AstraZeneca

Revised Clinical Study Protocol

Drug Substance AZD2281

Study Code D0810C00024

Edition Number 5

[redacted]

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

Sponsor:

AstraZeneca [redacted]

AstraZeneca Research and Development site representative

[redacted]

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No	Date of Local Amendment
1	[redacted]		
2			
3			
4			
5			

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change
1	[redacted]		
2			
3			
4			

[redacted]

[redacted]

PROTOCOL SYNOPSIS

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

International Co-ordinating Investigator

[redacted]

Study centre(s) and number of patients planned

PK Phase

For the Pharmacokinetic (PK) Phase of the study, approximately 20 patients, with advanced solid tumours refractory to standard therapies, will be enrolled from approximately 3 UK centres. Each centre will enrol approximately 6 patients. A minimum of 18 evaluable patients completing the two treatment periods for PK assessments will be required.

Determination of the number of patients required for the PK Phase of the study has assumed that there will be no more than 2 patients withdrawn between the two periods for PK assessments due to disease progression etc.

For the Continued Supply Phase of the study, it is anticipated that approximately 10-15 patients from the PK Phase of the study will wish to continue to receive the Gelucire® 44/14 (capsule) formulation of AZD2281.

Continued Supply Expansion Phase

Approximately, an additional 26 patients will be added to the Continued Supply Expansion Phase, of which 20 patients (Group 1) with confirmed genetic BRCA1/2 (gBRCA) ovarian or breast cancer will be randomised to either daily dosing with tablet or capsule formulation to assess the multiple dose safety profile of the Melt-extrusion (tablet) formulation in a comparative setting, and 6 patients (Group 2) with advanced solid tumours refractory to standard therapies will be recruited to directly compare the steady state PK of the capsule and the Melt-extrusion (tablet) formulation.

These patients will be recruited from 3 UK centres. Approximately 2-3 additional centres will be used to assist with recruitment of gBRCA ovarian and breast cancer patients.

Dose escalation phase of the continued supply expansion

The number of patients taking part in this part of the study will be up to approximately 185 patients (up to approximately 48 in the dose escalation phase dependent on the number of dose

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escalations required, and up to approximately 135 patients in the expansion phases ((Groups 6, 7 and 8), dependent on the number of expansion phases required), from 6-8 centres in the UK and an additional 4-6 centres in Europe and Australia. The dose escalation groups, of a minimum of 6 patients with any advanced solid tumour will be recruited to assess tolerability of increasing tablet doses. The groups will be recruited sequentially on the basis of tolerability, at increasing dose levels defined by the Safety review Committee (SRC). The dose escalation groups will be numbered Group 3, 4, 5, 5.1, 5.2 etc (Group 3 onwards). Following the assessment of tolerability of the 400 mg AZD2281 tablet (Group 5.1), approximately 45 patients with confirmed genetic BRCA1/2 ovarian or breast cancer will be randomised to the second expansion group (Group 6). In parallel, if 400 mg bid is tolerated, dose escalation will continue beyond 400 mg bid until the SRC agree that no further doses should be explored (Group 5.2, 5.3 etc). A further 30 patients with confirmed genetic BRCA1/2 ovarian or breast cancer may be randomised to the third expansion group (Group 7) once the final dose has been determined. The final dose investigated will be determined based on both tolerability and acceptability.

Following review of the data from Group 6, a further 60 patients (approximately) with confirmed genetic BRCA1/2 ovarian cancer will be recruited to the randomised tablet formulation continued supply expansion phase (Group 8).

Study period		**Phase of development**
Estimated date of first patient enrolled to the PK Phase	[redacted]	I
Estimated date of last patient completed PK Phase	[redacted]	I
Estimated date of first additional patient enrolled to Continued Supply Expansion Phase	[redacted]	I
Estimated date of last subject completed Continued Supply Expansion Phase	[redacted]	I
Estimated date of first additional patient enrolled to Dose escalation Phase	[redacted]	I
Estimated date of last subject completed Dose escalation Phase	[redacted]	I
Estimated date of last subject completed randomised tablet formulation continued supply expansion phase (Group 8)	[redacted]	I

[redacted]

Objectives

PK Phase

The primary objective of the PK Phase of this study is:

- To determine the comparative bioavailability of the new Melt-extrusion (tablet) formulation of AZD2281 compared to the existing Gelucire® 44/14 (capsule) formulation.

The secondary objectives of the PK Phase of this study are:

- To generate single dose PK data for the Melt-extrusion (tablet) formulation in man, and to generate information on dose linearity for the Melt-extrusion (tablet) formulation.

- To compare the extent of PARP inhibition achieved in peripheral blood mononuclear cells (PBMCs) following dosing of both the Melt-extrusion (tablet) formulation and existing Gelucire® 44/14 (capsule) formulation.

- To determine the safety and tolerability of AZD2281 for both the Melt-extrusion (tablet) formulation and Gelucire® 44/14 (capsule) formulations.

The Primary objective of the Continued Supply Phase of this study is:

- To enable patients to continue taking AZD2281. Safety and tolerability data will be collected to further determine the safety and tolerability of the Gelucire® 44/14 (capsule) formulation of AZD2281 in these patients.

Continued Supply Expansion Phase

The Primary objective of the Continued Supply Expansion Phase of this study is:

- To compare the safety and tolerability profile of the melt-extrusion (tablet) and Gelucire® 44/14 (capsule) formulation of AZD2281 in all patients.

The Secondary objective of the Continued Supply Expansion Phase of this study is:

- To compare (within individual patients in Group 2 and between patients in Group 1) the steady state exposure achieved with 200 mg bid Melt-extrusion (tablet) formulation and 400 mg bid Gelucire (capsule) formulation

- To describe the efficacy data observed in patients treated with the capsule and the Melt-extrusion (tablet) formulation.

Dose Escalation Phase of the continued supply expansion

The Primary objective is:

- To determine the safety and tolerability profile of higher doses than 200 mg bid, of the melt-extrusion (tablet) formulation (Groups 3 onwards) and to compare the safety and tolerability profile of higher doses than 200 mg bid, of the melt-extrusion (tablet) formulation with 400 mg bid Gelucire® 44/14 (capsule) formulation of AZD2281 (Group 6 and 7).

The Secondary objectives are:

- To determine the single dose and steady state exposures achieved with higher doses of AZD2281 melt-extrusion (tablet) formulation.

- To compare between patients the single dose and steady state exposures of AZD2281 achieved with selected tablet doses and the 400 mg bid capsule dose.

- To describe the efficacy data observed in patients treated with the Gelucire® 44/14 (capsule) formulation and the Melt-extrusion (tablet) formulation.

Exploratory Objectives

- To perform exploratory biomarker analysis and to correlate biomarker data with disease progression/response to therapy from optional archival tumour samples collected from the gBRCA patients enrolled into Group 6 and Group 7.

Randomised tablet formulation continued supply expansion phase (Group 8)

The Primary objective is:

- To determine the safety and tolerability profile of selected tablet dose schedules of the melt-extrusion (tablet) formulation.

The Secondary objectives are:

- To determine the single dose and steady state exposures achieved with the selected tablet dose schedules of AZD2281 melt-extrusion (tablet) formulation.

- To obtain a preliminary assessment of the effect of food on the exposure to AZD2281following dosing of the melt-extrusion (tablet) formulation.

- To describe the efficacy data observed in patients treated with the melt-extrusion (tablet) formulation.

Exploratory Objectives:

- To perform exploratory biomarker analysis and to correlate biomarker data with disease progression/response to therapy from optional archival tumour samples.

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- To further characterise the nature and profile of common low grade AEs associated with AZD2281 (nausea, vomiting and fatigue) to maximise understanding of these adverse events and inform future data collection and CRF design.

Study Design

PK Phase

The PK Phase of this study is an open-label, randomised two period cross over study. The purpose of this phase of the study is to establish the comparative bioavailability of the new Melt-extrusion (tablet) formulation compared with the current Gelucire® 44/14 (capsule) formulation. In addition single dose safety & tolerability data will be gathered for both formulations. Patients will be screened within 28 days of Day 1 of the first treatment period. Patients will take part in two randomised treatment periods each separated by a washout period of 6 to 14 days.

Cohort 1 will receive a single 50 mg dose of the Gelucire® 44/14 (capsule) formulation and a single 25 mg dose of the Melt-extrusion (tablet) formulation. Cohort 2 will receive a single 100 mg dose of the Gelucire® 44/14 (capsule) formulation and a single 50 mg dose of the Melt-extrusion (tablet) formulation. Cohorts 1 and 2 will be recruited consecutively, with Cohort 1 recruited first, immediately followed by Cohort 2. Patients will be randomised to treatment sequence. Cohort 3 will be recruited once PK analysis for Cohorts 1 and 2 has completed so as to be able to better define the higher dose level for the Melt-extrusion (tablet) formulation in Cohort 3. Patients in Cohort 3 will be randomised to treatment sequence and will receive a single 400 mg dose of the Gelucire® 44/14 (capsule) formulation and a dose of the new tablet formulation to be decided from the first two cohorts' data. The PK team at AstraZeneca will make the decision about the dose of the Melt-extrusion (tablet) formulation to be used in Cohort 3, following review of the PK and AUC data from Cohorts 1 and 2 confirming the exposure ratio between the Gelucire® 44/14 (capsule) and Melt-extrusion (tablet) formulations.

Continued Supply Phase

The Continued Supply Phase is scheduled 7 days after the end of treatment in the PK Phase. Following completion of the PK Phase, patients may continue to receive treatment with the Gelucire® 44/14 (capsule) formulation (400 mg orally twice daily [bid]) on a continuous basis as long as they remain free from intolerable toxicity and, in the Investigator's opinion, are receiving some clinical benefit from the treatment with AZD2281 and do not meet any other discontinuation criteria.

Continued Supply Expansion Phase

Once the PK team at AstraZeneca have confirmed the exposure ratio between the Gelucire® 44/14 (capsule) and Melt-extrusion (tablet) formulations, approximately, 26 additional patients will be recruited to the Continued Supply Expansion Phase: 20 patients (Group 1) with confirmed genetic BRCA1/2 ovarian or breast cancer will be randomised in a 1:1 ratio to

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receive either daily dosing with tablet or capsule formulation to assess the multiple dose safety profile of the Melt-extrusion (tablet) formulation in a comparative setting; a further 6 patients will be recruited to Group 2 which will directly compare the steady state PK of the capsule and the Melt-extrusion (tablet) formulation. All patients may receive continuous treatment with AZD2281 for as long as the Investigator believes they are receiving benefit.

Dose escalation phase of the continued supply expansion

To investigate the tolerability and pharmacokinetics (after a single dose and at steady state) of higher doses than 200 mg bid, of the AZD2281 melt-extrusion (tablet) formulation in patients with any advanced solid tumour, a minimum of 6 patients will be recruited to Group 3 and will receive 250 mg bid tablet dosing. Contingent upon demonstration of acceptable tolerability (according to pre-defined criteria) of the 250 mg bid tablet dose, a further 6 patients (minimum) will be recruited to the next Group and will receive increased bid tablet dosing. Dose escalation will continue, into additional groups of 6 patients minimum, at increasing dose levels defined by the SRC (see Figure 3). Following the assessment of tolerability of 400 mg AZD2281 tablet (Group 5.1), approximately 45 patients with confirmed genetic BRCA1/2 ovarian or breast cancer will be randomised to Group 6. Dose escalation will continue in parallel with Group 6 beyond 400 mg bid until the SRC agree that no further doses should be explored (Group 5.2, 5.3 etc). Once the final dose is established a further 30 patients with confirmed genetic BRCA1/2 ovarian or breast cancer may be randomised to Group 7. If, however, the MTD is 400 mg bid or lower, Group 6 will be the final group recruited to this study.

Depending on the outcome of the tolerability determination of Group 3 onwards (see Section 6.2.4.3), Group 6 will be conducted as follows:

- **If the highest tolerated tablet dose is greater than 250 mg bid**: Approximately 45 patients with gBRCA ovarian or breast cancer will be randomised 1:1:1 to either 400 mg bid capsule dosing, a tablet dose between 250mg and the higher tablet dose taken into the expansion that has been shown to be safe and tolerable or 400 mg bid AZD2281 tablet dose (or lower if 400 mg bid is not tolerated), to assess the multiple dose safety profile and pharmacokinetics of the Melt-extrusion (tablet) formulation in a comparative setting. Each arm must contain at least 10 gBRCA ovarian patients.

- **If 250 mg bid is the highest tolerated tablet dose:** Approximately 30 patients with gBRCA ovarian or breast cancer will be randomised 1:1 to either 400 mg bid capsule dosing or 250 mg bid tablet to assess the multiple dose safety profile and pharmacokinetics of the Melt-extrusion (tablet) formulation in a comparative setting. Each arm must contain at least 10 gBRCA ovarian patients.

If dose escalation continues beyond 400 mg bid, Group 7 may be conducted as follows:

- Approximately 30 patients with gBRCA ovarian or breast cancer will be randomised 1:1 to either 400 mg bid capsule dosing or a tablet dose (>400 mg bid)

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defined by the SRC, to assess the multiple dose safety profile and pharmacokinetics of the Melt-extrusion (tablet) formulation in a comparative setting. Each arm must contain at least 10 gBRCA ovarian patients.

All patients may receive continuous treatment with their allocated formulation of AZD2281 for as long as the Investigator believes they are receiving benefit.

Randomised tablet formulation continued supply expansion phase

Group 8 will be conducted as follows:

Approximately 60 patients with confirmed genetic BRCA1/2 ovarian cancer will be randomised 1:1:1:1 to one of the dosing schedules detailed below, to assess the multiple dose safety profile and pharmacokinetics of the Melt-extrusion (tablet) formulation in a comparative setting.

- 200mg tds tablet continuous dosing
- 250mg tds tablet 2 weeks on study drug, 1 week off study drug
- 400mg bid tablet 1 week on study drug, 1 week off study drug
- 400mg od tablet continuous dosing

All patients may receive continuous treatment with their allocated schedule of AZD2281 tablet for as long as the Investigator believes they are receiving benefit.

Target subject population

Patients with an advanced solid tumour, which is refractory to standard therapies or for which no suitable effective standard therapy exists. For the patients who will be recruited into Group 1, 6, or 7 or 8 and will receive continuous treatment with the melt-extrusion (tablet formulation) or Gelucire® 44/14 (capsule) formulation (Group 8 patients will receive tablet formulation only), the target population will be further defined as patients with confirmed genetic BRCA1/2 ovarian or breast cancer (Group 8, confirmed genetic BRCA1/2 ovarian only [including primary peritoneal and fallopian tube cancers]), a population that has previously been shown to benefit from AZD2281 and hence stay on treatment for longer. Use of this population therefore provides an opportunity to generate more robust, longer term safety data in comparison to the capsule formulation.

Investigational product, dosage and mode of administration

PK Phase

AZD2281 Gelucire® 44/14 (capsule) formulation will be administered at a dose of 50 mg, 100 mg or 400 mg orally.

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AZD2281 Melt-extrusion (tablet) formulation will be administered at a dose of 25 mg or 50 mg orally (Cohorts 1 & 2). The dose level for Cohort 3 will be determined from the analyses of the PK data from Cohorts 1 & 2.

Patients should fast for at least 2 hours prior to receiving their dose of either formulation of AZD2281. Patients should then refrain from eating or drinking for a further 2 hours after dosing due to the potential effect of food on absorption.

For both treatment periods patients should be dosed preferably at the same time each day. Patients will be advised to take AZD2281 with approximately 240 mL of water. The AZD2281 capsules should be swallowed whole and not chewed, crushed, dissolved or divided

Continued Supply Phase

Patients will have the option to take part in the Continued Supply Phase 7 days after the end of treatment in the PK Phase. AZD2281 – Gelucire® 44/14 (capsule) formulation – will be administered at a dose of 400 mg orally bid (ie, 8 capsules bid).

Continued Supply Expansion Phase (Group 1)

In Group 1, 20 gBRCA patients will be randomised to receive either the 200 mg bid melt-extrusion (tablet) formulation or the 400 mg bid Gelucire® 44/14 (capsule) formulation. These patients may continue to receive their randomised formulation (tablet or capsule) for as long as the investigator believes they are receiving benefit.

Continued Supply Expansion Phase (Group 2)

Group 2 patients will be randomised, using a two period crossover design, to receive either:

- Sequence 1: 200 mg bid AZD2281 tablets (2 tablets bid) for 1 week and 400 mg bid AZD2281 capsules for 1 week

OR

- Sequence 2: 400 mg bid AZD2281 capsules (8 capsules bid) for 1 week followed by 200 mg bid AZD2281 tablets (2 tablets bid) for 1 week

Patients randomised to either sequence may continue to receive 200 mg bid AZD2281 tablets (2 tablets bid) indefinitely, for as long as the investigator believes they are receiving benefit.

Following the plasma concentration determination of the PK samples obtained from Group 2 of the continued supply expansion phase, a within-patient comparison of tablet versus capsule steady state AUC and C_{max} will be performed to confirm the validity of the single dose PK modeling of steady state exposure. Following this analysis, patients continuing on 200 mg bid AZD2281 tablets may have their daily dose adjusted if required.

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Dose escalation phase of the continued supply expansion (Group 3 onwards)

In the first of the dose escalation groups, Group 3 patients will be treated with 250 mg bid AZD2281 tablet dose (2 x 100 mg and 2 x 25 mg tablets bid. Thereafter, dose escalation will continue at dose levels to be decided upon by the SRC. The dose will be administered indefinitely, for as long as the investigator believes they are receiving benefit.

Dose escalation phase of the continued supply expansion (Group 6)

Depending on the determination of tolerability of the tablet dose from Group 3 onwards, Group 6 patients will either receive:

- 400 mg bid capsule dose, 400 mg bid AZD2281 tablet dose (or lower if 400 mg bid is not tolerated) or a tablet dose between 250mg and the higher tablet dose taken into the expansion that has been shown to be safe and tolerable

OR

- 400 mg bid capsule dose or 250 mg bid tablet dose

Dose escalation phase of the continued supply expansion (Group 7)

If 400 mg bid AZD2281 tablet is tolerated and dose escalation continues to a dose defined by the SRC which is greater than 400 mg bid, Group 7 patients will receive:

- 400 mg bid capsule or the highest bid tablet dose deemed tolerable by the SRC following completion of the dose escalation phase

Randomised tablet formulation continued supply expansion phase (Group 8)

Group 8 patients will be randomised to receive one of the following tablet dosing schedules:

- 200mg tds tablet continuous dosing
- 250mg tds tablet 2 weeks on study drug, 1 week off study drug
- 400mg bid tablet 1 week on study drug, 1 week off study drug
- 400mg od tablet continuous dosing

Doses of AZD2281 should be taken at the same times each day, daily (OD) doses should be taken in the morning unless otherwise instructed, twice daily (BD) doses should be taken approximately 12 hours apart and three times (TDS) daily doses taken approximately 8 hours apart. All doses should be taken with approximately 240 mL of water.

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Patients will be instructed to take their doses of AZD2281 at least 2 hours after the last time they ate, and the patient should then refrain from eating for a further 2 hours due to the potential effect of food on absorption. For Group 8 patients (excluding Group 8 od schedule patients), and for all other patients (PK phase cohorts 1 and 2, and Groups 1-7) continuing to receive tablet doses following approval of Amendment 4, AZD2281 can be taken with a light meal and the time restrictions on eating will not apply.

For Group 8 od schedule patients an informal assessment of the effect of food on the PK of AZD2281 will be made. On Day 1 these patients must take their dose of AZD2281 at least 2 hours after the last time they ate, and then refrain from eating for a further 2 hours. On Day 8 patients must take their dose of AZD2281 within 30 minutes of eating breakfast. On all other days doses can be taken with a light meal, and no time restrictions are required.

All ongoing patients taking *capsule* doses of AZD2281 must continue to take their doses of AZD2281 at least 2 hours after the last time they ate, and then refrain from eating for a further 2 hours due to the potential effect of food on absorption of the capsule formulation.

The capsules/tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

The end of this study is defined as the date of the last visit of the last patient, occurring when all patients have completed study therapy.

For patients in the PK phase (cohorts 1 and 2) and Groups 1-7 data collection will continue until both the following criteria have been met:

- all gBRCA Group 1, 6 and 7 patients have progressed as per RECIST or AstraZeneca has determined that sufficient efficacy data has been collected
- all patients continuing on treatment have been assessed for safety for a minimum of 6 cycles (1 cycle being 28 days) or all patients have discontinued study treatment, whichever is the earlier.

When the above criteria are met the clinical database will be closed and only SAE data and investigator's assessment of response will be collected. All patients in the PK phase (cohorts 1 to 3) and Groups 1-7 can continue to receive study treatment until they meet any discontinuation criteria as per Section 5.5.1. Once all patients have completed 6 cycles, all protocol assessments can be stopped and patients should attend clinic visits according to routine clinical practice, approximately every 6-8 weeks. SAEs will continue to be reported to AstraZeneca in the usual way for patients who continue on AZD2281 until 30 days after study treatment is discontinued and followed-up as outlined in Section 5.5.2. Drug accountability should continue to be performed until the patient stops study treatment completely.

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For patients in Group 8 all data will be collected in the clinical database up to and including Cycle 6 for each patient. For patients continuing past Cycle 6 only AEs, SAEs, concomitant medication, laboratory data, dosing information will be collected in the database. Investigator's assessment of response will be assessed but not collected in the clinical database. All other protocol assessments do not need to be performed.

For patients in Group 8 all data collection will continue until both the following criteria have been met:

- all Group 8 patients have progressed as per RECIST or AstraZeneca has determined that sufficient efficacy data has been collected
- all Group 8 patients continuing on treatment have been assessed for safety for 12 cycles (or AstraZeneca has determined that sufficient safety data has been collected), or all patients have discontinued study treatment, whichever is the earlier.

When the above criteria are met the clinical database will close to new data. All patients in Group 8 can continue to receive study treatment until they meet any discontinuation criteria as per Section 5.5.1. Once the criteria above have been met and the database closed, all protocol assessments can be stopped and patients should attend clinic visits according to routine clinical practice, approximately every 6-8 weeks. SAEs will continue to be reported to AstraZeneca in the usual way for patients who continue on AZD2281 until 30 days after study treatment is discontinued and followed-up as outlined in Section 5.5.2. Drug accountability should continue to be performed until the patient stops study treatment completely

Duration of treatment

PK Phase

AZD2281 will be administered as a single dose of either formulation on Day 1 of each treatment period. Patients will have a minimum of 6 days (maximum 14 days) between receiving each treatment, thus this will equate to dosing on Day 1 and ≥ Day 8 of the study.

Each formulation of AZD2281 should be taken at the same time on each treatment day, with approximately 240 mL of water.

Continued Supply Phase

Providing the safety and tolerability of AZD2281 is acceptable, the patient will have the option to continue to receive Gelucire® 44/14 (capsule) formulation AZD2281 on an ongoing basis at a dose of 400 mg bid (ie, 8 capsules bid), continually.

Continued Supply Expansion Phase

Approximately, 185 additional patients will be recruited to the Continued Supply Expansion Phase:

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Investigating 200 mg bid tablet dose (Groups 1 and 2)

- 20 gBRCA patients will be recruited to Group 1 and treated with either 200 mg bid AZD2281 Melt-extrusion (tablet) formulation or 400 mg bid Gelucire® 44/14 (capsule) formulation, on an ongoing basis, to assess the multiple dose safety profile of the tablet formulation and determine the steady state pharmacokinetics in a comparative setting

- 6 patients will be recruited to Group 2 which will directly compare the steady state PK of 400 mg bid capsule and 200 mg bid Melt-extrusion (tablet) formulation before continuing on treatment with 200 mg bid tablets.

Investigating tablet doses higher than 200 mg bid (Groups 3-7)

- A minimum of 6 patients will be recruited to Group 3 which will assess the tolerability and pharmacokinetics of 250 mg bid AZD2281 melt-extrusion (tablet) formulation

- If 250 mg bid tablet dose is tolerated, a minimum of 6 patients will be recruited to Group 4 which will assess the tolerability and pharmacokinetics of 300 mg bid AZD2281 melt-extrusion (tablet) formulation

- If 300 mg bid tablet dose is tolerated, a minimum of 6 patients will be recruited to Group 5 which will assess the tolerability and pharmacokinetics of 350 mg bid AZD2281 melt-extrusion (tablet) formulation.

- If 350 mg bid tablet dose is tolerated, a minimum of 6 patients will be recruited to Group 5.1 which will assess the tolerability and pharmacokinetics of 400 mg bid AZD2281 melt-extrusion (tablet) formulation

- If 400 mg bid tablet dose is tolerated, dose escalations will continue in a minimum of 6 patients each time to Groups 5.2, 5.3 etc. Dose increases will be at the discretion of the SRC and will continue up a dose agreed by the SRC

- Approximately 45 patients will be randomised to Group 6 and treated with either 400 mg bid AZD2281 capsule dose, a tablet dose between 250mg and the higher tablet dose taken into the expansion that has been shown to be safe and tolerable, or 400 mg bid AZD2281 tablet dose (or lower if 400 mg bid is not tolerated). Each of these arms must contain approximately 15 patients of which at least 10 must be gBRCA ovarian patients

- If dose escalation continues beyond 400 mg bid, approximately 30 patients may be randomised to Group 7 with either 400 mg bid capsule dosing or a bid tablet dose (>400 mg bid) agreed by the SRC. Each of these arms will contain approximately 15 patients of which at least 10 must be gBRCA ovarian patients.

Investigating different tablet schedules (Group 8)

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Approximately 60 patients will be recruited into Group 8 to assess the safety and tolerability of AZD2281 in the following tablet dose schedules: -

- 200mg tds tablet continuous dosing
- 250mg tds tablet 2 weeks on study drug, 1 week off study drug
- 400mg bid tablet 1 week on study drug, 1 week off study drug
- 400mg od tablet continuous dosing

There is no maximum duration of treatment with either formulation of AZD2281. Patients will continue with AZD2281 treatment until objective disease progression or as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. Following the commencement of continuous daily treatment of either formulation, study safety assessments will continue to be performed until treatment discontinuation or study completion (see Section 10.5). If a patient remains on study treatment following the completion of the study, SAEs will continue to be collected until treatment discontinuation.

Once patients receiving AZD2281 have been discontinued from study treatment, other treatment options will be at the discretion of the Investigator.

Outcome variable(s):

PK Phase

- **Primary outcome variable**
  - C_{max}, AUC_{0-t} and AUC for each of the 2 formulations
  - The following PK parameters will also be derived and reported for each of the formulations: t_{max}, λz, $t_{1/2}$, CL/F, and Vz/F
- **Secondary outcome variables**
  - Pharmacodynamic (PD): PARP inhibition in PBMCs
  - Safety: AEs, physical examination, vital signs including blood pressure (BP) pulse and body temperature, electrocardiogram (ECG) and laboratory findings including clinical chemistry, haematology and urinalysis.

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Continued Supply Phase

- **Primary outcome variable**

  – Safety: AEs, physical examination, vital signs including BP, pulse and body temperature ECG and laboratory findings including clinical chemistry, haematology and urinalysis.

Continued Supply Expansion Phase (including dose escalation groups)

- **Primary outcome variable**

  – Safety (all patients): AEs, physical examination, vital signs including BP, pulse and body temperature ECG and laboratory findings including clinical chemistry, haematology and urinalysis.

- **Secondary outcome variables**

  – The following single dose PK parameters will be derived for the Melt Extrusion (tablet) formulation and the Gelucire® 44/14 (capsule) formulation: C_{max}, C_{min} and AUC_{0-8} (Group 8 tds schedule) , AUC_{0-12} (all patients on bd schedule) and AUC_{0-24} (Group 8 od schedule),

  – The following multiple dose PK parameters will be derived for the Melt Extrusion (tablet) formulation and the Gelucire® 44/14 (capsule) formulation: $C_{ss,max}$, $C_{ss,min}$ and AUC_{ss}

  – Efficacy: change from baseline in the sum of target lesions (as per RECIST), Progression-Free Survival (PFS), best overall response, CA-125 response

  – Preliminary assessment of the effect of food on the exposure of AZD2281 tablet (Group 8 patients only) – Day 8 : Day 1 Cmax and AUC_{0-24} ratios

- **Exploratory outcome variables**

  – Exploratory biomarker analysis of the activity of AZD2281 and correlation with disease progression/response to therapy will be conducted. If available, archival tumour samples from patients enrolled Group 6, 7 and 8 will be collected in order to achieve this objective.

Statistical methods

PK Phase

The primary objective of the PK Phase is to investigate the comparative bioavailability of the new Melt-extrusion (tablet) formulation of AZD2281 compared to the existing Gelucire® 44/14 (capsule) formulation. Secondary objectives are to generate single dose PK data for the

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Melt-extrusion (tablet) formulation in man and to generate information on dose linearity for the Melt-extrusion (tablet) formulation.

A PK/PD model which uses PARP inhibition in PBMCs as the PD endpoint, is also currently being developed and if this is successful, will be used to compare the PARP inhibition data from PBMC samples collected in this study following dosing of the two formulations with a view to demonstrating that a similar extent of PARP inhibition can be achieved following dosing of the two formulations.

Plasma concentration data, PK parameters and PARP inhibition data will be listed and summarised descriptively by dose level and formulation administered using the appropriate standard summary statistics. Within each cohort, comparative bioavailability will be estimated using an analysis of variance with factors for patient, formulation and period. The associated 90% confidence interval will also be calculated.

Safety variables will be listed and summarised descriptively.

Continued Supply Phase

Patients entering the continued supply phase following the PK phase, will continue to be followed for safety and tolerability, and data collected from such patients will be listed and summarised. No formal statistical analyses will be performed.

Continued Supply Expansion Phase

Approximately 185 additional patients will be recruited to the Continued Supply Expansion Phase.

Investigating 200 mg bid tablet dose (Groups 1 and 2)

The primary objective of the Continued Supply Expansion Phase will involve approximately 20 patients (Group 1) with confirmed genetic BRCA1/2 ovarian or breast cancer being randomised in a 1:1 ratio to either daily dosing with tablet or capsule formulation. This will allow the assessment of the multiple dose safety profile of the Melt-extrusion (tablet) formulation in a comparative setting. In terms of safety data, no formal statistical comparisons of data will be performed. Instead, data will be listed and summarised descriptively by formulation (tablet or capsule). Steady state pharmacokinetic and efficacy data will also be collected and summarised by formulation (tablet or capsule).

The secondary objectives of the Continued Supply Expansion Phase will involve an additional cohort of 6 patients (Group 2) being recruited to enable a direct within-patient comparison of the steady state PK of the capsule and the Melt-extrusion (tablet) formulation.

In addition, steady state PK will be assessed in the Group 1 population to determine multiple dose pharmacokinetic parameters for the melt extrusion (tablet) formulation and the Gelucire® 44/14 (capsule) formulation in man. Plasma concentration data and PK parameters will be listed and summarised descriptively using the appropriate standard summary statistics. In terms of the efficacy data, summaries and waterfall plots of percentage change from baseline

[redacted]

in sum of target lesions will be presented, and this data will also be analysed by analysis of covariance fitting baseline sum of target lesions as a continuous covariate and treatment group as a factor. Summary statistics will be presented for best overall response according to RECIST. PFS will be summarised using Kaplan-Meier estimates over time and will be displayed graphically.

Investigating tablet doses higher than 200 mg bid (Groups 3-7)

The primary objective of the dose escalation phase of the continued supply expansion is to determine the safety and tolerability profile of higher doses than 200 mg bid, of the melt-extrusion (tablet) formulation in groups of a minimum of 6 patients – (Groups 3 onwards), to compare the safety and tolerability profile of higher doses than 200 mg bid, of the melt-extrusion (tablet) formulation with 400 mg bid Gelucire® 44/14 (capsule) formulation of AZD2281 in approximately 45 gBRCA ovarian and breast cancer patients (Group 6) and to compare the safety and tolerability profile of higher dose AZD2281 tablet bid with 400 mg bid Gelucire® 44/14 (capsule) formulation of AZD2281 in approximately 30 gBRCA ovarian and breast cancer patients (Group 7). No formal statistical comparisons of safety data will be performed. Instead, data will be listed and summarised descriptively by dose.

The secondary objectives of the dose escalation within the continued supply expansion will involve:

- All patients from Group 3 to 5 contributing to an assessment of the single dose and steady state exposures achieved with higher doses than 200 mg bid, of AZD2281 melt-extrusion (tablet) formulation and all patients from Group 6 and 7 contributing to a comparison between patients of single dose and steady state exposures of AZD2281 achieved with selected tablet doses and the 400 mg bid capsule dose. Plasma concentration data and PK parameters will be listed and summarised descriptively using the appropriate standard summary statistics.

- To describe the efficacy data observed in patients treated with the Gelucire® 44/14 (capsule) formulation and the Melt-extrusion (tablet) formulation. Summaries and waterfall plots of percentage change from baseline in sum of target lesions will be presented, and this data will also be analysed by analysis of covariance fitting baseline sum of target lesions as a continuous covariate and treatment group as a factor. Summary statistics will be presented for best overall response according to RECIST. PFS will be summarised using Kaplan-Meier estimates over time and will be displayed graphically. Analyses will be performed in the overall population and in the gBRCA ovarian cancer subgroup.

- Correlative analyses of tumour biomarkers from archival biopsies will be reported outside the CSR.

Investigating different tablet schedules (Group 8)

The primary objective of the randomised tablet formulation continued supply expansion phase is to determine the safety and tolerability profile of selected dose schedules of the melt-

[redacted]

extrusion (tablet) formulation. No formal statistical comparisons of safety data will be performed. Instead, data will be listed and summarised descriptively by dose schedule.

The secondary objectives of the randomised tablet formulation continued supply expansion phase will involve:

- All patients from Group 8 contributing to an assessment of the single dose and steady state exposures of AZD2281 achieved with selected tablet dose schedules. Plasma concentration data and PK parameters will be listed and summarised descriptively using the appropriate standard summary statistics.

- To describe the efficacy data observed in patients treated with the Melt-extrusion (tablet) formulation. Summaries and waterfall plots of percentage change from baseline in sum of target lesions will be presented, and this data will also be analysed by analysis of covariance fitting baseline sum of target lesions as a continuous covariate and treatment group as a factor. Summary statistics will be presented for best overall response according to RECIST. PFS will be summarised using Kaplan-Meier estimates over time and will be displayed graphically. Analyses will be performed in the overall population.

- To obtain a preliminary assessment of the effect of food on the exposure of AZD2281.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
ADP	Adenosine diphosphate
AE	Adverse event (see definition in Section 7.3.1)
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANC	Absolute neutrophil count
API	Active pharmaceutical ingredient
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
ATM	Ataxia telangiectasia mutated
AUC	Area under curve
AUC_{ss}	Area under curve at steady state
BER	Base excision repair
BID	Twice daily
BP	Blood pressure
BRCA	Breast cancer gene type
BUN	Blood urea nitrogen
CI	Confidence interval
CL/F	Apparent clearance
C_{max}	Maximum concentration
CRF	Case Report Form (paper)
CRO	Clinical Research Organisation
CV	Coefficient of Variation
$C_{ss,max}$	Maximum concentration at steady state
$C_{ss,min}$	Minimum concentration at steady state
DAE	Discontinuation due to Adverse Event
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram

[redacted]

Abbreviation or special term	Explanation
ECOG	Eastern Co-operative Oncology Group
Ethics Committee (EC)	Synonymous to Institutional Review Board and Independent Ethics Committee
EU	European Union
F	Bioavailability (systemic availability of the administered dose)
FDA	Food and Drug Administration
gBRCA	Confirmed genetic BRCA mutation
G-CSF	Granulocyte Colony-Stimulating Factor
GGT	Gamma Glutamyltransferase
GCP	Good Clinical Practice
gmean	Geometric mean
GM-CSF	Granulocyte-Macrophage Colony Stimulating Factor
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus
HPLC-MS/MS	High performance liquid chromatography with tandem mass spectrometric detection
HPMC	Hydroxypropyl methyl cellulose
HRD	Homologous Recombination Deficiency
IATA	International Air Transport Association Dangerous Goods
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally.
INR	International Normalised Ratio
IPS	Investigational Product Supplies
λz	Elimination rate constant
LDH	Lactic Dehydrogenase
LHRH	Luteinizing Hormone-Releasing Hormone
LOQ	Limit of Quantification
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume

[redacted]

Abbreviation or special term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MTD	Maximum Tolerated Dose
mRNA	Messenger ribonucleic acid
NAD	Nicotine adenine dinucleotide
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
NQ	Non-quantifiable
OAE	Other Significant Adverse Event (i.e., adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment)
OD	Once daily
PAR	Poly- (ADP-ribose)
PARP	Poly- (ADP-ribose) polymerase
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamics
PFS	Progression-Free Survival
PK	Pharmacokinetics
R&D	Research and Development
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event (see definition in Section 7.3.2).
SAP	Statistical Analysis Plan
SD	Standard Deviation
SPC	Summary of Product Characteristics
SPE	Solid phase extraction
SRC	Safety Review Committee
Study Medication	Refers to both drug under investigation and comparators administered as part of the schedule
TDS	Three times daily
$t_{1/2}$	Terminal half-life
ULN	Upper Limit of Normal
Vz/F	Apparent Volume of Distribution during terminal phase
WBC	White Blood Cells

[redacted]

1. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

1.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 7.3.4.**

In the case of a medical emergency the Investigator may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development site shown below.

Name	Role in the study	Address & telephone number
[redacted]		

[redacted]

Name	Role in the study	Address & telephone number
[redacted]		

1.2 Overdose

There is currently no specific treatment in the event of overdose of AZD2281 and possible symptoms of overdose are not established.

The primary anticipated complications of over dosage may consist of bone marrow suppression. Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

- All overdose reports must be reported to AstraZeneca Patient Safety Department as soon as the Investigator becomes aware of it;
- An overdose with associated SAEs is recorded as the SAE diagnosis/symptoms on the relevant adverse event (AE) forms in the Case Report Form (CRF) only;
- An overdose with associated non-serious AEs is recorded as the AE diagnosis/symptoms on the relevant AE forms in the CRF and on the separate AstraZeneca "Clinical Study Overdose Report Form";
- An overdose without associated symptoms is only reported on the separate AstraZeneca "Clinical Study Overdose Report Form".

[redacted]

1.3 Pregnancy

All outcomes of pregnancy must be reported to AstraZeneca.

1.3.1 Maternal exposure

The outcomes of any conception occurring from the date of the first dose of study medication until 3 months after the last dose of study medication must be followed up and documented.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then Investigators or other site personnel must inform appropriate AstraZeneca representatives immediately but no later than the end of the next business day of when he or she becomes aware of it. The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the appropriate AstraZeneca Patient Safety data entry site within 30 calendar days.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

1.3.2 Paternal exposure

The outcomes of any conception occurring from the date of the first dose of study medication until 3 months after the last dose of study medication must be followed up and documented.

Male patients must refrain from fathering a child during the study and 3 months following the last dose, since the potential for chromosomal aberrations in male gametes, and possible teratogenicity effects thereof, has not yet been thoroughly investigated.

Pregnancy of subjects' partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

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2. INTRODUCTION

Investigators should be familiar with the AZD2281 Investigator Brochure (IB).

2.1 Background

2.1.1 PARP

Polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] or PAR polymerisation is a unique post-translational modification of histones and other nuclear proteins that contributes to the survival of proliferating and non-proliferating cells following deoxyribonucleic acid (DNA) damage. This event represents an immediate cellular response to DNA damage and involves the modification of glutamate, aspartate and lysine residues with the addition of long chains of Adenosine diphosphate (ADP)-ribose units, derived from Nicotine adenine dinucleotide (NAD)+, onto the DNA-binding proteins. The enzymes that catalyse this process, poly-(ADP)-ribose polymerases (PARPs), are critical regulatory components in DNA damage repair and other cellular processes. They now comprise a large and expanding family of 18 proteins, encoded by different genes, and display a conserved catalytic domain in which PARP 1 (113 kDa), the initial member, and PARP 2 (62 kDa) are so far the sole enzymes whose catalytic activity has been shown to be immediately stimulated by DNA strand breaks. Moreover, many of the identified family members interact with each other, share common partners and common sub-cellular localisations, suggesting functional redundancy and possibly fine-tuning in the regulation of post-translational modification of proteins.

The range of biological roles involving PARP proteins is wide. They include: DNA repair and maintenance of genomic integrity, regulation of protein expression at the transcriptional level, regulation of cellular replication and differentiation, regulation of telomerase activity, involvement in cell elimination pathway by necrosis and serving as a signal for protein degradation in oxidatively injured cells (Virag and Szabo 2002).

Of the various members of the PARP enzyme family, only PARP 1 and PARP 2 work as DNA damage sensor and signalling molecules. PARP 1 is a nuclear enzyme consisting of 3 domains; the N-terminal DNA binding domain containing 2 zinc fingers, the auto-modification domain and the C-terminal catalytic domain. It binds to both single and double stranded DNA breaks through the zinc-finger domain. PARP 1 catalyses the cleavage of NAD+ into nicotinamide and ADP-ribose, the latter is then synthesised to form branched nucleic acid-like polymers covalently attached to nuclear acceptor proteins. This branched ADP-ribose polymer is highly negatively charged, thereby affecting the function of the target proteins. Histones have been found to be acceptors of poly ADP-ribose; the negative charge leads to electrostatic repulsion between DNA and histones. This has been implicated in chromatin remodelling, DNA repair and transcriptional regulation. Other transcriptional factors and signalling molecules shown to be poly-ADP-ribosylated by PARP 1 are nuclear factor-KB, DNA-dependant protein kinase, p53, topoisomerase I, lamin B and PARP 1 protein itself.

PARP 1 activation leads to DNA repair through the base excision repair (BER) pathway, and cells deficient in PARP 1 have been shown to have delayed DNA repair function. Like PARP1, PARP 2 also responds to DNA damage and will similarly lead to single strand DNA repair. For both proteins, inactivation and cleavage promotes apoptosis and is part of the apoptotic cascade. Loss of PARP 1 activity in cells or in knockout mice leads to both radio and chemo-sensitisation. Moreover, increased PARP 1 activity has been found in many tumour types. The use of PARP inhibitors has confirmed that in combination an enhancement of the anti-tumour activity of radiation and DNA damaging cytotoxic agents occurs (Virag and Szabo 2002, Nguewa et al 2005). However, many of these inhibitors were of low potency and poor selectivity for PARP 1.

2.1.2 Homologous recombination deficiency and PARP

AZD2281 (previously referred to as KU-0059436 in earlier studies) is an inhibitor of PARP 1 and shows monotherapy activity in tumour cells with defective components of homologous recombination, which includes cells with the BRCA1-/- and BRCA2-/- genotype. Due to the molecular targeting of AZD2281 to specific subsets of tumours, this has raised the opportunity for relatively less toxic cancer monotherapy using such a PARP 1 inhibitor compared with conventional treatments, such as chemotherapy. AZD2281 displays anti-tumour activity to a variety of tumour cell lines and this sensitivity of the cells is known, in some instances and believed in others, to depend upon components of a defective homologous recombination capability. As a major example of this selective activity, the breast cancer (BRCA)-/- gene tumours (both BRCA1 and BRCA2) are seen to be highly sensitive to PARP inhibition. Recent studies indicate that PARP inhibition in BRCA1 and BRCA2 homozygous null cells, but not the isogenic BRCA heterozygous cells, leads to selective cell death. The BRCA1 and 2 genes encode proteins that are implicated in homologous DNA strand break repair, known as homologous recombination. BRCA1 or BRCA2 dysfunction profoundly sensitises cells to PARP inhibition, leading to chromosomal instability, cell cycle arrest and apoptosis (Farmer et al 2005). This sensitivity compared to unaffected heterozygous tissue provides a large therapeutic window for PARP inhibition.

The homologous recombination pathway involves a number of different proteins. Several of these have a strong disease linkage to a number of cancers when they are deficient ie, the well-known cancer-susceptibility proteins BRCA1 and BRCA2 as described above along with Ataxia Telangiectasia Mutated (ATM) and Mre11. For example, loss of BRCA due to inherited mutations results in a significant risk of developing breast and ovarian cancer, and is the best-known example of homologous recombination deficiency (HRD). Pre-clinical responses have been demonstrated in inherited (genetic) BRCA deficient tumours treated with AZD2281 and this has been validated clinically. However, loss of BRCA can also arise spontaneously during tumour formation, as can the loss of other HR proteins such as ATM, & MRE-11. Pre-clinically, similar sensitivity to AZD2281 of cancer cells has been observed whether HRD is based on deficiencies in BRCA1 or BRCA2 (inherited or spontaneous), or based on other HRDs such as ATM or MRE11. This similar sensitivity in pre-clinical models is expected to translate to similar responsiveness in the clinic. The broader HRD tumour populations include triple negative breast (~20%), serous ovarian (~50% of total ovarian), head and neck squamous cell (~ 40%), non-small cell lung (~30%) and colorectal (~15%).

[redacted]

2.1.3 Pre-clinical experience with AZD2281

The pre-clinical experience is fully described in the IB. Key findings are summarised below.

The AZD2281 molecule shows cellular activity in the low nM range with a cellular dose for 50% inhibition (IC50) of 2 nM in HeLa cells.

Distribution of AZD2281 is typical for an orally administered foreign compound, in the gastro-intestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. Metabolism data to date is limited and further investigations are ongoing. To date, several metabolites have been observed in pre-clinical studies, although their identification and activity have yet to be confirmed. Similar metabolite profiles were observed in the urine and faeces of male and female rats. Excretion is primarily via the faeces and to a lesser extent, the urine. In a study of [^{14}C]-AZD2281 in the rat, excretion was 76±13% in faeces and 20±11% in urine.

2.1.4 Toxicology and safety pharmacology summary

AZD2281 has been tested in a standard range of safety pharmacology studies ie, dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetized dog or any behavioural, autonomic or motor effects in the rat at the doses studied.

The toxicology studies indicate that the major target organ of toxicity is the bone marrow. Specific *ex vivo* work has been conducted exposing human bone marrow cells to AZD2281, which has confirmed that AZD2281 is also active against human marrow. However, the cytotoxic effect becomes evident at a higher concentration than that which fully ablates PARP activity (mean IC50 of 2.7 μM for myelosupression in n=4 human donors compared with 0.1 μM for total PARP-1 activity inhibition). These data along with the 28-day dog and rat studies show a myelotoxic effect that is mild-to-moderate and is reversible. Platelets appear first affected, followed by white blood cells. Twenty-six week repeat oral dose studies of AZD2281 in rat and dog have given similar results, with the drug being well tolerated and no drug-related mortality. Importantly, oncology clinics are well used to monitoring for the onset of such effects and are expert in their management.

AZD2281 was genotoxic in the rat micronucleus test. These findings are not uncommon for many therapeutic agents used in oncology and so do not present an unacceptable risk when appropriately clinically managed.

In the male fertility study in the rat, administration of AZD2281 to male rates at doses of 5, 15 or 40 mg/kg/day prior to puberty and throughout spermatogenesis had no adverse effect on mating performance, fertility, embryonic survival, sperm parameters, male reproductive tract organ weights or histological appearance of testes or epididymides. Dosing males with 1 or 40 mg/kg/day resulted in dosage-related slight toxicity. Dosing males with 5 mg/kg/day caused no significant effects.

[redacted]

In the embryofoetal development study in the rat, administration of AZD2281 to female rats during the period of major embryonic organogenesis at a dose of 0.5 mg/kg resulted in slight maternal toxicity. There was no effect on pregnant animals after dosing with 0.05 mg/kg/day. After dosing with 0.5 mg/kg/day, early embryofoetal survival and foetal weights were reduced with the occurrence of major eye and vertebrean/rib malformations and increased incidences of several visceral and skeletal minor abnormalities and variants. After dosing with 0.05 mg/kg/day, there was an associated increased incidence in a minor visceral abnormality and skeletal variant. There was also one foetus with a major eye malformation. A "no observed adverse effect" dose level for foetal abnormalities was not established.

2.1.5 Clinical experience

The clinical experience with AZD2281 is fully described in the IB and has been conducted with the Gelucire® 44/14 (capsule) formulation.

As of 20 November 2009, >950 patients suffering from ovarian, breast and a variety of other advanced solid tumours had been exposed to AZD2281 across the dose range 10 mg od to 600 mg bid, either as monotherapy (n=11 studies) or in combination with other chemotherapy agents (liposomal doxorubicin, cisplatin, DTIC, gemcitabine, gemcitabine+cisplatin, carboplatin, carboplatin+paclitaxel, paclitaxel, topotecan, irinotecan, or bevacizumab).

Data from these studies indicate that AZD2281 is generally well tolerated at doses up to 400 mg bid in patients with solid tumours. Administration of AZD2281 has been associated with:

- Laboratory findings and/or clinical diagnoses of
  - Anaemia, generally mild to moderate (CTCAE grade 1 or 2)
  - Neutropenia, predominantly mild to moderate (CTCAE grade 1 or 2)
  - Thrombocytopenia, generally mild to moderate (CTCAE grade 1 or 2), sometimes severe (CTCAE grade 3 or 4)
- Pneumonitis events with no consistent clinical pattern have been reported in a small number of patients
- Nausea and vomiting, generally mild to moderate (CTCAE grade 1 or 2), intermittent and manageable on continued treatment.
- Fatigue, generally intermittent of mild to moderate intensity (CTCAE grade 1 or 2).

AZD2281 appears to be generally well tolerated at PARP inhibitory dose levels in non-clinical toxicological testing and in the ongoing monotherapy clinical studies. Thus it represents a potential advance in the treatment of advanced cancers by directly inhibiting PARP-1 and hence tumour growth, either when used as monotherapy or in combination therapy with other cytotoxic agents (such as alkylating agents and the tecans).

[redacted]

Preliminary data from Phase I and Phase II studies of AZD2281 in combination with various chemotherapy agents indicate an increase in neutropenia, thrombocytopenia and anaemia compared to giving these agents alone. This bone marrow toxicity can be prolonged and recovery may be delayed. These findings are consistent with pre-clinical findings.

From the completed studies, there are no safety concerns noted for the renal or hepatic parameters measured and no clinically significant changes of concern relating to coagulation parameters. The changes in haematological parameters (haemoglobin, neutrophils, and thrombocytes) are as expected for monotherapy AZD2281 or can be explained by co-existing conditions/previous chemotherapy. Preliminary data from Phase I and Phase II studies of AZD2281 in combination with various chemotherapy agents indicate an increase in neutropenia, thrombocytopenia and anaemia compared to giving these agents alone. These findings are consistent with pre-clinical findings and are reflected in the more severe haematological events ie, CTCAE grade 4 neutropenia, febrile neutropenia and thrombocytopenia being reported as SAEs.

Final laboratory data from D0810C00002 (KU36-92) study has shown MCV increases in approximately 30% of patients in the study, especially with prolonged treatment with AZD2281 (≥6 cycles of treatment). The MCV elevations were mild to moderate in intensity, observed in the 200 mg bid dose cohort and above and were asymptomatic in nature. There was no obvious correlation of MCV with haemoglobin, platelets or WBC values for these patients, and there does not appear to be any clinical consequences. MCV has not been captured as a standard laboratory parameter within the AZD2281 Phase II studies D0810C00008 (KU36-44) and D0810C00009 (KU36-58), however elevations in MCV were also observed in a number of patients from these studies. The MCV elevations again appear to become progressively elevated over time. MCV has been included in many of the ongoing studies and will be included in future study protocols to allow further safety investigation.

Elevations in serum amylase were observed in approximately 15% of patients from final laboratory study data from D0810C00002 (KU36-92). The majority of these increases (13%) were mild to moderate (CTCAE grade 1 or 2) with no apparent link to clinical symptoms. The impact of AZD2281 on amylase and lipase is unclear and the parameters have been incorporated into ongoing protocols and will be measured in future protocols to allow further investigation. No new significant safety information has emerged from any other reported studies with respect to elevations in serum amylase.

2.1.6 Human pharmacokinetic summary

Following administration of single oral doses of AZD2281 (Gelucire® 44/14 [capsule] formulation) to cancer patients at doses of 10 to 600 mg, absorption is relatively rapid with maximum plasma concentrations achieved between 1 and 3 hours after dosing in the majority of patients. Following the peak, the plasma concentrations decline bi-phasically with a terminal half-life (based on sampling to 24 hours after dosing) of between 5 and 7 hours. The exposures achieved increase proportionally with dose at doses up to 100 mg but increase less than dose proportionally thereafter. The mean volume of distribution and plasma clearance are approximately 40 L and 4.55 L/h.

[redacted]

Following daily administration of AZD2281 on a once or twice daily basis, the pharmacokinetics (PK) showed no marked time dependency with steady state exposure being, respectively, approximately 20 and 50% higher than that following a single dose.

2.1.7 New Melt-Extrusion (tablet) formulation- Pre-clinical experience

The current Gelucire® 44/14 (capsule) formulation of AZD2281 is a large capsule (size zero) containing 50 mg of AZD2281. Dose finding studies are on going however; currently the clinical efficacious dose is projected to be between 200 mg and 400 mg bid. This will result in a daily dose between 8 and 16 large capsules. Attempts to increase the drug loading of this capsule and maintain similar exposure in pre clinical models have been unsuccessful. Therefore, an extensive formulation exercise has been undertaken to find a formulation with improved drug loading and bioavailability.

These formulation efforts have been focussed on improving the exposure of AZD2281 and after comparing potential drug delivery approaches, a formulation which renders the AZD2281 amorphous and presents the drug in a solid dispersion in copovidone (30% drug loading) was developed using a melt extrusion process. The milled extrudate is then blended with pharmacopoeial excipients and compressed into a tablet. The tablets are then film coated.

The Melt-Extrusion (tablet) formulation, when dosed to fasted dogs at a 100 mg dose, shows at least 2.4 times the C_{max} & AUC than the Gelucire® 44/14 (capsule) formulation. In addition the Melt-Extrusion (tablet) formulation showed reduced variability in dog with CV of ~ 20% as compared to ~ 50% for the Gelucire® 44/14 (capsule) formulation.

It is expected that the new Melt-Extrusion (tablet) formulation of AZD2281 should provide a more bioavailable and patient friendly formulation by minimising the number of dosage units and providing a more consistent PK profile.

2.2 Research hypothesis

PK Phase

The aim of the study is to test the hypothesis that the bioavailability of the new Melt-Extrusion (tablet) formulation is better in man than the existing Gelucire® 44/14 (capsule) formulation. Pre-clinical data in the dog supports an increase in bioavailability for the new Melt-Extrusion (tablet) formulation with a greater than two-fold increase of AUC compared to the existing Gelucire® 44/14 (capsule) formulation (Section 2.1.7). This study will test if this improvement in AUC in the dog can translate to an improvement in AUC in man and if so what increase in exposure can be achieved with the new Melt-Extrusion (tablet) formulation.

PK modelling of the plasma concentration data will be conducted in order to determine the dose of the Melt-Extrusion (tablet) formulation that would be predicted to give exposure (AUC_{ss}) to AZD2281 which would be within the range of exposures previously determined

[redacted]

for the Gelucire® 44/14 (capsule) formulation. The dose of the Melt-Extrusion (tablet) formulation determined will then be taken forward into the Phase III trial.

Pharmacodynamic assessments will be made to determine the extent of PARP inhibition achieved in peripheral blood mononuclear cells (PBMCs) after dosing with the Melt-Extrusion (tablet) formulation and the Gelucire® 44/14 (capsule) formulation of AZD2281.

AZD2281 Melt-Extrusion (tablet) formulation has an acceptable single dose safety and tolerability profile.

Continued Supply Phase and Expansion Phase

The primary objective of the Continued Supply Phase of this study is to enable patients recruited into the PK phase of the study to continue to receive treatment with AZD2281 (Gelucire® 44/14 (capsule) formulation) if they are free from intolerable toxicity and, in the investigator's opinion, are receiving some benefit. In addition, approximately 26 additional patients will be recruited to the Continued Supply Expansion Phase of which 20 gBRCA ovarian or breast cancer patients will be recruited to Group 1 to compare the multiple dose safety and tolerability profile of the Melt-extrusion (tablet) formulation and the capsule formulation.

The secondary objectives of the Continued Supply Expansion Phase will involve 6 patients (Group 2) being recruited to directly compare the steady state PK of the capsule and the Melt-extrusion (tablet) formulation as well as to assess the safety of the tablet formulation. Steady state PK will also be assessed in the Group 1 population to determine multiple dose pharmacokinetic parameters for the melt extrusion (tablet) formulation and Gelucire® 44/14 (capsule) formulation. In addition, efficacy will be investigated and summarised in the two treatment arms of the Group 1 population.

The primary objective of the continued supply expansion phase will be expanded to investigate the safety and tolerability of higher doses than 200 mg bid, of the tablet formulation, by including several groups (Groups 3 onwards) of a minimum of 6 patients with any advanced solid tumour, 45 gBRCA breast or ovarian cancer patients (Group 6), 30 gBRCA breast or ovarian cancer patients (Group 7) and 60 gBRCA ovarian patients (Group 8). The secondary objectives of the expansion phase is to determine the single dose and steady state exposures achieved with higher doses than 200 mg bid, of AZD2281 melt-extrusion (tablet) formulation. Efficacy observed in patients treated with the capsule and the Melt-extrusion (tablet) formulation will also be described for patients recruited to Group 6, 7 and 8.

2.3 Rationale for conducting this study

The current clinical formulation of AZD2281 is the active pharmaceutical ingredient (API) dispersed in a Gelucire® 44/14 matrix, and filled into size 0 white hydroxypropyl methyl cellulose (HPMC) capsules at a 10% drug loading to achieve unit dose strength of 50 mg. A large number of capsules are therefore required to achieve a 400 mg bid daily dose (16 capsules per day), and consequently patient compliance and convenience may be

compromised. As such, there are constraints associated with dosing patients who require high doses of AZD2281.

To alleviate the dosing constraints of the Gelucire® 44/14 (capsule) formulation, AstraZeneca developed a melt-extrusion tablet (Melt-Extrusion [tablet] formulation) designed to deliver the therapeutic dose of AZD2281 in fewer and smaller dose units. Comparative to the Gelucire® 44/14 (capsule) formulation, the new Melt-Extrusion (tablet) formulation has higher drug loading, at least a 2-fold improvement in bioavailability and reduced PK variability in Beagle dogs, and is expected to have food-independent exposure. The melt-extruded tablet will be produced using a copovidone matrix, and pharmacopoeial tablet excipients.

Due to the genotoxic nature of AZD2281, the comparative bioavailability study will be conducted in a cancer patient population. The objectives of this study are to generate single dose PK data for the Melt-Extrusion (tablet) formulation in man, to generate information on dose linearity for the Melt-Extrusion (tablet) formulation and to compare, in man, the exposure achieved after dosing the Melt-Extrusion (tablet) formulation with that achieved following dosing of the Gelucire® 44/14 (capsule) formulation.

The dose of the Melt-Extrusion (tablet) formulation determined in this study is to be taken forward into the Phase III trial. The current study requires that patients fast for at least 2 hours prior to receiving their dose of either formulation of AZD2281 and for 2 hours following treatment. However, as it is possible that the new Melt-Extrusion (tablet) formulation may not be affected by food as much as the Gelucire® 44/14 (capsule) formulation, a further food interaction study is to be conducted with the Melt-Extrusion tablet.

The objective of the continued supply expansion phase of the study as set out in the previous protocol amendment is to explore the safety and tolerability of AZD2281 following multiple dosing of a melt-extrusion tablet formulation. The 200 mg bid AZD2281 tablet dose was selected, based upon pharmacokinetic modelling of the single dose tablet exposure data obtained from the PK phase of the study, as a dose which would best match the range of steady state exposures ($C_{ss\ max}$ and AUC_{ss}) previously observed following 400 mg bid AZD2281 capsule dosing.

Analysis of data from the on-going continuous supply expansion phase has shown that the 200 mg bid tablet dose does achieve exposures within the range of those seen following dosing at 400 mg bid AZD2281 with the capsule formulation. A direct intra-subject comparison of steady state exposure has shown that, although the gmean $C_{ss\ max}$ achieved following these doses of the two formulations was very similar, the gmean AUC_{ss} was approximately 20% lower following the tablet dose. The 200 mg bid tablet dose was very well tolerated but seemed to demonstrate lower anti-tumour activity compared to the 400 mg bid capsule dose.

As a result of these data, in order to identify a tablet dose which will be both tolerated by patients and provide comparable clinical activity to the 400 mg bid capsule dose, the safety and tolerability of higher doses of the tablet formulation, commencing at 250 mg bid, will be explored. This investigation of higher tablet doses will also support greater understanding of

[redacted]
the single and steady state pharmacokinetics of AZD2281 following dosing with the tablet formulation.

2.4 Benefit/risk and ethical assessment

The target population is patients with an advanced solid tumour which is refractory to standard therapies or for which no suitable effective standard therapy exists. It is anticipated that there is limited clinical benefit for such patients.

There is, however, strong preclinical evidence that deficiencies in homologous recombination DNA repair are associated with susceptibility to PARP inhibition. There is also increasing clinical evidence that AZD2281 has anti-tumour activity in patients with defective DNA repair – HRD. Although there are diagnostic methods to identify patients with some germline HRD (BRCA1 & BRCA2), currently there is no validated diagnostic method for many of the other genes involved in HRD and it is believed that many of the common tumour types (eg, colorectal, lung, breast, ovarian, head & neck cancers) have sub-groups of patients with a HRD phenotype. The hypothesised percentage of broader HRD tumour populations include triple negative breast (~20%), serous ovarian (~50% of total ovarian), head and neck squamous cell (~ 40%), non-small cell lung (~30%) and colorectal (~15%). Clinical study findings to date indicate that AZD2281 is generally well tolerated at doses up to and including the MTD of 400 mg bid in patients with various solid tumours.

In view of the observed and modelled pharmacokinetic properties of the tablet formulation, it is expected that a tablet dose of 250 mg bid would deliver a mean steady state AUC which would be 20% higher than that delivered by the 200 mg bid tablet dose with slightly higher C_{max} values compared to the 400 mg bid capsule dose. At this dose level, it is expected that the tolerability profile of the tablet formulation would be similar to the 400 mg capsule dose, which has proven to be generally well-tolerated in a number of clinical studies in the monotherapy setting. Thus, the 250 mg bid tablet dose is considered to be an appropriate dosing regimen to initiate and continue with a dose escalation to identify the maximum tolerated dose of the tablet formulation. Any higher tablet doses would be carefully considered only if lower doses have been declared tolerable. Given the potential advantages of the tablet formulation in terms of convenience and potentially similar or better efficacy along with a favourable and manageable toxicity profile, it would be clinically and ethically justified to explore higher tablet doses.

In view of the potential for AZD2281 to have anti-tumour activity in the HRD cancer population, the current study is designed to allow for patients to continue on AZD2281 therapy after completion of the PK Phase and continued supply expansion phase of the protocol until clinical progression of disease. Patients may, however, stop treatment at any time if they choose to do so or if the Investigator believes it is in the best interest of the patient to stop treatment with AZD2281. Additionally, in the event of unmanageable toxicity, directions for reducing or stopping dosing with AZD2281 are provided.

There is strong pre-clinical evidence that deficiencies in homologous recombination are associated with susceptibility to PARP inhibition (Section 2.1). Biomarker research on

[redacted] archival tumour tissue, from patients in this study, may help develop this hypothesis clinically and ultimately ensure that AstraZeneca will be able to prospectively identify patients most likely to benefit from treatment with AZD2281.

3. STUDY OBJECTIVES

3.1 Primary objectives

Table 1 PK Phase Primary Objective

To determine the comparative bioavailability of the new Melt-extrusion (tablet) formulation of AZD2281 compared to the existing Gelucire® 44/14 (capsule) formulation.

Dependent Variables	Description
Pharmacokinetic assessment	To determine the comparative bioavailability of the new Melt-extrusion (tablet) formulation of AZD2281 compared to the existing Gelucire® 44/14 (capsule) formulation.

Table 2 Continued Supply Phase and Expansion Phase Primary Objective

To enable patients to continue to receive treatment with AZD2281. Safety and tolerability data will be collected to further determine the safety and tolerability of the Gelucire® 44/14 capsule formulation of AZD2281 in these patients. In the Continued Supply Expansion Phase the primary objective is to compare the safety and tolerability profile of the melt-extrusion (tablet) and Gelucire ® 44/14 (capsule) formulations of AZD2281 in Groups 1, 6 and 7 and determine safety and tolerability of the tablet formulation in Groups 2,3, 4,5 and 8.

Dependent Variables	Description
Safety and tolerability (Group 1 to 8)	AEs, physical examination, vital signs including blood pressure (BP), pulse and body temperature, electrocardiogram (ECG) and laboratory findings including clinical chemistry, haematology and urinalysis.

[redacted]

3.2 Secondary objectives

Table 3 PK Phase Secondary Objectives

Dependent Variables	Description
Pharmacokinetics	To generate single dose PK data for the Melt-Extrusion (tablet) formulation in man and to generate information on dose linearity for the Melt-Extrusion (tablet) formulation
Pharmacodynamics	To compare the extent of PARP inhibition achieved in PBMCs following dosing of both the Melt-Extrusion (tablet) formulation and Gelucire® 44/14 (capsule) formulations
Safety and Tolerability	AEs, physical examination, vital signs including BP and pulse and body temperature, ECG and laboratory findings including clinical chemistry, haematology and urinalysis.

Table 4 Continued Supply Expansion Phase Secondary Objective

Dependent Variables	Description
Steady State PK in Group 2	To generate PK data for both the capsule and the tablet formulation in the same patient to allow a direct comparison of the steady state pharmacokinetic parameters for capsule and tablet formulations.
Pharmacokinetics in Group 1, 3 4, 5, 5.1… 6, 7 and 8	To generate single dose (except Group 1) and steady state PK data for both the capsule and the tablet formulation in man. To obtain a preliminary assessment of the effect of food on the exposure to AZD2281 tablet Group 8 patients only).

[redacted]

Table 4 Continued Supply Expansion Phase Secondary Objective

Dependent Variables	Description
Efficacy (Groups 1, 6, 7 and 8)	
Change from baseline in the sum of target lesions	Determined from radiological scans using RECIST criteria
Best overall response	Best tumour response determined by RECIST (CR, PR, SD or PD)
Progression-Free Survival	Progression free survival is defined as the time from randomisation to the earlier date of objective assessment of progression (per RECIST criteria) or death (by any cause in the absence of progression)
CA-125 Response	CA-125 response determined by GCIG criteria

3.3 Continued Supply Expansion Phase Exploratory Objectives

Optional archival tumour sample

Group 6, 7 and 8 patients will be asked to supply an archival tumour sample which will be required for exploratory biomarker analysis of activity of AZD2281. This is not mandatory and will not affect patients' eligibility for the study.

Dependent Variables

Biomarker data from optional archival tumour samples.

Description

Dependent upon number of samples and quantity of tissue obtained, may include measurements such as RNA, DNA and protein for biomarkers such as PARP1, BRCA1/2 and ATM.

'Nausea, vomiting & fatigue' questionnaire (Group 8 patients only)

Dependent Variables

Data collated from 'nausea, vomiting and fatigue' questionnaire.

Description

Questionnaires will be completed by site staff for any patient spontaneously reporting or with an ongoing AE of nausea, vomiting or fatigue to further characterise the nature and profile of low grade AEs associated with AZD2281.

[redacted]

4. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

4.1 Overall study design and flow chart

4.1.1 PK Phase

The PK Phase of this study is an open-label, randomised, two-period, crossover study in patients with advanced solid tumours refractory to standard therapies or for whom no suitable effective standard therapy exists. The purpose of this phase of the study is to establish the comparative bioavailability of the new Melt-Extrusion (tablet) formulation compared to the current Gelucire® 44/14 (capsule) formulation. In addition safety and tolerability data will be gathered for both formulations.

Patients will be screened within 28 days of Day 1 of the first treatment period. Written informed consent will be obtained prior to any study procedures. Demographic information, medical and surgical history, ECOG performance status and concomitant medication will be recorded. Safety assessments will be performed (AEs, laboratory tests [haematology, clinical chemistry and urinalysis], vital signs, body weight, ECG and physical examination). Eligibility criteria will be checked.

Patients will take part in two treatment periods each separated by a washout period of 6-14 days. Patients will be randomised into either Sequence 1 or Sequence 2 (assigned 1:1) as follows:

- Sequence 1 will receive AZD2281 Gelucire® 44/14 (capsule) formulation followed by AZD2281 Melt-Extrusion (tablet) formulation (Treatment A followed by Treatment B);

- Sequence 2 will receive AZD2281 Melt-Extrusion (tablet) formulation followed by AZD2281 Gelucire® 44/14 (capsule) formulation dose (Treatment B followed by Treatment A).

Patients should fast for at least 2 hours prior to receiving their dose of either formulation of AZD2281. Patients should then refrain from eating or drinking for a further 2 hours after dosing due to the potential effect of food on absorption.

For both treatment periods patients should be dosed preferably at the same time each day. Patients will be advised to take AZD2281 with approximately 240 mL of water. The AZD2281 capsules/tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

[redacted]

Cohort 1 will receive a single 50 mg dose of the Gelucire® 44/14 (capsule) formulation and a single 25 mg dose of the Melt-Extrusion (tablet) formulation. Cohort 2 will receive a single 100 mg dose of the Gelucire® 44/14 (capsule) formulation and a single 50mg dose of the Melt-Extrusion (tablet) formulation. Cohorts 1 and 2 will be recruited consecutively, with Cohort 1 recruited first, immediately followed by Cohort 2. Patients will be randomised to treatment sequence. Cohort 3 will be recruited once PK analysis for Cohorts 1 and 2 has completed so as to be able to better define the higher dose level for the Melt-Extrusion (tablet) formulation in Cohort 3. Patients in Cohort 3 will be randomised to treatment sequence and will receive a single 400 mg dose of the Gelucire® 44/14 (capsule) formulation and a dose of the new formulation to be decided from the first two cohorts' data. The PK team at AstraZeneca will make the decision about the dose of the Melt-Extrusion (tablet) formulation to be used in Cohort 3, following review of the PK and AUC data from Cohorts 1 and 2 confirming the exposure ratio between the Gelucire® 44/14 (capsule) and Melt-Extrusion (tablet) formulations.

For Cohorts 1 and 2, patients will be recruited consecutively: Cohort 1 will be recruited first, immediately followed by Cohort 2. All patients will be randomised to treatment sequence following enrolment. Patients in Cohort 3 will be randomised to treatment sequence at the dose determined following analysis of PK data from Cohorts 1 and 2.

Treatment Periods

On the first day of each treatment period, safety assessments will be performed prior to dosing (laboratory tests [haematology, clinical chemistry and urinalysis], vital signs and body weight [body weight only at Treatment Period 1, Day 1], ECG, physical examination, AEs and concomitant medications) and ECOG performance status recorded. Patients will be given a single dose of either AZD2281 formulation (Sequence 1 or Sequence 2) on the morning of Treatment Period 1 (Day 1) and Treatment Period 2 (Day 8). Blood samples for the determination of plasma concentrations of AZD2281 will be collected pre-dose and at 0.5, 1.0, 1.5, 2, 3, 4, 6, 8 & 10 hours for both treatment periods. Patients may remain in hospital on the first day of Treatment Periods 1 and 2. In addition, patients who live a distance from the hospital may also stay in the hospital or nearby the hospital for Treatment Period 1, Day 2 and Treatment Period 2, Day 9.

On Treatment Period 1 (Day 2) and Treatment Period 2 (Day 9), safety assessments will be performed - vital signs, AEs and concomitant medications. A blood sample for AZD2281 analysis will be taken 24 hours post-dose.

On Treatment Period 1 (Day 3) and Treatment Period 2 (Day 10), safety assessments will be performed - vital signs, AEs and concomitant medications. A blood sample for AZD2281 analysis will be taken 48 hours post-dose.

Treatment periods will be separated by a washout period of 6–14 days from the first AZD2281 dose.

[redacted]

PK Phase Follow-up Visit

All patients will return for a post-study visit 7 days from the time of last dose for laboratory tests (haematology, clinical chemistry and urinalysis), vital signs (pulse and BP), ECG, and a physical examination.

AEs will be recorded from the date of consent until the post-study visit as detailed in Section 7.3.3.

The timing of procedures for each study period is presented in Section 7.2.

4.1.2 Continued Supply Phase

4.1.2.1 Continued Supply Phase following PK Phase

The Continued Supply Phase is scheduled 7 days after the end of treatment in the PK Phase. Following completion of the PK Phase, patients may continue to receive treatment with the Gelucire® 44/14 (capsule) formulation (400 mg orally bid [ie, 8 capsules bid]) on a continuous basis as long as they remain free from intolerable toxicity and, in the Investigator's opinion, are receiving some clinical benefit from treatment with AZD2281 and do not meet any other discontinuation criteria.

4.1.2.2 Continued Supply Expansion Phase

Once the PK team at AstraZeneca have confirmed the exposure ratio between the Gelucire® 44/14 (capsule) and Melt-extrusion (tablet) formulations, approximately 26 additional patients will be recruited to the Continued Supply Expansion Phase:

- Approximately 20 gBRCA patients will be recruited to Group 1 to assess the multiple dose safety profile of the Melt-extrusion (tablet) formulation in a comparative setting. The patients will be randomised on a 1:1 ratio to the following active treatment arms:
  - Treatment A: 200 mg bid AZD2281 Melt-extrusion (tablet) formulation
  - Treatment B: 400 mg bid AZD2281 Gelucire® 44/14 (capsule) formulation
  - Randomisation will be stratified based on primary tumour type (breast cancer or ovarian cancer).
- 6 patients will be recruited to Group 2 which will directly compare the steady state PK of the capsule and the Melt-extrusion (tablet) formulation. The patients will be randomly assigned a treatment sequence as follows:
  - Treatment Sequence 1: 200 mg bid AZD2281 Melt-extrusion (tablet) formulation until Day 8 followed by 400 mg bid AZD2281 Gelucire® 44/14 (capsule) formulation until Day 15

[redacted]

- Treatment Sequence 2: 400 mg bid AZD2281 Gelucire® 44/14 (capsule) formulation until Day 8 followed by 200 mg bid AZD2281 Melt-extrusion (tablet) formulation until Day 15

- After Day 15, all 6 patients will receive 200 mg bid AZD2281 melt-extrusion (tablet) formulation until treatment discontinuation.

4.1.2.3 Dose escalation within the continued supply expansion phase

To investigate higher doses of the AZD2281 melt-extrusion (tablet) formulation, up to approximately 48 additional patients will be recruited to the expansion phase in sequential groups:

- A minimum of 6 patients will be recruited to Group 3 which will assess the tolerability and pharmacokinetics of 250 mg bid AZD2281 tablet dose

- If 250 mg bid tablet dose is tolerated, a minimum of 6 patients will be recruited to Group 4 to assess the tolerability and pharmacokinetics of 300 mg bid AZD2281 tablet dose

- If 300 mg bid tablet dose is tolerated, a minimum of 6 patients will be recruited to Group 5 to assess the tolerability and pharmacokinetics of 350 mg bid AZD2281 tablet dose

- If 350 mg bid tablet dose is tolerated, a minimum of 6 patients will be recruited to Group 5.1 to assess the tolerability and pharmacokinetics of 400 mg bid AZD2281 tablet dose

- If 400 mg bid tablet dose is tolerated, dose escalations will continue in a minimum of 6 patients each time to Groups 5.2, 5.3 etc. Dose increases will be at the discretion of the SRC and will continue until the SRC agree that no further doses should be explored.

All dose escalation groups will recruit a minimum of 6 patients. As the dose of AZD2281 tablets at 200 mg bid has already shown to be well-tolerated and the average $AUC_{0\text{-}12,}$ following 250 mg bid tablet dosing, is predicted to be similar to that following 400 mg bid capsule dosing, the study will recruit the 250 mg bid tablet dose group of 6 patients in parallel. This will also be applicable to the subsequent dose escalation groups if the SRC considers this appropriate based on the available safety information.

Once entered into the study, patients will commence 250 mg bid AZD2281 tablet dosing on Day 1 and pharmacokinetic sampling will be performed to obtain PK information after the first dose and at steady state. After the first 3 patients to start treatment have received one cycle of treatment (28 days) the SRC will review all of the available data. If, at this stage, no patient has experienced DLT then 6 new patients will be enrolled into Group 4 at 300 mg bid AZD2281 tablet dose. If one patient in group 3 experiences DLT before all 6 patients have

[redacted]

completed the 1st cycle, the decision to dose escalate will be deferred until all 6 patients in the group have completed 1 cycle or 28 days of treatment. If no further DLTs are observed in the group then the SRC may dose escalate as appropriate. The same will apply for dose escalation in the subsequent groups. If 2 or more patients in any single group experience DLT the dose will be considered not tolerated. If 2 or more patients experience DLT in the group after the decision has been made to recruit to the next dose level, the dose will still be considered not tolerable, the recruitment to the next dose level stopped and patients within that next group will have their dose reduced to the MTD.

In each group the following therefore applies:

- If no DLT, proceed to next dose group
- If 1 patient experiences a DLT continue until all 6 patients have received 28 days of study treatment before deciding whether to escalate to the next dose level
- If ≥2 patients out of the group of 6 experience a DLT within the first 28 days of treatment, dose is considered not tolerable.

There will be no intra-patient dose escalation of AZD2281 in this study. If a patient experiences AZD2281 related toxicity, their daily dose of AZD2281 may be reduced or with-held. If the toxicity improves or resolves, the patient may be restarted on AZD2281 at either their initial dose or at a reduced dose. However once a patient has received a reduced dose, re-escalation of AZD2281 to their initial dose level will not be permitted, without prior discussion with the AZ study physician (see Section 6.2.4).

4.1.2.4 Randomised comparison between tablet and capsule

Following the completion of the dose escalation tolerability assessment up to 400 mg bid AZD2281, approximately 45 patients will be randomised to Group 6 to assess the multiple dose safety profile of the Melt-extrusion (tablet) formulation in a comparative setting. The patients will be randomised on a 1:1:1 ratio to the following active treatment arms:

- Treatment A: A tablet dose between 250mg and the higher tablet dose taken into the expansion that has been shown to be safe and tolerable
- Treatment B: 400 mg bid dosing with AZD2281 Gelucire® 44/14 (capsule) formulation
- Treatment C: 400 mg bid AZD2281 tablet dose (or lower if 400 mg bid is not tolerated).

If dose escalation continues beyond 400 mg bid, following the completion of the dose escalation tolerability assessment up to a dose defined by the SRC, approximately 30 patients may be randomised to Group 7 to assess the multiple dose safety profile of the Melt-extrusion (tablet) formulation in a comparative setting. The patients will be randomised on a 1:1 ratio to the following active treatment arms:

- Treatment A: The highest bid tablet dose deemed tolerable by the SRC following the dose escalation phase

- Treatment B: 400 mg bid capsule

Randomisation will be stratified based on primary tumour type (breast cancer or ovarian cancer). There must be at least 10 gBRCA ovarian patients in each arm.

Regardless of the formulation the patient is treated with or the treatment group assigned to, all patients may receive continuous treatment with the assigned formulation for as long as they remain free from intolerable toxicity and, in the Investigator's opinion, are receiving some clinical benefit from AZD2281 and do not meet any other discontinuation criteria.

Patients who experience NCI-CTCAE of grade 3 or 4 toxicity and meet the criteria outlined in Section 5.5.1 for AZD2281 will have their study medication stopped. The safety follow-up should be continued as outlined in the study schedule.

Once patients receiving AZD2281 have been discontinued from study medication, other treatment options will be at the discretion of the Investigator.

4.1.2.5 Randomised comparison between different tablet dose schedules

Following the completion of Group 6, approximately 60 confrimed gBRCA1/2 ovarian cancer patients will be randomised to Group 8 to assess the multiple dose safety profile of the Melt-extrusion (tablet) formulation in differing dose schedules. The patients will be randomised on a 1:1:1:1 ratio to the following dosing schedules:

- Schedule A: 200mg tds tablet continuous dosing

- Schedule B: 250mg tds tablet 2 weeks on study drug, 1 week off study drug

- Schedule C: 400mg bid tablet 1 week on study drug, 1 week off study drug

- Schedule D: 400mg od tablet continuous dosing

All patients may receive treatment for as long as they remain free from intolerable toxicity and, in the Investigator's opinion, are receiving some clinical benefit from AZD2281 and do not meet any other discontinuation criteria.

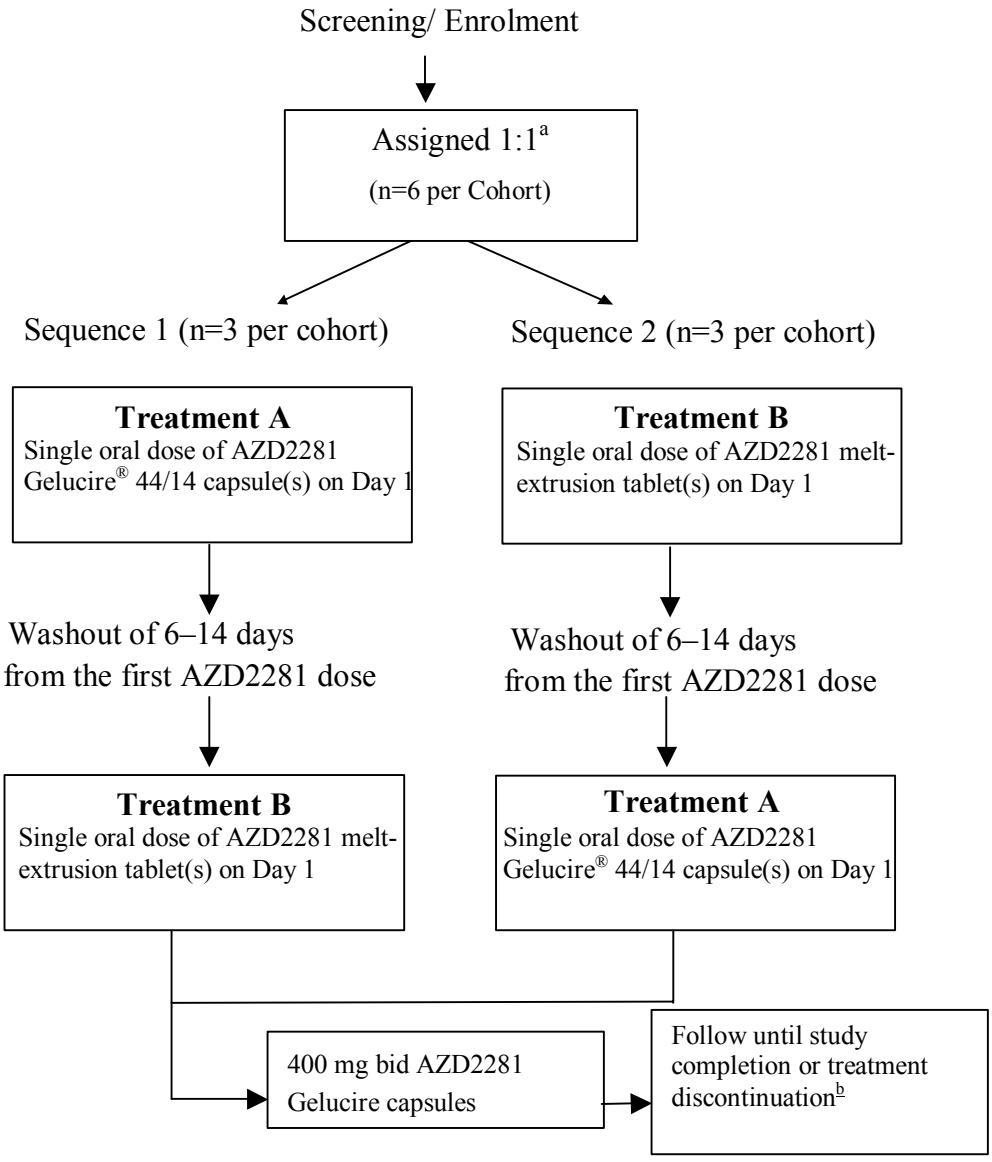
Patients who experience NCI-CTCAE of grade 3 or 4 toxicity and meet the criteria outlined in Section 5.5.1 for AZD2281 will have their study medication stopped. The safety follow-up should be continued as outlined in the study schedule.

Once patients receiving AZD2281 have been discontinued from study medication, other treatment options will be at the discretion of the Investigator.

[redacted]

4.1.3 Study Flow Chart and Study Schedule

Figure 1 Study flow chart for PK Phase

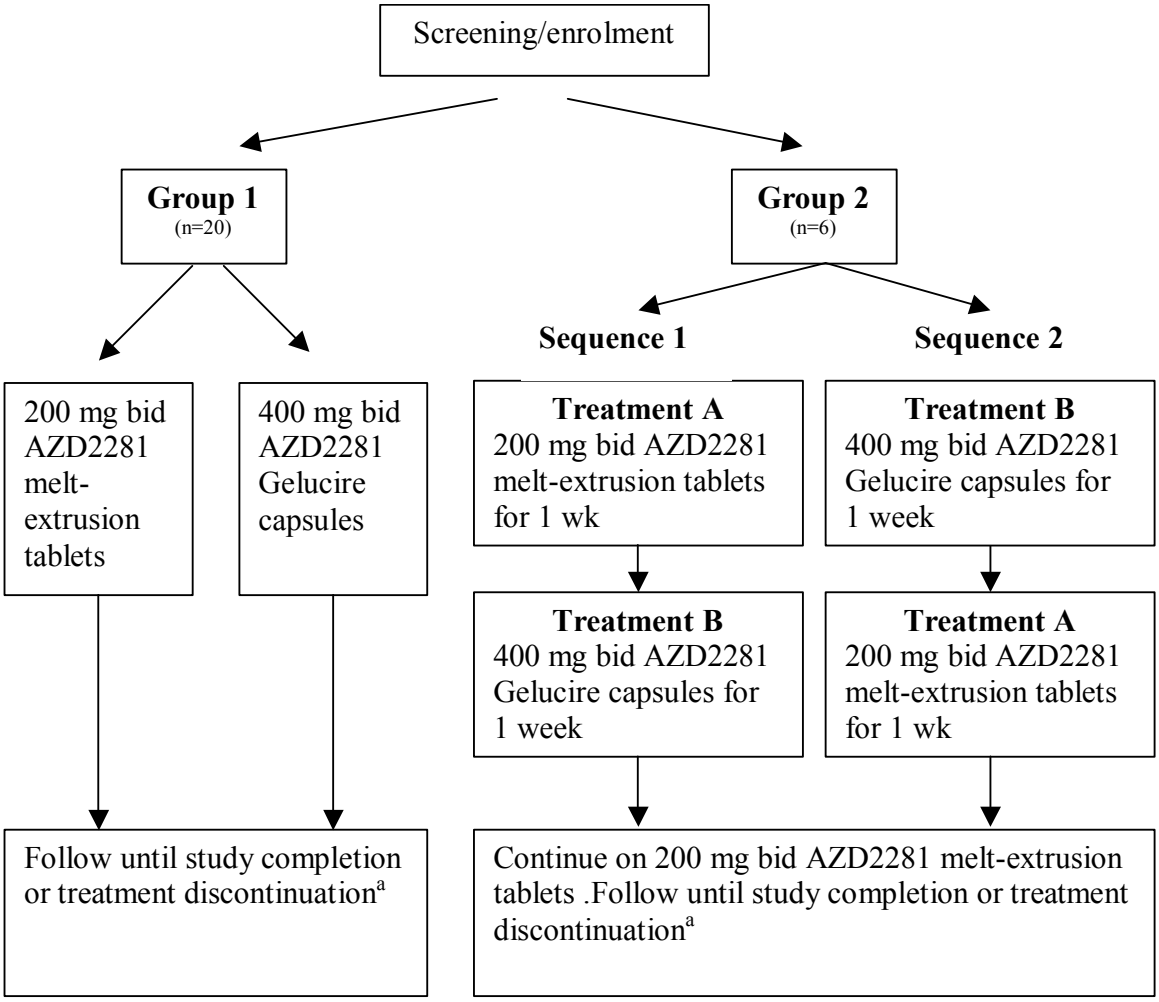


[a] Patients will be screened, enrolled into the study and randomly assigned 1:1 to each treatment sequence. Cohort 1 will be recruited first, immediately followed by Cohort 2. Cohort 3 will be recruited following determination of dose from PK data for Cohorts 1 and 2.

[b] Patient may continue on AZD2281 for as long as the patient is free of intolerable toxicity and is, in the opinion of the investigator, deriving some clinical benefit. If the patient remains on treatment following study completion, SAEs will continue to be collected until treatment is discontinued

[redacted]

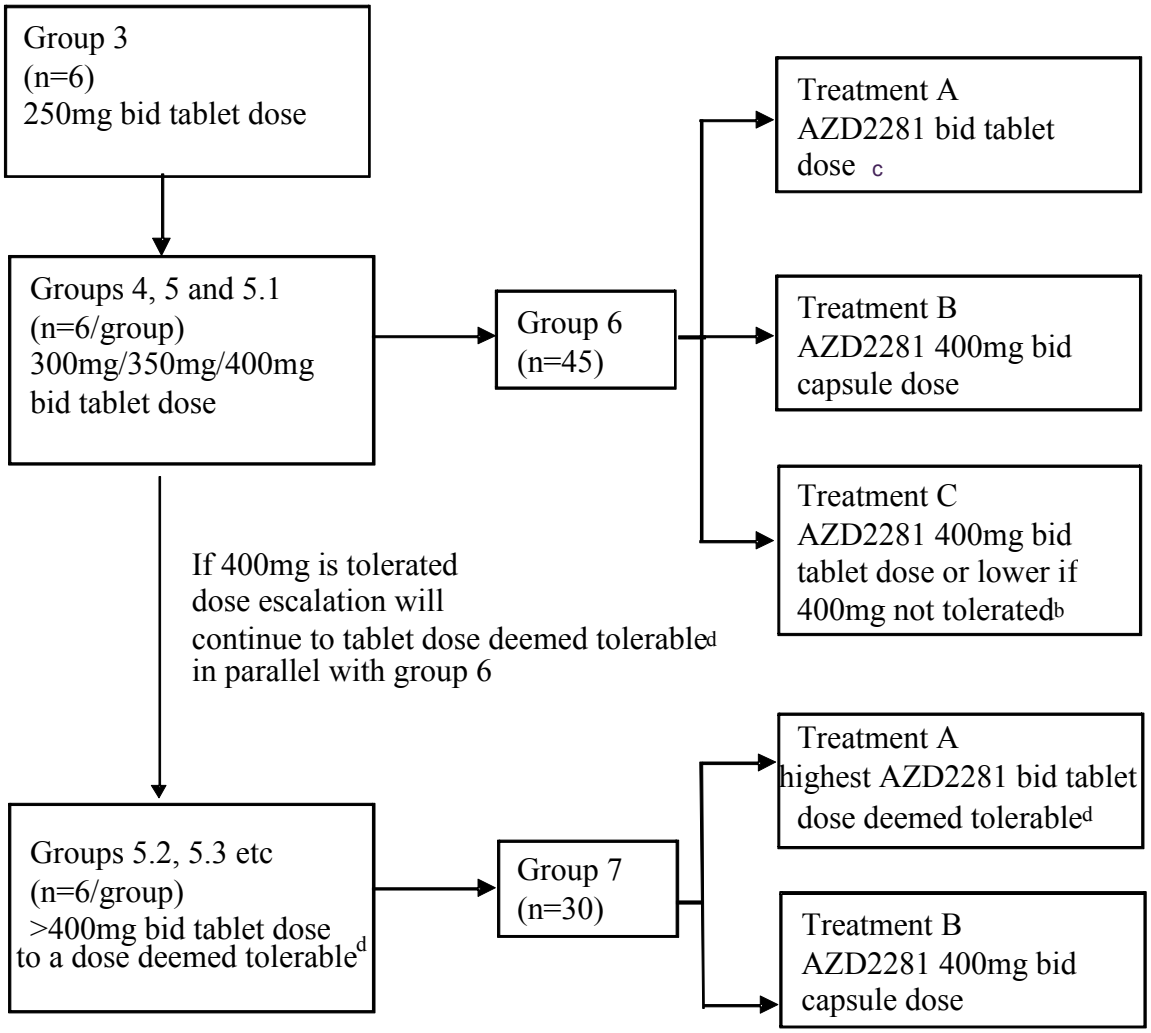
Figure 2 Study flow chart for Continued Supply Expansion Phase

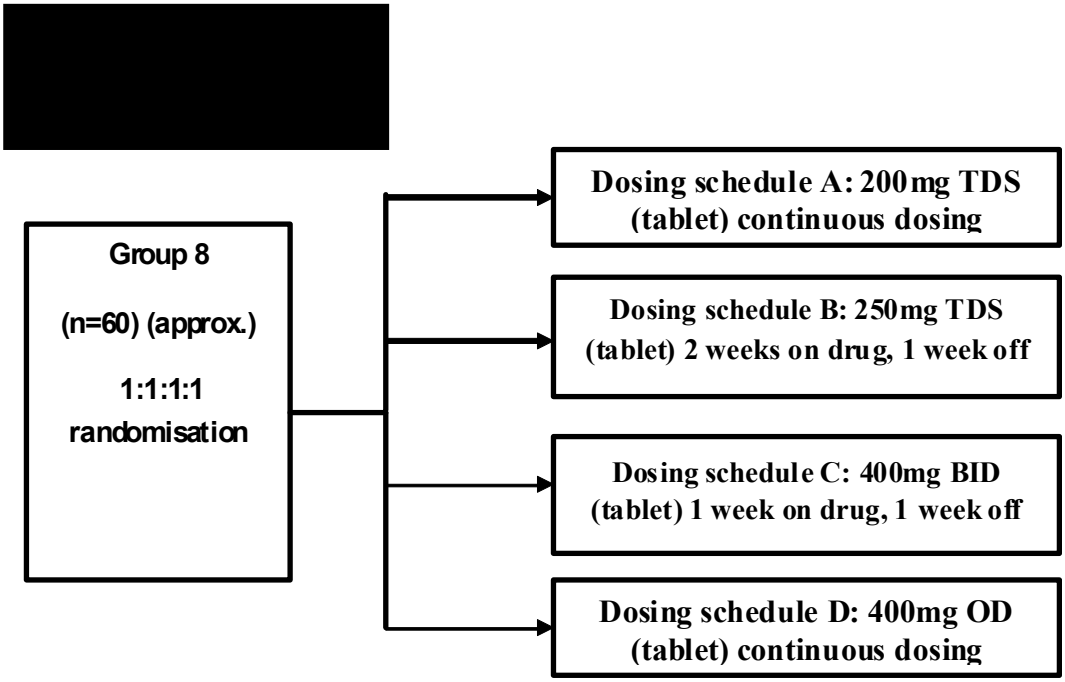


[a] Patient may continue on AZD2281 for as long as the patient is free of intolerable toxicity and is, in the opinion of the investigator, deriving some clinical benefit. If the patient remains on treatment following study completion, SAEs will continue to be collected until treatment is discontinued

[redacted]

Figure 3 Study flow chart for dose escalation phase in the Continued Supply Expansion [a]





[a] For all treatment groups, the patient may continue on their assigned AZD2281 formulation for as long as the patient is free of intolerable toxicity and is, in the opinion of the investigator, deriving some clinical benefit. If the patient remains on treatment following study completion, SAEs will continue to be collected until treatment is discontinued.

[b] If 300 mg bid tablet dose is not tolerated, then the Treatment C arm will not be included in group 6 and approximately 30 patients will be randomised 1:1 to either Treatment A or B.

[c] A tablet dose between 250mg and the higher tablet dose taken into the expansion that has been shown to be safe and tolerable

[d] The final doses to be explored in the dose escalation phase and expansion phase will be agreed by the SRC

[redacted]

Table 5 Study schedule for PK Phase

Visit	Screening		PK Phase: Treatment Period 1			PK Phase: Treatment Period 2			Post PK Phase Follow-up [a] 7 days since last dose	Continued Supply Phase: Continuous treatment[b] 7 days after end of PK Phase	Continued Supply Phase: Final Follow-up[k] 30 days since last dose	Treatment Discontinuation
Day	**-28 to -1**	**-7 to -1**	**1**	**2**	**3**	**8**	**9**	**10**				
Informed consent	X											
Demographics	X											
Medical and surgical history	X											
Inclusion/exclusion criteria	X	X										
Physical exam[c]	X		X[d]			X			X	X	X	X
Vital signs, body weight[e]	X		X[d]	X	X	X	X	X	X	X	X	X
ECOG performance status	X		X[d]			X				X	X	X
ECG[f]		X	X			X			X	X	X	X
Haematology / clinical chemistry	X		X[d]			X			X	X	X	X
Pregnancy test[g]		X										
Pharmacokinetics[h]			X	X	X	X	X	X				
Pharmacodynamics[i]			X	X		X	X					
Urinalysis	X		X[d]			X			X	X	X	X

[redacted]

Table 5 Study schedule for PK Phase

Visit	Screening		PK Phase: Treatment Period 1			PK Phase: Treatment Period 2			Post PK Phase Follow-up [a] 7 days since last dose	Continued Supply Phase: Continuous treatment[b] 7 days after end of PK Phase	Continued Supply Phase: Final Follow-up[k] 30 days since last dose	Treatment Discontinuation
Day	-28 to -1	-7 to -1	1	2	3	8	9	10				
Adverse Events[j]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
AZD2281 dispensed/returned			X			X			X	X		

[a] Following the last dose of AZD2281 in the PK Phase, patients should have a post-study visit within 7 days.

[b] The Continued Supply Phase is scheduled 7 days after the end of the PK Phase. Patients may then continue to receive treatment with the Gelucire® 44/14 (capsule) formulation (at 400 mg orally bid [ie, 8 capsules bid]). Patients that wish to continue onto the Continued Supply Phase of the study will have safety assessment performed approximately every 28 days (28 days = 1 cycle). There will be the exception of patients being seen less after the first three monthly reviews - if the Investigator considers the patient to be tolerating AZD2281 well, in which case patients should be assessed by the Investigator at least quarterly with interim telephone contact and monthly laboratory assessments (undertaken by local hospital / General Practitioner). Once the PK team at AstraZeneca have confirmed the exposure ratio between the Gelucire® 44/14 (capsule) and Melt-Extrusion (tablet) formulations, patients may be given the option to switch from the Gelucire® 44/14 (capsule) formulation (400 mg orally bid) to receive the equivalent Melt-Extrusion (tablet) formulation of AZD2281.

[c] Height at screening only. Physical examination to be performed throughout the study.

[d] If assessed within 7 days before enrolment and meets the stated eligibility criteria (if applicable), it need not be repeated on Day 1 of cycle 1 unless Investigator believes that it is likely to have changed significantly.

[e] Vital signs include BP, pulse and body temperature. Patient is to be in the supine position for BP and pulse. Body weight will be measured at screening, Treatment Period 1, Day 1 and on the Final Follow-up Visit.

[f] ECGs are required within 7 days prior to start of study, at the start of each treatment period and at 7-day follow-up and if patient continues into Continued Supply Phase at least monthly for the first three months and at 30-day follow-up and when clinically indicated, see Section 7.3.5.2. ECG should be performed once the patient has been in the supine position for at least 5 minutes in each case.

[redacted]

[g] Pre-menopausal women of child-bearing potential must have a negative urine or serum pregnancy test within 7 days prior to Day 1 of Treatment Period 1. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.

[h] Blood samples for the determination of plasma concentrations of AZD2281 will be collected pre-dose and at 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 24 & 48 hours. Patients may remain in hospital on Treatment Period 1, Day 1 and Treatment Period 2, Day 8. In addition, patients who live a distance from the hospital may also stay in the hospital or nearby the hospital for Treatment Period 1, Day 2 and Treatment Period 2, Day 9..

[i] PD Samples will be collected in each treatment period at pre-dose and then at 3, 10 and 24 hours post dose of AZD2281.

[j] AEs must be collected from the time of informed consent, throughout the treatment period and up to and including the follow-up period (7 days for PK Phase, 30 days for Continued Supply Phase). All new AEs/SAEs occurring during the follow-up period must be reported and followed up until resolution (if SAEs they must be reported to AstraZeneca within 24 hours). All ongoing AEs must be monitored until resolution unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. After discontinuation from treatment, patients must be followed up for all existing and new AEs for 30 calendar days (if SAEs, they must be reported to AstraZeneca within 24 hours) and followed until resolution unless, in the opinion of the Investigator, the condition is unlikely to resolve due to the patient's underlying disease.

[k] The Follow-up Visit should be done 30 days from treatment discontinuation/last dose of study medication.

[redacted]

Table 6 Study Schedule: Expansion of continued supply phase (Groups 1 and 2)

Visit	Screening	2	3	4	5	6	7	8	9	10[i]	Final Follow-up (30 days after Treatment Discontinuation)	Treatment Discontinuation
Day[a]	**-28 to -1**	**1**	**8**	**15**	**29**	**57 (+/- 2)**	**85 (+/- 2)**	**113 (+/- 2)**	**141 (+/- 2)**	**169 (+/- 2)**		
Informed consent	X											
Demographics	X											
Medical and surgical history	X											
Inclusion/exclusion criteria	X											
Pregnancy test[j]	X											
Randomisation		X										
Physical exam	X	X[a]			X	X	X	X	X	X	X	X
Vital signs, body weight[b]	X	X[a]			X	X	X	X	X	X	X	X
ECOG performance status	X	X[a]			X	X	X	X	X	X	X	X
ECG[c]	X	X			X	X					X	
Haematology / clinical chemistry	X	X[a]			X	X	X	X	X	X	X	X
Urinalysis	X	X[a]			X	X	X	X	X	X	X	X
Adverse Events[d]	X	X			X	X	X	X	X	X	X	X

[redacted]

Table 6 Study Schedule: Expansion of continued supply phase (Groups 1 and 2)

Visit	Screening	2	3	4	5	6	7	8	9	10[i]	Final Follow-up (30 days after Treatment Discontinuation)	Treatment Discontinuation
Day[a]	**-28 to -1**	**1**	**8**	**15**	**29**	**57 (+/- 2)**	**85 (+/- 2)**	**113 (+/- 2)**	**141 (+/- 2)**	**169 (+/- 2)**		
Concomitant medications	X	X			X	X	X	X	X	X	X	X
AZD2281 dispensed/returned		X	Group 2	Group 2	X	X	X	X	X	X	X	X
Pharmacokinetics			X[e, f]	X[e, f]	Group 1[e]							
Tumour Assessment[h]	Group 1					Group 1[g]		Group 1[g]		Group 1[g]		
Blood sampling for CA-125	Group 1	Group 1[k]				Group 1[k]		Group 1[k]		Group 1[k]		

[a] If assessed within 7 days before enrolment and meets the stated eligibility criteria (if applicable), it need not be repeated on Day 1 of cycle 1 unless Investigator believes that it is likely to have changed significantly.

[b] Vital signs include BP, pulse and body temperature will be measured at least monthly for a minimum of 6 cycles of treatment, at least every 2 months thereafter, and on final follow up visit until study completion or treatment discontinuation. Patient is to be in the supine position for BP and pulse. Body weight will be measured at screening, Day 1 and on the Final Follow-up Visit. Height will be measured at screening only.

[c] ECGs are required within 7 days prior to start of study medication, at least monthly for the first three months and at 30-day follow-up and when clinically indicated, see Section 7.3.5.2. ECG should be performed once the patient has been in the supine position for at least 5 minutes in each case. ECG Traces will be stored with the CRFs and collected by the monitor.

[d] AEs must be collected from the time of informed consent, throughout the treatment period and up to and including the follow-up period. All ongoing AEs must be monitored until resolution unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. After discontinuation from treatment, patients must be followed up for all existing and new AEs for 30 calendar days (if SAEs, they must be reported to AstraZeneca within 24 hours) and followed until resolution unless, in the opinion of the Investigator, the condition is unlikely to resolve due to the patient's underlying disease.

[redacted]

[e] For the 20 additional gBRCA patients that are recruited to Group 1, blood samples will be collected immediately prior to the first dose of the day on day 8, day 15 and day 29 and post the first dose of the day on day 29 between 0 - 0.5 hours, 0.5 to 1.5 hours, 1.5 - 3 hours, 3 - 6 hours and 6 - 12 hours.

[f] For the 6 additional patients that are recruited to Group 2, PK sampling will occur on both day 8 and day 15 at the following timepoints within each day: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hours after morning dosing.

[g] For the additional 20 gBRCA patients recruited to the Continued Supply Expansion Phase and assigned to Group 1, follow-up tumour assessments will be performed every 8 weeks (+/-1 week) until disease progression. Any other sites at which new disease is suspected should also be appropriately imaged. If scans are performed outside of scheduled visit ± 1 week window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Patients must be followed until progression regardless of whether study treatment is discontinued or delayed and/or protocol violation. A repeat scan is needed at the next scheduled tumour assessment (at least ≥ 4 weeks) for confirmation of a PR or CR by RECIST. Radiological examinations performed in the conduct of the study should be retained at site as source data and may be collected by the sponsor if required.

[h] For the additional 20 gBRCA patients recruited to the Continued Supply Expansion Phase and assigned to Group 1, the imaging modalities used for RECIST assessment will be CT or MRI scans of chest, abdomen and pelvis for breast cancer and abdomen and pelvis for ovarian cancer with other regions as clinically indicated for the assessment of disease. An historical scan meeting the RECIST criteria as defined in Appendix F can be used for baseline assessment, but this must be performed no more than 28 days before the first dose of study medication.

[i] After the follow up visit at the end of the 6th cycle of treatment (Visit 10), this visit should be repeated every 8 weeks until either the patient discontinues study treatment or the study is completed (see Section 10.5).

[j] Pre-menopausal women of child-bearing potential must have a negative urine or serum pregnancy test within 7 days prior to Day 1 of Treatment Period 1. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.

[k] Blood samples for CA-125 analysis should be taken prior to the morning dose of study medication.

[redacted]

Table 7 Study Schedule: Dose escalation phase of the continued supply expansion (Groups 3-8)

Visit	**Screening**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**[j]	**Treatment Discontinuation**	**Final Follow-up (30 days after Treatment Discontinuation)**
Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**43 (+/- 2)**	**57 (+/- 2)**	**71 (+/- 2)**	**85 (+/- 2)**	**113 (+/- 2)**	**141 (+/- 2)**	**169 (+/- 2)**		
Informed consent	X														
Demographics	X														
Medical and surgical history	X														
Inclusion/exclusion criteria	X														
Pregnancy test[k]	X	X													
Randomisation		X													
Physical exam [q]	X	X[a]	X	X	X	X		X		X	X	X	X	X	X
Vital signs, body weight[b q]	X	X[a]	X	X	X	X		X		X	X	X	X	X	X
ECOG performance status [q]	X	X[a]	X	X	X	X		X		X	X	X	X	X	X
ECG[c q]	X	X[a]				X		X							X
Haematology / clinical chemistry	X	X[a]	X	X	X	X	Group 3-5[m]	X	Group 3-5[m]	X	X	X	X	X	X
Urinalysis [r]	X	X[a]	X	X	X	X		X		X	X	X	X	X	X

[redacted]

Table 7 Study Schedule: Dose escalation phase of the continued supply expansion (Groups 3-8)

Visit	**Screening**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13** [j]	**Treatment Discontinuation**	**Final Follow-up (30 days after Treatment Discontinuation)**
Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**43 (+/- 2)**	**57 (+/- 2)**	**71 (+/- 2)**	**85 (+/- 2)**	**113 (+/- 2)**	**141 (+/- 2)**	**169 (+/- 2)**		
Adverse Events[d, p]	X	X	X	X	X	X		X		X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X		X		X	X	X	X	X	X
AZD2281 dispensed/returned		X				X		X		X	X	X	X	X	X
Pharmacokinetics		X[e]	X[e]	X[e]		X[f, g]		Group 6 & 7 [n]							
Pharmacokinetics (Group 8 only)		X[o]	X[o]					X[o]							
Archival tumour sample for biomarker analysis	Group 6, 7 & 8 [n]														
Tumour Assessment [i]	Group 6, 7 & 8							Group 6, 7 & 8 [h]			Group 6, 7 & 8 [h]		Group 6 & 7 [h]		
Blood sampling for CA-125	Group 6, 7 & 8	Group 6, 7 & 8[l]						Group 6, 7 & 8[l]			Group 6, 7 & 8[l]		Group 6 & 7 [l]		

[a] If assessed within 7 days before enrolment and meets the stated eligibility criteria (if applicable), it need not be repeated on Day 1 of cycle 1 unless Investigator believes that it is likely to have changed significantly.

[redacted]

[b] Vital signs include BP, pulse and body temperature will be measured at least monthly for a minimum of 6 cycles of treatment, at least every 2 months thereafter, and on final follow up visit until study completion or treatment discontinuation. Patient is to be in the supine position for BP and pulse. Body weight will be measured at screening, Day 1 and on the Final Follow-up Visit. Height will be measured at screening only.

[c] ECGs are required within 7 days prior to start of study medication, Day 29, Day 57 and at 30-day follow-up and when clinically indicated, see Section 7.3.5.2. ECG should be performed once the patient has been in the supine position for at least 5 minutes in each case. ECG Traces will be stored with the CRFs and collected by the monitor.

[d] AEs must be collected from the time of informed consent, throughout the treatment period and up to and including the follow-up period. All ongoing AEs must be monitored until resolution unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. After discontinuation from treatment, patients must be followed up for all existing and new AEs for 30 calendar days (if SAEs, they must be reported to AstraZeneca within 24 hours) and followed until resolution unless, in the opinion of the Investigator, the condition is unlikely to resolve due to the patient's underlying disease.

[e] For all patients enrolled into Groups 3 to 7 blood samples will be collected on Day 1 at the following timepoints: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hours after morning dosing and on day 8 and Day 15 at the following timepoints: Pre-dose and 1 hour after morning dosing.

[f] For the additional patients that are recruited to Groups 3 onwards, blood samples will be collected on Day 29 at the following timepoints: pre-dose and post-dose between 0 - 0.5 hours, 0.5 to 1.5 hours, 1.5 - 3 hours, 3 - 6 hours, 6 – 8, and 8-12 hours.

[g] For the additional patients that are recruited to Group 6 and 7**,** blood samples will be collected on Day 29 and Day 57 at the following timepoints: pre-dose and post-dose between 0 - 0.5 hours, 0.5 to 1.5 hours, 1.5 - 3 hours, 3 - 6 hours, 6 – 8, and 8-12 hours.

[h] For the additional patients recruited to Group 6,7 and 8, follow-up tumour assessments will be performed every 8 weeks (+/-1 week) until disease progression or study end (Tumour assessments for Group 8 patients should be stopped after Cycle 5). Any other sites at which new disease is suspected should also be appropriately imaged. If scans are performed outside of scheduled visit ± 1 week window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Patients must be followed until progression regardless of whether study treatment is discontinued or delayed and/or protocol violation. A repeat scan is needed at the next scheduled tumour assessment (at least ≥ 4 weeks) for confirmation of a PR or CR by RECIST. Radiological examinations performed in the conduct of the study should be retained at site as source data and may be collected by the sponsor if required.

[i] For the additional patients recruited to Group 6, 7 and 8, the imaging modalities used for RECIST assessment will be CT or MRI scans of chest, abdomen and pelvis for breast cancer and abdomen and pelvis for ovarian cancer with other regions as clinically indicated for the assessment of disease. An historical scan meeting the RECIST criteria as defined in Appendix F can be used for baseline assessment, but this must be performed no more than 28 days before the first dose of study medication.

[j] After the follow up visit at the end of the 6th cycle of treatment (Visit 13), this visit should be repeated at least every 8 weeks until either the patient discontinues study treatment or the study is completed (clinical database is closed) (see Section 10.5).

[k] Pre-menopausal women of child-bearing potential must have a negative urine or serum pregnancy test within 28 days prior to Day 1 and Day 1 (prior to treatment). In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.

[l] Blood samples for CA-125 analysis should be taken prior to the morning dose of study medication for ovarian cancer patients only.

[m] Haematology and clinical chemistry will also be performed on Day 43 and 71 for Group 3, 4 and 5 patients.

[n] For the additional patients recruited to Group 6, 7 and 8, archival tumour samples will be requested. This is not mandatory and will not affect the enrolment of the patients into the study if not available. The sample can be collected at any time during the study.

[o] For all patients enrolled into Group 8 blood samples will be collected at the following timepoints:
OD schedule

[redacted]

Day 1: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 hours after dosing
Day 8: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 hours after dosing
Day 57: pre-dose, 0 – 0.5, 0.5 – 1.5, 1.5 – 3, 3 – 6, 6 – 8, 8 – 12 hours after dosing
BD schedule:
Day 1: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hours after dosing
Day 8: pre-dose, 0 – 0.5, 0.5 – 1.5, 1.5 – 3, 3 – 6, 6 – 8, 8 – 12 hours after dosing
Day 57: pre-dose, 0 – 0.5, 0.5 – 1.5, 1.5 – 3, 3 – 6, 6 – 8, 8 – 12 hours after dosing
TDS schedule:
Day 1: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 hours after dosing
Day 8: pre-dose, 0 – 0.5, 0.5 – 1.5, 1.5 – 3, 3 – 6, 6 – 8 hours after dosing
Day 57: pre-dose, 0 – 0.5, 0.5 – 1.5, 1.5 – 3, 3 – 6, 6 – 8 hours after dosing

[p] Questionnaire will be completed by site staff for any Group 8 patient spontaneously reporting or with an ongoing AE of nausea, vomiting or fatigue.

[q] For Group 8 patients these assessment should be stopped after Cycle 6.

r Urinalysis dipstick only performed post baseline where clinically indicated.

[redacted]

4.1.4 Safety Review Committee (SRC)

After at least the first 3 patients have been treated for 28 days with AZD2281 tablets within groups 3 onwards, the SRC will evaluate the safety, tolerability and any available pharmacokinetic data for AZD2281 and decide the next dose.

The SRC will consist of:

- Study Team Physician, who will chair the committee, or delegate
- International Principal Investigator or delegate and other Principal Investigators as required
- At least one other physician from the following:
  - Global Safety Physician or delegate
  - Medical Science Director or delegate
  - Senior physician from another project

In addition, the Study Pharmacokineticist, Study Statistician, Patient Safety Scientist and Study Delivery Leader will be invited as appropriate. Further internal or external experts may be consulted by the SRC as necessary. The Global Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion.

The SRC will review and assess all available safety data together with available PK data to make a decision on the dose for the next cohort of subjects. Safety information from later cycles of therapy in addition to cycle 1 data may be considered to assess this relative comparison of toxicity. The decision may be to escalate no further, to give the intended escalation dose or a greater/smaller dose increment which may involve an additional dose escalation step. If 400 mg bid tablet dose is tolerable, higher doses could be considered by the SRC.

The decision of the SRC on the next dose will be taken in consensus between the physicians. If consensus cannot be reached then the International Principal Investigator, who has the ultimate responsibility for the safety of the subjects, will take the final decision on the next dose level or whether to stop the study. The Medical Science Director, who may need to consider other factors, will be involved in this decision. The decisions and decision-making of the SRC on the next dose level will be documented and provided to the International Principal Investigator and Pharmacist prior to the commencement of dosing in the next group.

For details on dose limiting toxicities refer to Section 6.2.4.3.

[redacted]

4.2 Rationale for study design, doses and control groups

This study is intended to establish the comparative bioavailability of AZD2281 Melt-Extrusion (tablet) formulation to AZD2281 Gelucire® 44/14 (capsule) formulation.

Due to the genotoxic nature of AZD2281, this comparative bioavailability study will be conducted in a cancer patient population. A placebo group has been excluded as this would be unethical and the study is non-comparator as there are no assessments of efficacy.

The doses of 50 mg, 100 mg and 400 mg of the current Gelucire® 44/14 (capsule) formulation have been selected as they span the potential Phase II doses (100 mg bid and 400 mg bid) plus a lower dose (50 mg) at a previously defined linear part of exposure/dose relationship. Melt-Extrusion (tablet) formulation doses for Cohorts 1 and 2 have been selected based on assumption that a 2-fold increase in exposure seen in preclinical studies in the dog will translate into a 2 fold increase in man. The Melt-Extrusion (tablet) formulation dose for Cohort 3 will be selected once the comparative bioavailability of the Melt-Extrusion (tablet) formulations in Cohorts 1 and 2 have been determined.

Following completion and review of the first 3 cohorts, 200 mg bid AZD2281 has been chosen as the Melt-extrusion (tablet) formulation dose for continuous treatment. This has been based on modelling of single dose plasma concentration data and subsequent prediction of the tablet dose required to give multiple dose AZD2281 exposure similar to that previously seen following the 400 mg bid Gelucire® 44/14 capsule dose. Additional patients will be recruited to provide reassurance on the safety and steady state exposure of the Melt-extrusion 200 mg bid dose.

Analysis of data from the on-going continuous supply expansion phase has shown that the 200 mg bid tablet dose does achieve exposures within the range of those seen following dosing at 400 mg bid AZD2281 with the capsule. A direct intra-subject comparison of steady state exposure has shown that although the gmean $C_{ss\ max}$ achieved following these doses of the two formulations was very similar, the gmean AUC_{ss} was approximately 20% lower following the tablet dose. The 200 mg bid tablet dose was very well tolerated but seemed to demonstrate lower anti-tumour activity compared to the 400mg bid capsule dose.

The addition of patients to the Continued Supply Expansion Phase is primarily intended to:

- Provide data to validate the predictions of steady state exposures following administration of Melt-extrusion (tablet) formulation at 200 mg bid
- Provide single dose and steady state exposure data following administration of Melt-extrusion (tablet) formulation at doses above 200 mg bid
- Provide safety data for the Melt-extrusion (tablet) formulation when given over an extended treatment period. This will be achieved by treating patients with ovarian and breast tumours associated with germline mutations in the BRCA 1 or BRCA 2 genes. From previous studies, median time on treatment prior to progression

[redacted]

approached 6 months, suggesting that this population will be suitable for assessing the longer-term safety and tolerability of the tablet formulation compared to 400 mg bid capsule formulation.

5. STUDY SELECTION CRITERIA

Patient population should be selected without bias.

Investigator(s) must keep a record of patients who entered pre-trial screening but were never enrolled eg, patient screening log. Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

5.1 Inclusion criteria

For inclusion in the study, patients must fulfil all of the following criteria.

1. Provision of fully informed consent prior to any study specific procedures;

2. Patients must be > 18 years of age;

3. Histologically confirmed malignant advanced solid tumour, which is refractory to standard therapies (except Group 8 patients who must not be platinum refractory) or for which no suitable effective standard therapy exists. If a diagnosis based on a histological sample is not available, a diagnosis based on cytology is allowed for those tumour entities in which this method is a generally accepted alternative;

4. Eastern Co-operative Oncology Group (ECOG) Performance status 0 – 1 (see Appendix D);

5. Patients must have adequate organ and bone marrow function measured within 7 days prior to administration of study treatment as defined below:

   - Haemoglobin ≥ 10.0 g/dL and no blood transfusions in the 4 weeks prior to randomisation (Group 8 only) ≥ 9.0 g/dL (all other groups)
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - No dysplastic features on peripheral blood smear (Group 8 only)
   - White blood cells (WBC) > 3x10^9/L
   - Platelet count ≥ 100 x 10^9/L
   - Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)

[redacted]

- Aspartate transanimase (AST [SGOT])/Alanine transanimase (ALT [SGPT]) ≤ 2.5 x ULN unless liver metastases are present in which it must be ≤ 5x ULN

- Serum creatinine ≤ 1.5 x ULN;

6. Patients must have a life expectancy ≥ 16 weeks;

7. Female patients must have evidence of non-childbearing status: negative urine or serum pregnancy test within 7 days of study treatment for women of childbearing potential, or postmenopausal status.

   Postmenopausal is defined by any one of the following:

   - natural menopause with last menses >1 year ago;

   - radiation-induced oophorectomy with last menses >1 year ago;

   - chemotherapy-induced menopause with >1 year interval since last menses;

   - serum follicle stimulating hormone, luteinising hormone and plasma oestradiol levels in the post menopausal range for the institution;

   - or surgical sterilisation (bilateral oophorectomy or hysterectomy).

8. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.

Inclusion criterion that applies to the additional gBRCA ovarian or breast cancer patients being assigned to Group 1, 6, 7 and 8 in the Continued Supply Expansion Phase:

9. Patients must have solid tumours originating from the ovary or breast with a confirmed genetic BRCA1/2 mutation (Group 8 gBRCA ovarian [including primary peritoneal and fallopian tube] cancer patients only). The mutation must be confirmed as a loss of function mutation ie, a known deleterious or suspected deleterious mutation, the exact sequence variant must be recorded on the CRF and a redacted copy of the genetic diagnosis available at site.

10. Patients must have at least one lesion, not previously irradiated, that can be accurately measured as ≥10 mm in the longest diameter with spiral computed tomography (CT) scan or as ≥20 mm with conventional techniques (conventional CT or MRI) and which is suitable for accurate repeated measurements.

5.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled.

[redacted]

1. Patients receiving any chemotherapy, radiotherapy (except for palliative reasons), or any other anti-cancer therapy within 4 weeks from the last dose prior to study randomisation (or a longer period depending on the defined characteristics of the agents used). Patients may continue the use of bisphosphonates for bone metastases, and corticosteroids provided the dose is stable before and during the study and these must have been started at least 4 weeks prior to the beginning of study treatment. Patients will be allowed to continue on hormone replacement therapy and on Luteinizing Hormone-Releasing Hormone (LHRH);

2. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to enrolment;

3. Major surgery within 2 weeks of starting the study and patients must have recovered from any effects of any major surgery;

4. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, unstable spinal cord compression (untreated and unstable for at least 28 days prior to study entry), superior vena cava syndrome, pure red cell aplasia, or any psychiatric disorder that prohibits obtaining informed consent

5. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication (e.g. invasive pancreatic cancer, partial bowel obstruction or malabsorption);

6. Pregnant or breastfeeding women;

7. Immunocompromised patients, eg, patients who are known to be serologically positive for human immunodeficiency virus (HIV) and are receiving antiviral therapy;

8. Patients with known hepatic disease (ie, Hepatitis B or C);

9. Persistent toxicities (NCI-CTCAE grade 2 or greater) caused by previous cancer therapy (excluding alopecia).

10. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site);

11. Previous randomisation of treatment in the present study;

[redacted]

12. Treatment with any investigational product during the last 14 days (or a longer period depending on the defined characteristics of the agents used);

13. Patients with a known hypersensitivity to AZD2281 or any of the excipients of the product (Co-povidone, Gelucire);

14. Patients currently experiencing seizures or who were currently being treated with only anti-epileptics for seizures (use of anti-epileptic drugs to control pain is allowed in patients not suffering from seizures unless drug is excluded due to CYP3A4 induction - phenytoin, carbamazepine, phenobarbital, see Section 6.3.1.

15. Patients receiving the following classes of inhibitors of CYP3A4 (see Section 6.3.1 for guidelines and wash out periods).

    – Azole antifungals

    – Macrolide antibiotics

    – Protease inhibitors

16. Patients with myelodysplastic syndrome/acute myeloid leukaemia (Group 8 only).

17. Patients who are platinum refractory (Group 8 only).

18. Patients who have previously received a PARP inhibitor (including AZD2281) (Group 8 only).

5.3 Restrictions

1. Patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 3 months after last dose of study drug(s).

   Condom with spermicide

   and one of the following

   oral contraceptive or hormonal therapy (eg, hormone implants)

   Placement of an intra-uterine device (see Appendix G as consideration should be given to the type of device/system used)

   Appendix G provides details of acceptable birth control methods to be used within the study.

[redacted]

2. Male patients must refrain from fathering a child or donating sperm during the study and for 3 months following the last dose of AZD2281.

3. No other chemotherapy or other novel agent is to be permitted during the course of the study for any patient. Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present.

4. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with AZD2281 are unknown and therefore they should not be administered to patients in any treatment group.

5. *In vitro* data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of AZD2281 is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, to ensure patient safety all patients must avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity (see Section 6.3.1) from the time they enter the screening period until 30 days after the last dose of study medication.

6. Refrain from eating star fruit (averrhoa carambola) while taking the study medication.

7. Patients who are blood donors should not donate blood during the study, and for 3 months after the last dose of study medication.

8. PK phase only (cohorts 1 to 3) (N/A for Groups 1-8): Patients should not lie down during the absorption phase (from dose administration until 2 hours after dosing).

5.4 Procedures for handling incorrectly included patients

Patients that do not meet the inclusion/exclusion criteria for a study should not, under any circumstances, be enrolled into the study – there can be no exceptions to this rule.

Where patients that do not meet the study criteria are enrolled in error, incorrectly randomised, or where patients subsequently fail to meet the criteria for the study post enrolment, the procedures included in the protocol for the discontinuation of such patients must be followed. Once the error is identified a discussion must occur between the AstraZeneca Study Team Physician and the Investigator regarding whether to continue or discontinue the patient from the study. Once a decision is made, Investigators need to ensure they comply with all applicable requirements for human patient protection and ethical review. The AstraZeneca Study Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached with the Investigator in terms of how to manage the patient going forward, the patient should have their study medication stopped and be discontinued from the study.

[redacted]

5.5 Discontinuation of patients

5.5.1 Criteria for discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient are given below:

Discontinuation from the study:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment;
- Risk to patients as judged by the Investigator and/or AstraZeneca;
- Severe non-compliance to protocol as judged by the Investigator and/or AstraZeneca;
- Incorrectly enrolled patients, ie, the patient does not meet the required inclusion/exclusion criteria for the study;
- The patient becomes pregnant;
- Patient lost to follow-up.

Discontinuation from study treatment:

- **PK Phase**: Any NCI-CTCAE grade 3 or 4 events that have not reverted to NCI-CTCAE grade 1 or less within 2 weeks (14 days)
- **Continued Supply Phase**: Any NCI-CTCAE grade 3 or 4 events that have not reverted to NCI-CTCAE grade 1 or less within 4 weeks (28 days). (At the Investigator's discretion, following dose interruption, patients may be considered for dose reductions, providing they have not already undergone the maximum number of dose reductions allowed for guidelines see Table 9 and Table 10 for AZD2281. However, if upon re-challenging with AZD2281 at the lowest reduced dose any NCI-CTCAE grade 3 or 4 AEs recur, the patient must be discontinued (refer to Section 6.2.3.2).

5.5.2 Procedures for discontinuation of a patient from the study

A patient that discontinues will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s) at 7-day follow-up for the PK Phase and at 4 weeks post-discontinuation for the Continued Supply Phase for the evaluations outlined in Table 5. After discontinuation of study medication, the Principal Investigator (PI)/sub-Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. In addition, they will record on the CRF the date of discontinuation, the reasons, manifestation and treatment at the time of discontinuation. If

[redacted]

patients discontinue study treatment, AstraZeneca must be informed immediately. Patients will be required to attend the treatment discontinuation visit. The patient should return all study medication.

After discontinuation of the study medication at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the Investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up (see Sections 7.3.3 and 7.3.3.10). All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 7.3.3.10) and followed to resolution as above. Patients should attend a visit at least 30 days after discontinuing study medication for the collection and/or completion of AE information. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the Investigator assesses as possibly related to the study medication should also be reported as an AE.

5.5.3 Patient replacement policy

Replacement of ineligible and non-evaluable patients will be dependent on discussion with AstraZeneca. An evaluable patient is defined as a patient who:

- Met all of the inclusion and exclusion criteria specified in Sections 5.1 and 5.2 within the specified time frame;
- Provided a full PK profile (N.B. if a full PK profile has not been provided then the number of missing PK samples and the corresponding collection time points will be reviewed by AstraZeneca to confirm if the patient is to be replaced);
- Had his/her CRF completed, received and accepted.

No patient numbers will be reallocated; any new patients (replacing ineligible or non-evaluable patients) will be enrolled and assigned the next available patient number.

6. STUDY CONDUCT

6.1 Patient enrolment and randomisation

The Principal Investigator will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.
2. Assign potential patient a unique enrolment number, beginning with "E".
3. Determine patient eligibility. See Sections 5.1 and 5.2.

[redacted]

4. Register the screening of a patient by e-mail to the clinical research organisation (CRO) and AstraZeneca, as detailed in the CRF.

If patients have discontinued their participation in the study then they cannot re-enter into the study.

6.1.1 Procedures for randomisation

Eligible patients will be randomised in a 1:1 ratio (Sequence 1: Sequence 2) for Cohorts 1, 2 and 3 and Group 2 of the Continued Supply Expansion Phase. The actual treatment sequence given to individual patients will be determined by separate randomisation schemes for each cohort.

Eligible patients will be randomised in a 1:1 ratio (Treatment A: Treatment B) for Group 1 of the Continued Supply Expansion Phase.

Eligible patients will be randomised in a 1:1 or 1:1:1 ratio (Treatment A: Treatment B: and Treatment C (if applicable)) for Group 6 of the Continued Supply Expansion Phase.

Eligible patients will be randomised in a 1:1:1:1 ratio (Schedule A: Schedule B: Schedule C: Schedule D) for Group 8, Randomised Tablet Formulation Continued Supply Expansion Phase.

A blocked randomisation will be generated and all centres will use the same list in order to minimise any imbalance in the number of patients assigned to each treatment group. The randomisation scheme will not be stratified for the randomisation of treatment sequences. However, the randomisation of treatment arms for Group 1, 6 and 7 patients in the Continued Supply Expansion Phase will be stratified according to primary tumour type (either breast cancer or ovarian cancer). For Group 6 and 7 both gBRCA breast and gBRCA ovarian patients will be randomised. However, there should be at least 10 gBRCA ovarian patients enrolled per treatment arm; therefore recruitment may be closed to non-ovarian cancer patients before ovarian cancer patients.

Patient eligibility will be established before treatment randomisation. Patients will be randomised strictly consecutively, as patients are eligible for randomisation. Once the eligibility of a patient has been confirmed, the Investigator (or nominated assistant) should contact the Centralised Randomisation Centre by telephone for allocation of randomised treatment sequence or treatment arm and randomisation number. Patients will be identified to the Centralised Randomisation Centre using patient initials, enrolment number and date of birth and which Group the patient is intended to be randomised in to. The Centralised Randomisation Centre will inform the Investigator of the treatment sequence or treatment arm to be allocated to the patient at the randomisation visit.

[redacted]

6.2 Treatments

6.2.1 Identity of investigational product(s)

AstraZeneca Pharmaceuticals Investigational Products will supply AZD2281, for oral use only, to the Investigator in two presentations. The first presentation is a banded white HPMC size 0 capsule, with a nominal fill weight of 500 mg. The capsules contain a 10% w/w suspension of the drug substance (AZD2281) in a waxy solid (Gelucire 44/14®). The second presentation is green, film-coated tablets containing either 25 mg, 100 mg or 200 mg AZD2281 which will be used in the PK phase and continued supply expansion phase. Tablets are prepared by compression of an amorphous solid dispersion of the drug substance in a carrier polymer prepared by melt extrusion, after blending with common pharmaceutical excipients. AZD2281 will be supplied in white high-density polyethylene (HDPE) bottles with child resistant tamper evident closures.

Table 8 Identity of Investigational Product

Investigational product[a]	Dosage form and strength	Manufacturer	Study Phase
AZD2281 (Gelucire® 44/14 [capsule] formulation)	50 mg capsule	Patheon Inc	Phase I (PK & Continued supply phase)
AZD2281 (Melt-extrusion [tablet] formulation)	25, 100 & 200 mg tablets	Soliqs	Phase I (PK Phase & continued supply expansion phase)

[a] Descriptive information for AZD2281 Gelucire® 44/14 (capsule) and Melt-extrusion (tablet) formulations can be found in the IB

6.2.2 Labelling, storage and accountability

Each bottle will have a label permanently affixed to the outside and will be labelled in accordance with Good Manufacturing Practice and local regulations, stating that the material is for clinical trial/investigational use only and should be kept out of reach of children.

For the Continued Supply Phase, labels will include blank lines for quantity of capsules to be taken, patient enrolment code (E-code) and date of dispensing. Instructions stating that the AZD2281 capsules should be taken at approximately the same time each morning and evening will be included. Following Amendment 4, all labels will instead include the text 'To be taken as directed by your doctor', and patients will be provided with specific dosing instructions.

All study medication must be kept in a secure place under appropriate storage conditions and may only be dispensed by a pharmacist or a qualified designee. The investigational product label on the bottle specifies the appropriate storage and shipment. Investigational product should not be stored under refrigerated conditions.

[redacted]

The medication provided for this study is for use only as directed in the protocol. All unused drugs will be accounted for and retained until advised otherwise. The study personnel will account for all drugs dispensed and returned. Certificates of delivery and destruction must be maintained by the study site.

6.2.3 Doses and treatment regimens

6.2.3.1 PK Phase

Patients will take part in two treatment periods each separated by a 6 to 14-day washout period. Eligible patients will be randomised in a 1:1 ratio (Sequence 1 [Treatment AB]: Sequence 2 [Treatment BA]) for Cohorts 1 and 2. Cohort 3 will be recruited following analysis of PK data from Cohorts 1 and 2. Eligible patients will be randomised in a 1:1 ratio (Sequence 1: Sequence 2).

- Treatment A: Patients will receive a single oral dose of AZD2281 Gelucire® 44/14 (capsule) formulation on Day 1;
- Treatment B: Patients will receive a single oral dose of AZD2281 Melt-Extrusion (tablet) formulation on Day 1.

Cohort 1 will receive a single 50 mg dose of the Gelucire® 44/14 (capsule) formulation and a single 25 mg dose of the Melt-Extrusion (tablet) formulation. Cohort 2 will receive a single 100 mg dose of the Gelucire® 44/14 (capsule) formulation and a single 50 mg dose of the Melt-Extrusion (tablet) formulation. Cohorts 1 and 2 will be recruited consecutively, with Cohort 1 recruited first, immediately followed by Cohort 2. Patients will be randomised to treatment sequence. Cohort 3 will be recruited once PK analysis for Cohorts 1 and 2 has completed so as to be able to better define the higher dose level for the Melt-Extrusion (tablet) formulation in Cohort 3. Patients in Cohort 3 will be randomised to treatment sequence and will receive a single 400 mg dose of the Gelucire® 44/14 (capsule) formulation and a dose of the Melt-Extrusion (tablet) formulation to be decided from the first two cohorts' data. The PK team at AstraZeneca will make the decision about the dose of the Melt-Extrusion (tablet) formulation to be used in Cohort 3, following review of the PK and AUC data from Cohorts 1 and 2 confirming the exposure ratio between the Gelucire® 44/14 (capsule) and Melt-Extrusion (tablet) formulations.

The capsules or tablets should be swallowed whole and not chewed, crushed or divided. Patients will take the study drugs with a total of 240 mL of water, and must consume all the fluid.

6.2.3.2 Continued Supply Phase and Expansion Phase

Continued Supply Phase

The Continued Supply Phase is scheduled 7 days after the end of the PK Phase. Gelucire® 44/14 (capsule) formulation AZD2281 will be administered orally at a dose of 400 mg bid (ie, 8 capsules bid) on a continuous basis.

[redacted]

Continued Supply Expansion Phase

Once the PK team at AstraZeneca have confirmed the exposure ratio between the Gelucire® 44/14 (capsule) and Melt-extrusion (tablet) formulations, approximately 26 additional patients will be recruited to the Continued Supply Expansion Phase: 20 patients with confirmed genetic BRCA1/2 ovarian or breast cancer will be randomised to either daily dosing with tablet or capsule formulation to assess the multiple dose safety profile of the Melt-extrusion (tablet) formulation in a comparative setting and 6 patients will be recruited to Group 2 which will directly compare the steady state PK of the capsule and the Melt-extrusion (tablet) formulation.

Following determination of the AZD2281 plasma concentrations in the samples obtained from the patients in Group 2 of the Continued Supply Expansion Phase, a within-patient comparison of tablet versus capsule steady state AUC and C_{max} will be performed in order to validate the predictions of steady state exposure previously performed from the single dose data obtained from the patients in the PK Phase. Following this analysis, patients continuing on 200 mg bid AZD2281 tablets may have their daily dose adjusted if required. In addition, further patients will be recruited into the study to assess safety, tolerability and pharmacokinetics of higher doses than 200 mg bid, of the melt-extrusion (tablet) formulation. Initially, a minimum of 6 patients (Group 3) will be treated with 250 mg bid (2 x 100 mg and 2 x 25 mg tablets bid) AZD2281 tablet dose. If tolerated, a further group of 6 patients (minimum) will be recruited to the next Group and will receive increased bid tablet dosing. Dose escalation will continue, into additional groups of 6 patients minimum, at increasing dose levels up to a dose defined by the SRC.

Depending on the determination of tolerability of the tablet dose from Groups 3 onwards, Group 6 patients will either receive:

- 400 mg bid capsule dose, 400 mg bid tablet dose (or lower if 400 mg bid is not tolerated) or a tablet dose between 250mg and the higher tablet dose taken into the expansion that has been shown to be safe and tolerable

OR

- 400 mg bid capsule dose or 250 mg bid tablet dose

If 400 mg bid AZD2281 tablet is tolerated and dose escalation continues to a dose defined by the SRC, Group 7 patients will receive:

- 400 mg bid capsule or highest bid tablet dose deemed tolerable by the SRC following completion of the dose escalation phase

<u>Group 8 patients - to further investigate the safety profile and pharmacokinetics of AZD2281 melt-intrusion (tablet) formulation, approximately 60 patients with gBRCA ovarian cancer will be randomised 1:1:1:1 to one of the dosing schedules detailed below:</u>

- <u>200mg tds tablet continuous dosing</u>

[redacted]

- 250mg tds tablet 2 weeks on study drug, 1 week off study drug
- 400mg bid tablet 1 week on study drug, 1 week off study drug
- 400mg od tablet continuous dosing

Patients will continue with their assigned AZD2281 treatment as long as they remain free from intolerable toxicity and, in the Investigator's opinion, are receiving some clinical benefit from treatment with AZD2281 and do not meet any other discontinuation criteria. Following the commencement of continuous treatment of either formulation, study safety assessments will be performed monthly for the first 6 months and then every 8 weeks until treatment discontinuation or study completion (closure of the clinical database - see Section 10.5). If a patient remains on study treatment following the completion of the study (closure of the clinical database), SAEs will continue to be collected until treatment discontinuation.

If the data demonstrate that one treatment arm is significantly more efficacious, then patients who are ongoing on treatment in the less efficacious arm may be permitted to switch to the more efficacious treatment arm following agreement of the investigator and the AZ study physician.

Doses of AZD2281 should be taken at the same times each day, daily (OD) doses should be taken in the morning unless otherwise instructed, twice daily (BD) doses should be taken approximately 12 hours apart and three times (TDS) daily doses taken approximately 8 hours apart. All doses should be taken with approximately 240 mL of water.

Patients will be instructed to take their doses of AZD2281 at least 2 hours after the last time they ate, and the patient should then refrain from eating for a further 2 hours due to the potential effect of food on absorption. For Group 8 patients (excluding Group 8 od schedule patients), and for all other patients (PK phase cohorts 1 and 2, and Groups 1-7) continuing to receive tablet doses following approval of Amendment 4, AZD2281 can be taken with a light meal and the time restrictions on eating will not apply.

For Group 8 od schedule patients an informal assessment of the effect of food on the PK of AZD2281 will be made. On Day 1 these patients must take their dose of AZD2281 at least 2 hours after the last time they ate, and then refrain from eating for a further 2 hours. On Day 8 patients must take their dose of AZD2281 within 30 minutes of eating breakfast. On all other days doses can be taken with a light meal, and no time restrictions are required.

All ongoing patients taking *capsule* doses of AZD2281 must continue to take their doses of AZD2281 at least 2 hours after the last time they ate, and then refrain from eating for a further 2 hours due to the potential effect of food on absorption of the capsule formulation.

The capsules/tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

[redacted]

If vomiting occurs shortly after the AZD2281 capsules/tablets are swallowed, the dose should only be replaced if all of the intact capsules/tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (eg, as a result of forgetting to take the capsules/tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

6.2.4 Management of toxicity of AZD2281

6.2.4.1 PK Phase

It is unlikely for patients to experience any toxicities related to a single dose administration of AZD2281. However, dosing must be interrupted if any NCI-CTCAE grade 3 or 4 AE occurs which the Investigator considers to be related to administration of AZD2281. The patient should not enter the second treatment period in their sequence until the toxicity has resolved to at least NCI-CTCAE grade 1. If this has not resolved to at least NCI-CTCAE grade 1 during the maximum 2 weeks (14 days) dose interruption period, the patient must permanently discontinue treatment with AZD2281.

6.2.4.2 Continued Supply Phase and Expansion Phase

Any toxicity observed during the course of the study will be managed by interruption of the dose if deemed appropriate by the Investigator. Repeat dose interruptions are to be allowed as required, for a maximum of 4 weeks (28 days) on each occasion. AZD2281 must be interrupted until the patient recovers completely or the toxicity reverts to NCI-CTCAE version 3.0 grade 1 or less.

Where toxicity recurs following re-challenge with AZD2281, and where further dose interruptions are considered inadequate for management of toxicity, then the patient is to be considered for dose reduction or must permanently discontinue treatment with AZD2281.

Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 AE occurs which the Investigator considers to be related to administration of AZD2281. If this has not resolved to at least NCI-CTCAE grade 1 during the maximum 4 weeks (28 days) dose interruption period, and/or the patient has already undergone the maximum number of dose reductions allowed, the patient must permanently discontinue treatment with AZD2281. If toxicity is appropriately resolved, then the patient should restart treatment with AZD2281 but with a dose reduction according to Table 9 and Table 10. If the event recurs with the same severity, treatment should be interrupted again and, on resolution, a further dose reduction made (see Table 9 and Table 10). If, on re-starting treatment, the event continues to occur, the patient must permanently discontinue AZD2281.

Management of new or worsening pulmonary symptoms: If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality occurs, an interruption in AZD2281 dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality

[redacted]

is observed on CT imaging and symptoms resolve, then AZD2281 treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca Study Delivery Physician.

Management of leukopaenia and/or anaemia: An exception to the management of AZD2281-related toxicity is the occurrence of leukopaenia and/or anaemia. In this case, the AE should be managed as deemed appropriate by the investigator (growth factor, transfusions), without interruption in study drug or change in dose. However, growth factors must be discontinued once the AE has recovered to grade 1 or better. They may be resumed, if necessary, if leukopaenia/anaemia develops again and discontinued once it recovers.

Management of leukopaenia and/or anaemia (Group 8 and ongoing patients): An exception to the management of AZD2281-related toxicity is the occurrence of leukopaenia and/or anaemia. In this case, the AE should be managed as deemed appropriate by the investigator (e.g. G-CSF or blood transfusions). However, growth factors must be discontinued once the AE has recovered to grade 1 or better. They may be resumed, if necessary, if leukopaenia/anaemia develops again and discontinued once it recovers. In addition:

- Patients who develop a requirement for repeated blood transfusions within 4-6 weeks should be dose reduced.
- Patients who develop grade 3 anaemia should be dose reduced.

Management of prolonged haematological toxicities including anaemia, neutropaenia or thrombocytopaenia whilst on study treatment:

- If any study treatment is interrupted/delayed because of one or more of the following:
- ≥2 week interruption/delay in study treatment due to CTC grade >2 neutropaenia
- ≥2 week interruption/delay in study treatment due to CTC grade >2 thrombocytopaenia
- ≥2 week interruption/delay in study treatment due to CTC grade >2 anaemia and or development of blood transfusion dependence

Weekly blood counts should be performed during the study treatment interruption/delay. If the levels have still not recovered to CTC Grade ≤1 after 4 weeks of dose interruption, the patient should be referred to a haematologist for further investigations. Bone marrow analysis or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Development of myelodysplastic syndrome should be reported as an SAE and full reports must be provided by the Investigator for documentation on the Patient Safety database.

[redacted]

The dose of AZD2281 must not be adjusted under any other circumstances unless AstraZeneca gives prior agreement. Once the dose of AZD2281 has been reduced under no account should it be re-escalated.

AZD2281 should be discontinued for a minimum of 7 days before a patient undergoes therapeutic palliative radiation treatment.

All dose reductions and interruptions, and the reasons for the reductions/interruptions are to be recorded in the CRF.

Table 9 Dose reductions for AZD2281 (Group 3-7)

Reduction	**Dose Level**[a] Capsule Formulation	**Dose Level**[a] Tablet Formulation
Initial Dose Level	400 mg bid	Dose reduce in steps of at least 50mg bid to a minimum daily dose of 100 mg bid after which the patient should be withdrawn from study treatment. A maximum of 3 dose reductions is allowed.
1st dose reduction due to NCI-CTCAE grade 3 or 4 treatment related SAE/AEs	200 mg bid	
2nd dose reduction due to NCI-CTCAE grade 3 or 4 treatment related SAE/AEs	100 mg bid	
3rd Dose Reduction due to NCI-CTCAE grade 3 or 4 treatment-related SAEs/AEs.	No reduction allowed – withdraw patient	

[a] AZD2281 is not to be decreased below 100 mg bid

[redacted]

Table 10 Dose reductions for AZD2281 (Group 8)

Starting Dose	**Schedule A: 200mg tds continuous**	**Schedule B: 250mg tds 2 weeks on, 1 week off**	**Schedule C: 400mg bid 1 week on, 1 week off**	**Schedule D: 400mg od continuous**
Initial dose level	200mg tds	250mg tds	400mg bd	400mg od [a]
Dose reduction 1	150mg tds	200mg tds	300mg bd	350mg od
Dose reduction 2	100mg tds	150mg tds	250mg bd	300mg od
Dose reduction 3	100mg bd	100mg tds	200mg bd	250mg od

[a] As an alternative to the first dose reduction the dose for 400mg od schedule the dose may be taken in the evening to manage adverse events if appropriate (e.g. nausea).

At each dose reduction the dosing schedule remains the same (continuous or intermittent at the same schedule as per randomisation), only the dose (mg) is changed.

6.2.4.3 Dose limiting toxicities

Dose limiting toxicity (DLT) will be defined as any of the following events that is determined to be possibly or probably related to AZD2281 (as determined by the investigator) and occurring during the first cycle of treatment (28 days), irrespective of whether the toxicity resolved:

- ANC < 0.5 x10^9/L lasting for > 5 days, or ANC < 0.5x10^9/L with neutropenic fever/sepsis.
- Platelet count < 25 x 10^9/L.
- Any other drug-related non-haematological grade 3/4 toxicity, with the exceptions of fatigue, nausea and vomiting, diarrhoea, myalgia or arthralgia unless appropriate prophylactic or therapeutic measures have been administered.
- Unfavourable tolerability profile compared to 400 mg bid capsule profile used in monotherapy in terms of gastrointestinal toxicities and fatigue (grade 3/4)
- Inability to tolerate the cycle of therapy due to toxicity.
- Grade 2 cardiac or neurological toxicity.
- Any toxicity, which in the judgement of the Sponsor and Investigator is viewed as DLT.

[redacted]

- If any haematological or non-haematological toxicities have not resolved (≤ Grade 1 CTCAE or baseline levels) within 2 weeks, the patient may be considered to have a DLT and may be discontinued from the trial.

In order to define DLT, patients should not be prophylactically prescribed growth factor support, antiemetics, anti-diarrhoeals or antipyretics during cycle 1 of therapy.

If a patient experiences grade 3 or greater nausea and/or vomiting, diarrhoea, medical intervention should occur, including prophylactic administration of these agents for subsequent doses as indicated.

Patients with dose-limiting toxicity after cycle 2 who have documented clinical benefit (stable disease or an objective response) may continue to be treated at a reduced dose level. Any patient in whom a DLT occurs during any cycle will have his or her treatment held until toxicity resolves to baseline or grade 1 or better. Upon resolution, therapy may be re-instituted at the next lower dose level when clinically indicated. Treatment may be delayed up to 2 weeks to allow sufficient time for recovery from toxicities.

6.3 Concomitant and post-study treatment(s)

6.3.1 AZD2281 and CYP3A4

The use of any natural/herbal products or other "folk remedies" should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded in the Case Report Form (CRF).

AZD2281 is an investigational drug for which no data on *in vivo* interactions are currently available. Based on *in vitro* data and clinical exposure data, AZD2281 is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. *In vitro* data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of AZD2281 is CYP3A4 and consequently, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving AZD2281.

While this is not an exhaustive list, it covers the known potent inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfanavir

For patients taking any of the above, the required wash-out periods prior to starting AZD2281 is one week:

In addition, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4 inducers should be avoided:

[redacted]

- Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil and St John's Wort (Hypericum perforatum)

For patients taking any of the above, the required wash-out periods prior to starting AZD2281 are:

- phenobarbitone 5 weeks, and for any of the others, 3 weeks.

If the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the investigator must contact the AstraZeneca Study Physician. A decision to allow the patient to continue in the study will be made on a case-by-case.

6.3.2 Other Concomitant Medications

Any medications, with the exceptions noted in Section 6.3.5 below, which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the Investigator, providing the medications, the doses, dates and reasons for administration are recorded in the CRF.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the comments section of the corresponding AE report.

Anticoagulant Therapy: Patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time (International Normalised Ratio [INR] and activated partial thromboplastin time [APTT]) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

Anti-emetics/Anti-diarrhoeals: Prophylactic anti-emetics and/or anti-diarrhoeals will not routinely be given. Should a patient develop nausea, vomiting and/or diarrhoea, which, in the Investigator's opinion, is considered related to the study medication, then appropriate prophylactic treatment may be given.

The prophylactic use of granulocyte colony stimulating factors (G-CSF) is not allowed in any cycle during the study. They should only be used after relevant toxicity has occurred. In this case, their use is permitted at the Investigator's discretion and according to local hospital guidelines. The reason for use, doses and dates of treatment should be recorded in the CRF. Patients who are on recombinant human erythropoietin prior to trial entry may continue on this therapy. For Group 8 patients receiving recombinant human erythropoietin prior to trial entry, this must be discussed with the AZ physician prior to entry. The use of recombinant erythropoietin for patients not currently receiving erythropoietin and who have symptomatic anaemia during treatment may be considered upon discussion with AZ.

The reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate section of the CRF.

[redacted]

All medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the trial or until 30 days from the end of the last protocol treatment and different from the trial medication must be documented.

6.3.3 Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the Investigator does not feel that these are indicative of clinical disease progression during the study period.

6.3.4 Administration of other anti-cancer agents

Patients must not receive any concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates for bone disease and corticosteroids provided the dose is stable before and during the study and were started at least 4 weeks prior to beginning study treatment.

6.3.5 Medications that may NOT be administered

No other chemotherapy, immunotherapy or other novel agent is to be permitted while the patient is receiving study medication.

6.4 Treatment compliance

During the PK Phase compliance will be assured by supervised administration of the investigational product by the Investigator or his delegate.

The administration of all medication (including investigational products) must be recorded in the appropriate sections of the CRFs.

During the Continued Supply Phase, patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer AZD2281. Compliance of the first dose and dose taken on the day of any study visit of AZD2281 will be assured by supervised administration by the Investigator or delegate. Study site pharmacy staff will make capsule and tablet counts at regular intervals during treatment. All patients must return their bottle(s) of AZD2281 at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses.

Patients must return all containers and any remaining capsules and tablets at the end of the study

6.4.1 Accountability

The medication provided for this study is for use only as directed in the protocol. It is the Investigator/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, so as to ensure that:

- Deliveries of such products from AstraZeneca are correctly received by a responsible person;

[redacted]

- Such deliveries are recorded;
- Study treatments are handled and stored safely and properly as stated on the label;
- Study treatments are only dispensed to study patients in accordance with the protocol.

The study personnel will account for all study medications dispensed and returned.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the study treatment was dispensed, the quantity and date of dispensing and unused study treatment returned to the Investigator. This record is in addition to any drug accountability information recorded on the CRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the Investigator or a pharmacist, and copies retained in the Investigator site file.

7. COLLECTION OF STUDY VARIABLES

7.1 Recording of data

The Investigator will ensure that all data collected in the study are provided to AstraZeneca. He/she ensures the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the paper Case Report Form (pCRF) and according to any instructions provided.

The Principal Investigator will provide AstraZeneca with all data produced during the study from the scheduled study assessments. He/she ensures the accuracy, completeness, legibility, and timeliness of the data reported to AstraZeneca in the pCRF and in all required reports.

7.2 Screening and demography procedures

7.2.1 Screening

The following assessments and procedures should be performed within 28 days prior to first dose of study treatment. For details of the schedule and nature of the assessments, see below.

- Study eligibility (Inclusion/Exclusion criteria) (within 28 days and 7 days prior to study treatment start);
- Signed informed consent (within 28 days prior to study treatment start);
- Demographics (date of birth, gender, and race) (within 28 days prior to study treatment start);
- Serum or urine pregnancy test for women of childbearing potential (within 28 days prior to study treatment start);

[redacted]

- Medical and surgical history (within 28 days prior to study treatment start), including previous cancer and radiotherapy and history of blood transfusions in the previous 6 months;
- Current and concomitant medications including previous cancer therapies (if applicable) (within 28 days and 7 days prior to study treatment start);
- Physical examination, ECOG performance status, vital signs (BP, pulse and body temperature), body weight and height (within 28 days prior to study treatment start);
- ECG (within 7 days prior to study treatment start);
- Haematology, clinical chemistry and urinalysis (within 28 days prior to study treatment start);
- AE recording(within 28 days and 7 days prior to study treatment start);

The following assessments will only be performed for those patients who will be participating in Group 1 , 6, 7 and 8 of the Continued supply phase expansion:

- Tumour assessment (CT or MRI scans of chest, abdomen and pelvis for breast cancer and abdomen and pelvis for ovarian cancer with other regions as clinically indicated for the assessment of disease). An historical scan meeting the RECIST criteria as defined in Appendix F can be used for baseline assessment, but this must be performed no more than 28 days before the first dose of study medication.
- CA-125 (within 28 days prior to study treatment start) in ovarian cancer patients only

7.2.2 On trial assessments

7.2.2.1 PK Phase

For the PK Phase, patients will attend the clinic for the first 3 days of each treatment period (Treatment Period 1 and Treatment Period 2) and the following assessments will be performed in each treatment period at time points specified in the study schedule (see Table 5).

- Physical examination including ECOG performance status (Treatment Period 1: Day 1; Treatment Period 2: Day 8), vital signs (Treatment Period 1: Days 1 to 3; Treatment Period 2: Days 8 to 10) and body weight (Treatment Period 1: Day 1);
- ECG (Treatment Period 1: Day 1; Treatment Period 2: Day 8);
- PK blood sampling (taken as close to the nominal time-point as possible; (Treatment Period 1: Days 1 to 3; Treatment Period 2: Days 8 to 10);

[redacted]

- PD blood sampling (PBMCs) pre-dose and at, 3, 10, & 24 hours; (Treatment Period 1: Days 1 to 2; Treatment Period 2: Days 8 to 9);
- Haematology, clinical chemistry and urinalysis (Treatment Period 1: Day 1; Treatment Period 2: Day 8);
- AZD2281 dispensed/returned (Treatment Period 1: Day 1; Treatment Period 2: Day 8);
- AE and concomitant medications (every visit).

It is essential that PK blood sampling is conducted as close as possible to study plan timings. To ensure that the assessments are carried out according to this order, and that PK sampling is conducted at the appropriate time it will be necessary to arrange the assessment procedures so that the PK assessments fall on/or around the correct timing. The actual time of collection of all PK samples must be recorded.

7.2.2.2 PK Phase Follow-Up Visit

Following the last dose of AZD2281 in the PK Phase, patients should have a post-study visit at 7 days.

The following assessments will be performed at time points specified in the study schedule (see Table 5).

- Physical examination including vital signs;
- ECG;
- Haematology, clinical chemistry and urinalysis;
- AZD2281 dispensed/returned;
- AE and concomitant medications (any AEs should have returned to baseline before patients proceed to commence the Continued Supply Phase)

7.2.2.3 Continued Supply Phase and Continued Supply Expansion Phase

Patients in the Continued Supply Phase and Expansion Phase of the study will have the following assessment performed approximately every 28 days for the first 24 weeks and then at least every 56 days thereafter (28 days = 1 cycle) until treatment discontinuation or study completion (closure of the clinical database). If the patient is still benefiting from taking AZD2281 following study completion, then treatment can be continued. and any new SAEs must be reported to AZ.

The following assessments are included:

- Physical examination including ECOG performance status and vital signs;

- ECG at baseline, Day 1 (if baseline ECG performed greater than 7 day prior to Day 1), end of cycle 1 and cycle 2, when clinically indicated and at final follow-up assessment;
- Haematology, clinical chemistry and urinalysis;
- AZD2281 dispensed/returned;
- AE and concomitant medications (including blood product transfusions and g-CSF support)

For Group 8 patients, physical examination, ECOG performance status, vital signs and ECG assessments should be stopped after Cycle 6 and urinalysis by dipstick should be performed post baseline only if clinically indicated.

Once the PK team at AstraZeneca have confirmed the exposure ratio between the Gelucire® 44/14 (capsule) and Melt-extrusion (tablet) formulations approximately 26 additional patients will be recruited to the Continued Supply Expansion Phase: 20 patients with confirmed genetic BRCA1/2 ovarian or breast cancer will be randomised to either daily dosing with tablet or capsule formulation to assess the multiple dose safety profile of the Melt-extrusion (tablet) formulation in a comparative setting and 6 patients will be recruited to Group 2 which will directly compare the steady state PK of the capsule and the Melt-extrusion (tablet) formulation. To investigate safety, tolerability and pharmacokinetics of higher doses than 200 mg bid, of AZD2281 tablet formulation, up to a further 48 patients (approximately) will be recruited to sequential groups. Following the assessment of tolerability of 400 mg AZD2281 tablet (Group 5.1), approximately 45 patients with confirmed genetic BRCA1/2 ovarian or breast cancer will be randomised to Group 6. Dose escalation will continue in parallel with Group 6 beyond 400 mg bid until the SRC agree that no further doses should be explored (Group 5.2, 5.3 etc). Once the final dose is established a further 30 patients with confirmed genetic BRCA1/2 ovarian or breast cancer may be randomised to Group 7. If, however, 400 mg bid is not deemed tolerable, Group 6 will be the final group recruited to this study. Patients in Group 6 and 7 will be randomised to either twice daily dosing with AZD2281 tablet or capsule formulation to assess the multiple dose safety profile of the Melt-extrusion (tablet) formulation in a comparative setting. A further 60 patients (approximately) with confirmed genetic BRCA1/2 ovarian cancer will be randomised into Group 8 to determine the safety and tolerability profile of selected dose schedules of the melt-extrusion (tablet) formulation.

Additional assessments for Group 1 include:

- Blood sampling for determination of AZD2281 plasma concentration at the following timepoints: immediately prior to the first dose of the day on Day 8, Day 15 and Day 29 and post the first dose of the day on day 29 between 0 - 0.5 hours, 0.5 to 1.5 hours, 1.5 - 3 hours, 3 - 6 hours and 6 - 12 hours

Additional assessments for Group 1, 6, 7 and 8 include:

[redacted]

- Tumour marker CA-125 will be assessed locally from blood samples taken at screening, visit 2 and every 8 weeks thereafter (applicable to ovarian cancer patients only). For Group 8 patients this assessment should stop at the end of cycle 5.

- Tumour assessments (CT or MRI scans of chest, abdomen and pelvis for breast cancer and abdomen and pelvis for ovarian cancer with other regions as clinically indicated for the assessment of disease). For Group 8 patients this assessment should stop at the end of cycle 5.

Additional assessments for Groups 2, 3, 4, 5, 5.1…..6 and 7 include:

- Blood sampling for determination of AZD2281 plasma concentration at the following timepoints: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hours after dosing at:

  – Group 2 – Day 8 and Day 15

  – Group 3 to 7 – Day 1

- Blood sampling for determination of AZD2281 plasma concentration at the following timepoints: Pre-dose and 1 hour after morning dose

  – Groups 3 to 7 – Day 8 and Day 15

- Blood sampling for determination of AZD2281 plasma concentration at the following timepoints: immediately prior to the first dose of the day and post the first dose of the day between 0 - 0.5 hours, 0.5 to 1.5 hours, 1.5 - 3 hours, 3 - 6 hours, 6 – 8 hours and 8 – 12 hours

  – Group 3 to 5 – Day 29

  – Group 6 and 7 – Day 29 and Day 57

Additional assessments for Group 8 include:

- Blood sampling for determination of AZD2281 plasma concentration for each dose schedule at the following timepoints:

  od schedule:

  – Day 1: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 hours after dosing

  – Day 8: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 hours after dosing

  – Day 57: pre-dose, 0 – 0.5, 0.5 – 1.5, 1.5 – 3, 3 – 6, 6 – 8, 8 – 12 hours after dosing

[redacted]

bd schedule:

- Day 1: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hours after dosing
- Day 8: pre-dose, 0 – 0.5, 0.5 – 1.5, 1.5 – 3, 3 – 6, 6 – 8, 8 – 12 hours after dosing
- Day 57: pre-dose, 0 – 0.5, 0.5 – 1.5, 1.5 – 3, 3 – 6, 6 – 8, 8 – 12 hours after dosing

tds schedule:

- Day 1: pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 hours after dosing
- Day 8: pre-dose, 0 – 0.5, 0.5 – 1.5, 1.5 – 3, 3 – 6, 6 – 8 hours after dosing
- Day 57: pre-dose, 0 – 0.5, 0.5 – 1.5, 1.5 – 3, 3 – 6, 6 – 8 hours after dosing

- Tumour tissue samples for biomarker analysis for Group 6, 7 and 8 patients (optional). If available, an adequately sized (minimum of 2mm x 2mm) archival tissue paraffin block from resection or a core biopsy from the primary tumour should be provided. This must have been taken at or since the time of diagnosis but prior to study entry. Alternatively, slides prepared from the block can be provided. This material may be used for the elucidation of mechanism of response, understanding the mode of action of AZD2281 and improving the understanding of disease progression.

There is no maximum duration of treatment with AZD2281. Patients will continue with their assigned AZD2281 treatment as long as they remain free from intolerable toxicity and, in the Investigator's opinion, are receiving some clinical benefit from the treatment with AZD2281 and do not meet any other discontinuation criteria. Once patients on AZD2281 have been discontinued from treatment, other treatment options will be at the discretion of the Investigator.

7.2.2.4 Final Follow-Up

The Follow-up Visit should be done 30 days from treatment discontinuation/last dose of study medication

- Physical examination including ECOG performance status, vital signs and body weight;
- ECG;
- Haematology, clinical chemistry and urinalysis;
- AE and concomitant medications.

[redacted]

For Group 8 only: physical examination, ECOG performance status, vital signs and body weight and ECG assessments should only be performed at the follow up visit if the patient discontinued treatment prior to Cycle 6. Urinalysis need only be performed if clinically indicated.

Any serious and/or non-serious AEs ongoing at the time of the Discontinuation Visit or which have occurred during the defined 30-day follow-up period must be followed-up (in accordance with Section 7.3.3.10). Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the Investigator, until resolution, unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the CRF.

7.3 Safety

It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The Principal Investigator is responsible for ensuring this.

7.3.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

7.3.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), at any dose of the study drugs, that fulfils one or more of the following criteria:

- Results in death;
- Is immediately life-threatening;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

[redacted]

- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For reporting purposes, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and is reported in an expedited manner. Any organism, virus or infectious particle (for example prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

7.3.3 Recording of adverse events

AEs will be collected from time of signed informed consent until their final follow-up visit. SAEs will continue to be collected if a patient remains on treatment after their final study visit until 30 days after study treatment is discontinued. All AE/SAEs will be monitored until resolution unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

7.3.3.1 Variables

The following variables will be recorded on the CRFs provided. A description of the event, including its date of onset and resolution, whether it constitutes a SAE or not, any action taken (eg, changes to study treatment, other treatment given, and follow-up tests) and outcome, should be provided along with the Investigator's assessment of causality (the relationship to the study treatment[s] and study procedures).

Severity of AE

The severity of any AE will be graded according to the NCI-CTCAE, version 3, where applicable.

For each episode, the highest severity grade attained should be reported.

If an AE occurs that is not listed in the NCI-CTCAE booklet, the Investigator will evaluate its severity using the definitions in the table below.

Table 11 Definition of Severity of Adverse Events

Severity	Description
Mild	Grade 1 – Does not interfere with the patient's usual function (awareness of symptoms or signs, but easily tolerated (acceptable)).
Moderate	Grade 2 – Interferes to some extent with the patient's usual function (enough discomfort to interfere with the usual activity (disturbing)).

[redacted]

Table 11 Definition of Severity of Adverse Events

Severity	Description
Severe	Grade 3 – Interferes significantly with the patient's usual function (incapacity to work or to do usual activities (unacceptable).
Life-threatening	Grade 4 – Results in risk of death, organ damage or permanent disability (unacceptable)
Death	Grade 5 – Event has a fatal outcome

Note: It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE

A copy of the CTCAE version can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov)

Causality

The Investigator will assess causal relationship between Investigational Product and AEs, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

7.3.3.2 Adverse Events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit?" or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.3.3.3 Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they fulfil any of the SAE criteria or are the reason for stopping treatment with the investigational product. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as

additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Clinically relevant deterioration in non-protocol-mandated measurements will be reported as AE(s).

Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value).

7.3.3.4 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the type of cancer for which the study drugs are being studied. It may be an increase in the severity of the cancer or an increase in the symptoms of the cancer. Expected progression of the patient's cancer and/or expected progression of signs and symptoms of the cancer, unless more severe in intensity or more frequent than expected for the patient's condition, should not be reported as an AE. Any events that are unequivocally due to progression of disease must not be reported as an AE.

The development of new metastases, or progression of existing metastases to the primary cancer under study, should be considered as disease progression and not an AE. Signs and symptoms clearly associated with metastases present at study entry should not be reported as AEs unless they are newly emergent (ie, not previously observed in the patient), judged by the Investigator to be unusually severe or accelerated, or if the Investigator considers deterioration of disease related signs and symptoms to be caused directly by the study medication.

7.3.3.5 New cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 7.3.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

7.3.3.6 Lack of efficacy

When there is deterioration in the condition for which the study treatment(s) is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

7.3.3.7 Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

[redacted]

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the CRF but should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 7.3.2 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death CRF'.

- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety Department within the usual timeframes.

7.3.3.8 Overdose

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 1.2, Procedures in case of overdose, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

7.3.3.9 Pregnancy

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 1.3. Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

7.3.3.10 Follow-up of unresolved adverse events

Any AEs/SAEs that are unresolved at the patient's last AE assessment (ie, 7 or 30 day follow up visit) in the study are followed up by the Investigator for as long as medically indicated. After data cut-off, any ongoing AEs will be recorded as ongoing. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

7.3.3.11 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the study treatment, or to the study procedure(s). All SAEs will be recorded in the CRF. SAEs will be recorded from the time of informed consent.

The Investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

[redacted]

For studies in countries implementing the European Union (EU) Clinical Trials Directive, informing Ethics Committees and Regulatory Authorities will be performed by AstraZeneca. If any SAE occurs in the course of the study, then Investigators or other site personnel inform appropriate AstraZeneca representatives immediately but no later than the end of the next business day of when he or she becomes aware of it.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform appropriate AstraZeneca representatives of any follow-up information on a previously reported SAE immediately but no later than the end of the next **business day** of when he or she becomes aware of it.

Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative and any other relevant supporting documentation (eg, ECG, laboratory results, autopsy report).

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the appropriate AstraZeneca Patient Safety data entry site within **one business day** for fatal and life threatening events and within **five calendar** days for other SAEs. If the report arrives late in the day, it can be sent the following morning. If the report arrives during a weekend or public holiday, the information is forwarded as early as possible on the first business day following the weekend or holiday. The clock start date is then the next business day.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

7.3.4 Laboratory safety assessment

Full haematology assessments for safety (haemoglobin, red blood cells [RBC], platelets, mean corpuscular volume [MCV], mean corpuscular haemoglobin concentration [MCHC], mean corpuscular haemoglobin [MCH], WBC, differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils), ANC, and coagulation [APTT and international normalised ratio {INR}]) will be performed.

Biochemistry assessments for safety (sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], AST, ALT, urea, total protein, albumin, lactic dehydrogenase [LDH]) will be performed.

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

For blood volume see Section 8.1.

[redacted]

7.3.5 Physical examination and vital signs

For timing of individual measurements refer to study schedule (see Table 5, Table 6 and Table 7).

Full physical examinations will be performed including height (screening only), BP, pulse, and body temperature at the screening visit and as outlined in the study schedules. Body weight will be measured once at the start of the PK Phase on Day 1. For patients enrolled into the Continued Supply Expansion Phase, body weight will be measured at screening, Day 1 and on the final follow-up visit.

Performance status will be assessed using the ECOG scale (reference: Appendix D) at baseline and as outlined in the study schedules. The same observer should assess performance status each time.

7.3.5.1 Pulse and blood pressure

At each study visit, supine BP and pulse will be measured using a semi-automatic BP recording device with an appropriate cuff size. The date and time of collection and measurement will be recorded on the appropriate CRF.

Measurements will be made after the patient has been resting supine for a minimum of 5 minutes. Two readings should be taken and the average recorded.

7.3.5.2 Resting 12-lead ECG

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. All 12-lead ECGs should be recorded while the patient is in the supine position. The Investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the Investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the CRF. ECGs are required within 7 days prior to start of study, end of cycle 1 and cycle 2, when clinically indicated and at final follow-up assessment. If the patient continues into Continued Supply Phase, ECGs are required at baseline (could be same as the follow-up assessment for the PK Phase), at least monthly for the first three months and at 30-day follow-up, and when clinically indicated. A copy of the ECG indicating the study number and without patient identifiers will be included with the patient's CRF for collection by the study monitor.

7.3.5.3 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential at screening. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

[redacted]

7.3.5.4 Urinalysis

A urinalysis will be performed at the beginning of each Treatment Period and at post-PK follow-up visit using a dipstick for blood and protein. Other abnormal results should be collected if appropriate. Microscopic analysis will be performed by the hospital's local laboratory if clinically indicated. If patients continue into Continued Supply Phase urinalysis will be performed at least monthly for the first three months, at treatment discontinuation and 30-day follow-up. For patients enrolled into the Continued Supply Expansion Phase, urinalysis will be performed as per the schedule in Table 6 and Table 7. For Group 8 urinalysis by dipstick should be performed at baseline and then only if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required.

7.3.5.5 CT or MRI scans (RECIST)

The RECIST guidelines (Therasse et al 2000) for measurable, non-measurable, target and non-target lesions, and the objective tumour response criteria (complete response (CR), partial response (PR), Stable disease (SD) or progression of disease (PD)) are presented in Appendix F. The RECIST criteria will be used to programmatically determine best overall response, PFS and duration of response. Patients with non-measurable disease only at baseline are excluded from Group 1 within the Continued supply phase expansion.

Baseline and follow-up contrast-enhanced CT scans of chest, abdomen and pelvis for breast cancer and abdomen and pelvis for ovarian cancer with other regions as clinically indicated for the assessment of disease. All baseline radiological tumour assessments must be performed no more than 28 days before the start of study treatment. Scans that were performed as part of standard of care prior to signature of the informed consent form can be analysed for the purposes of the study if they were performed within the correct time frame and of sufficient quality. Subsequent tumour assessments according to RECIST should be performed at the end of every 2 months (8 weeks +/-1 week) according to the planned study schedule (see Table 6 and Table 7) up to objective progression by RECIST. Any other sites at which new disease is suspected should also be appropriately imaged. Patients must be followed until RECIST disease progression. (Group 8 only: RECIST assessments should stop after Cycle 5).

Radiological examinations performed in the conduct of the study should be retained at site as source data and may be collected by the sponsor if required.

All measurable lesions confirmed and assessed by radiological methods (CT or MRI scans) up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions, recorded and measured at baseline, and at the time points specified in the protocol.

Non-target lesions will also be monitored throughout the study, and an overall assessment of response will be made; complete response, incomplete response/stable disease or progression. Details of any new lesions will also be recorded.

[redacted]

Tumour assessment will be performed in accordance with the protocol schedule until evidence of one of the following:

- Progression of disease by RECIST
- Death without evidence of progression
- Withdrawal of consent

If a patient has any palliative radiotherapy to a lesion, that lesion should not be included in assessment of response, but should be assessed for progression.

A patient will be determined to have progressed if they have progression of target lesions, clear progression of existing non-target lesions, or the appearance of one or more new lesions.

Disease progression will be determined as the appearance of one or more new soft tissue and visceral lesions, including lymph nodes with LD> 1.5cm. Patients with appearance of new or worsening of any effusion including ascites will not be determined to have disease progression, unless it is considered to be clinically significant by the investigator and confirmed on radiology.

Unequivocal malignant disease not identified prior to starting study treatment on additional anatomical imaging (eg, computed tomography (CT), magnetic resonance imaging (MRI) or bone scan confirmed by X-ray), prompted by symptoms is considered disease progression and should be recorded as new lesions.

If a patient demonstrates CA-125 progression determined by a 2 fold increase from the baseline CA-125 (if above the ULN at baseline) or 2 fold greater than the ULN (if below the ULN at baseline) on two occasions 7 or more days apart a patient will have an unscheduled RECIST assessment (CT/MRI) to assess for objective disease progression by RECIST. If progression is not confirmed by RECIST ideally the patient should continue on treatment until the next study assessment unless they fulfil another reason for withdrawal.

If a patient presents with disease related bowel obstruction they should be assessed by CT or MRI according to the RECIST criteria for tumour progression. If the CT or MRI findings are consistent with tumour progression in the view of the investigator, taking into account changes in CA-125 levels indicative of progression according to the GCIG criteria, then this should be recorded as new lesions, or captured appropriately for target or non target lesion if present at base-line at this location.

If an unscheduled radiological and clinical tumour assessment is performed, and the patient has not progressed according to RECIST criteria, the next scheduled tumour assessment should still be performed at the planned time (as detailed in the study plan) relative to the date of first dose of AZD2281 and treatment should continue.

[redacted]

If at any time progression is uncertain, patients may continue on treatment until the next scheduled assessment (ie, 8 weeks later +/- 1 week) or may have an unscheduled assessment earlier than this, if considered appropriate by the investigator.

Death will be regarded as a progression event in those patients who die before disease progression.

Lesions must be assessed using the same method and technique on each occasion. Lesions will be recorded on the CRF page in the same order as they were recorded at screening. Details of any new lesions will also be collected. Response will be calculated in comparison to the baseline tumour measurements obtained before starting treatment. Progression will be calculated in comparison to when the tumour burden was at a minimum. Overall visit response will be recorded on the CRF.

Methods of assessment

Response will be assessed using RECIST criteria in patients who have measurable disease (see Appendix F). Categorisation of overall visit response will be based on RECIST using the following response categories: CR, PR, SD, and PD (see Appendix F). In the case of stable disease, measurements must have met the stable disease criteria at least once after randomisation for a minimum interval of 7 weeks.

To be assigned a status of PR or CR, changes in tumour assessments must be confirmed at the next scheduled tumour assessment no less than 4 weeks after the criteria for response were met.

Although CA-125 is measured in this study it will not be directly used for assessing objective response or progression and patients should be continued on treatment until confirmed RECIST progression.

Derivation or calculation of outcome variable

Best overall response will be calculated as the best response recorded from date of enrolment (taking as reference for progressive disease the smallest measurements recorded since the treatment started) for each patient, and will be used for the summaries of objective response. Best overall response will be determined programmatically based on the RECIST criteria.

7.3.5.6 CA-125 plasma samples

All patients with ovarian cancer will supply plasma samples for CA-125 (2 mLs) at screening and at visit 2 and every 8 weeks thereafter prior to receiving AZD2281. (Group 8 only: assessment should be stopped after Cycle 5)

7.3.5.7 Tissue tumour samples for biomarker analysis

Group 6, 7 and 8 patients will be asked to supply an archival tumour sample for biomarker analysis. This will be optional. If available, an adequately sized (minimum of 2mm x 2mm) archival tissue paraffin block from resection or a core biopsy derived from the diagnostic

[redacted]

tumour or metastatic site should be provided. This must have been taken at or since the time of diagnosis but prior to study entry. Alternatively, slides prepared from the block can be provided. This material may be used for, but not restricted to, the elucidation of mechanism of response, understanding the mode of action of AZD2281 and improving the understanding of disease progression.

7.4 Pharmacokinetic measurements

For timing of individual samples refer to the study plan (Table 5, Table 6 and Table 7).

7.4.1 Determination of drug concentration in biological samples

Blood samples for the determination of AZD2281 plasma concentrations will be collected on Days 1–3 of Treatment Periods 1 & 2. For both treatments Periods samples will be 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 AZD2281. Patients may remain in hospital on Treatment Period 1, Day 1 and Treatment Period 2, Day 8. In addition, patients who live a distance from the hospital may also stay in the hospital or nearby the hospital for Treatment Period 1, Day 2 and Treatment Period 2, Day 9 as this will cover the 48-hour period of PK sampling.

Blood samples will be collected for the determination of AZD2281 plasma concentrations during the continued supply phase from the 20 additional gBRCA patients assigned to Group 1 to explore steady state kinetics. Samples will be collected immediately prior to the first dose of the day on days 8, 15 and 29 and after the first dose of the day on day 29 between 0 - 0.5 hours, 0.5 - 1.5 hours, 1.5 to 3 hours, 3 - 6 hours and 6 - 12 hours. In addition, blood samples will also be collected from the 6 additional patients assigned to Group 2. Samples will be collected on both day 8 and day 15 at the following timepoints within each day: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hours after dosing.

In addition, blood samples will also be collected from the additional patients assigned to Groups 3 onwards. Samples will be collected as specified in the study schedule (see Table 7) and in Section 7.2.2.3.

Samples for the measurement of AZD2281 will be analysed using solid phase extraction (SPE) followed by high performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS). Samples analysis will be performed by Covance Laboratories Ltd., Otley Road, Harrogate, North Yorkshire HG3 1PY UK. Details of all assays used, and performance of the assays during the analysis of study samples, will be referred to in the clinical study report.

Sample collection, processing and shipping procedures are detailed in Appendix E.

All samples will be analysed within the timeframe after collection for which the stability in the samples has been validated and found acceptable: this is 12 months for AZD2281. Results from samples that have been stored longer than the period stated will not be reported.

[redacted]

Selected samples will be re-analysed to measure AZD2281 and these data will be used to establish the reproducibility of the assay measurements in samples from individuals in order to support the validity of the data generated in the original analysis.

Samples may also be analysed to determine the presence and/or identity of metabolite(s) of AZD2281, in which case they will be retained for a maximum of 5 years following finalisation of the Clinical Study Report. Any results of such analyses will be reported separately from the Clinical Study report.

Samples will be disposed of either after the Bioanalytical report has been finalised or after any determination of metabolite plasma concentrations has been completed.

7.5 Pharmacodynamic measurements

Patients recruited to the PK Phase will participate in pharmacodynamic (PD) studies with blood sampling to isolate PBMCs for analysis for PARP inhibition, Samples will be collected in each treatment period at pre-dose and then at 3, 10 and 24 hours post dose of AZD2281.

Sample collection and processing procedures will be detailed in a laboratory manual.

7.6 Exploratory Biomarker Research on Archival Tumour Samples

Archival tumour samples from consenting patients will have been taken at or since the time of diagnosis but prior to study entry and donation of samples involves no further biopsy procedures.

The tumour samples will preferably be in the form of a formalin fixed paraffin embedded block (tissue derived from the diagnostic tumour or metastatic site) or if this is not possible as slides (prepared 5 micron sections from the archival tumour block). Sections should be mounted on to clean "Superfrost" glass slides. These slides are produced commercially and are ready treated (electrostatically charged). All samples should be shipped at ambient temperature. The samples and data from this research will be coded and not labelled with any personal details. Each sample will be identified with the study and patient enrolment number. In this way biomarker data may be correlated with clinical data, samples destroyed in the event of withdrawal of consent and regulatory audit enabled. However, only the investigator will be able to link the biomarker sample to the individual patient.

The coded samples may be made available to groups or organisations working with AstraZeneca on this research or as part of the development drug project. However, the samples and any results will remain the responsibility of AstraZeneca at all times. AstraZeneca will not give samples, sample derivatives or data derived from the samples to any other parties except as required by law.

Any biomarker data generated will be generated in real time during the study and will have unknown clinical significance. AstraZeneca will not provide biomarker results to patients, their family members, any insurance company, an employer, clinical study investigator,

[redacted]

general physician or any other third party unless required to do so by law. The patient's samples will not be used for any other purpose other than those described in the protocol.

8. BIOLOGICAL SAMPLING PROCEDURES

8.1 Volume of blood

The total volume of blood that will be drawn from each patient in the PK Phase of this study is as follows:

Table 12 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples[b]	Total volume (mL)[d]
Pharmacokinetics		4.0	24	96
Cannula overage[a]		1.0	20	20
Safety	Clinical chemistry	6.0[c]	3[b]	18
	Haematology	10.0[c]	3[b]	30
Pharmacodynamics		12	8	96
Total		33	58	243

[a] For withdrawal from cannula prior to PK sampling
[b] Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments.
[c] These are approximate volumes that are subject to site-specific change
[d] Total volume is based on patients completing the PK Phase of the study

Patients that wish to participate in the Continued Supply Phase and Expansion Phase of the study with have routine safety bloods; at a frequency in line with the Institutions Clinical practice. It is recommended that this is at least monthly (ie, 16 mL of blood each month).

For those patients participating in the Continued Supply Expansion Phase of the study additional 4 mL blood samples for pharmacokinetic analysis will be taken. For patients assigned to:

- Group 1: 8 samples will be taken with a total volume of 40 ml of blood (including cannula overage)
- Group 2: 24 samples will be taken with a total volume of 120 ml of blood (including cannula overage).
- Group 3 to 5: 23 samples will be taken with a total volume of 115 ml of blood (including cannula overage).

[redacted]

- Group 6: 30 samples will be taken with a total volume of 150 ml of blood (including cannula overage)
- Group 7: 30 samples will be taken with a total volume of 150 ml of blood (including cannula overage)
- Group 8: up to a maximum of 33 samples (depending on AZD2281 dose schedule) will be taken with a total volume of 165 ml of blood (including cannula overage)

For Group 1, 6, 7 (ovarian patients) and 8, additional 2 ml blood samples will be taken for CA-125 analysis every 8 weeks until objective disease progression. (Group 8 only: assessment should be stopped after Cycle 5)

8.2 Handling, storage and destruction of biological samples

For sample processing, handling and shipment see Investigators Laboratory Manual.

8.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B (materials containing or suspected to contain infectious substances that do not meet Category A) criteria (see International Air Transport Association Dangerous Goods [IATA] 6.2 Regulations Guidance in Appendix C).

Any samples identified as Infectious Category A materials should not be shipped and no further samples should be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

8.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full trace ability of collected biological samples from the patients while in storage at the centre until shipment and keeps documentation of receipt of arrival.

The sample receiver keeps full trace ability of the samples while in storage and during use until used or disposed.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use is registered in AstraZeneca bio bank system during the entire life cycle.

[redacted]

8.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of biological samples donated the samples will be disposed/destroyed, if not already analysed and documented.

If collection of the biological samples is a voluntary part of the study then the patient may continue in the study. If the collection of the biological samples is mandatory then the patient will be discontinued from the study as this will require the patient to withdraw their consent for the whole study.

The Principal Investigator:

- Ensures patients withdrawal of informed consent is notified immediately to AstraZeneca;
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed/destructed and the action documented;
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

AstraZeneca ensures the central laboratory (ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

In the event that analysis/research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

AstraZeneca ensures that any biological samples remaining after analysis have been performed may be repatriated upon request or kept until the end of the period specified in the informed consent.

9. ETHICAL AND REGULATORY REQUIREMENTS

9.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

[redacted]

9.2 Patient data protection

9.2.1 Genetic Data

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

In the PK Phase of the study, AstraZeneca will only collect PD samples for evaluation of PARP inhibition. AstraZeneca will not perform any additional genetic analysis on these PD samples and will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

All data protection and confidentiality principles are applicable to the exploratory research on archival tumour samples.

9.3 Ethics and regulatory review

An Ethics Committee must approve the final study protocol, including the final version of the Informed Consent Form(s) and any other written information to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee must be given in writing. The Investigator must submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee must approve all advertising used to recruit patients for the study.

AstraZeneca must approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol must be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

The distribution of any of these documents to the national regulatory authorities will be handled by AstraZeneca.

AstraZeneca is responsible for informing the Regulatory Authority of SAEs/SUSARs as per local country regulations and guidelines. AstraZeneca will be responsible for safety regulatory reporting.

For all countries except the US and Canada, AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements. For the US and Canada, each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator.

9.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study;
- Ensure that the patients are notified that they are free to discontinue from the study at any time;
- Ensure that the patient are given the opportunity to ask questions and allowed time to consider the information provided;
- Obtain and document the patient's signed and dated informed consent before conducting any procedure specifically for the study;
- Ensure the original, signed Informed Consent Form is stored in the Investigator's Study File;
- Ensure a copy of the signed Informed Consent Form is given to the patient.

9.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment. If required a new version of the study protocol (Amended Protocol) will be written.

The amendment must be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements must be followed for amended protocols.

[redacted]

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 9.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee must approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

9.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

10. STUDY MANAGEMENT BY ASTRAZENECA (OR DELEGATE)

10.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities;
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the Investigator.

10.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures utilised. They will also discuss the procedures associated with the collection of samples and mandatory biomarker research with a representative of AstraZeneca. The requirements for the collections of the patients' sample will also be made clear.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

10.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s);
- Confirm that facilities remain acceptable;
- Confirm that the investigational team is adhering to the protocol that data are being accurately and timely recorded in the CRFs, and that investigational product accountability checks are being performed;
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) incl. verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts);
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed/destructed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

10.3.1 Source data

Refer to Clinical Study Agreement for location of source data.

10.4 Study agreements

The Principal Investigator at each centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

Agreements between AstraZeneca and the Principal Investigator must be in place before any study-related procedures can take place, or patients be enrolled.

[redacted]

10.5 Study timetable and end of study

The study is expected to start in October 2008 and the PK Phase to be completed by end of February 2009. The Continued Supply Expansion Phase is expected to be completed by Q2 2014.

The end of this study is defined as the date of the last visit of the last patient, occurring when all patients have completed study therapy.

For patients in the PK phase (cohorts 1 and 2) and Groups 1-7 data collection will continue until both the following criteria have been met:

- all gBRCA Group 1, 6 and 7 patients have progressed as per RECIST or AstraZeneca has determined that sufficient efficacy data has been collected
- all patients continuing on treatment have been assessed for safety for a minimum of 6 cycles (1 cycle being 28 days) or all patients have discontinued study treatment, whichever is the earlier.

When the above criteria are met the clinical database will be closed and only SAE data and investigator's assessment of response will be collected. All patients in the PK phase (cohorts 1 - 3) and Groups 1-7 can continue to receive study treatment until they meet any discontinuation criteria as per Section 5.5.1. Once all patients have completed 6 cycles, all protocol assessments can be stopped and patients should attend clinic visits according to routine clinical practice, approximately every 6-8 weeks. SAEs will continue to be reported to AstraZeneca in the usual way for patients who continue on AZD2281 until 30 days after study treatment is discontinued and followed-up as outlined in Section 5.5.2. Drug accountability should continue to be performed until the patient stops study treatment completely.

For patients in Group 8 all data will be collected in the clinical database up to and including Cycle 6 for each patient. For patients continuing past Cycle 6 only AEs, SAEs, concomitant medication, laboratory data, dosing information will be collected in the database. Investigator's assessment of response will be assessed but not collected in the clinical database. All other protocol assessments do not need to be performed

For patients in Group 8 all data collection will continue until both the following criteria have been met:

- all Group 8 patients have progressed as per RECIST or AstraZeneca has determined that sufficient efficacy data has been collected
- all Group 8 patients continuing on treatment have been assessed for safety for 12 cycles (or AstraZeneca has determined that sufficient safety data has been collected), or all patients have discontinued study treatment, whichever is the earlier.

[redacted]

When the above criteria are met the clinical database will close to new data. All patients in Group 8 can continue to receive study treatment until they meet any discontinuation criteria as per Section 5.5.1. Once the criteria above have been met and the database closed, all protocol assessments can be stopped and patients should attend clinic visits according to routine clinical practice, approximately every 6-8 weeks. SAEs will continue to be reported to AstraZeneca in the usual way for patients who continue on AZD2281 until 30 days after study treatment is discontinued and followed-up as outlined in Section 5.5.2. Drug accountability should continue to be performed until the patient stops study treatment completely.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD2281.

11. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data should be recorded in English onto the CRFs in black ink. Any corrections should be made legibly and initialled and dated by approved personnel (correction fluid or covering labels must not be used).

CRFs will be double data-entered into the study database, and the data will be checked for missing, invalid or inconsistent data points. Data queries arising from these checks will be sent to the Investigator for response and signature.

Once all data queries have been resolved, the study will be declared to be "clean", and the study database will be locked ready for statistical analysis.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

12. EVALUATION AND CALCULATION OF PHARMACOKINETIC, PHARMACODYNAMIC, SAFETY AND STATISTICAL ANALYSIS BY ASTRAZENECA

12.1 Pharmacokinetic/Pharmacodynamic evaluation

12.1.1 Calculation or derivation of Pharmacokinetic variables

The PK analyses of the AZD2281 plasma concentration data will be performed by (or on behalf of) Clinical Pharmacology & DMPK, Alderley Park, AstraZeneca.

For the PK Phase, non-compartmental methods will be used for the evaluation of the AZD2281 plasma concentration-time data for each subject on each dosing occasion. The maximum plasma concentration (C_{max}) and the time of the maximum concentration (t_{max}) will be determined by visual inspection of the concentration-time profiles. Where possible the

[redacted]

terminal rate constant (lambda z) will be calculated by log linear regression of the terminal portion of the concentration-time profiles. Where there are sufficient data, the terminal half-life ($t_{1/2}$) will be calculated as ln 2/lambda z. The area under the plasma concentration-time curve up to the last quantifiable sample ($AUC_{(0-t)}$) will be calculated using the linear trapezoidal rule and, where appropriate, $AUC_{(0-t)}$ will be extrapolated to infinity using lambda z to obtain AUC. The apparent clearance (CL/F) will be determined from the ratio of dose/AUC. The apparent volume of distribution (Vz/F) will be calculated by dividing dose by (AUC x lambda z).

For the patients in Group 1 of the Continued supply phase, non-linear mixed effects modelling will be used for the evaluation of the AZD2281 steady state plasma concentration-time data to determine the maximum steady state drug concentration in the plasma during the dosing interval ($Css_{,max}$), the minimum steady state drug concentration in plasma ($Css_{,min}$) and the area under the plasma concentration-time curve during the dosing interval at steady state (AUCss). For those patients in Group 2, non-compartmental methods will be used for the evaluation of the steady state plasma concentration-time data to determine $Css_{,max}$, $Css_{,min}$ and AUCss.for both the Melt Extrusion (tablet) formulation and the Gelucire® 44/14 (capsule) formulation. For the patients in Groups 3 to 8 non compartmental methods will be used to determine single dose C_{max}, C_{min} and AUC_{0-8} /AUC_{0-12} / AUC_{0-24} and non-linear mixed effects modelling will be used to determine steady state Css_{max}, Css_{min}, and AUCss.

12.2 Calculation or derivation of safety variable(s)

12.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuations due to AEs (DAEs). Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered OAEs and reported as such in the Clinical Study Report.

Examples of these maybe marked haematological and other laboratory abnormalities and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

12.3 Calculation or derivation of efficacy variable(s)

A secondary objective of the Continued Supply Expansion Phase is to summarise the efficacy of AZD2281 on patients who receive tablet compared to patients who receive capsules. This will be achieved by measuring the % change in tumour burden compared with baseline, Best Objective Response, PFS and CA-125 response. Analyses will be performed in the overall population and in the gBRCA ovarian cancer subgroup.

The RECIST criteria will be used to programmatically determine % change in tumour burden compared with baseline, Best Objective Response and PFS.

[redacted]

12.3.1 Change from baseline in the sum of target lesions

This will be determined by calculating the % change in tumour burden, determined from the sum of longest diameters in target lesions measured per RECIST, at each follow-up tumour assessment compared with baseline.

12.3.2 Best Overall Response (by RECIST)

Categorisation of best overall response will be based on the RECIST criteria (Appendix F) using the following response categories: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Best overall response will be calculated as the best response recorded from date of enrolment (taking as reference for progressive disease the smallest measurements recorded since the treatment started) for each patient, and will be used for the summaries of objective response. Best overall response will be determined programmatically based on the RECIST criteria.

A best overall response of CR means that a response of CR is recorded at one visit and confirmed by repeat imaging at the next scheduled visit. A CR that was not confirmed because the next scheduled scan was after the data cut-off will be counted as a CR. Similarly for PR. In the case of SD, follow-up measurements must have met the SD criteria for a minimum interval of 7 weeks after randomisation.

12.3.3 Progression Free Survival

PFS is defined as the time from randomisation to the earlier date of assessment of objective progression (per RECIST criteria) or death by any cause in the absence of progression. Patients without a progression event and still alive at the time of analysis will be censored at the time of their last evaluable objective tumour assessment. This includes patients who are lost to follow up or who withdraw consent.

If at any follow-up visit > 1/3 of the target lesions recorded at baseline are missing then target lesion response will be not-evaluable (NE) (unless the sum of the longest diameters [LDs] of non-missing target lesion LDs would result in PD).

If ≤ 1/3 of lesions recorded at baseline are missing then the results will be scaled up (based on the baseline sizes) to give an estimated sum of diameters and this will be used in calculations.

A complete response will not be permissible at a visit response where there is missing data.

Objective progression is defined as at least a 20% increase in sum of longest diameters of the target lesions (compared to previous minimum sum) or an overall non-target lesion assessment of progression or a new lesion.

Patients are to have radiological scans until objective progression, regardless of whether they discontinue their randomised therapy or take another anti cancer therapy prior to progression. Tumour assessments for Group 8 patients should be stopped after Cycle 5 (week 16). Dates of progression and death will be defined as follows:

- The actual date of progression will be used in the analysis regardless of whether the patient had previously discontinued all or part of their randomised therapy, started another anti cancer therapy, the event occurred between scheduled visits or previous

visits were not evaluable due to partially, or completely missing tumour assessments. This also applies to patients who die in the absence of progression.

- If radiological assessments take place on multiple dates at a visit then the date of progression used for analysis will be the earliest of target lesions or non-target lesion or new lesion dates, regardless of which component contributed to progression.

12.3.4 CA-125 response (GCIG criteria; Rustin et al 2004; http://ctep.cancer.gov/resources/gcig/respdef_nov2005.doc)

Patients will be evaluable for CA-125 response if:

- Diagnosed with ovarian cancer
- a pre-treatment CA-125 level (taken within 2 weeks prior to starting treatment) is at least twice the upper limit of normal, and
- there is no more than a 10% fall in CA-125 between the two pre-treatment samples
- the same assay method is used for each sample from the same patient

A response according to CA-125 will be considered to have occurred if there is at least a 50% reduction in CA-125 levels from the last pre-treatment sample. The response must be confirmed and maintained for at least 28 days. The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response.

12.4 Statistical methods and determination of sample size

12.4.1 Statistical evaluation

In order to be able to fully evaluate the effects of the study drugs, the data will be presented individually and summarised using appropriate summary statistics. Details of all listings and summaries to be provided will be included in a comprehensive Statistical Analysis Plan (SAP). This will be prepared and finalised before database lock.

Statistical summaries will be produced by or under the guidance of UK Biostatistics at AstraZeneca Research and Development (R&D) using SAS version 8.1 and, where appropriate, additional validated software.

12.4.2 Description of variable in relation to hypotheses

12.4.2.1 Screening and demographic measurements

The screening and demographic variables will not address any study objectives per se. They define the population being included in the study and thus contribute to the interpretation of the results of the study.

[redacted]

All demographic data, medical history and details of medications taken before and during the study will be summarised and listed using appropriate summary statistics. Data will be summarised across all patients.

Medications will be coded using the AstraZeneca Drug Dictionary.

12.4.2.2 Safety measurements

The safety data will address the secondary objective to assure the safety of all patients by assessment of pulse, BP, ECG, laboratory data and AEs.

12.4.2.3 Adverse event data

AE variables are collected as a free text description of the AE and coded using the Medical Dictionary for Regulatory Activities (MedDRA). They will be assessed at the Preferred Term and System Organ Class levels. Other information used in the assessments will be the start and stop date of the AE (if available), maximum NCI-CTCAE grade, whether the event was serious or not and whether the AE was thought, in the opinion of the Investigator, to be associated with the study drug. The definitions of these categories are given in Section 7.4. All AE data will be listed for all patients. Separate listings of all SAEs, deaths, discontinuations or other significant AEs will be presented.

12.4.2.4 Laboratory safety measurements

All laboratory safety data, incorporating haematology, clinical chemistry and urinalysis data will be listed, with deviations from the range explicitly noted. Numerical laboratory data will be summarised by treatment using standard summary statistics.

12.4.2.5 Pulse and blood pressure

Absolute pulse and BP data will be listed and summarised using standard summary statistics by treatment.

12.4.2.6 Other safety data

Physical examination details and ECG data will be listed.

12.4.2.7 Continued Supply Expansion Phase

The primary objective of the Continued Supply Expansion Phase is to assess the multiple dose safety profile of the Melt-extrusion (tablet) formulation in a comparative setting. In terms of safety data, no formal statistical comparisons of data will be performed. Instead, data will be listed and summarised descriptively by formulation (tablet or capsule). Steady state pharmacokinetic and efficacy data will also be collected and summarised by formulation (tablet or capsule).

The secondary objectives of the Continued Supply Expansion Phase (Group 2) is to enable a direct within-patient comparison of the steady state PK of the capsule and the Melt-extrusion (tablet) formulation.

[redacted]

In addition, steady state PK will be assessed in the Group 1 population to determine multiple dose pharmacokinetic parameters for the melt extrusion (tablet) formulation and the Gelucire® 44/14 (capsule) formulation in man. Plasma concentration data and PK parameters will be listed and summarised descriptively using the appropriate standard summary statistics. In terms of efficacy data, summaries and waterfall plots of percentage change from baseline in sum of target lesions will be presented, and this data will also be analysed by analysis of covariance fitting baseline sum of target lesions as a continuous covariate and treatment group as a factor. Summary statistics will be presented for best overall response according to RECIST. PFS will be summarised using Kaplan-Meier estimates over time and will be displayed graphically.

Dose escalation phase within the continued supply expansion

The number of patients taking part in this part of the study will be approximately 185.

The primary objective of the dose escalation phase of the continued supply expansion is to determine the safety and tolerability profile of higher doses than 200 mg bid, of the melt-extrusion (tablet) formulation in groups of a minimum of 6 patients – (Groups 3 onwards) and to compare the safety and tolerability profile of higher doses than 200 mg bid, of the melt-extrusion (tablet) formulation with 400 mg bid Gelucire® 44/14 (capsule) formulation of AZD2281 in approximately 45 gBRCA ovarian and breast cancer patients (Group 6) and in 30 gBRCA ovarian and breast cancer patients (Group 7). The primary objective in the randomised tablet formulation continued supply expansion phase (Group 8) is to determine the safety and tolerability profile of selected tablet dose schedules of the melt-extrusion (tablet) formulation. No formal statistical comparisons of safety data will be performed. Instead, data will be listed and summarised descriptively by dose.

The secondary objectives of the dose escalation within the continued supply expansion will involve:

- All patients from Groups 3 onwards contributing to an assessment of the single dose and steady state exposures achieved with higher doses than 200 mg bid of AZD2281 melt-extrusion (tablet) formulation and all patients from Group 6 and 7 contributing to a comparison between patients of single dose and steady state exposures of AZD2281 achieved with selected tablet doses and the 400 mg bid capsule dose. Plasma concentration data and PK parameters will be listed and summarised descriptively using the appropriate standard summary statistics.

- A preliminary assessment of the effect of food by comparison of the Day 8 and Day 1 Cmax and AUC_{0-24} data from patients in the 400 mg od cohort of Group 8.

- To describe the efficacy data observed in patients treated with the Gelucire® 44/14 (capsule) and the Melt-extrusion (tablet) formulations. Summaries and waterfall plots of percentage change from baseline in sum of target lesions will be presented, and this data will also be analysed by analysis of covariance fitting baseline sum of target lesions as a continuous covariate and treatment group as a factor. Summary

[redacted]

statistics will be presented for best overall response according to RECIST. PFS will be summarised using Kaplan-Meier estimates over time and will be displayed graphically. Analyses will be performed in the overall population and in the gBRCA ovarian cancer subgroup.

12.4.3 Description of analysis sets

There will be 2 analysis sets considered in this study: the safety analysis set and the PK analysis set. The safety analysis set will include all patients who have taken at least one dose of the trial medication. The PK analysis set will include all patients who completed both treatment periods of the PK Phase of the study and who have evaluable PK data. However, PK parameters will be calculated for all individuals where plasma concentration data is available.

Data from the patients who withdraw or are discontinued from the study, or who have missing values for other reasons, will be included in the analysis in such a way as to minimize any possible bias.

A strategy for dealing with PK data from the PK Phase of the study that is affected by protocol deviations will be agreed upon by the study team physician, pharmacokineticist, and statistician before any formal statistical analysis is performed.

12.4.4 Methods of statistical analysis

12.4.4.1 Pharmacokinetics

For both the PK phase and the Continued Supply Expansion Phase, plasma concentration data and PK parameters will be listed and summarised descriptively by dose level and formulation administered using the appropriate standard summary statistics.

Within each cohort of the PK phase, the comparative bioavailability of the Melt-extrusion (tablet) formulation compared to the Gelucire® 44/14 (capsule) formulation will be estimated using an analysis of variance with factors for patient, formulation and period. The associated 90% confidence interval will also be calculated. Prior to analysis, C_{max} and AUC values will be log-transformed.

All data will be listed and summarised as described in Section 12.6.1.

The plasma concentration-time data will be presented graphically via both individual and mean plots. Where plots are provided, an appropriate measure of variation may also be included.

12.4.4.2 Archival tumour tissue samples (optional for Group 6, 7 and 8 patients only)

Data arising from the exploratory biomarker analysis from Group 6, 7 and 8 patients will be detailed in a separate exploratory analysis SAP and reported outside of the main CSR.

[redacted]

12.4.4.3 Nausea, vomiting and fatigue data (Group 8 patients only)

Data arising from the characterisation of the common low grade AEs associated with AZD2281 (nausea, vomiting and fatigue) will be reported outside of the main CSR.

12.4.5 Determination of sample size

This study is an investigation of the comparative bioavailability of a new Melt-Extrusion (tablet) formulation of AZD2281 compared to the current Gelucire® 44/14 (capsule) formulation. There are no formal statistical analyses of the data planned and no formal sample size calculations have therefore been performed. The size of this study is based upon the desire to gain adequate PK information on the Melt-Extrusion (tablet) formulation whilst exposing as few patients as possible to study procedures.

Within the continued supply expansion phase, tablet doses (commencing at 250 mg bid) with potentially higher average exposure values than the 400 mg capsule dose will be explored and thus, in group 6 and 7 of the continued supply expansion, approximately 15 patients per arm (including at least 10 gBRCA ovarian cancer patients) are required to assess the safety and tolerability of these doses. In addition, as an exploratory measure of clinical activity, to rule out a significant difference between the melt-extrusion (tablet) formulation and the Gelucire® 44/14 (capsule) formulation, change in tumour size at eight weeks will be compared between the tablet dose arm(s) and the 400 mg bid capsule dose arm.

In Group 8, approximately 15 patients per treatment arm will be randomised. In a similar way as per the earlier expansion groups, change in tumour size will be evaluated.

12.5 Interim analysis

During the PK phase of the study an interim analysis will be performed on recorded safety and PK data retrieved from Cohorts 1 and 2 before proceeding to Cohort 3 randomisation. The objective of such an analysis is to better define the higher dose level for the Melt-extrusion (tablet) formulation in Cohort 3.

During the Continued Supply Expansion Phase, an interim analysis of safety data will be performed following the completion of 3 cycles of treatment with the tablet formulation for all patients. The objective of such an analysis is to get an early indication of the emerging safety profile of the tablet formulation. In addition, the steady state plasma concentration data obtained from Group 2 will be analysed once all PK sampling in this group has completed to provide reassurance that the tablet dose being used for continuous dosing is providing the equivalent steady state exposure as the capsule formulation.

Data from the Continued Supply Expansion Phase will be evaluated on an on-going basis to monitor emerging safety and efficacy profile of the tablet formulation.

[redacted]

12.6 Data presentation

12.6.1 Pharmacokinetics

The AZD2281 plasma concentration data and PK parameters will be listed individually for each patient and summarised according to the dose and formulation (capsule or tablet) received. Summaries will be constructed appropriately for the cohorts of the PK Phase and Continued Supply Expansion Phase.

Summaries of AZD2281 plasma concentration at each time point will present:

- The geometric mean (gmean, calculated as exp [μ], where μ is the mean of the data on a log scale);
- Coefficient of variation (CV, calculated as 100 x $\sqrt{}$ [exp(s^2)-1], where s is the standard deviation of the data on a log scale);
- Gmean ± standard deviation (SD) (calculated as exp[$\mu \pm s$]);
- Arithmetic mean calculated using untransformed data;
- SD calculated using untransformed data;
- Minimum;
- Maximum;
- Number of observations.

Summaries of AZD2281 AUC, AUC_{0-t} ,C_{max} ,$C_{ss,max}$, $C_{ss,min}$ and AUC_{ss} will present:

- The gmean (calculated as exp [μ], where μ is the mean of the data on a log scale);
- Coefficient of variation (CV, calculated as 100 x $\sqrt{}$ [exp(s^2)-1], where s is the standard deviation of the data on a log scale);
- Arithmetic mean calculated using untransformed data;
- SD calculated using untransformed data;
- Minimum;
- Maximum;
- Number of observations.

Summaries of AZD2281 CL/F, $t_{1/2}$ and Vz/F should present:

- Arithmetic mean;
- SD;
- Minimum;
- Maximum;
- Number of observations.

Summaries of AZD2281 t_{max} will present:

- Median;
- Minimum;
- Maximum;
- Number of observations.

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 gmean, CV, gmean ± SD, arithmetic mean and SD will be calculated by substituting the limit of quantification (LOQ) for values which are NQ;
- If more than 50 %, but not all, of the concentrations are NQ, the gmean, CV, gmean ± SD, arithmetic mean and SD will be reported as not calculable (NC);
- If all the concentrations are NQ, the gmean and arithmetic mean will be reported as NQ and the CV, gmean ± SD and SD as NC.

If the calculation of the gmean – SD results in a value less than the LOQ, NQ will be displayed.

12.6.2 Safety data

All AEs will be listed for each patient and summarised for each treatment by body system and preferred term assigned to the event using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary. AEs will also be assigned a maximum NCI-CTCAE grade by the Investigator and summaries will be performed by maximum NCI-CTCAE grade using NCI CTCAE Version 3.

All laboratory safety data, incorporating haematology, clinical chemistry and urinalysis data will be listed for each patient. Haematology and clinical chemistry values outside the standard reference ranges will be highlighted. Numerical laboratory data will be summarised by the dose and formulation (capsule or tablet) received. Summaries will be constructed

[redacted]

appropriately for the cohorts of the PK Phase and Continued Supply Expansion Phase. Standard summary statistics (mean, standard deviation, minimum, median, maximum, and number of subjects) will be produced. NCI-CTCAE shift tables of laboratory parameters will be produced.

Pulse and BP will be listed by patient and summarised by the dose and formulation (capsule or tablet) received. Summaries will be constructed appropriately for the cohorts of the PK Phase and Continued Supply Expansion Phase. Standard summary statistics for the absolute value at each protocol time and the change from screening baseline to all subsequent protocol assessments will be produced.

ECG and physical examination details will be listed individually by patient.

12.6.3 Efficacy data

The efficacy data from Group 1, 6, 7 and 8 of the Continued Supply Expansion Phase will be summarised by dose, formulation (capsule or tablet) and schedule and is described below.

Summaries and waterfall plots of percentage change from baseline in sum of target lesions will be presented, and this data will also be analysed by analysis of covariance fitting baseline sum of target lesions as a continuous covariate and treatment group as a factor. Summary statistics will be presented for best overall response according to RECIST. PFS will be summarised using Kaplan-Meier estimates over time and will be displayed graphically.

Summaries of CA-125 response and the corresponding percentage change from baseline, will also be presented.

Summaries will be presented for the overall population and for the gBRCA ovarian cancer subgroup.

12.7 Data monitoring committee- not applicable

13. LIST OF REFERENCES

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Rustin GJS, Quinn M, Thigpen T, Du Bois A, Pujade-Lauraine E, Jakobsen A, et al. New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). J Natl Cancer Inst 2004;96(6):487-488

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Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J Nat Cancer Inst 2000;92(3):205-216

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Appendix B
Additional Safety Information

[redacted]

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment

Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine

Intensive treatment in an emergency room or at home for allergic bronchospasm

Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse.

[redacted]

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

Is this a recognised feature of overdose of the drug?

Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix C
IATA 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Cat A pathogens are eg. Ebola, Lassa fever virus

are to be packed and shipped in accordance with IATA Instruction 602

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Cat B pathogens are eg. Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

UN 3373 – Biological Substance, Category B

are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

Clinical trial samples will fall into Cat B or exempt under IATA regulations.

Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).**

Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.

IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.

Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D
Performance Status (ECOG/Karnofsky Scale)

[redacted]

1. PERFORMANCE STATUS (ECOG/KARNOFSKY SCALE)

1.1 Example of Performance Status (ECOG/KARNOFSKY SCALE)

DESCRIPTION	ECOG GRADE	KARNOFSKY EQUIVALENT	
Fully active, able to carry on all pre-disease performance without restriction.	0	100	Normal, no complaints; no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, i.e. light housework, office work.	1	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self but unable to carry on normal activity or to do work.
Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2	60	Requires occasional assistance but is able to care for most of personal needs.
		50	Requires considerable assistance and frequent medical care.
Capable of only limited self care, confined to bed or chair more than 50% of waking hours.	3	40	Disabled; requires special care and assistance.
		30	Severely disabled; hospitalisation is indicated although death not imminent.
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4	20	Very ill; hospitalisation and active supportive care necessary.
		10	Moribund.

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Appendix E
Handling and Shipment of Pharmacokinetic Samples

[redacted]

1. INSTRUCTIONS FOR HANDLING PHARMACOKINETIC SAMPLES

1.1 Collection and handling of pharmacokinetic blood samples

Venous blood samples (4 mL) will be collected into tubes containing LITHIUM HEPARIN anticoagulant at the times shown in the study plan and thoroughly mixed. Pharmacokinetic sample tubes will be clearly labelled with the compound name, study number, subject enrolment code, cohort number, treatment period, study day, date of sample collection and nominal time-point. The date and time of sample collection will be recorded on CRFs.

Venous blood samples taken into LITHIUM HEPARIN anticoagulant will be centrifuged at 2000G for 10 minutes at room temperature within 30 minutes of collection, to provide plasma for analysis of AZD2281. Following centrifugation, each plasma sample should be divided into 2x ~1 mL aliquots, each aliquot transferred to a separate individually labelled cryo vial and stored at –20ºC within 1 hour of blood collection. Plasma samples should be stored at -20ºC or below at all times until analysis. One aliquot will be shipped for analysis while one will be retained at site as a back-up sample. On successful receipt and analysis of the first aliquot, the second aliquot will be destroyed.

1.2 Shipment of pharmacokinetic plasma samples

Plasma samples must be kept at a temperature of –20 ºC or below (using a freezer or dry ice) whilst being shipped and should be packed securely to avoid breakage during transit. Samples should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that the samples will remain frozen for at least 72 hours to allow for delays in shipment. Arrival at Covance at the weekend and public holidays must be avoided.

[redacted]

URGENT

[redacted]

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[redacted]

Appendix F
Guidelines for Evaluation of Objective Tumour Response Using RECIST Criteria (Response Evaluation Criteria in Solid Tumours)

[redacted]

1. INTRODUCTION

This appendix details the implementation of RECIST Guidelines for the D0810C00024 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Only patients with measurable disease at baseline should be included in studies where objective tumour response is the primary end-point. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable: Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with spiral Computed Tomography (CT) scan or as ≥20 mm with conventional techniques (Conventional CT or Magnetic Resonance Imaging (MRI)) and which have not previously been irradiated.

Non-measurable:

- All other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan)
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions.
- Previously irradiated lesions*
- Skin lesions assessed by clinical examination
- Brain metastasis
- Superficial and palpable lesions assessed by clinical examination or photography.

Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as Non-Target Lesions (NTL) at baseline and followed up as part of the NTL assessment.

Target lesions: A maximum of 10 measurable lesions (with a maximum of 5 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline.

[redacted]

Non-Target lesions: All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

3. METHODS OF MEASUREMENT

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

Table 1 Summary of Methods of Assessment

Target Lesions	Non-Target Lesions and New Lesions
CT (preferred) MRI	CT (preferred) MRI Clinical examination X-ray, Chest x-ray Ultrasound Endoscopy and laparoscopy

3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and new lesions.

In the D0810C00024 study it is recommended that CT examinations of the thorax, abdomen and pelvis for breast cancer, and pelvis and abdomen for ovarian cancer, with other anatomical regions as clinically indicated for the type of disease, will be used to assess tumour burden at baseline and follow-up time points. CT examination with intravenous (i.v.) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

3.2 Clinical examination

In the D0810C00024 study, clinical examination will not be used as part of RECIST assessment for TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

[redacted]

3.3 X-ray

3.3.1 Chest X-ray

In the D0810C00024 study, chest x-ray assessment will not be used as part of RECIST assessment for TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

3.3.2 Plain X-ray

In the D0810C00024 study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4 Ultrasound

In the D0810C00024 study, ultrasound examination will not be used as part of RECIST assessment for TL as it is not a reproducible method and does not provide an accurate assessment of tumour size. Ultrasound examination can, however, be used to assess NTL and to identify the presence of new lesions.

If new or worsening clinical symptoms occur and an ultrasound is performed then new lesions or progression of the existing lesions need to be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

In the D0810C00024 study, endoscopy and laparoscopy will not be used as part of RECIST assessment for TL as they are not validated in the context of tumour measurements. However, endoscopy and laparoscopy can be used for assessment of NTL and to identify the presence of new lesions.

3.6 Tumour markers

In the D0810C00024 study tumour markers will not be used as part of RECIST assessment for TL.

In studies where tumour markers (e.g. CA-125 in ovarian cancer) are being collected for separate analysis these will not contribute to tumour response based on RECIST assessment.

3.7 Cytology and histology

In the D0810C00024 study histology will not be used as part of the RECIST assessment.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens or appears during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

[redacted]

3.8 Imaging techniques not covered in the RECIST guidelines and not used in studies using RECIST tumour assessment

3.8.1 Isotopic bone scan

In the D0810C00024 study isotopic bone scans will not be used to assess bone lesions as part of RECIST assessment due to insufficient specificity.

Bone lesions identified on an isotopic bone scan and confirmed by CT, MRI or x-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment. If new bone lesions or worsening bone symptoms occur and a bone scan is performed, then worsening of disease needs to be confirmed by CT, MRI or x-ray.

3.8.2 PET scan

In the D0810C00024 study PET scans will not be used for assessment of tumour response, as PET evaluations do not form part of the RECIST framework.

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

All baseline tumour assessments must adequately assess tumour burden and should be performed no more than 28 days before the start of study treatment and ideally should be performed as close as possible to the start of study treatment. Any other sites at which new disease is suspected should also be adequately imaged at follow-up. Follow-up assessments will be performed every 8 weeks (+/- 1 week) after randomisation.

Bias in analysis can occur if one treatment group is examined more often or sooner than the other. If an unscheduled radiological and/or clinical tumour assessment is performed, and the patient has not progressed, the next scheduled tumour assessment should still be performed at the planned time (as detailed in the study plan). This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

4.2 Target lesions (TL)

4.2.1 Documentation of target lesions

A maximum of 10 measurable lesions (with a maximum of 5 lesions per organ), representative of all lesions involved, should be identified as TL at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (by methods documented in Section 3 of this Appendix).

The site and location of each TL should be documented as well as the longest diameter (LD) of each TL. All measurements should be recorded in metric notation using a ruler, calipers, or electronic calipers etc. At baseline the sum of the LD for all TL will be calculated and reported as the baseline sum LD. At follow-up visits the sum of the LD for all TL will be calculated and reported as the follow-up LD.

[redacted]

Special cases:

- If a TL splits into two or more parts, then the sum of the LDs of those parts is recorded.
- If two or more TL merge then the LD of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL becomes too small to measure accurately, then an estimate as close to the size as possible should be provided. The minimum size that can be recorded for a single lesion is 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide as close an estimate as possible of the size of the lesion.
- For TL measurable in 2 or 3 dimensions, always report the longest diameter.
- When a TL has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL at the investigational site:

Table 2 Overall Visit Response for Target Lesions

Complete Response (CR)	Disappearance of all TL since baseline
Partial Response (PR)	At least a 30% decrease in the sum of the LD of TL, taking as reference the baseline sum LD
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of TL, taking as reference the smallest sum LD recorded since the treatment started
Not Evaluable (NE)	Only relevant if any of the TL were not assessed or not evaluable or had a lesion intervention

4.3 Non-Target lesions (NTL)

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be

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recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table 3 Overall Visit Response for Non-Target Lesions

Complete Response (CR)	Disappearance of all NTL since baseline
Incomplete Response (IR)/ Stable Disease (SD)	Persistence of one or more NTL
Progression (PD)	Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression must be clinically significant for the physician to consider changing (or stopping) therapy
Not Evaluable (NE)	Only relevant when one or some of the NTL have not been assessed and in the Investigator's opinion they are not able to provide an evaluable overall NTL assessment
Not Applicable (NA)	Only relevant if there are no NTL at baseline

4.4 New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTL or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If the lesion is still present it should be recorded as a new lesion on the date it was first observed.

4.5 Evaluation of Overall Visit Response and Best Overall Response

Table 4 Overall Visit Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR (or NA)	No	**CR**
CR	IR/SD	No	**PR**
PR	CR, IR/SD (or NA)	No	**PR**
SD	CR, IR/SD (or NA)	No	**SD**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**
NE	Non-PD	No	**NE**
Non-PD	NE	No	**NE**

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease
IR = incomplete response, NE = not evaluable, NA = not applicable

The best overall response is the best response recorded from the start of treatment until disease progression.

Overall visit response and best overall response will be derived as part of the study analysis by the Sponsor from TL measurements, overall assessment of NTL and presence/absence of new lesions.

5. CONFIRMATION OF RESPONSE

According to RECIST Guidelines the main goal of confirmation of objective response is to minimize the risk of over-estimation of the response rate. This aspect of response evaluation is particularly important in non-randomized studies where response is the primary endpoint.

In the D0810C00024 study, confirmation of response (CR or PR) is determined by the study protocol to be performed at the next scheduled RECIST assessment 8 weeks (certainly no less than 4 weeks) following the date the criteria for response were first met.

6. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

6.1 CT Scan

CT scans of the neck, thorax, abdomen, and pelvis should be contiguous throughout the anatomical region of interest.

The type of CT scanner is important regarding the slice thickness and minimum sized lesions. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the thorax, abdomen, and pelvis.

CT examination with i.v. contrast media administration is the preferred method. This is to accentuate vascular structures from adjacent lymph node masses and to help enhance liver and other visceral metastases. The method of administration of i.v. contrast agents is variable. Contrast agent timing should be aimed at the portal-venous phase of the liver. In patients in whom the abdomen and pelvis have been imaged, oral contrast agents should be given to distinguish the bowel from other soft tissue masses. A consistent method should be used on subsequent examinations for any given patient.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed then CT without i.v. contrast is an option for the thorax, abdomen and pelvis examination. For brain lesions assessment, MRI is the preferred method.

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All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

6.2 MRI Scan

MRI is entirely acceptable and capable of providing images in different anatomical planes. It is important therefore that when it is used lesions must be measured in the same anatomical plane using the same imaging sequences on subsequent examinations. MRI scanners vary in the images produced. For a particular patient the same scanner should be used during the study assessment.

Moreover, many patients with advanced malignancy are in pain, so their ability to remain still for the duration of a scan sequence, in the order of 2-5 minutes is limited. Any movement during the scan time leads to motion artifacts, degradation of image quality such that the examination will probably be useless.

For these reasons, CT is the imaging modality of choice.

7. REFERENCES

Therasse et al 2000
Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumours. Journal of the National Cancer Institute. 2000 Feb 2;92(3):205-216.

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Appendix G
Acceptable Birth Control Methods

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ACCEPTABLE BIRTH CONTROL METHODS

Olaparib is regarded as a compound with medium/high foetal risk.

Patients of childbearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 3 months after last dose of study drug(s).

Acceptable Non-hormonal birth control methods include

- Total sexual abstinence. Abstinence must be for the total duration of the trial and the drug washout period.
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
- Tubal occlusion plus male condom with spermicide
- IUD plus male condom + spermicide. Provided coils are copper-banded

Acceptable hormonal methods

- Etonogestrel implants (e.g., Implanon, Norplan) + male condom with spermicide
- Normal and low dose combined oral pills + male condom with spermicide
- Norelgestromin / EE transdermal system + male condom with spermicide
- Intravaginal device + male condom with spermicide (e.g., EE and etonogestrel)
- Cerazette (desogestrel) + male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.