   (b) (4)   on the bioavailability of your product;

you may use [(b) (4)] %w/w or some other levels you deem appropriate to support your proposed specification limit for [(b) (4)].

b. In order to conduct the study described above, [(b) (4)] formulations of Olaparib capsules with various percentages of [(b) (4)] will have to be manufactured. We recommend that the percentage of [(b) (4)] in the [(b) (4)] formulations be quantified just prior to administration to patients and at the end of the study. You may also measure [(b) (4)] levels of the target and clinical [(b) (4)] batches over a period of time to supplement the stability data that you are gathering.

c. Submit, no later than 19-May-2014, the date when study data/results will be submitted.

On the day of a teleconference with FDA to discuss the above IR comments (5/21/2014), the Applicant submitted a preliminary response document as an amendment to the NDA. The Applicant's submission can be summarized as follows:

- A proposal to a limit of NMT [(b)(4)]% for [(b) (4)];
- [(b) (4)] exhibited a [(b) (4)] solubility in all media compared to [(b) (4)];
- The presence of [(b)(4)]% [(b) (4)] resulted in a [(b)(4)]% decrease in solution concentration relative to [(b) (4)] alone. The presence of [(b)(4)]% and [(b)(4)]% [(b) (4)] resulted in [(b)(4)]% and [(b)(4)]% reductions respectively in solution concentration.
- In a dog bioavailability study, [(b) (4)] exhibited a [(b)(4)]% lower olaparib AUC_{0-12h} and a [(b)(4)]% lesser C_{max} compared to [(b) (4)].
- A GI-Sim software model predicts that a reduction in olaparib solution concentration greater than [(b)(4)]% is required before a significant reduction in bioavailability occurs.

It was agreed at the meeting that a [(b) (4)] limit of NMT [(b)(4)]% would ensure that a precipitous fall in solubility of olaparib does not occur in-vivo.

Reviewer's Comments

The biopharmaceutics-related data in the package submitted to the NDA following discussion of the [(b) (4)] levels in the finished product are acceptable to the Biopharmaceutics Review team, provided the CMC team finalizes the product shelf life issues based on [(b) (4)] levels.

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA # 206-162

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**206-162** (IND# 75918 & (b) (4))	**Proposed Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	V	**Generic Name**	Olaparib
Medical Division	Oncology	**Drug Class**	PARP inhibitor
OCP and Genomics Reviewer	Elimika Pfuma, Pharm.D. /Ph.D.	**Proposed Indication**	Maintenance treatment of adult patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline BRCA (gBRCA) mutation as detected by an FDA-approved test who are in response (complete response or partial response) to platinum-based chemotherapy
OCP Team Leader	Qi Liu, Pharm D.	**Dosage Form**	50 mg capsules
Genomics Team Leader	Rosane Charlab Orbach, PhD	**Dosing Regimen**	**Proposed:** 400 mg BID
Pharmacometrics Reviewers	Hongshan Li, PhD		
Pharmacometrics Team Leader	Liang Zhao, PhD and Ping Zhao, PhD		
Date of Submission	3-February-2014	**Route of Administration**	Oral
Estimated Due Date of OCP Review		**Sponsor**	AstraZeneca
Medical Division Due Date		**Priority Classification**	Priority Review

Clinical Pharmacology Information

	"X" if included at filing	Number of studies submitted (*numbers in smaller font were already counted in another section*)	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	5		
I. Clinical Pharmacology				
Mass balance:	X	1		Trial 10
Isozyme characterization:	X	4		
Blood/plasma ratio:	X	1		
Plasma protein binding:	X	2		

Pharmacokinetics -	**X**	**8**		**Trials 1, 2, 7, 8, 9, 10, 12 and 24**
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**8**		
Dose proportionality -				
fasting / **non-fasting single dose**:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				**Preliminary report of Effect of strong CYP3A4 inhibitor and inducer will be submitted by Day 120**
In-vivo effects of primary drug:				
In-vitro:	**X**	**10**		**Transporter substrate /inhibitor (6 studies and CYP substrate/inhibitor/induction**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD - QT Study:				**Preliminary QT data to be submitted by Day 120**
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**		**Trial 7**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**X**	**2**		**Population PK model**
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				**Preliminary report to be submitted by Day 120**
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies	**X**	**1**		**PBPK Model**
Genotype/phenotype studies	**X**	**3**		
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**37**		

Clinical Pharmacology Filing Form for NDA 206162 - NME   2

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?		X		
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			Missing datasets already requested in IR
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Applicant is applying for waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Applicant is applying for waiver
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			No exposure–response information is in the proposed label

Clinical Pharmacology Filing Form for NDA 206162 - NME   3

	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? <u>Yes</u>

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Elimika Pfuma, Pharm.D. / Ph.D.   10-March-14
Clinical Pharmacology and Genomics Reviewer   Date

Qi Liu, PhD   10-March-14
Clinical Pharmacology Team Leader   Date

Rosane Charlab Orbach, PhD   10-March-14
Genomics Team Leader   Date

Hongshan Li, PhD   10-March-14
Pharmacometrics Reviewer   Date

Liang Zhao, PhD and Ping Zhao, PhD   10-March-14
Pharmacometrics Team Leaders   Date

Clinical Pharmacology Filing Form for NDA 206162 - NME   4