AstraZeneca

Statistical Analysis Plan

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A Randomised, Open-label, Three-part, Phase I Study 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 Tumours

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Global Product Statistician	PPD	PPD Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under plasma concentration-time curve from zero to infinity
AUC_{0-t}	Area under plasma concentration-time curve from zero to the last measurable time point
$AUC_{0-\tau}$	Area under plasma concentration-time curve over the dosing interval, τ
bd	Twice daily (Latin: *bis die*)
BP	Blood pressure
C_{avg}	Average plasma drug concentration over the dosing interval
$C_{ss,avg}$	Average plasma drug concentration over the dosing interval at steady state
CI	Confidence interval
CL/F	Apparent plasma clearance following oral administration
CL_{ss}/F	Apparent plasma clearance following oral administration at steady state
C_{max}	Maximum plasma drug concentration
$C_{ss,max}$	Maximum plasma drug concentration at steady state
$C_{ss,min}$	Minimum plasma drug concentration at steady state
CRF	Case record form
CSR	Clinical Study Report
CTC	Common terminology criteria (derived from National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4)
CV	Coefficient of variation
dECG	Digital electrocardiogram
ECG	Electrocardiogram
FI	Fluctuation index
%GCV	Geometric %CV
IP	Investigational Product
LOQ	Limit of quantification
λ_z	Terminal rate constant
MedDRA	Medical Dictionary for Regulatory Activities
NC	Not calculable
NQ	Non quantifiable
PD	Pharmacodynamics
PK	Pharmacokinetics
PR	PR interval of ECG
QRS	QRS interval of ECG

Abbreviation or special term	Explanation
QT	QT interval of ECG
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's correction
QTcF	QT interval corrected for heart rate using Fridericia's correction
QTcI	QT interval corrected for heart rate using individual-specific correction
R&D	Research and Development
RR	RR interval of ECG
SAE	Serious adverse event
SD	Standard deviation
$t_{½}$	Terminal half-life
t_{max}	Time to reach maximum plasma concentration
$t_{ss,max}$	Time to reach maximum plasma concentration at steady state
$t_{ss,min}$	Time to reach minimum plasma concentration at steady state
V_z/F	Apparent volume of distribution

AMENDMENT HISTORY

Date	Brief description of change
6 May 2014	Update to Global Product Statistician signatory.
Edition Number 2.0	ECG categories updated in section 4.2.4.
	Updated Table 2 to include steady state / multiple dose PK parameters.
	Updated list of abbreviations with steady state PK parameters.
8 May 2014	Updated date format on page 1.
Edition Number 2.1	Replaced '6th May 2014' on signature pages with 'Date'.

1. STUDY DETAILS

1.1 Study objectives

Primary objective

- To investigate the effect of food on the pharmacokinetics (PK) of olaparib following oral dosing of the tablet formulation in patients with advanced solid tumours.

Secondary objectives

- To investigate the effect of olaparib on the QT interval corrected for heart rate (QTc) following single (Part A) and multiple (Part B) oral dosing of the tablet formulation in patients with advanced solid tumours.

- To assess the safety and tolerability of olaparib following oral dosing of the tablet formulation in patients with advanced solid tumours.

1.2 Study design

This is a 3-part study in patients with advanced solid tumours:

- Part A will determine the effect of food on the PK of olaparib and the effect of olaparib on the QT interval following a single oral dose of olaparib tablets;

- Part B will determine the effect of olaparib on the QT interval following multiple oral dosing of olaparib tablets;

- Part C will allow patients continued access to olaparib tablets after the PK and QT phases (Parts A & B) and will provide for additional safety data collection.

A total of 48 patients are planned to be enrolled at approximately 8 sites in Western Europe; approximately 42 evaluable patients will be expected to complete the study.

Part A of this study is a randomised, open-label, 2-treatment period crossover study in approximately 48 patients with advanced solid tumours. Each patient will receive a single oral dose of olaparib tablets 300 mg in each of 2 treatment periods (once in the overnight fasted state and once immediately following a high-fat meal at breakfast time), with at least 5 and no more than 14 days (washout) between doses. Digital ECG (dECG), PK assessments, and safety assessments will be obtained for up to 72 hours post-dose in each treatment period. Additionally, during the first treatment period, patients will undergo baseline dECG assessments on Day -1 (ie, the day prior to dosing) at clock times matched to planned/scheduled dECG assessment times on the dosing day (Day 1). Patients will check into the clinic on the evening of Day -2 (first treatment period) or the evening of Day -1 (second treatment period) and remain resident until 24 hours after each dose of olaparib tablets (Day 2). The dECGs performed on Day 1 in each treatment period will be clock-

matched to the actual times that the Day -1 dECGs are performed in the first treatment period. Patients will return to the clinic for assessments on Days 3 and 4 of each treatment period. On Day 1 of Part A patients should be fasted over the same time period as Day -1.

Part B of this study is an open-label study in the same patients who participated in Part A. Upon completion of Part A, following a washout period (of at least 5 days and no more than 14 days between the last dose in Part A and Day -1 of Part B) and providing the patient continues to meet the study entry criteria, each patient will receive olaparib tablets 300 mg bd for 5 days. Patients will check into the clinic on the evening of Day -2. On Day -1, baseline dECG assessments will be performed at clock times matched to planned/scheduled dECG assessment times on Day 5. Patients will be discharged from the clinic on the evening of Day -1. Patients will self-administer their olaparib doses under fasted conditions (from 1 hour prior to 2 hours after the olaparib dose) from Day 1 up to the morning of Day 4 on an outpatient basis. On the evening of Day 4, patients will check back into the clinic, and will receive their Day 4 evening dose. On the morning of Day 5, patients will receive their Day 5 morning dose after an overnight fast and will remain fasting for 4 hours post-dose. Patients will undergo dECG and PK assessments pre-dose and for 12 hours post-dose. The dECGs performed on Day 5 will be clock-matched to the actual times that the Day -1 dECGs are performed. Patients will be discharged from the clinic after completing 12-hour assessments on Day 5, and will self-administer their evening Day 5 dose of olaparib tablets. On Day 5 of Part B patients should be fasted over the same time period as Day -1.

On completion of Part B, patients may be entered into Part C and continue to take olaparib tablets (300 mg bd) if they and the investigator agree that this is appropriate. Patients should start Part C immediately after the last dose received in Part B. Patients will have weekly clinic visits for the first 4 weeks; thereafter visits will be every 4 weeks. Part C will be of 12 months' duration from the date the last patient enters this part of the study.

During and after Part C, patients may continue to take olaparib tablets. After the end of Part C patients will be seen as per their normal routine clinical schedule and no clinical data will be collected, other than serious adverse events (SAEs) and drug dispensing/accountability.

Patients will return to the clinic for follow-up assessments either 30 days (±7 days) after their last dose (regardless of whether the last dose is in Part A, Part B, Part C, or the continued access phase after Part C). If a patient discontinues olaparib tablets during Part C, they will also attend a study treatment discontinuation visit.

Patients aged ≥18 years with advanced solid tumours who are refractory to standard therapy and are able to eat a high-fat meal will be recruited.

1.3 Number of patients

The study has been sized to provide an estimate of the difference between olaparib PK parameters in the fed and fasted states. Based on the estimate of within-patient standard deviation (SD) for log AUC from Studies D0180C00002 and D0180C00003 of 0.26, and assuming a true food effect difference of 5%, 42 evaluable volunteers (21 per-sequence) will

give 90% power of showing that the 90% confidence interval (CI) for the food effect (ratio of geometric least-squares means of AUC or C_{max} in the fed state to the fasted state) lies entirely within the range of 0.8 to 1.25.

A total of 48 patients will be entered to ensure that 42 evaluable patients complete the study. nQuery v7.2 was used for the sample size calculations.

2. ANALYSIS SETS

2.1 Definition of analysis sets

There will be 3 analysis sets considered in this study:

- The safety analysis set will include all patients who receive at least one dose of olaparib.

- The PK analysis set will include all patients who receive an olaparib dose and provide evaluable PK profiles in at least 1 treatment period i.e. fed (A) or fasted (A).

  If a patient has a major protocol deviation that affects the evaluability of the PK profile in any treatment period, then the patient will not form part of the PK analysis for that treatment period.

- The QT analysis set will include all patients who have at least 1 evaluable time-matched QT/QTc interval value at a scheduled time point, time-matched between Day -1(baseline) and Day 1(treatment periods 1 or 2) for Part A, or time matched between Day -1(baseline) and Day 5 for Part B.

2.2 Violations and deviations

Important protocol deviations will be agreed by the study team physician, pharmacokineticist and statistician before any statistical analysis is performed.

Patients who withdraw from the study following dosing, but prior to study completion, will be included in the PK analysis provided they have evaluable profiles over the planned collection period. Patients with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for meaningful analysis.

If a patient vomits within approximately 3 hours after dosing with olaparib tablets, all PK sampling may be omitted for that treatment period but the safety assessments should continue as per the study schedule. The patient may continue in the study and proceed with Part A, if applicable, and then on to Part B and Part C.

Important protocol deviations include changes to the procedures that may impact the quality of the data, or any circumstances that can alter the evaluation of the PK. Examples include,

but may not be limited to, vomiting following oral dosing occurring within the time frame of 2 times the median t_{max}, sample processing errors that lead to inaccurate bioanalytical results, incomplete dose administered, incomplete PK profile collected, and/or use of disallowed concomitant medication. In the case of an important protocol deviation, affected PK data collected will be excluded from the summaries and statistical analyses, but will still be reported in the study result listings. Important deviations will be listed and summarised in the Clinical Study Report (CSR).

3. PRIMARY AND SECONDARY VARIABLES

Primary variables

The primary PK outcome variables to be calculated for olaparib are described below. All PK parameters for Parts A & B will be summarised descriptively. For Part A, AUC, (or AUC_{0-t}, if AUC is not adequately estimable), C_{max} and t_{max} will also be statistically analysed.

- Single-dose PK parameters will be calculated for olaparib during each treatment period in Part A:
  - C_{max} Maximum plasma concentration obtained directly from the observed concentration versus time data
  - t_{max} Time to maximum plasma concentration obtained directly from the observed concentration versus time data
  - AUC_{0-t} Area under the plasma concentration-time curve from zero to the time of the last measurable concentration, calculated by linear up/log down trapezoidal summation
  - λ_z Terminal rate constant estimated by log-linear least squares regression of the terminal part of the concentration-time curve
  - AUC Area under the plasma concentration-time curve from zero (pre-dose) extrapolated to infinity calculated by linear up/log down trapezoidal summation and extrapolated to infinity by the addition of the last quantifiable concentration divided by the terminal rate constant: $AUC_{0-t}+C_{last}/\lambda_z$
  - $t_{1/2}$ Terminal half-life. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile
  - CL/F Apparent plasma clearance
  - V_z/F Apparent volume of distribution
- Multiple-dose PK parameters will be calculated for olaparib on Day 5 of Part B:

- $C_{ss,max}$ Maximum plasma concentration obtained directly from the observed concentration versus time data
- $t_{ss,max}$ Time to maximum plasma concentration obtained directly from the observed concentration versus time data
- $C_{ss,min}$ Minimum plasma concentration obtained directly from the observed concentration versus time data
- $t_{ss,min}$ Time to minimum plasma concentration obtained directly from the observed concentration versus time data
- $AUC_{0-\tau}$ Area under the plasma concentration-time curve over the dosing interval, τ, calculated by linear up/log down trapezoidal summation
- $C_{ss,avg}$ Average concentration over the dosing interval calculated as $AUC_{0-\tau/\tau}$
- FI Fluctuation index, calculated as $[(C_{ss,max}-C_{ss,min})/C_{ss,avg}]\times 100\%$
- CL_{ss}/F Apparent plasma clearance

The PK analysis of the plasma concentration data for olaparib will be done at AstraZeneca R&D. The actual sampling times will be used in the final PK parameter calculations, except for the pre-dose sample for which the time will be set to zero. All PK computations will be performed using Phoenix™ for WinNonlin. Additional PK parameters may be determined if deemed appropriate.

Secondary variables

The pharmacodynamic (PD) analyses of the dECG data will be performed by ERT, with the exception of the derivation of QTcI (Quintiles will derive QTcI as described below). ERT standard operating procedures (SOPs) and Work Instructions will be used as the default methodology if not otherwise specified.

- Pharmacodynamic (PD) variables i.e. ECG intervals (including QT and QTc interval) will be reported based on the continuous dECG measurements:
  - RR
  - HR
  - PR
  - QRS

- QT

The QT interval will be corrected for RR (the duration of a heart beat) to obtain corrected (QTc) variables:

- QTcF (Fridericia correction)
- QTcB (Bazett correction)
- QTcI (Individual correction)

The general formula for QTc that will be used is:

$QTc=QT/RR^{b}$

with the QT intervals expressed in milliseconds and the RR interval in seconds.

Different factors for b in the formula above will be used:

(i) For QTcF b=1/3

(ii) For QTcB b=1/2

(iii) For QTcI individual values of b_i will be estimated for each patient from the study data.

For the estimates of the individual-specific correction factors, the estimate of individual slopes, b_i, a fixed effects linear model for patient i, part p, and time point t will be used:

$$\log(QT_{i,p,t})=a_{i,p}+b_i \log(RR_{i,p,t})$$

The corrected QT is then obtained by:

$$QTcI_{i,p,t}=QT_{i,p,t} / ((RR_{i,p,t})^{bi})$$

The estimation will be based on the pooled data from the drug-free days: Day -1 in Part A, and Day -1 in Part B.

Additional methods of QT correction may also be applied.

To obtain a single PD value at each specified time point, the mean of the triplicate values at that time point will be used.

For change from baseline (pre-dose): Baseline is defined as the pre-dose measurement taken on the same day that the post-dose measurements are taken. This also applies to Day -1 in Part A and Part B, despite no dose being administered.

For change from baseline (time-matched day -1): Baseline for the PD data in Part A is defined as Day -1 of treatment period 1 in Part A, and baseline for the PD data in Part B is defined as Day -1 in Part B. For each patient, the change-from-baseline in a PD variable at each time point will be calculated as the difference between the mean of the replicate value at each post-dose time point and the mean of the time-matched replicate value at the corresponding baseline.

- Safety and tolerability will be assessed by:
  - Assessment of adverse events (AEs), graded by CTCAE (v4.03)
  - Physical examination
  - Vital signs (including BP and pulse)
  - Standard 12 lead ECGs
  - Evaluation of laboratory parameters (clinical chemistry, haematology, and urinalysis)

Adverse events (AEs) will be classified according to the terminology of Medical Dictionary for Regulatory Activities (MedDRA), Version 16. AEs will also be assigned a maximum CTC grade by the Investigator.

Each adverse event will be assigned to the period of the study in which they started as follows: The baseline period is the time between enrolment into the study and receipt of the first dose of study treatment. The treatment period is the time between receipt of the first dose of study drug and the follow-up assessment at the end of the study. The treatment period is divided into Part A, Part B and Part C, with Part A being subdivided according to which food condition study treatment was received under. AEs occurring in the baseline period will be listed only and will not be included in any summary tables.

Table 1 Adverse event occurrence

Adverse event occurrence	Period assigned	Study treatment (food condition)
Date and time before first treatment with olaparib	Baseline period	Not applicable
Date and time the same as or greater than the date and time of the first treatment with olaparib but before date and time of second treatment	Treatment period 1 (Part A)	Fed [OR] Fasted, dependent on treatment sequence
Date same as or greater than date of first treatment with olaparib but prior to date of second treatment; but time is missing	Treatment period 1 (Part A)	Fed [OR] Fasted, dependent on treatment sequence
Date and time the same as or greater than the date and time of the second treatment with olaparib, but prior to the date and time of Part B treatment, or up to (and including) 30 days after the last dose date (where the patient does not enter Part B)	Treatment period 2 (Part A)	Fed [OR] Fasted, dependent on treatment sequence
Date same as or greater than date of second treatment with olaparib, but prior to the date and time of first Part B treatment, or up to (and including) 30 days after the last dose date (where the patient does not enter Part B); but time is missing	Treatment period 2 (Part A)	Fed [OR] Fasted, dependent on treatment sequence
Date and time the same as or greater than the date and time of the first Part B treatment with olaparib, but prior to the date of optional Part C treatment, or up to (and including) 30 days after the last dose date (where the patient does not enter Part C)	Part B	Olaparib 300 mg bd
Date same as or greater than date and time of first Part B treatment with olaparib, but prior to the date of optional Part C treatment, or up to (and including) 30 days after the last dose date (where the patient does not enter Part C); but time is missing	Part B	Olaparib 300 mg bd
Date same as or greater than start date of optional Part C treatment with olaparib (time not recorded in Part C), up to (and including) 30 days after the last dose date	Part C	Olaparib

4. ANALYSIS METHODS

4.1 General principles

Statistical summaries and analyses will be performed by Quintiles under the direction of the Biostatistics Group, AstraZeneca using SAS® version 8.1 or higher and, where appropriate, additional validated software.

After the last patient has completed the treatment period in Part B, the database for Parts A & B of the study will be locked and the data will be reported in a Part A and Part B CSR. AstraZeneca anticipates receiving regulatory questions relating to QT effect of olaparib in relation to a marketing authorisation application. In the event that Part A and Part B are not completed at the time of receipt of the questions, an analysis of the available Part A and Part B data may be performed to enable AstraZeneca to respond within the permitted time frame. On completion of Part C, a further database lock will occur and the Part C data will be reported in a separate Part C CSR.

All individual data as recorded in the final study database will be provided by Quintiles Data Management.

The treatments will be labelled in all summaries and listings as:

- "Fasted (A)"
- "Fed (A)"
- "Olaparib 300 mg bd (B)"
- "Olaparib 300 mg bd (C)"

and defined as follows:

- Fasted: Olaparib 300 mg (2x150 mg tablets) administered in fasted state (Part A).
- Fed: Olaparib 300 mg (2x150 mg tablets) administered in fed state following high-fat meal (Part A).
- Olaparib 300 mg bd: Olaparib 300 mg (2x150 mg tablets) twice daily for 5 days (Part B).
- Olaparib 300 mg bd: Olaparib 300 mg (2x150 mg tablets) twice daily (Part C).

The 2 treatment sequences, to which patients will be randomised in Part A, will be labelled as:

- "Fed/Fasted (A)"
- "Fasted/Fed (A)"

and defined as follows:

- Fed/Fasted: Olaparib 300 mg (2x150mg tablets) administered in high-fat fed state in period 1 and in fasted state in period 2.

- Fasted/Fed: Olaparib 300 mg (2x150mg tablets) administered in fasted state in period 1 and in high-fat fed state in period 2.

The number of patients screened and included in the safety analysis set will be summarised. Demographic and baseline characteristics will be summarised and listed for the safety analysis set.

For qualitative demographic and safety variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented.

Quantitative demographic and safety variables will be summarised using descriptive statistics, including n, mean, SD, median, minimum, and maximum values. Where appropriate, assessments will be summarised by visit.

Treatment duration will be summarised for Part C only. Treatment duration is based on the dates of first and last dose relating to Part C.

Study day will be calculated as follows:

- Days prior to first dose: Study day=date – first dose date.

- Days on or after first dose: Study day=date – first dose date+1.

Where date is missing, but is required in the calculation of *time to randomisation*, date will be imputed as 01 i.e. 1st of the month. Otherwise no imputations will be made for any missing data, unless agreed by the study team.

Quantitative PK variables will be summarised using descriptive statistics, including n, arithmetic mean, SD, coefficient of variation (%CV), median, minimum, and maximum values. Additionally, geometric means and geometric %CV (%GCV) will be reported as described in Table 2. The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The %GCV is calculated as $100 \cdot \sqrt{(\exp(s^2)-1)}$ where s is the SD of the data on a log scale. Mean, SD, %CV, geometric mean, and %GCV will not be calculated for t_{max}; t_{max} will be summarised by median, minimum and maximum.

For all PK data, descriptive statistics will follow the rounding conventions described in Table 2. Coefficients of variation (%CV and %GCV) will always be reported to 1 decimal place. Ratios and any corresponding confidence intervals (CIs) that are obtained during inferential statistical analysis shall be reported to 2 decimal places.

The plasma concentrations will be reported to the same precision as the source data.

Table 2 Reporting accuracy of pharmacokinetic data

Variable / Parameter	Data	Mean	SD	%CV & %GCV	Median	Min	Max	Differences/ Ratios & CIs
Plasma concentrations	As reported	+1sf	+1sf	1dp	+1sf	3sf	3sf	
Single dose parameters								
C_{max}	As reported	+1sf	+1sf	1dp	+1sf	3sf	3sf	2dp
t_{max}	As reported	NA	NA	NA	2dp	2dp	2dp	2dp
AUC	3sf	4sf	4sf	1dp	4sf	3sf	3sf	2dp
AUC_{0-t}	3sf	4sf	4sf	1dp	4sf	3sf	3sf	2dp
CL/F	3sf	4sf	4sf	1dp	4sf	3sf	3sf	
Vz/F	3sf	4sf	4sf	1dp	4sf	3sf	3sf	
thalf	3sf	4sf	4sf	1dp	4sf	3sf	3sf	
lamdaz	4sf	5sf	5sf	1dp	5sf	3sf	3sf	
Multiple dose (steady state) parameters								
$C_{ss,max}$	As reported	+1sf	+1sf	1dp	+1sf	3sf	3sf	
$t_{ss,max}$	As reported	NA	NA	NA	2dp	2dp	2dp	
$C_{ss,min}$	As reported	+1sf	+1sf	1dp	+1sf	3sf	3sf	
$t_{ss,min}$	As reported	NA	NA	NA	2dp	2dp	2dp	
$C_{ss,avg}$	As reported	+1sf	+1sf	1dp	+1sf	3sf	3sf	
$AUC_{0-\tau}$	3sf	4sf	4sf	1dp	4sf	3sf	3sf	
FI	0dp	1dp	NA	NA	NA	1dp	1dp	
CL_{ss}/F	3sf	4sf	4sf	1dp	4sf	3sf	3sf	

sf Significant figures.
dp Decimal places.

For descriptive statistics of concentrations, non-quantifiable (NQ) values of plasma concentrations will be handled as follows:

- If, at a given time point, 50% or less of the plasma concentrations are NQ, the mean, SD, geometric mean, %CV, and %GCV will be calculated by substituting the limit of quantification (LOQ) for values which are NQ.
  - olaparib: use low range LOQ = 0.0005 µg/ml
- If more than 50%, but not all, of the concentrations are NQ, the mean, geometric mean, SD, %CV, and %GCV will be reported as not calculable (NC).

- If all the concentrations are NQ, the geometric mean and mean will be reported as NQ and the SD, %CV, and %GCV as NC.

The PK parameters will be reported as described in Table 2.

The PK data will be presented by treatment for Part A (food condition) and Part B (olaparib 300 mg bd).

The PD analysis (QT/QTc interval analysis) and the PD summaries, figures, and data listings will be the responsibility of the Quintiles biostatistician.

Additionally, dECG data from this study will be pooled with data from another study(ies). The methodology will be described separately, and the data analysed separately by AstraZeneca using statistical methods and PK/PD modeling.

4.2 Analysis Methods

4.2.1 Screening and demographic measurements (Parts A & B, and Part C)

Disposition of patients

For Parts A & B a summary table will be presented specifying the number of patients enrolled, randomised, who received treatment, who completed study, and who terminated prematurely. Data will be summarised by treatment sequence and across all patients (Part A) and olaparib 300 mg bd (Part B).

For Part C a summary table will be presented specifying the number of patients who received treatment, who completed study and who terminated prematurely. Data will be summarised across all patients.

In addition, the number of patients included in each analysis set (Parts A & B only) as well as important protocol deviations will also be summarised within separate tables. Data will be summarised by treatment sequence for Part A and across all patients (Part A) and olaparib 300 mg bd (Part B), and across all patients for Part C.

Demographic data

Descriptive statistics will be presented for age. In addition, frequencies and percentage of patients will be tabulated for the categorical variables age group, sex, race and ethnic group in the same table. Data will be summarised by treatment sequence and across all patients (Part A) and olaparib 300 mg bd (Part B), and across all patients for Part C.

Concomitant medication

Concomitant medications will be summarised by the coded terms in separate tables according to whether the medication is allowed or disallowed. The number of patients receiving a medication will be summarised by treatment for Part A and across all patients for Parts A & B, and separately across all patients for Part C of the study. A medication taken during the course of the study is considered concomitant. A patient is only counted once if receiving the

medication more than once. For detailed information regarding concomitant treatments see Sections 5.6.1 and 5.6.2 of the protocol.

Other baseline data

Other demographic and baseline data, including past treatments and surgery, will be listed and summarised by treatment sequence and across all patients for Parts A & B, and across all patients for Part C.

Treatment Compliance (Part C only)

Study site pharmacy staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the case record form (CRF). Dates of missed or held doses will be recorded on the CRF.

Estimated compliance is derived from the actual administration days divided by the total planned administration days (last dose date - first dose date + 1), (accounting for dose interruptions).

4.2.2 Pharmacokinetic parameters (Parts A & B)

All PK data received will be presented in data listings, and summaries will be presented for patients in the PK analysis set. Data from patients excluded from the PK analysis set will be included in the data listings, but not in the summaries. Extra measurements (such as unscheduled or repeat assessments) will also not be included in summary tables, but will be included in patient listings. Presentations will be by treatment as defined previously.

In addition, the plasma concentration data and the PK data will be explored graphically. The following plots will be presented:

- Individual plots of olaparib concentration versus time. Time on x-axis with linear scale, concentration on y-axis with *log scale*. There will be one plot per patient showing 3 profiles, one for each treatment (ie, one for fed state, one for fasted state, and one for olaparib 300 mg bd).

- Individual plots of olaparib concentration versus time. Time on x-axis with linear scale, concentration on y-axis with *linear scale*. There will be one plot per patient showing 3 profiles, one for each treatment (ie, one for fed state, one for fasted state, and one for olaparib 300 mg bd).

- Geometric mean (± geometric SD, if appropriate) of olaparib plasma concentration versus time. The geometric mean for each treatment (ie, fed state, fasted state, and olaparib 300 mg bd) to be shown in different symbols. Time on x-axis with linear scale and concentration on y-axis with *log scale*. Repeat and include Fed (A) and Fasted (A) only.

- Geometric mean (± geometric SD, if appropriate) of olaparib plasma concentration versus time. The geometric mean for each treatment (ie, fed state, fasted state, and olaparib 300 mg bd) to be shown in different symbols. Time on x-axis with linear scale and concentration on y-axis with *linear scale*. Repeat and include Fed (A) and Fasted (A) only.

- Individual plots of olaparib concentration versus time. Time on x-axis with linear scale, concentration on y-axis with *log scale*. All patient profiles for fed state on one plot, repeat for fasted state with patient profiles on one plot. Part A data only.

- Scatter plot of AUC, AUC_{0-t} and C_{max} on separate plots presenting ratio of fed : fasted with patient number denoted on x-axis.

- Geometric mean and 90% CI for the ratio of fed : fasted, plotted separately for AUC, AUC_{0-t} and C_{max}

4.2.3 Food effect analysis (Part A only)

Following log-transformation using natural logarithms, C_{max}, AUC and AUC_{0-t} will be analysed using a mixed effect analysis of variance (ANOVA) model, fitting terms for sequence, patient within sequence, period and treatment (where treatment represents food condition i.e. fed or fasted). Patient within sequence will be treated as a random effect in the model.

Point estimates and adjusted 90% CIs for the difference between treatments, for C_{max}, AUC and AUC_{0-t}, will be constructed based on the following treatment comparisons:

- Fed compared to Fasted

Each confidence interval will be based on the t distribution. The sum of squares of the residuals in the linear model will be used to estimate the variance, which is assumed to be equal for both treatments.

The point estimate and adjusted 90% CIs will then be exponentially back transformed to provide point and confidence interval (CI) estimates for the ratio of interest. No food effect on the PK of olaparib will be concluded if the 2-sided 90% CIs for the ratios of AUC (or AUC_{0-t} as previously noted) and C_{max} are within the range of 0.80 to 1.25.

The analysis will be performed using SAS procedure MIXED in the following manner:

```
PROC MIXED DATA=.;

    CLASS patient sequence period treatment;

    MODEL logY=sequence period treatment;

    RANDOM patient(sequence);
```

ESTIMATE 'Fed vs. Fasted' treatment -1 1 / CL ALPHA=0.10;

RUN;

QUIT;

Where logY is log(AUC), log(C_{max}) and log(AUC_{0-t}) and treatment is coded as 0 = "Fed" and 1 = "Fasted".

Assumptions of normality and constancy of variance will be explored in all analyses and, if necessary, an appropriate transformation (eg, rank) or non-parametric technique (eg, Mann-Whitney test) will be used to validate the results of the main analysis.

Results of this analysis will be presented in an overview table. The original SAS output of this PROC MIXED will be presented in an additional appendix.

An analysis of t_{max} using the Wilcoxon Signed Rank Test, and the Lehmann median estimator of difference and 90% CIs will also be presented for the following treatment comparisons:

- Fed compared to Fasted

4.2.4 Pharmacodynamic parameters (Parts A & B)

All data received will be presented in data listings. Pharmacodynamic summaries will be presented for patients in the QT analysis set by treatment and study day for Part A, and study day for Part B. Data from patients excluded from the QT analysis set will be included in the data listings, but not in the summaries. Extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables, but will be included in patient listings.

The PD variables (absolute values and change from baseline (pre-dose)) will be listed and summarised using descriptive statistics (n, mean, SD, median, minimum, and maximum). Change from baseline (time-matched day -1) in PD variables will also be listed. The QT/QTc outliers are defined as QT/QTc values following dosing that are greater than 450 ms or are increases from baseline (pre-dose) greater than 30 ms. QT/QTc outliers will be highlighted in the data listings and summarised using the following categories:

- values that are
  - >450 ms
  - >480 ms
  - >500 ms

and

- Values that are increases from baseline (pre-dose) of

- >30 ms
- >60 ms
- >90 ms

Box-plots of QTcB, QTcF and QTcI will be presented for absolute values and change from baseline (pre-dose), separately for Part A and Part B.

Patient profile plots of RR, HR, PR, QRS, QT, QTcB, QTcF and QTcI will be presented for absolute values and change from baseline (both pre-dose and time-matched day -1), separately for Part A and Part B.

The number and percentage of patients who meet the ECG outlier criteria at any assessment after start of investigational product (IP) will be tabulated by treatment for Part A ("Fed (A)" and "Fasted (A)"), and by study day for Part B ("Day -1 (B)" and "Day 5 (B)").

4.2.5 Safety parameters (Parts A & B, and Part C)

Safety variables

All safety analyses will be performed on the safety analysis set.

Where more than one measurement was made at baseline, the last non-missing pre-dose value will be taken as the baseline measurement.

If the baseline measurement is missing then the last non-missing pre-dose value will be taken as baseline.

Treatment exposure

Treatment exposure data will be collected for patients in Parts B and C. For Part B the mean daily dose will be summarised. For Part C the duration of treatment exposure, dose interruptions and reductions, mean daily dose and adherence will be summarised and listed.

Adverse events

All AEs will be listed for each patient, and will be summarised for Parts A & B, and separately for Part C of the study. In addition, the following summary tables will be presented by treatment (food condition (Part A) and olaparib 300 mg bd (Part B)) and across all patients for Part A, and across all patients only for Part C.

- Summary of number (%) of patients who had at least one adverse event in any category (Any AE, any causally related AE, any AE of CTCAE grade 3 or higher, any causally related AE of CTCAE grade 3 or higher, any AE with outcome = death, any causally related AE with outcome=death, any SAE (including events with outcome = death), any causally related SAE (including events with outcome = death), any SAE causing discontinuation of IP, any causally related SAE causing discontinuation of IP, any AE leading to discontinuation of IP, any causally related

AE leading to discontinuation of IP, any other significant AE, any other causally related significant AE).

- In addition, a summary of number (%) of AEs in any category (episode level) will also be presented.
- Summary of number (%) of patients who had at least 1 AE by preferred term, arranged by system organ class.
- Summary of number (%) of patients who had at least 1 AE by system organ class and preferred term presented by maximum reported CTCAE grade.
- Summary of number (%) of patients who had at least 1 olaparib/other causally related AE by preferred term.
- Summary of number (%) of patients who died, summary of number (%) of patients with an AE with outcome = death. In addition, a listing of deaths, and a listing of key information for AEs with outcome = death will be presented .
- Summary of SAEs (episode level) by preferred term, arranged by system organ class.
- Summary of number (%) of patients with SAEs by preferred term, arranged by system organ class. In addition, a listing of key information for SAEs, and a listing of key information for SAEs with outcome other than death will be presented.
- Summary of number (%) of patients who had an AE leading to discontinuation of IP, by system organ class and preferred term. In addition, a listing of key information for AEs leading to discontinuation of IP will be presented.
- Summary of number (%) of patients with any other significant AE by category. In addition, a listing of key information for other significant adverse events will be presented.

Part C only:

- Summary of number (%) of patients with an AE leading to olaparib dose reduction / interruption, by system organ class and preferred term.

Clinical laboratory variables (haematology, clinical chemistry, coagulation, urinalysis)

Project-specific reference ranges will be applied.

All laboratory safety data, incorporating haematology, clinical chemistry, coagulation (aPTT and INR will be collected at baseline in Part A) and urinalysis data will be listed for each patient and summarised where appropriate. Haematology, clinical chemistry and coagulation values outside the standard reference ranges will be highlighted in the listings. Numerical

laboratory data (absolute and change from baseline (Screening)) will be summarised by treatment (fed (A), fasted (A), olaparib 300 mg bd (B)) using standard summary statistics (mean, standard deviation, minimum, median, maximum, and number of patients). The only exception to this rule is for Screening and Follow-up assessments which will be summarised by treatment sequence for Part A and across all patients for Parts A & B, and across all patients for Part C.

Shift tables summarising the change from baseline to maximum CTC grade and to maximum value will be presented for haematology and clinical chemistry in Parts A & B and Part C. For urinalysis a shift table comparing baseline to the maximum value will be presented for Parts A & B only.

Vital signs and oral temperature

For Parts A & B, pulse, systolic and diastolic BP, height, weight and oral temperature will be listed by patient and summarised by treatment and part (fed (A), fasted (A), olaparib 300 mg bd (B)) using standard summary statistics for the absolute value at each protocol time and the change from baseline (Screening) to all subsequent protocol assessments. The only exception to this rule is for Screening and Follow-up assessments which will be summarised by treatment sequence and across all patients.

For Part C assessments will be summarised across all patients by study day.

ECG and physical examination

ECG and physical examination details will be listed individually by patient for Parts A & B, and will be summarised by treatment and part (fed (A), fasted (A), olaparib 300 mg bd (B)).

Physical examinations conducted during Part C will not be captured on the eCRF, but new or aggravated physical findings implying deterioration compared with baseline will be reported as an AE.

5. INTERIM ANALYSES (NOT APPLICABLE)

6. CHANGES OF ANALYSIS FROM PROTOCOL

There are no changes to the planned analysis from the protocol.

7. REFERENCES

CTCAE v4.03 2010
Common Terminology Criteria for Adverse Events Version 4.03 2010. Available from URL: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed 03 April 2013.

Food and Drug Administration 2002
United States Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry -Food-Effect Bioavailability and Fed Bioequivalence Studies. December 2002

8. APPENDIX (NOT APPLICABLE)