AstraZeneca

Revised Clinical Study Protocol

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00039

[redacted]

A randomized, double-blinded, multicentre phase II study to assess the efficacy of olaparib (AZD2281, KU-0059436) in combination with paclitaxel versus paclitaxel in patients with recurrent or metastatic gastric cancer who progress following first-line therapy

Sponsor: [redacted]

AstraZeneca Research and Development site representative [redacted]

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	[redacted]		
2			
3			
4			
Administrative change No.			
1			

[redacted]

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PROTOCOL SYNOPSIS

A randomized, double-blinded, multicentre phase II study to assess the efficacy of olaparib (AZD2281, KU-0059436) in combination with paclitaxel versus paclitaxel in patients with recurrent or metastatic gastric cancer who progress following first-line therapy

International Co-ordinating investigator

[redacted]

Study centre(s) and number of patients planned

Approximately 6-8 centres will be required for this study. Approximately 240 patients will be enrolled in this study to achieve 120 patients randomized.

Study period	Phase of development
[redacted]	

Objectives

The primary objectives of this study are:

- To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by progression-free survival (PFS), in all patients with recurrent and metastatic gastric cancer who progress following first-line therapy.
- To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by progression-free survival (PFS) in patients with recurrent and metastatic gastric cancer whose tumours are defined as homologous recombination deficient (HRD) by way of loss of expression of ATM protein ("ATM-negative patients") who progress following first-line therapy.

The secondary objectives of this study are:

- To determine the safety and tolerability of olaparib when given in combination with paclitaxel in patients with recurrent and metastatic gastric cancer who progress following first-line therapy.

- To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by overall survival (OS), response rate (RR) and percentage change in tumour size at Week 8, in all patients with recurrent and metastatic gastric cancer who progress following first-line therapy.

- To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by overall survival (OS), response rate (RR) and percentage change in tumour size at Week 8 in ATM-negative patients with recurrent and metastatic gastric cancer who progress following first-line therapy.

- To conduct a preliminary assessment of the effects of olaparib when given in combination with paclitaxel on the time to deterioration of disease related symptom and HRQoL as assessed by the EORTC QLQ-C30 + -STO22 questionnaires.

The exploratory objectives of this study are:

- To explore potential biomarkers in archival tumour in order to understand the utility of homologous recombination deficiency (HRD) markers as a predictor of response to olaparib.

- To explore potential biomarkers (such as but not limited to mutational status) in archival tumour, and in optional baseline plasma/serum samples, which may influence the development of cancer and/or response to study treatment.

- To obtain an optional blood sample for DNA extraction for future pharmacogenetic analysis into genes that may influence response, e.g. distribution, safety, tolerability and efficacy of olaparib and/or agents used in combination and/or as comparators.

Study design

This study is a phase II randomized, double-blinded study of olaparib plus paclitaxel vs. paclitaxel plus matching placebo (paclitaxel monotherapy) in patients with recurrent and metastatic gastric cancer who progress following first-line chemotherapy.

Approximately 120 patients will be randomized onto this study. It is expected that 60 patients will be ATM-positive and 60 patients will be ATM-negative. The ATM-positive arm will close after 60 patients have been enrolled, after which only ATM-negative patients will be recruited, up to 60 ATM-negative patients. It is expected that approximately 240 total patients will require screening because the prevalence of ATM-negativity is assumed to be approximately 20-25%.

Both ATM-positive and ATM-negative patients will be randomized to one of two arms:

- Paclitaxel + olaparib
- Paclitaxel + matching placebo (paclitaxel monotherapy)

Tumour evaluation using RECIST v1.1 will be conducted at screening (within 28 days prior to date of randomisation) and every 8 weeks relative to date of randomisation, up to Week 40 then every 16 weeks until objective disease progression. It is important to follow the assessment schedule as closely as possible to prevent bias in the analysis that can occur if one treatment group is assessed more often or sooner than the other. Patients will be evaluated by RECIST until objective progression and then followed up for survival unless they withdraw consent. If a patient discontinues study medication prior to objective disease progression, they should continue to be assessed using RECIST until disease progression and then followed up for survival, unless they withdraw consent.

The imaging modalities used for RECIST assessment will be CT or MRI scans of chest, abdomen and pelvis.

A mandatory archived paraffin embedded tumour sample will be collected from all patients to assess ATM status, and ATM status must be known prior to enrolment. Additional analyses for HRD markers and other related biomarkers may be performed on residual tissue (optional; subject to consent).

Optional blood samples for exploratory biomarkers and pharmacogenetic analyses will be obtained from consenting patients and stored for exploratory purposes.

Target patient population

Patients with recurrent and metastatic gastric cancer, as defined by metastatic or recurrent/refractory disease who progress following first-line chemotherapy. Patients must have assessable disease at baseline by imaging methods (CT or MRI).

Investigational product, dosage and mode of administration

Doses of olaparib or matching placebo should be taken at least one hour after food, and the patient should then refrain from eating for a further two hours due to potential effect of food on absorption.

Olaparib or matching placebo will be administered at a dose of 100 mg orally twice daily, throughout each cycle (28 days) at the same times each day, with a glass of water.

Comparator, dosage and mode of administration

Paclitaxel, 80 mg/m^2 will be administered as an intravenous (IV) infusion over 1 hour on Days 1, 8 and 15 of a 28-day cycle, and should be given one hour after the olaparib dose.

Paclitaxel is commercially available and will be supplied by AstraZeneca.

Duration of treatment

Patients will be administered paclitaxel within normal clinical practice, and it is expected that patients will receive between 6-10 cycles of paclitaxel + olaparib or paclitaxel + matching placebo. There is no maximum duration of treatment with olaparib/matching placebo. Patients will continue to receive paclitaxel + olaparib or paclitaxel + matching placebo on a 28-day cycle schedule as described above, until they demonstrate objective disease progression, unless in the Investigator's opinion they are benefiting from treatment and do not meet any other discontinuation criteria.

Patients who experience Common Terminology Criteria for Adverse Events (CTCAE) of grade 3 or 4 toxicity and meet the criteria outlined in Section 5.5.5 will have their study medication reduced or stopped, and restarted according to study guidelines. The safety follow-up should be continued as outlined in the Study Schedule (see Table 1and Table 2).

If patients are discontinued from randomised treatment for reasons other than objective disease progression, they should continue to be followed for confirmed progressive disease (RECIST) and survival according to the study schedule, unless consent is withdrawn.

After the combination treatment including paclitaxel is stopped, patients will continue with olaparib or matching placebo monotherapy until objective progression as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. The olaparib or matching placebo dose will be increased to the recommended monotherapy dose of 200 mg bd, or matched placebo commencing on the day following the scheduled completion of the last cycle of chemotherapy (i.e. 28 days after the first of the three pacliatxel doses in this cycle) as long as the specified criteria for bone marrow, hepatic and renal function are met (see Section 4.1) otherwise the tablet dose (100 mg or matched placebo bd) will be maintained until these criteria are met at a subsequent scheduled visit, at which time the olaparib or matching placebo dose should be increased to 200 mg bd or placebo to match, until objective disease progression by RECIST v1.1 as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. Once patients receiving olaparib or matching placebo have been discontinued from study treatment, other treatment options will be at the discretion of the Investigator. Patients will be unblinded after the final analysis. No cross over to olaparib is permitted.

Outcome variable(s):

Primary outcome variable

- PFS as evaluated by RECIST v1.1.

Secondary outcome variables

- Safety: Adverse events (AEs), physical examination, vital signs (including blood pressure (BP) and pulse), electrocardiogram (ECG) and laboratory findings including clinical chemistry, haematology and urinalysis (if clinically indicated)

- Efficacy: OS, ORR and percentage change in tumour size at Week 8 as evaluated by RECIST**;** the time to deterioration of disease related symptom and HRQoL as assessed EORTC QLQ-C30 + -STO22.

Exploratory outcome variables

- Measurement of HRD factors (including but not limited to ATM, BRCA-1, MDC-1, and PARP) to correlate outcome with study therapy (optional).

- Collection of pre-treatment blood (serum and plasma) sample for potential future identification of biomarkers (circulating DNA or protein markers) that are predictive of response to treatment (optional).

- Retrospective host pharmacogenetic analysis (optional).

Statistical methods

The co-primary objectives of this study will be to assess the efficacy of olaparib in combination with paclitaxel, compared with paclitaxel alone in 1) patients with recurrent and metastatic gastric cancer who progress following first-line therapy (overall population); and 2) patients with recurrent and metastatic gastric cancer whose tumours are defined as HRD by negative ATM staining by IHC (ATM-negative), who progress following first-line therapy, by assessing PFS.

The secondary objectives of this study will be to assess the efficacy of olaparib in combination with paclitaxel, compared with paclitaxel alone in the 1) overall population; and 2) ATM-negative population, by assessing ORR, OS and change in tumour size at 8 weeks.

It is assumed that patients who are ATM-negative will show a greater response to olaparib than patients who are ATM-positive. As the prevalence of ATM-negative patients is assumed to be approximately 25% of the overall population (AstraZeneca, unpublished) and this study population will have a 50% prevalence, analyses of endpoints in the overall population will be calculated using weighted estimates of the ATM-negative and ATM-positive patients. Weights w_1 and w_2 (proportion of ATM-negative patients and ATM-positive patients respectively) will be estimated from the screening records (up until the ATM-positive group is closed to recruitment). For calculation of Confidence Intervals, the variance will take into account the variance of both groups.

The PFS analyses will be performed when approximately 104 progression events have occurred (and approximately 50 events in the ATM-negative population). If the true HR is 0.55 (likely to correspond to an 80% prolongation of PFS) in the ATM-negative population, this analysis will have approximately 80% power to demonstrate a statistically significant difference for PFS, assuming a 10% one-sided significance level. Assuming a true prevalence of 25% for the ATM-negative group, if the true HR in the ATM-positive group is 0.65, then this study will have 80% power to detect a weighted overall HR of 0.62 (likely to correspond to a 61% prolongation of PFS), assuming a 10% one-sided significance level. This trial has been sized using one-sided 10% significance levels as it is a Phase II study looking for a

signal of improved efficacy. If a one-sided p-value <0.1 is observed for the comparison of PFS between the paclitaxel + olaparib vs. paclitaxel + matching placebo in either of the co-primary populations, the results will be regarded as promising (but not definitive) in the relevant population as there is less than 1 in 5 probability that such a result could have been detected if there was truly no treatment effect. Assuming 50 events in the ATM-positive population occur, an observed HR of <0.69 will achieve a one-sided p-value <0.1. Similarly, assuming 104 events overall and a 25% prevalence of HRD-negative (to be assessed from screening log), an observed weighted HR of <0.75 will achieve a p-value of <0.1.

Assuming non-uniform recruitment and a median PFS of 3 months (Emi et al 2008) in the control group, if approximately 120 patients (60 per arm) are recruited over 15 months it is expected that 104 events will occur approximately 6 months following recruitment of the last patient.

All efficacy data will be analyzed on an intention-to-treat (ITT) basis using randomized treatment, except for ORR and percentage change in tumour size at Week 8, which will be analyzed using an 'evaluable-for-response' population (a sub-population of the ITT) that will exclude patients who do not have measurable disease at entry. There will be two co-primary analysis populations: the first will be based on the full analysis set (FAS) and will include all randomized patients; the second will comprise the subset of randomized that are ATM-negative. These patients will be identified from the analyses of ATM protein staining by IHC, on sections taken from archival tumour blocks.

PFS, ORR and percentage change in tumour size at Week 8 will be assessed using RECIST v1.1 assessments (RECIST assessments to be carried out at screening, and then at Week 8, Week 16 and every 8 weeks thereafter relative to date of randomisation, until Week 40, at which time assessments will be carried out every 16 weeks until objective disease progression as defined).

Numerical (standardised) score data for the 2-item global QoL scale and the 5 disease related multi-item symptom subscales (dysphagia, eating restriction, stomach pain, reflux, anxiety) will be summarized by treatment arm (data from the EORTC QLQ-C30 +-STO22 questionnaires). Kaplan Meier plots of Time to deterioration by treatment group will be presented for each of the six endpoints.

Best objective response, safety data and tumour biomarker data will be summarised descriptively and will not be formally analysed.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
ATM	Ataxia-Telangiectasia Mutation
bd	Twice daily
BP	Blood Pressure
BRCA	Breast cancer gene type
CI	Confidence Interval
CR	Complete response
CRF	Case Report Form
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DNA	Deoxyribonucleic acid
DUS	Disease under study
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FAS	Full Analysis Set
GCP	Good Clinical Practice
HDPE	High-density polyethylene

Abbreviation or special term	Explanation
HR	Hazard Ratio
HRD	Homologous Recombination Deficiency
HRQoL	Health related quality of life
IATA	International Air Transport Association Dangerous Goods
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
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.
IP	Investigational product
IRB	Institutional Review Board
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LSLV	Last Patient Last Visit
MRI	Magnetic resonance imaging
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
ORR	Objective Response Rate
OS	Overall Survival
PAR	Polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)]
PARP	Polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] polymerisation
PFS	Progression-Free Survival
PGx	Pharmacogenetic research
PI	Principal investigator
PP	Per protocol
PR	Partial Response
PRO	Patient reported outcome
QoL	Quality of life
RBC	Red blood cells

Abbreviation or special term	Explanation
RR	Response Rate
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event (see definition in Section 6.4.2).
SAP	Statistical Analysis Plan
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

1.1.1 Polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] polymerisation (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 et al 2002).

Of the various members of the PARP enzyme family, only PARP 1 and PARP 2 have been shown to 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 utilised to

synthesise 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. Like PARP1, PARP 2 also responds to DNA damage and is similarly involved in 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 et al 2002; Nguewa et al 2005).

1.1.2 Homologous recombination deficiency and PARP

Olaparib (AZD2281, KU-0059436) is an inhibitor of PARP 1 and shows monotherapy activity in tumour cells with defective components of homologous recombination (HRD) pathway, which includes cells with the BRCA1-/- and BRCA2-/- genotype, as well as those with low ataxia-telangiectasia mutation (ATM) gene expression. Due to the molecular targeting of olaparib 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. For further information please refer to the current version of the olaparib Investigator's Brochure.

1.1.3 Pre-clinical experience

The pre-clinical experience is fully described in the current version of the olaparib Investigator's Brochure.

1.1.4 Toxicology and safety pharmacology summary

Olaparib has been tested in a standard range of safety pharmacology studies e.g. 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 target organ of toxicity is the bone marrow.

Further information can be found in the current version of the olaparib Investigator's Brochure.

1.1.5 Clinical experience

Olaparib appears to be generally well tolerated in patients with various solid tumours at doses up to and including 400 mg twice daily, as monotherapy. To date, more than 500 patients suffering from ovarian, breast, pancreatic, melanoma and a variety of other recurrent and metastatic solid tumours had been exposed to olaparib across the dose range 10 mg once daily to 600 mg twice a day, either as monotherapy or in combination with other chemotherapy agents, including paclitaxel and carboplatin/paclitaxel.

Administration of olaparib has been associated with cases of:

- Laboratory findings and/or clinical diagnoses of:
  - Anaemia, generally mild to moderate (CTC grade 1 or 2)
  - Neutropenia, predominantly mild to moderate (CTC grade 1 or 2)
  - Thrombocytopenia, generally mild to moderate (CTC grade 1 or 2), sometimes severe (CTC grade 3 or 4)
- Nausea and vomiting, generally mild to moderate (CTC grade 1 or 2), intermittent and manageable on continued treatment.
- Fatigue, generally intermittent, of mild to moderate intensity (CTC grade 1 or 2).

Pneumonitis events with no consistent clinical pattern have been reported in a small number of patients.

At present, the number of patients exposed to olaparib is small, and safety and efficacy data is limited. In an ongoing phase I study of paclitaxel + olaparib, continuous doses of olaparib 100 mg bd were well-tolerated when given with paclitaxel 80 mg/m^2 weekly (AstraZeneca, unpublished). These events will continue to be monitored to assess frequency and severity as patient exposure increases. These events suggest an emerging safety profile for olaparib that supports further studies in cancer patients. The clinical experience with olaparib is fully described in the current version of the olaparib Investigator's Brochure.

1.1.6 Gastric Cancer

Gastric cancer is the fourth-most common cancer and is the second-most common cause of cancer death worldwide. In 2000, there were almost one million cases of gastric cancer diagnosed world-wide, with 650,000 deaths (Crew et al 2006). Although the prognosis for patients with localized disease is good, patients with advanced or metastatic disease have a five-year overall survival of less than 20% (Theuer et al 2000). Screening programs, specifically in Asia where the incidence of gastric cancer is highest, have lead to fewer patients diagnosed at a late-stage. However most patients in Europe and the United States are diagnosed with advanced, incurable disease.

Recently, emerging data suggests that in addition to standard cytotoxic chemotherapy, including 5-fluorouracil, capecitabine, oxaliplatin, cisplatin, S-1, or irinotecan, targeted therapy may be of clinical benefit in a percentage of patients. Approximately 20% of patients with gastric cancer will express ErbB2 (Her-2) on the tumour surface (Im et al 2009; Bang et al 2009), suggesting a targeted therapeutic option that was studied in a randomized trial recently completed, in which patients whose tumours expressed Her-2 were treated with trastuzumab (Herceptin; Roche-Genentec). In this study, survival was extended by less than three months in patients treated with trastuzumab (Van Cutsem et al 2009). Despite these results, 80% of patients remain trastuzumab-ineligible, and additional targeted therapies are warranted. Other subpopulations of gastric cancer patients that may benefit from targeted therapy may include those with mutations or errors in HRD genes, such as ATM, as demonstrated by the recent identification of a group of such patients with limited or absent expression of ATM.

The biological approach of the study described implies that targeted therapies such as olaparib can be successful in gastric cancer, specifically when given with conventional cytotoxic or standard-of-care agents.

1.2 Research hypothesis

Olaparib in combination with paclitaxel improves progression-free survival compared to paclitaxel alone in patients with recurrent and metastatic gastric cancer who have progressed following first-line therapy, and patients whose tumours are ATM-negative will show a greater response to olaparib in combination with paclitaxel than patients who are ATM-positive.

1.3 Rationale for conducting this study

Currently, there are few specific treatment options for patients with recurrent and metastatic gastric cancer who progress following first-line therapy. The taxanes, including paclitaxel, are now a mainstay in the treatment of recurrent and metastatic gastric cancer. However paclitaxel alone fails to provide an adequate treatment for the majority of patients. The identification of the group of patients who have recurrent and metastatic gastric cancer with limited or absent expression of ATM is under investigation; recent data suggests that patients with gastric cancer may fail to express ATM in up to 25% of cases (AstraZeneca; unpublished data). Such patients may specifically benefit from the use of PARP-1 inhibiting agents such as olaparib in the setting of ATM-negativity. Previous studies with olaparib have shown objective tumour responses in breast and ovarian cancer patients from resistant populations with BRCA mutations. In addition to patients with BRCA mutations, it has been shown that additional patients in these populations have loss of BRCA protein function through a variety of other mechanisms. In preclinical models from cells with low BRCA and ATM expression, these abnormalities lead to an increased sensitivity to olaparib. Therefore this study has been designed and sized to assess efficacy in the overall gastric cancer population, but in addition to assess the efficacy in the gastric cancer patient population with ATM-negativity to investigate whether ATM status is predictive of improved response to olaparib in combination with paclitaxel.

1.4 Benefit/risk and ethical assessment

Gastric cancers frequently recur after primary treatment. At recurrence, these cancers are generally incurable. The goals of treatment for recurrent and metastatic gastric cancer are to improve survival, prolong PFS and promote good quality of life. In the current study, all patients will receive a weekly regimen of paclitaxel at a dose and schedule with proven efficacy. Weekly paclitaxel has become a widely-acceptable second-line treatment of patients with recurrent and metastatic gastric cancer. It is believed that olaparib may have enhanced anti-tumour activity in the ATM-negative recurrent and metastatic gastric cancer population and, as such, serves as a rational therapy offering the possibility of improving upon the efficacy of paclitaxel administered alone. The current study aims to provide a clearer understanding of how to provide effective therapies to those who will benefit most.

In view of the potential for olaparib to have anti-tumour activity in the gastric cancer population, the current study is designed to allow for patients to continue on olaparib monotherapy after completion of protocol doses of paclitaxel until progression of disease. However, patients may 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 olaparib.

There is strong preclinical evidence that deficiencies in homologous recombination are associated with susceptibility to PARP inhibition. Biomarker research on archival tumour tissue, from patients in this study, may confirm this hypothesis clinically and ultimately ensure that AstraZeneca will be able to prospectively identify patients most likely to benefit from treatment with olaparib. Analyses of archival tumour samples from patients will be used to identify the HRD subset population of patients in this study, as defined by ATM staining by IHC; archival tumour will also be analysed to determine other HRD core factors that may influence response to therapy.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objectives of this study are:

- To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by Progression Free Survival (PFS), in all patients with recurrent and metastatic gastric cancer who progress following first-line therapy.

- To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by Progression Free Survival (PFS) in patients with recurrent and metastatic gastric cancer whose tumours are defined as homologous recombination deficient (HRD) by way of loss of expression of ATM protein (“ATM-negative patients”) who progress following first-line therapy.

2.2 Secondary objectives

The secondary objectives of this study are:

- To determine the safety and tolerability of olaparib when given in combination with paclitaxel in patients with recurrent and metastatic gastric cancer who progress following first-line therapy.

- To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by overall survival (OS), response rate (RR) and percentage change in tumour size at Week 8, in all patients with recurrent and metastatic gastric cancer who progress following first-line therapy.

- To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by overall survival (OS), response rate (RR) and percentage change in tumour size at Week 8 in ATM-negative patients with recurrent and metastatic gastric cancer who progress following first-line therapy.

- To conduct a preliminary assessment of the effects of olaparib when given in combination with paclitaxel on the time to deterioration of disease related symptom and health related quality of life (HRQoL) as assessed by the EORTC QLQ-C30 +-STO22 questionnaires.

2.3 Exploratory objectives

The exploratory objectives of this study are:

- To explore potential biomarkers in archival tumour in order to understand the utility of homologous recombination deficiency (HRD) markers as a predictor of response to olaparib.

- To explore potential biomarkers (such as but not limited to mutational status) in archival tumour, and in optional baseline plasma/serum samples, which may influence the development of cancer and/or response to study treatment.

- To obtain an optional blood sample for DNA extraction for future pharmacogenetic analysis into genes that may influence response, e.g. distribution, safety, tolerability and efficacy of olaparib and/or agents used in combination and/or as comparators.

3. STUDY PLAN AND PROCEDURES

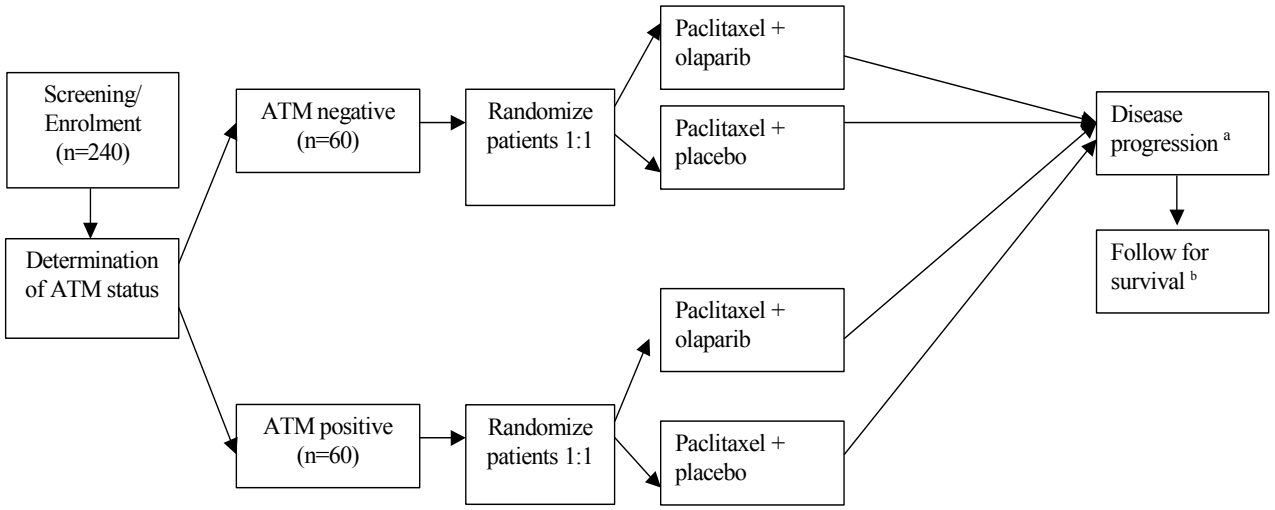
This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

Once the number of ATM positive patients, as described in this protocol, have been recruited, then only ATM negative patients may be entered in the remaining part of the study.

Due to the incidence of ATM negativity (20 - 25%), approximately 240 patients will need to be screened to obtain 60 ATM negative patients entered in the study. To avoid patients, who are ATM positive, undergoing unnecessary screening assessments investigators will be able to pre-screen for ATM status prior to obtaining the main consent from the patients for this study. Investigators must obtain a signed and dated pre-screening consent form prior to assessing potential patients for their ATM status in order to pre-screen for ATM status.

Figure 1 Study Flow Chart



[a] Tumour assessment using RECIST performed at Week 8 and every 8 weeks until Week 40, and then every 16 weeks relative to date of randomization, until objective disease progression. Patients must be followed until objective progression regardless of whether study treatment is discontinued or delayed and/or protocol violations.

[b] Once patient has discontinued all study treatment and shown objective disease progression, survival contacts are every 8 weeks.

Table 1 Study Schedule – Screening (see section 6.2 for further details)

Visit	**1**	
Day	**-28 to -1**	**-7 to -1**
Informed consent	X	
Demographics	X	
Medical and surgical history	X	
Previous cancer therapy	X	
Inclusion/exclusion criteria	X	
Collection of archival tumour sample (mandatory)	X	
ATM status (mandatory)	X	
Physical examination	X	
Vital signs, body weight, height (Includes BP [supine position], pulse and temperature)	X	
ECOG performance status	X	
ECG		X
Haematology/clinical chemistry/urinalysis	X	
Pregnancy test [a]	X	
Tumour assessment (CT or MRI according to RECIST v1.1) [b]	X	
Adverse events (from time of consent)	X	
Concomitant medications	X	

[a] Pre-menopausal women of child-bearing potential must have a negative urine or serum pregnancy test within 28 days prior to starting treatment and a confirmatory test before treatment at visit 2. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.

[b] RECIST assessments will be performed using CT or MRI scans of chest, abdomen, and pelvis. Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and

symptoms of individual patients. Baseline assessments should be performed no more than 28 days prior to date of randomisation, and ideally should be performed as close as possible to the start of study treatment.

Table 2 Study schedule – on treatment and follow up (see section 6.2 for further details)

Visit number	2	3	4	5	6	7	8	9	Subsequent visits - every 4 weeks [a] Visit No. 10 onwards	Treatment Discontinuation	Follow-up 30 days after last dose of study medication	Survival Every 8 weeks following objective disease progression
Day	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**Day 1 – next visit period (e.g. day 57, 85)**			
Visit Window		±1d	±1d	±1d	±1d	±1d	±1d	±1d	±2d	±3d	±3d	±3d
Physical exam	X[b]				X				X	X		
Vital signs, body weight (Includes BP [supine position], pulse and temperature	X[b]	X	X	X	X	X	X	X	X	X	X	
ECOG performance status	X[b]				X				X	X	X	
ECG [c]									X[c]		X	
Haematology/clinical chemistry/urinalysis [d]	X[b]	X	X	X	X	X	X	X	X	X	X	
Pregnancy test before treatment	X											
Circulating biomarker sample (optional) [e]	X											
Blood sample for pharmacogenetics (optional) [f]	X											

Visit number	2	3	4	5	6	7	8	9	Subsequent visits - every 4 weeks [a] Visit No. 10 onwards	Treatment Discontinuation	Follow-up 30 days after last dose of study medication	Survival Every 8 weeks following objective disease progression
Day	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**Day 1 – next visit period (e.g. day 57, 85)**			
Visit Window		±1d	±1d	±1d	±1d	±1d	±1d	±1d	±2d	±3d	±3d	±3d
Tumour assessment (CT or MRI according to RECIST v1.1) [g]									X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	
Randomisation	X											
Olaparib or matching placebo dispensed/returned	X				X				X	X		
Pacltaxel infusion [h]	X	X	X		X	X	X		X			
HR Quality of life assessment [i]	X				X				X	X	X	
Post discontinuation cancer therapy											X	X
Survival [j]												X

[a] Visit to take place on Day 1 of a 4 week (28 day) visit period.

[b] If assessed within 7 days before randomisation 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.

[c] ECG performed at baseline(day-7 to -1), at 8 weeks (day 57), at final follow-up and if clinically indicated at any other time, see Section 6.4.7. ECG should be performed once the patient has been in the supine position for at least 5 minutes in each case.

[d] Hematology/clinical chemistry should be performed on Day 1, 8 and 15 of a 28-day cycle prior to paclitaxel infusion. Urinalysis should be performed if clinically indicated.

[e] Two x 4 mL blood sample, processed into serum and plasma take prior to first dose.

[f] This sample will be taken, any time from enrolment to commencement of dosing, but may be taken at any visit until the last study visit.

[g] RECIST assessments will be performed using CT or MRI scans of chest, abdomen, and pelvis. Follow-up assessments will be performed every 8 weeks relative to date of randomization, up to Week 40 then every 16 weeks until objective disease progression as defined by RECIST 1.1. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

[h] Paclitaxel will be administered as an IV infusion over 1hour on Day 1, 8 and 15 of a 28-day cycle.

[i] The questionnaires should be completed prior to any study-related assessments being performed at the study visit. If the patient discontinues therapy for reasons other than RECIST progression, HRQoL assessments should continue until RECIST progression is confirmed.

[j] Assessment for survival should be made every 8 weeks following objective disease progression. Survival information may be obtained via telephone contact.

3.2 Rationale for study design, doses and control groups

This Phase II study will be randomised and double-blind in order to minimise bias when assessing whether olaparib in combination with paclitaxel shows better efficacy (PFS, OS, ORR and percentage change in tumour size at Week 8) when compared to paclitaxel alone (paclitaxel + matching placebo) in patients with recurrent and metastatic gastric cancer, both overall and with ATM-negative HRD. The primary endpoint of PFS is chosen as is felt to be clinically meaningful in the setting of recurrent and metastatic gastric cancer.

There is no accepted standard therapy for patients with recurrent and metastatic gastric cancer who have progressed following first-line therapy, and no curative therapy. Because the implication of HRD status is unknown with respect to its effect on response to olaparib, a study that assesses both the overall population and the ATM-negative population is proposed. A prevalence of 25% is expected for ATM-negativity. The doses selected for olaparib and paclitaxel are based upon current safety data from an ongoing phase 1 study of continuous olaparib + weekly paclitaxel in which olaparib has been tolerated by patients at 100 mg/dose PO bd for 28 days continuously, and paclitaxel has been tolerated by patients at 80 mg/m^2 IV weekly on days 1, 8 and 15 of a four-week cycle. This is also an accepted dose of paclitaxel given on this schedule in this patient population. Once the combination treatment including paclitaxel is stoppted, the dose of olaparib will be escalated to the accepted monotherapy dose of 200 mg bd.

4. PATIENT SELECTION CRITERIA

The patient population should be selected without bias.

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

Each patient should 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.

4.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

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

2. Recurrent or metastatic gastric cancer that has progressed following first-line therapy

3. Confirmed ATM status from archival tumour sample. A formalin fixed, paraffin embedded tumour sample (usually provided at diagnosis) from the primary or recurrent cancer **must** be available from each patient for central testing of ATM staining by IHC.

4. Patients must be ≥18 years of age.

5. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:

   - Haemoglobin ≥ 9.0 g/dL
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - White blood cells (WBC) > 3 x 10^9/L
   - Platelet count ≥ 100 x 10^9/L
   - Total bilirubin ≤ 1.5 x institutional upper limit of normal
   - AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case it must be ≤ 5x ULN
   - Serum creatinine ≤ 1.5 x institutional upper limit of normal (ULN)

6. ECOG performance status ≤ 2 (see Appendix F).

7. Patients must have a life expectancy ≥ 16 weeks.

8. Evidence of non-childbearing status for women of childbearing potential, or postmenopausal status: negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on day 1.

   Postmenopausal is defined as:

   - Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments,
   - LH and FSH levels in the post menopausal range for women under 50,
   - radiation-induced oophorectomy with last menses >1 year ago,
   - chemotherapy-induced menopause with >1 year interval since last menses,
   - or surgical sterilisation (bilateral oophorectomy or hysterectomy).

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

10. At least one lesion (measurable and/or non-measurable) that can be accurately assessed by imaging (CT/MRI) at baseline and follow up visits.

For inclusion in the optional genetic research (additional blood samples for pharmacogenetic sample), patients must fulfil the following criterion :

11. Provision of informed consent for genetic research.

If a patient declines to participate in the genetic research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they consent to that part.

4.2 Exclusion criteria

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

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

2. Previous randomisation in the present study.

3. More than one prior chemotherapy regimen for the treatment of gastric cancer in the metastatic or recurrent setting.

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

5. Any previous treatment with a PARP inhibitor, including olaparib.

6. Any previous treatment with a taxane, including paclitaxel and docetaxel, in the metastatic or recurrent setting.

7. Patients with second primary cancer, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for ≥5 years.

8. Patients receiving any systemic chemotherapy, radiotherapy (except for palliative reasons), within 2 weeks from the last dose prior to study treatment (or a longer period depending on the defined characteristics of the agents used). The patient can receive a stable dose of bisphosphonates for bone metastases, before and during the study as long as these were started at least 4 weeks prior to treatment.

9. Patients receiving the following classes of inhibitors of CYP3A4 (see Section 5.6.1 for guidelines and wash out periods):

   - Azole antifungals
   - Macrolide antibiotics
   - Protease inhibitors

10. Ongoing toxicities (>CTCAE grade 2) caused by previous cancer therapy.

11. Intestinal obstruction or CTCAE grade 3 or grade 4 upper GI bleeding within 4 weeks before study treatment.

12. Clinically significant (i.e. active and untreated or symptomatic) heart disease (e.g. congestive heart failure, symptomatic coronary artery diseases, cardiac arrhythmias, etc) or myocardial infarction within past 12 months.

13. Interstitial pneumonia or diffused symptomatic fibrosis of the lungs.

14. 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 treatment.

15. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

16. 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, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.

17. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

18. Pregnant and breastfeeding women.

19. Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV).

20. Patients with known active hepatic disease (i.e. Hepatitis B or C).

21. Patients with a known hypersensitivity to olaparib, paclitaxel or any of the excipients of the product.

22. Patients with uncontrolled seizures.

For the optional pharmacogenetics sample only:

- Previous allogeneic bone marrow transplant.

- Blood transfusion in the last 120 days prior to entry to the study.

For procedures for withdrawal of incorrectly enrolled patients see Section 5.3

5. STUDY CONDUCT

5.1 Restrictions during the study

Contraception

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 three months after last dose of study drug(s), including:

- Condom with spermicide

And one of the following:

- Oral contraceptive or hormonal therapy (e.g. hormone implants)
- Placement of an intra-uterine device (see Appendix E as consideration should be given to the type of device/system used)

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

Other Concomitant treatment

1. No other chemotherapy, hormonal therapy (HRT is acceptable) or other novel agent is to be permitted during the course of the study treatment for any patient (the patient can receive a stable dose of corticosteroids during the study as long as these were started at least 4 weeks prior to treatment, as per exclusion criteria above). 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.

2. Live virus and bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

3. Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity (see Section 5.6.1) from the time they enter the screening period until 30 days after the last dose of study medication. In vitro data have shown that the principal enzyme responsible for the formation of the three main metabolites of olaparib is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown this restriction is required to ensure patient safety.

5.2 Patient enrolment and randomisation and initiation of investigational product

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 4.1 and 4.2.

4. The randomisation code (patient number) will be obtained through IVRS or IWRS.

As patients are screened for the study, they must be allocated an enrolment code (E-code). The E-code is a 7-digit number made up of the centre number and the patient number within that particular centre (e.g., the first patient screened at centre number 0001 would be assigned the E-code E0001001, the second patient screened would be E0001002 and so on). This number is the patient's unique identifier and is used to identify the patient on the eCRFs.

Once the number of ATM positive patients, as described in this protocol, have been recruited, then only ATM negative patients may be entered in the remaining part of the study. To avoid patients, who are ATM positive, undergoing unnecessary screening assessments investigators will be able to pre-screen for ATM status. Investigators must obtain a signed and dated pre-screening consent form prior to assessing potential patients for their ATM status in order to pre-screen for ATM status. These patients will not be assigned an E-code and no data will be collected on the clinical database, until confirmation of ATM negative status and signed consent for the main study. Investigator must maintain a pre-screening log in ISF.

Randomisation codes will be assigned strictly sequentially as patients are eligible for randomisation.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

5.2.1 Procedures for randomisation

Eligible patients will be randomised in a 1:1 ratio (olaparib:matching placebo). The actual treatment given to individual patients will be determined by a randomisation scheme. The randomisation scheme will be produced by a computer software program called GRand (AZ Global Randomisation system) that incorporates a standard procedure for generating random numbers.

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 randomization scheme will be stratified by ATM status.

Patient eligibility will be established before treatment randomisation. Once the eligibility of a patient has been confirmed, the Investigator (or nominated assistant) should follow the manual provided to instruct them on how to allocate the randomised therapy. Patients will be identified using patient initials, E-code and date of birth. The manual provided to the site will detail the process of what treatment to allocate at randomisation and also what to do for subsequent dispensing visits. If a patient reduces his or her dose, the Investigator (or nominated assistant) must ensure that they complete the label so that it indicates the reduced dose that the patient is receiving.

If a patient discontinues participation in the study, then their enrolment/randomisation code cannot be reused.

5.3 Procedures for handling patients incorrectly randomised

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or randomised. There can be no exceptions to this rule.

Where patients that do not meet the selection criteria are randomised in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Delivery Team Physician and the investigator regarding whether to continue or discontinue the patient from treatment. 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 Delivery Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped and be withdrawn from the study.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

Olaparib and matching placebo treatment will be blinded.

The study medication will be labelled in accordance with the randomisation scheme. The active and placebo tablet will be identical and presented in the same packaging to ensure blinding of the study medication.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator(s) or pharmacists from either the IVRS or in the form of de-code envelopes. Routines for this will be described in the manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The

investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product

The Investigational Products Supply (IPS) section of AstraZeneca will supply olaparib or matching placebo to the investigator as green film coated tablets containing either 25mg or 100mg.

Investigational product[a]	Dosage form and strength	Manufacturer
Olaparib	25 mg tablet 100mg tablet	AstraZeneca
Placebo to match olaparib	Tablet	AstraZeneca

[a] Descriptive information for olaparib can be found in the Investigator's Brochure

Paclitaxel will be supplied by AstraZeneca. Descriptive information for paclitaxel can be found in the local package insert supplied with the drug.

5.5.2 Doses and treatment regimens

For all centres, olaparib or matching placebo tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain sufficient medication for at least 28 days plus overage. Olaparib or matching placebo will be dispensed to patients on Day 1 and every 28 days thereafter until the patient completes the study, withdraws from the study or closure of the study.

Patients will be administered olaparib or matching placebo orally twice daily (bd) at 100 mg continually. Four x 25 mg olaparib (or 1 x 100mg olaparib) or matching placebo tablets should be taken at the same times each morning and evening of each day, approximately 12 hours apart with a glass of water.

Patients will be instructed to take their doses of olaparib or matching placebo at least one hour after food, and the patient should then refrain from eating for a further two hours due to potential effect of food on absorption. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

If vomiting occurs shortly after the olaparib or matching placebo tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of two hours after that scheduled dose time. If greater than two 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.

Patients will continue with olaparib or matching placebo until objective disease progression (determined by RECIST v1.1) as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

Paclitaxel should be given at least 1 hour after the patient has taken their olaparib or matching placebo morning dose. Paclitaxel will be administered as an intravenous (IV) infusion over 1 hour at 80 mg/m^2 weekly on days 1, 8 and 15 of a four-week schedule.

Patients will be administered paclitaxel in line with normal clinical practice. It is expected that patients will receive between 6 and 10 cycles of paclitaxel; there is no maximum duration of treatment with olaparib or matching placebo. After the combination treatment including paclitaxel is stopped, patients will continue with olaparib or matching placebo monotherapy until objective disease progression as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. The olaparib or matching placebo dose will be increased to 200 mg bd, or matched placebo commencing on the day following the scheduled completion of the last cycle of chemotherapy (i.e. 28 days after the first of the three paclitaxel doses in this cycle) as long as the specified criteria for toxicity are met (see Section 5.5.5).

All patients should be premedicated (as per local standard practice) prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel.

Patients will be unblinded after the final analysis. No cross over to olaparib is permitted.

5.5.3 Labelling

Investigational Product Supplies (IPS), AstraZeneca, will label each bottle of olaparib and/or matching placebo. 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. Labels will include blank lines for quantity of tablets to be taken, patient enrolment code (E-code) and date of dispensing. The label will also state that olaparib or matching placebo tablets should be taken as instructed by the investigator at approximately the same time each morning and evening.

5.5.4 Storage

All study drugs 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 and the Investigator Brochure specifies the appropriate storage and shipment.

5.5.5 Management of toxicity

Any toxicity observed during the course of the study will be managed by interruption of olaparib and/or paclitaxel, as deemed appropriate by the Investigator. Each patient should receive three paclitaxel doses in a four-week period as toxicity permits however interruption or dose modification of paclitaxel must follow labelled recommendations where appropriate (for example, myelosuppression). Interruption of olaparib for paclitaxel-specific toxicities (for example, peripheral neuropathy) should be avoided.

Treatment with paclitaxel may continue at the full dose of 80 mg/m^2 (unless previously dose reduced) on Days 1, 8 and 15 of each cycle as long as the following criteria are met, else paclitaxel should be held until restoration of ANC and platelet count:

- ANC $\geq 1.5 \times 10^9$/L
- Platelets $\geq 100 \times 10^9$/L

In the event that a patient has not recovered sufficiently to enable the next chemotherapy cycle to start, then the cycle should be delayed until the toxicity has recovered sufficiently to allow further dosage. The maximum cycle delay is permitted in 28 days. In the event that only the paclitaxel needs to be held and the patient is still receiving continuous dosing of olaparib, then the start of the chemotherapy cycle should be delayed, however the patient should continue the olaparib doses during the delay period, unless any other criteria requires doses to be omitted.

Further dose modifications are described in Table 3, Table 4, Table 5 and Table 6.

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in olaparib 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 is observed on CT imaging and symptoms resolve, then olaparib 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 Team Physician.

5.5.5.1 Management of haematological toxicity (paclitaxel and olaparib)

At the first occurrence of haematological toxicity, both olaparib and paclitaxel should be held until resolution of toxicity. At the resolution of the first occurrence of any of these toxicities, no change should be made to dose. At the second occurrence, upon resolution of toxicity, olaparib should be reduced by the 1st dose reduction to 100 mg bd days 1-14 of a 28-day cycle (Table 3). If despite this change, at the third occurrence, upon resolution of toxicity,

paclitaxel should be reduced by the first dose reduction to 65 mg/m^2/dose (Table 4). At the fourth occurrence, upon resolution of toxicity, olaparib should be reduced by the 2nd dose reduction to 100 mg bd days 1-7 of a 28-day cycle (Table 3). If despite these changes, toxicity recurs, the patient should be withdrawn from the treatment.

Refer to Table 5 for specific dose modification guidance regarding haematological toxicity.

Please note that for simultaneous toxicities (for example, neutropenia and thrombocytopenia), if either olaparib or paclitaxel has been recently held or dose-reduced, and a second toxicity develops, the event should be considered singular and no further dose modification should be made, providing that both toxicities resolve within 28 days. However, sequential toxicities (for example, neutropenia followed by thrombocytopenia) should follow Table 5; if a recent dose reduction has been made, a second modification may be required before beginning the next cycle.

Table 3 Dose reductions for olaparib or matching placebo when combined with paclitaxel

Reduction	Dose Level
Initial Dose Level	100 mg bd days 1-28 of a 28-day cycle
1st dose reduction [a]	100 mg bd days 1-14 of a 28-day cycle
2nd dose reduction [a]	100 mg bd days 1-7 of a 28-day cycle
3rd Dose reduction	No reduction allowed; withdraw patient

[a] Dose must not be re-escalated even if toxicities have resolved.

Table 4 Dose reductions for paclitaxel

Reductions	Dose Level
Initial dose level	80 mg/m^2 on days 1, 8 and 15 of a 28 day cycle
1st dose reduction [a]	65 mg/m^2 on days 1, 8 and 15 of a 28 day cycle
2nd dose reduction	No additional reduction allowed; stop paclitaxel

[a] Dose may be re-escalated to full dose once toxicities have resolved, depending on toxicity (see below for exceptions).

Filgrastim or PEG-filgrastim may be used at the investigator's discretion.

In addition, paclitaxel should be permanently reduced to 65 mg/m^2/dose in case of the following haematological toxicities:

- Febrile neutropenia (temperature ≥ 38.5°C, ANC < 1.0 x 10^9/L), requiring hospitalisation and IV antibiotics.

- Bleeding associated with platelet count of ≤ 40 x 10^9/L or any platelet count of ≤ 20 x 10^9/L.

5.5.5.2 Management of non-haematological treatment-related adverse events attributable to olaparib

Non-hematological CTCAE grade 3 and 4 toxicities observed during the course of the study and attributable to olaparib will first be managed by interruption of the dose. Repeat dose interruptions are to be allowed as required. The maximum duration of any dose interruption is 28 days. If an interruption of longer than 28 days is required, the patient should be withdrawn. When olaparib is interrupted, the patient must either recover completely or the toxicity must revert to NCI CTCAE ≤ grade 1 or to the baseline CTCAE grade before restarting treatment. Patients whose NCI CTCAE grade 3 or 4 event does not resolve to ≤ grade 1 or to the baseline CTCAE grade after a full 28 day dose interruption should be withdrawn from the study.

Where toxicity recurs following re-challenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, then dose reduction or withdrawal is indicated.

Upon appropriate resolution of the toxicity (i.e. to CTCAE grade 1 or to baseline CTCAE grade), the patient should restart treatment with olaparib but with a 50% dose reduction (as per Table 3).

If the event recurs with the same severity, treatment should be interrupted again and, on resolution, a further dose reduction made.

5.5.5.3 Management of non-haematologic treatment related adverse events attributable to paclitaxel

Treatment with paclitaxel may be continued on Day 1, 8, 15 of each cycle as long as each of the following criteria are met:

- AST ≤ 5 x ULN
- Bilirubin < 27 μmol/L (1.6 mg/dL)

If any of the following criteria are met:

- AST > 5 x ULN and ≤ 10 x ULN
- Bilirubin 27-43 μmol/L (1.6-2.5 mg/dL)

then hold paclitaxel until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 65 mg/m^2. Dose may return to full dose (80 mg/m^2) in subsequent cycles. If paclitaxel is withheld for >1 cycle (4 weeks) the patient should not restart paclitaxel.

In the case of CTCAE grade 3 neuropathy, paclitaxel should be withheld and then resumed at 65 mg/m^2 on resolution to CTCAE grade 1 or less.

Paclitaxel should be permanently discontinued for the following non-haematological toxicities:

- Severe hypersensitivity reactions.
- CTCAE grade 3 or 4 neuropathy lasting more than 4 weeks.
- CTCAE grade 3 or 4 neuropathy recurring after dose reduction.
- AST and/or ALT CTCAE grade 3 or above (CTCAE grade 4 or above in case of liver metastases) lasting more than 7 days.
- Bilirubin CTCAE grade 3 or above.

Dose delays of paclitaxel as a consequence of non-haematological toxicities:

The treatment of a patient can be postponed for up to 4 weeks (one cycle) if the patient has not recovered to CTCAE grade 1 or less non-haematological toxicity at the beginning of cycle (day 1).

Dose reductions of paclitaxel as a consequence of non-haematological toxicities:

For non-haematological toxicities other than those mentioned above and excluding nausea, vomiting and asthenia:

- If CTCAE grade 3, patients should have a permanent dose reduction to 65 mg/m^2
- Patients who experience CTCAE grade 4 non-haematological toxicity may have their dose held for up to 4 weeks (one cycle) to permit recovery to CTCAE grade 3 or below followed by a permanent dose reduction to 65 mg/m^2

Hypersensitivity reactions:

Discontinue paclitaxel infusion for significant hypersensitivity reactions defined as:

- Hypotension requiring pressor therapy.
- Angiodema.
- Respiratory distress requiring bronchodilator therapy.
- Generalised urticaria.

For other hypersensitivity reactions, paclitaxel may be discontinued at the discretion of the investigator.

Any significant hypersensitivity reaction and any hypersensitivity reaction requiring treatment discontinuation should be reported as an AE or SAE.

The following management of hypersensitivity reactions is recommended or local standard practice:

- Administer cholorpheniramine 10 mg IV, or equivalent.
- Administer adrenaline (or its equivalent) sub-cutaneous every 15-20 minutes until the reaction subsides or a total of 6 doses given.
- If hypotension is present that does not respond to adrenaline, administer IV fluids.
- If wheezing is present that is not responsive to adrenaline, administration of nebulized salbutamol solution (or equivalent) is recommended.

Although corticosteroids have no effect on the initial reaction, they have been shown to block "late" allergic reactions to a variety of substances. Thus, methylprednisolone 125 mg IV (or its equivalent) may be administered to prevent recurrent or ongoing allergy manifestations.

Patients should not be re-challenged with paclitaxel in case of a severe hypersensitivity reaction. These patients should be discontinued from treatment with paclitaxel.

Table 5 Summary of guidance on the management of toxicity for olaparib or matching placebo and paclitaxel

Toxicity	Olaparib or matching placebo	Paclitaxel
Haematological toxicities		
Neutropenia ANC > 1 x 10^9/L and < 1.5 x 10^9/L	No action required.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at original dose. If withheld for > 28 days patient should not restart paclitaxel.

Toxicity	Olaparib or matching placebo	Paclitaxel
Neutropenia ANC ≤ 1 x 10^9/L	1st occurrence Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at original dose level. If symptoms do not recover to ≤ CTCAE grade 1, discontinue olaparib.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at original dose. If withheld for > 28 days patient should not restart paclitaxel.
	2nd occurrence Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at 1st reduced dose level. If symptoms do not recover to ≤ CTCAE grade 1, discontinue olaparib.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at original dose. If withheld for > 28 days patient should not restart paclitaxel.
	3rd occurrence Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at 1st reduced dose level. If symptoms do not recover to ≤CTCAE grade 1, discontinue olaparib.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at reduced dose of 65 mg/m^2. If withheld for >28 days patient should not restart paclitaxel.
	4th occurrence Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at 2nd reduced dose level. If symptoms do not recover to ≤CTCAE grade 1, discontinue olaparib.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at a dose of 65 mg/m^2. If withheld for >28 days patient should not restart paclitaxel.

Toxicity	Olaparib or matching placebo	Paclitaxel
Febrile neutropenia (temperature ≥ 38.5°C, ANC < 1.0 x 10^9/L), requiring hospitalisation and IV antibiotics	Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at original dose level. If symptoms do not recover to ≤ CTCAE grade 1, discontinue olaparib.	Permanent dose reduction to 65 mg/m^2.
Bleeding associated with platelet count of ≤ 40 x 10^9/L or any platelet count of ≤ 20 x 10^9/L	Withhold dose for up to 28 days until recovery to ≤CTCAE grade 1 then resume at original dose level. If symptoms do not recover to ≤CTCAE grade 1, discontinue olaparib.	Permanent dose reduction to 65 mg/m^2.
Platelets > 20 x 10^9/L and < 100 x10^9/L	No action required.	Reduce dose to 65 mg/m^2, may be re-escalated at next cycle.
Peripheral neuropathy		
CTCAE grade 2	No change	Start next course with dose reduced by 1 dose level (65 mg/m^2)
CTCAE grade 3	Withhold dose for up to 1 cycle (4 weeks) until recovery to ≤CTCAE grade 1 then dose reduce by 1 dose level. If symptoms do not recover, discontinue olaparib	Withhold paclitaxel for minimum of 1 cycle (4 weeks) until recovery to ≤CTCAE grade 1 then dose reduce subsequent cycles to 65 mg/m^2. If symptoms recur after dose reduction discontinue paclitaxel

Toxicity	Olaparib or matching placebo	Paclitaxel
Hepatotoxicity	Withhold dose for up to 1 cycle (4 weeks) until recovery to ≤CTCAE grade 1 then dose reduce by 1 dose level. If symptoms do not recover to ≤CTCAE grade 1, discontinue olaparib	Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 65 mg/m^2. Dose may return to full dose (80 mg/m^2) in subsequent cycles. If withheld for > 1 cycle (4 weeks) patient should not restart paclitaxel – AST > 5 x ULN and ≤ 10 x ULN – Bilirubin 27-43 μmol/L (1.6 – 2.5 mg/dL Stop paclitaxel – AST and/or ALT CTCAE grade 3 or above (CTCAE grade 4 or above in case of liver metastases) lasting more than 7 days – Bilirubin CTCAE grade 3 or above
Other non-haematological toxicities (excludes nausea, vomiting, asthenia) that are not listed above		
CTCAE grade 3	Withhold dose for up to 1 cycle (4 weeks) until recovery to ≤ CTCAE grade 1, reduce by 1 dose level	Permanent dose reduction to 65 mg/m^2
CTCAE grade 4	Withhold dose for up to 1 cycle (4 weeks) until recovery to ≤CTCAE grade 1, reduce by 1 dose level	Withhold dose for up to 1 cycle (4 weeks) until recovery to CTCAE grade 3 or below, permanent dose reduction to 65 mg/m^2
CTCAE grade 3 or 4 allergic reaction/hypersensitivity that is clearly attributable to paclitaxel	No change	Stop paclitaxel

5.5.5.4 Management of Toxicity (Monotherapy Only)

When olaparib or matching placebo is given as monotherapy (upon completion or discontinuation of paclitaxel), the dose will be increased to 200 mg orally bd. Treatment must be interrupted, with dose reductions as detailed in the Table 6.

Table 6 Dose reductions for olaparib or matching placebo (monotherapy)

Reduction	Dose Level
Initial Dose Level	200 mg bd
1st dose reduction due to NCI-CTCAE grade 3 or 4 treatment related SAE/AEs [a]	100 mg bd
2nd dose reduction due to NCI-CTCAE grade 3 or 4 treatment related SAE/AEs [a]	100 mg od
3rd Dose Reduction due to NCI-CTCAE grade 3 or 4 treatment related SAEs/AEs	No reduction allowed; withdraw patient

[a] Dose must not be re-escalated even if toxicities have resolved.

With the exception of the cases discussed above, the dose of olaparib or matching placebo must not be adjusted under any other circumstances unless AstraZeneca gives prior agreement.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

5.6 Concomitant and post-study treatment(s)

5.6.1 Olaparib 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 electronic Case Report Form (eCRF).

Olaparib is an investigational drug for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data, olaparib 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 three main metabolites of olaparib is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib. 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, idnavir, saquinavir, telithromycin, clarithromycin and nelfanvir

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

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

- Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil and St. John's Wort

For patients taking any of the above, the required wash-out periods prior to starting olaparib 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 basis.

5.6.2 Other Concomitant Medications

Any medications, with the exceptions noted in Section 5.6.5 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 eCRF.

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

Anticoagulant Therapy: Patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time (INR and 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 reason(s) for the use, doses and dates of treatment should be recorded in the patient’s medical records and appropriate section of the eCRF.

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.

5.6.3 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.

5.6.4 Administration of other anti-cancer agents

Patients must not receive any other 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 they were started at least 4 weeks prior to beginning study treatment.

5.6.5 Medications that may NOT be administered

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

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form.

5.7 Treatment compliance

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

Patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer olaparib or matching placebo. Compliance of the first dose and dose taken on the day of any study visit of olaparib or matching placebo will be assured by supervised administration by the investigator or delegate. Study site pharmacy staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the Investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of olaparib or matching placebo at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded on the eCRF.

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

5.7.1 Accountability

The study drug provided for this study is for use only as directed in the study 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.
- 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. Certificates of delivery and return should be signed.

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 eCRF. 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.

5.8 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse Event.
- Severe non-compliance to study protocol.
- Any CTC grade 3 or 4 events that have not reverted to CTC grade 1 or less within 4 weeks (28 days). See Section 5.5.5for management of dose modifications.
- Objective progression according to RECIST criteria.

  Note: Patients may continue to receive study treatment following objective progression provided that, in the opinion of the investigator, the patient is benefiting from the treatment and does not meet any other discontinuation criteria.

5.8.1 Procedures for discontinuation of a patient from investigational product

A patient that decides to discontinue investigational product will always be asked about the reason(s) for discontinuation and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (see sections 6.4.3 and 6.4.4), and remaining study drug or placebo should be returned by the patient.

Any patient discontinuing investigational product should be seen at 30 days post-discontinuation for the evaluations outlined in the study schedule. The patient's tumour status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment. After discontinuation of study medication, the principal Investigator/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 eCRF the date of discontinuation, the reasons, manifestation and treatment at the time of discontinuation. If patients discontinue study treatment, the AstraZeneca monitor must be informed immediately. Patients will be required to attend the treatment discontinuation visit. The patient should return all study medication (olaparib or placebo).

After discontinuation of the study medication at any point in the study, all ongoing AEs and 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 6.4.3 and 6.4.4). 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 6.4.4) and followed to resolution as above. Patients should be contacted at least 30 days after discontinuing study medication to collect and /or complete 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.

Any patient, who has not yet shown objective disease progression should continue to be followed as per RECIST v1.1 as detailed in Section 6.2.3.4.

All patients must be followed for survival, unless they withdraw consent.

If a patient is withdrawn from study, see Section 5.9.

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4), and study drug or placebo should be returned by the patient.

Reasons for withdrawal 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 i.e. the patient does not meet the required inclusion/exclusion criteria for the study.
- The patient becomes pregnant.
- Patient lost to follow-up.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The RAVE Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement.

6.2 Data collection and enrolment

6.2.1 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.

- Signed informed consent for the study; this will include an optional consent form for circulating biomarker research and a separate consent for pharmacogenetics research.
- Date of birth, race and ethnicity.
- Menopausal status; serum or urine pregnancy test for women of childbearing potential (within 28 days prior to study treatment start and a confirmatory test before treatment at visit 2).
- Confirmed ATM status from a formalin fixed paraffin embedded tumour tissue sample.

- Medical and surgical history.
- Current and concomitant medications including previous cancer therapies (if applicable).
- Physical examination; ECOG performance status, vital signs (blood pressure and pulse, body temperature), body weight and height.
- Haematology, clinical chemistry and urinalysis.
- Tumour assessment (scans of the abdomen/pelvis/other sites as clinically indicated for assessment of disease [CT/MRI]), performed within 28 days prior to randomisation.
- Adverse events must be captured from time of consent.

The assessments and procedures of ECG should be performed within 7 days prior to first dose of study treatment.

The Principal investigator/sub-investigator should adhere to the study plan, procedures and perform tests/observations in accordance with the protocol.

6.2.2 On trial assessments

Olaparib is self-administered by the patient twice daily as instructed continuously. The visit schedule is based on 28 days periods. Patients will attend the clinic on day 1 (1st day of treatment), 8, 15, 22, 29, 43, 50, 57 and every 28 days thereafter and the following assessments will be performed at time points specified in the study schedule (see Table 1and Table 2)

- Physical examination including ECOG performance status (day 1 of each 4 week period) and vital signs every visit.
- ECG on Day 57 only (i.e. +8 weeks from stating study treatment).
- Haematology, clinical chemistry and urinalysis (if clinically indicate).
- Serum or urine pregnancy test for women of childbearing potential (prior to treatment on day of first treatment).
- AE and concomitant medications (every visit).
- Tumour assessments via CT or MRI (every 8 weeks until Week 40, then every 16 weeks, relative to date of randomisation until objective disease progression).
- Completion of EORTC QLQ-C30 +-STO22 questionnaires (day 1 of each 4-week period)

- Blood sample for circulating biomarker analysis (optional).

- A pharmacogenetic sample will be obtained from consenting patients and stored for long-term experimental pharmacogenetic analysis (optional).

Patients will continue with olaparib or matching placebo until radiological objective disease progression by RECIST v1.1 or as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 5.8. Once patients on olaparib or matching placebo have been discontinued from treatment, other treatment options will be at the discretion of the investigator. No cross over to olaparib is permitted.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of the 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 will be evaluated until objective disease progression by RECIST, as per the study schedule (see Table 1and Table 2), and then followed for survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

The imaging modalities used for RECIST assessment will be CT or MRI scans of chest, abdomen and pelvis. Any other sites at which new disease is suspected should also be appropriately imaged. The radiological examinations performed in the conduct of this study should be retained at site as source data and be available for collection by the sponsor for centralised review.

6.2.2.1 Archival tumour tissue for biomarker analysis

ATM Status

Archival tumour tissue samples must be collected and analysed for ATM status during the screening period. An archival tumour tissue paraffin sample from the primary tumour or metastases should be provided according to the investigator laboratory manual. This sample will have been collected anytime since the time of original diagnosis. Samples will be analysed for ATM status via IHC. These samples must be sent to the central laboratory prior to randomization, to determine ATM status.

Exploratory analysis on tumour samples

Any residual material remaining after ATM status has been determined will be used to investigate expression of other HRD factors, such as but not limited to BRCA-1, MDC-1 and PARP.

Please refer to the investigator laboratory manual for further details of archival tissue collection, shipping and storage.

6.2.2.2 Blood sample for circulating biomarker (optional)

All consenting patients will supply plasma and serum samples for biomarker research ; Plasma for circulating tumour DNA, serum for defensive sample for future exploratory research. These blood samples (2 x 4 mL) will be taken pre-dose on Cycle 1 Day 1. For sample processing, handling and shipment see investigators Laboratory Manual. The analysis will be performed by AstraZeneca or an AstraZeneca approved laboratory.

6.2.2.3 Pharmacogenetic research sample (optional)

An optional pharmacogenetic sample (9 mL) will be obtained from consenting patients and stored for long-term pharmacogenetic analysis. The sample will be taken preferably after randomisation on Cycle 1 Day 1 or at a subsequent visit. Patients do not have to consent to this optional sample in order to participate in the study.

6.2.3 Follow-up procedures

6.2.3.1 Treatment discontinuation visit

Patients should be discontinued from study treatment if any discontinuation criteria are fulfilled (see Section 5.8). The assessments to be carried out at the visit are detailed in the study schedule (see Table 1and Table 2)

6.2.3.2 Final follow up visit

A final follow up visit should be conducted 30 days after the last dose of olaparib or matching placebo. 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 Sections 6.4.3, 6.4.4). 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 eCRF.

6.2.3.3 Survival visit

Assessments for survival should be made every 8 weeks following objective disease progression. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected. Survival data will be collected up to the time of the final PFS analysis and thereafter patients may continue to be followed for OS dependant on the PFS data.

In addition, patients should be contacted in the week following the data cut-off for the primary and final survival analyses to provide complete survival data.

6.2.3.4 CT or MRI scans (RECIST)

Subsequent tumour assessments according to RECIST should be performed at the end of every 8 weeks (±1 week) up to 40 weeks then every 16 weeks (±1 week) according to the

planned study schedule (see Table 1 and Table 2) 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.

6.3 Efficacy

This study will assess the efficacy of olaparib when given in combination with paclitaxel, compared with matching placebo + paclitaxel, in all patients with recurrent and metastatic gastric cancer who progress following first-line therapy, as well as in those who are ATM-negative, as assessed by PFS. Assessment of PFS will be made using RECIST v1.1 (section 6.3.2).

6.3.1 Efficacy variable

Please see Table 7 for efficacy variables by objective. :

Table 7 Efficacy and Variables

Objective	Variable
Primary	
To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by progression-free survival (PFS), in all patients with recurrent and metastatic gastric cancer who progress following first-line therapy.	Progression-free survival
To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by progression-free survival (PFS) in patients with recurrent and metastatic gastric cancer whose tumours are defined as homologous recombination deficient (HRD) by way of loss of expression of ATM protein ("ATM-negative patients") who progress following first-line therapy.	Progression-free survival
Secondary	
To determine the safety and tolerability of olaparib (AZD2281) when given in combination with paclitaxel in patients with recurrent and metastatic gastric cancer who progress following first-line therapy.	Frequency and severity of AEs and SAEs
To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by overall survival (OS), response rate (RR) and percentage change in tumour size at Week 8, in all patients with recurrent and metastatic gastric cancer who progress following first-line therapy.	Overall survival Response rate Percentage change tumour size at Week 8

Objective	Variable
To assess the efficacy of olaparib when given in combination with paclitaxel compared with paclitaxel alone as defined by overall survival (OS), response rate (RR) and percentage change in tumour size at Week 8 in ATM-negative patients with recurrent and metastatic gastric cancer who progress following first-line therapy.	Overall survival Response rate Percentage change tumour size at Week 8
To conduct a preliminary assessment of the effects of olaparib when given in combination with paclitaxel on the time of deterioration of disease related symptom and health relate quality of life (HRQoL) as assessed by the EORTC QLQ-C30 + -STO22 questionnaires.	STODYS (dysphagia), STOEAT (eating restriction), STOPAIN (stomach pain), STOFX (reflux), STOANX (anxiety) sub-scales Global QoL sub-scale

6.3.2 Tumour Evaluation

RECIST 1.1 criteria will be used to assess patient response to treatment by determining progression-free survival (PFS), overall survival (OS), objective response rates (ORR), and percentage change in tumour size at Week 8. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) are presented in Appendix D.

The methods of assessment of tumour burden used at baseline, CT or MRI scans of chest, abdomen and pelvis must be used at each subsequent follow-up assessment.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments every 8 weeks relative to date of randomisation, until week 40, at which time assessments will be carried out every 16 weeks until objective disease progression as defined by RECIST v1.1. See Study Schedule (Table 1and Table 2) for further details.

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression as defined by RECIST v1.1.

Categorisation of objective tumour response assessment will be based on the RECIST v1.1 criteria of response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

For patients with non-measurable disease only at baseline, categorisation of objective tumour response assessment will be based on the RECIST v1.1 criteria of response: CR (complete response), PD (progression of disease) and Non CR/Non PD.

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTL (non-target lesion) 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 repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

Following progression, patients should continue to be followed up for survival weeks as outlined in the Study Schedule (see Table 1and Table 2).

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in section 3.1 and CT/MRI scans in section 6.2.3.4.

6.4 Safety

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

6.4.1 Definition of adverse events

An adverse event 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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). 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.

For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected.

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

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e. screening, 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.
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

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

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse Events will be collected from time of signed informed consent throughout the treatment period and up to and including the 30-day follow-up period.

SAEs will be recorded from the time of informed consent.

No AE data will be collected during the pre-screening process.

Follow-up of unresolved adverse events

Any AEs/SAEs that are unresolved at the patient's last AE assessment (i.e. 30-day follow up visit) in the study are followed up by the investigator for as long as medically indicated (see section 5.8.1). 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.

Post Follow-up adverse events

After study treatment completion (i.e. after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow up period (30 days). If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify AstraZeneca, Patient Safety.

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and / or post study completion then as a minimum all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe (section 6.4.4).

Variables

The following variables will be collect for each AE:

- AE (verbatim).

- The date when the AE started and stopped.
- The NCI CTCAE grade and any grade changes
- Whether the AE is serious or not.
- Investigator causality rating against the olaparib/placebo (yes/no), paclitaxel (yes/no) and study procedures/other medications (yes/no).
- Action taken with regard to olaparib/placebo and/or paclitaxel.
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE.
- Date investigator became aware of serious AE.
- Reason that AE is serious ("due to").
- Date of hospitalisation.
- Date of discharge.
- Probable cause of death.
- Date of death.
- Autopsy performed.
- Description of AE.

Severity of AE

The grading scales found in the revised National Cancer Institute (NCI) CTCAE version 3.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation is the CTCAE criteria that convert mild, moderate and severe events into CTCAE grades should be used

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

For each episode, all changes to the CTCAE grade attained should be reported.

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 6.4.2. 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.

Causality collection

The investigator will assess causal relationship between Investigational Product and each Adverse Event, 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/placebo/combination drug?"

Causal relationship will also be assessed for other medication and study procedures. Note that for AEs 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.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient 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 eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to the 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.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product, placebo and combination drug.

If deterioration in a laboratory value/vital sign/ECG is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign/ECG will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

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.

Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product(s) is being studied. It may be an increase in the severity of the disease under study and/or an increase in the symptoms of the disease. 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 be considered as disease progression and not as an AE. Any events that are unequivocally due to disease progression should not be reported as an AE during the study.

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 6.4.2). 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.

Lack of efficacy

When there is deterioration in the condition for which the study treatment(s) is being used (recurrent and metastatic gastric cancer) 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.

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:

- 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 eCRF 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 6.4.4 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 of eCRF'.

- 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 within the usual timeframes.

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives within one day i.e. 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 the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigator(s) or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e. immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site personnel how to proceed.

6.4.5 Laboratory safety assessment

Blood samples for determination of clinical chemistry, haematology and coagulation will be taken at the times indicated in the Study Schedule (see Table 1 and Table 2).

The following laboratory variables will be measured:

Full haematology assessments for safety (haemoglobin, red blood cells [RBC], platelets, mean corpuscular volume [MCV], mean corpuscular haemoglobin concentration [MCHC], mean corpuscular haemoglobin [MCH], white blood cells [WBC], differential white cell count and absolute neutrophil count) should be performed at each visit and when clinically indicated. Coagulation (activated partial thromboblastin time [APTT] and international normalised ratio

[INR]) will be performed at baseline and if clinically indicated unless the patient is receiving warfarin.

Biochemistry assessments for safety (sodium, potassium, calcium, magnesium, glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, albumin, lactic dehydrogenase [LDH]) amylase and lipase will be performed.

Urinalysis should be performed at screening and if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required.

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

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

For blood volumes see Section 7.1

6.4.6 Physical examination

For timing of individual measurements refer to the Study Schedule (see Table 1and Table 2).

A complete physical examinations will be performed including an assessment of the following:

Height (screening only), BP, pulse, and temperature at the screening visit and as outlined in the study schedule. Weight will be measured according to the study schedule.

Performance status will be assessed using the ECOG scale (see Appendix F) at screening and as outlined in the study schedule. The same observer should assess performance status each time.

6.4.7 ECG

6.4.7.1 Resting 12-lead ECG

ECGs are required within 7 days prior to starting study treatment, at 8 weeks after starting study treatment and at the follow up visit after patient has discontinued study medication and when clinically indicated.

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 eCRF. ECGs are required within 7 days prior to starting study treatment, at 8 weeks after starting study treatment and at the final follow up visit and when clinically indicated. A copy of the ECG indicating the study number and E-code will be included in the study file.

6.4.8 Vital signs

6.4.8.1 Pulse and blood pressure

Supine BP and pulse rate will be measured using a semi-automatic BP recording device with an appropriate cuff size, after patient has rested for at least 10 minutes. For the timing of assessments refer to the Study Schedule (see Table 1 and Table 2)

The date and time of collection and measurement will be recorded on the appropriate eCRF.

6.4.9 Other Safety Assessments

6.4.9.1 Serum or urine pregnancy test

Two pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential one within 28 days prior to the start of study treatment and the other on Day 1 of the study prior to commencing treatment. 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.

6.5 Patient reported outcomes (PRO)

6.5.1 European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 + -STO22 Questionnaires

Health related QoL is important in gastric cancer because most patients are symptomatic when diagnosed and the disease is usually incurable. Patients who survived gastric cancer surgery may continue to suffer from symptomatic, nutritional or functional problems. Even when treatment improves overall or progression-free survival this benefit can be counterbalanced by the burden of treatment and or its potential effect on patients' HRQoL (Ajani et al 2007).

In this study patient-reported disease related symptoms and health-related quality of life (HRQoL) will be evaluated using the validated EORTC QLQ-C30 + -STO22 questionnaires. The questionnaire has been developed to assess HRQoL (Aaronson et al 1993) and is the most commonly used cancer-specific tool in oncology (Garret et al 2002). It has undergone extensive testing and validation as well as detailed cross-cultural testing and validation (Aaronson et al 1993) and has been used in gastric cancer trials (Ajani et al 2007).

The EORTC QLQ-C30 comprises 30 questions designed for all cancer types. Questions can be grouped into 5 multi-item functional scales (physical, role, emotional, cognitive and social); 3 multi-item symptom scales (fatigue, pain, nausea and vomiting); a 2-item global

QoL scale; 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea) and 1 item on the financial impact of the disease.

The -STO22 is a well-validated module developed specifically for patients with gastric cancer (Vickery et al 2001, Blazeby et al 2004) and has also been validated for use in Asian patients (Huang et al 2007, Morita et al 2008). It consists of 22 questions which can be grouped into 5 disease related multi-item symptom scales (dysphagia, eating restriction, stomach pain, reflux, anxiety) and 4 single items (dry mouth, body image, hair loss, taste problem).

Time to deterioration of disease related symptoms scales and global QoL scale will be investigated. For further information see section 11.1.2.

6.5.2 Administration of PRO questionnaires

Each centre must allocate the responsibility for the administration of the PRO questionnaires to a specific individual (eg, a research nurse, study coordinator) and if possible assign a back-up to cover holidays. Relevant training in administration of the questionnaires will be provided. The paper PRO questionnaires should be administered and completed in the clinic as described in this section and per the study plan.

It is important that the significance and relevance of the data are explained carefully to participating patients so that they are motivated to comply with data collection (Fallowfield et al 1987)

The instructions for completion of the PRO are as follows:

- It must be completed prior to any other study procedures (following informed consent) and before discussion of patient progress to avoid biasing the responses to the questions
- It must be completed in private by the patient
- The patient should be given sufficient time to complete at their own speed
- The patient should not receive help from relatives, friends or clinic staff to answer the questionnaire. However, if the patient is unable to read the questionnaire (eg, is blind or illiterate) the questionnaire may be read out by trained clinic staff and responses recorded
- On completion of the questionnaire it should be handed back to the person responsible for PROs who should check for completeness
- Only 1 answer should be recorded for each question.
- Data from the questionnaire will be transcribed at site to the eCRF.

Details of non-compliance with questionnaire completion will be captured in the eCRF.

6.6 Pharmacogenetics (optional)

6.6.1 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from the patients at Visit 2 after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may discontinue investigational product due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 8 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples [a]	Total volume (mL)
Safety	Clinical chemistry	6[b]	10[c]	60
	Haematology	10[b]	10[c]	100
Pharmacogenetics (optional)		9	1	9
Circulating biomarker sample (optional)		4	2	8
Total		29	23	177

[a] Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments.
[b] These are approximate volumes that are subject to site-specific change.
[c] Number of samples is based on patients on average completing 4 cycles of combination therapy.

No more than 29mL of blood will be taken at any individual visit for a patient.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

Biological samples for future research can be retained at R&D site/CRO, on behalf of AstraZeneca for a maximum of 25 years following the Last Patient's Last Visit in the study. The results from future analysis will not be reported in the Clinical Study Report but separately in a Scientific Report or Scientific Publication.

7.2.1 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 25 years, from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

7.3 Labelling and shipment of biohazard samples

The Principal investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual, see Appendix C 'IATA 6.2 Guidance Document'.

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

7.4 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 traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

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

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

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

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 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 ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

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.

AstraZeneca 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

8.3 Institutional Review Board (IRB) and regulatory review

An IRB should approve the final study protocol, including the final version of the Informed Consent Form(s) including optional biomarker and /or pharmacogenetic sample consents and any other written information and/or materials to be provided to the patients.

The investigator will ensure the distribution of these documents to the applicable IRB and to the study site staff.

The opinion of the IRB should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The IRB should approve all advertising used to recruit patients for the study.

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

If required by local regulations, the protocol should be re-approved by the IRB 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.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, IRBs and Principal investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the 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 so that he/she can meet these reporting requirements.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Include information on any optional biomarker or pharmacogenetic sampling.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent Form(s) is/are stored in the investigator's Study File.
- Ensure a copy of the signed Informed Consent Form is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB.

Once the number of ATM positive patients, as described in this protocol, have been recruited, then only ATM negative patients may be entered in the remaining part of the study. To avoid patients, who are ATM positive, undergoing unnecessary screening assessments investigators will be able to pre-screen for ATM status. Investigators must obtain a signed and dated pre-screening consent form prior to assessing potential patients for their ATM status in order to pre-screen for ATM status.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the National 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 and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment should be approved by each IRB and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal investigator(s). For distribution to IRB see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's IRB should 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 IRB.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an IRB 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, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 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.
- Determine availability of appropriate patients for the study.
- 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.

9.2 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 (i.e. IVRS) and the WBDC system utilised.

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).

9.3 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 eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that investigational product accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., 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 of/destroyed 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.

9.3.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.4 Study agreements

The Principal investigator at each centre should 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 terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

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

9.4.1 Archiving of study documents

The investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.5 Study timetable and end of study

The end of this study is defined as the date when all patients receiving olaparib or placebo have been followed for a minimum period of 6 months since start of treatment or the date of the final analysis of the data, whichever is the later. At this time point, the clinical study database will close to new data. Patients are however permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the investigator, they are continuing to receive benefit from treatment with olaparib.

[redacted]

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 olaparib or if results from any other study with olaparib adversely affect the risk/benefit profile of the investigational product.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by Cognizant.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by Cognizant.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

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

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

Patients will undergo regular tumour assessments until documented objective disease progression as defined by RECIST v1.1. (see Appendix D).

At each visit patients will be programmatically assigned a RECIST visit response of CR, PR, SD or PD depending on the status of their disease compared to baseline and previous assessments.

If a patient has had a tumour assessment, which cannot be evaluated, then the patients will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

For TL measurements, if ≤ 1/3 of the TL sizes are missing then a scaling up rule will be applied as follows:

- 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 (this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the baseline sum of diameters excluding the lesions that are missing and determining at what rate the lesions are changing)

- If > 1/3 of lesions recorded at baseline are missing then the target lesion response will be NE. However, if the sum of non-missing target lesion diameters would result in PD (i.e. if using a value of 0 for missing lesions the sum of diameters has still increased by > 20% or more compared to the smallest sum of diameters on study and has an absolute increase ≥ 5mm PD takes precedence over NE

- A visit response of CR will not be allowed if any of the TL data is missing

11.1.1 Primary Endpoint

Progression-free survival (PFS)

PFS is defined as the time from the date of randomisation until objective disease progression as defined by RECIST v1.1 or death (by any cause in the absence of progression).

Patients who have not progressed or died at the time of the statistical analysis will be censored at the time of their last evaluable RECIST assessment. If a patient has no RECIST follow up assessments or has no evaluable baseline assessment and is still alive at the time of the analysis then they will be censored at 0 days for PFS.

If a patient discontinues treatment prior to progression and/or receives a subsequent therapy prior to progression then these patients will continue to be followed until evidence of

objective disease progression as defined by RECIST v1.1 and their PFS time will be derived as defined above.

11.1.2 Secondary Endpoints

Overall survival

Overall survival is defined as the time from the date of randomisation until death by any cause.

Patients who have not died at the time of the statistical analysis will be censored at the time they were last known to be alive.

Objective response rate (ORR)

ORR is defined as the percentage of patients who have at least one visit response of CR or PR prior to any evidence of progression (as defined by RECIST v1.1).

A visit response of CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be <10mm to be considered non-pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions.

An 'evaluable-for-response' population will be derived for the analysis of ORR and will exclude patients who do not have measurable disease at entry.

Percentage change in tumour size at Week 8

The tumour size is the sum of the longest diameters of the target lesions. The percentage change in tumour size at Week 8 will be assessed using the ratio of the Week 8 tumour size over the baseline tumour size for each patient.

Data handling rules and methods for missing data and other scenarios will be fully described in the SAP.

An 'evaluable-for-response' population will be derived for the analysis of percentage change in tumour size at Week 8 and will exclude patients who do not have measurable disease at entry.

Patient reported outcome

The EORTC QLQ-C30 + -STO22 will be scored according to the EORTC scoring manual, (Fayers et al 1995). Each scale will be transformed to a 100 point scale as per the manual.

For each of the symptom and QoL scales, a change in scores from baseline of at least 10 points can be considered as a clinically relevant or a minimally important difference (Osoba et al 2005). A visit response will be calculated for each subscale Table 9.

Table 9 Visit Response

Subscale	Change from baseline	Visit Response
STODYS (dysphagia), STOEAT (eating restriction), STOPAIN (stomach pain), STOFX (reflux), STOANX (anxiety). Global QoL	≥ +10	Improved
	≤ -10	Deterioration
	Otherwise	No change

Overall deterioration or improvement must be sustained for at least 21 days. At the conclusion of the trial, the following criteria will be used to assign a best overall response to treatment based on the individual visit responses (Table 10).

Table 10 Overall Response to Treatment

Overall score response	Criteria
Improved	Two visit responses of "improved" a minimum of 21 days apart without an intervening visit response of "deterioration".
No change	Does not qualify for overall score response of "improved". Two visit responses of either "no change" or "improved" and "no change" a minimum of 21 days apart without an intervening visit response of "deterioration".
Deterioration	Does not qualify for overall score response of "improved". A visit response of "deterioration" without a response of "improved" or "no change" within 21 days.
Other	Does not quality for one of the above.

Time to deterioration of STODYS (dysphagia), STOEAT (eating restriction), STOPAIN (stomach pain), STOFX (reflux), STOANX (anxiety) and Global QoL will be calculated.

For each subscale, if less than 50% of the subscale items are missing, the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscale (Fayers et al 1995). If at least 50% of the items are missing, that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded.

11.1.3 Additional endpoints to be summarized

The following endpoints will not be formally analysed but will be summarised.

Best Objective Response

In summaries of Best Objective Response, for the case of SD, follow up assessments must have met the SD criteria for a minimum interval of 6 weeks following date of randomisation.

[redacted]

Duration of response

Duration of response is defined as the date of first documentation of response (CR/PR) until the date of disease progression as defined by RECIST v1.1 or death (by any cause in the absence of disease progression).

11.2 Calculation or derivation of safety variable(s)

11.2.1 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 DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these may be 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. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

All Efficacy data will be analysed on an intention-to-treat (ITT) basis using randomised treatment, except for ORR and Change in tumour Size, which will be analysed using an 'evaluable-for-response' population (a sub-population of the ITT) that will exclude patients who do not have measurable disease at entry.

12.1.2 Safety analysis set

Safety data will not be formally analysed. All patients who received at least one dose of olaparib or matching placebo and for whom any post-dose data are available will be included in the safety population. Throughout the safety results sections, erroneously treated patients (e.g., those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set. This is a subset of the FAS, which includes all patients who received at least one dose of study medication. Treatment group comparisons will be based on the initial dose of study treatment actually received. If a patient discontinues study medication and starts another anti-cancer therapy, all subsequent safety data for that patient after the 30 day follow up period will be excluded from the assessment of safety.

12.2 Methods of statistical analyses

A comprehensive statistical analysis plan (SAP) will be prepared before unblinding of the data.

RECIST will be used to assess tumours at Screening, week 8, week 16 and then every 8 weeks relative to date of randomisation, until Week 40, at which time assessments will be carried out every 16 weeks until disease progression, death, or withdrawal from consent.

The outcome variable to be analysed will be the objectively programmed assessment of response (based on the investigational site assessment and programmatically defined using the in-house algorithm) and not the investigators overall opinion, which will also be captured on eCRF. Any differences between the two will be highlighted and discussed in the clinical study report.

The co-primary objectives of this study will be to assess the efficacy of olaparib in combination with paclitaxel, compared with paclitaxel alone in 1) patients with recurrent and metastatic gastric cancer who progress following first-line therapy (overall population) and 2) patients with recurrent and metastatic gastric cancer whose tumours are defined as homologous recombination deficient (HRD) by way of loss of expression of ATM protein ("ATM-negative patients") who progress following first-line therapy, by assessing PFS.

The secondary objectives of this study will be to assess the efficacy of olaparib in combination with paclitaxel, compared with paclitaxel alone in the 1) overall population and 2) ATM-negative population, by assessing ORR, OS and percentage change in tumour size at Week 8.

It is assumed that patients who are ATM-negative will show a greater response to olaparib than patients who are ATM-positive. As the prevalence of ATM-negative patients is assumed to be approximately 25% of the overall population (AstraZeneca, unpublished) and this study population will have a 50% prevalence, analyses of endpoints in the overall population will be calculated using weighted estimates of the ATM-negative and ATM-positive patients. Weights w_1 and w_2 (proportion of ATM-negative patients and ATM-positive patients respectively) will be estimated from the screening records (up until the ATM-positive group is closed to recruitment). For calculation of Confidence Intervals, the variance will take into account the variance of both groups.

No adjustments for multiplicity have been made in sizing the study but this will be taken into account when interpreting the data.

Confidence intervals for the treatment effects will be critical in interpretation of results from this trial. Results of secondary outcome variables need to be broadly consistent with primary outcomes.

12.2.1 Progression-free Survival

12.2.1.1 PFS in the overall population

To achieve an estimated HR that is representative of the overall population, a weighted estimate of the overall HR ('$HR_{overall}$') will be calculated using the estimated HR in the ATM-negative population ('$HR_{ATM\ negative}$') and the estimated HR in the ATM-positive population ('$HR_{ATM\ positive}$'):

$$ln(HR_{overall}) = w_1 ln(HR_{ATM\ negative}) + w_2 ln(HR_{ATM\ positive})$$

where weights w_1 and w_2 (proportion of ATM-negative patients and ATM-positive patients respectively) will be estimated from the screening records (up until the ATM-positive group is closed to recruitment).

For calculation of Confidence Intervals, the overall variance (log scale) will take into account the variance of both groups (that are independent), and thus be calculated as:

$$var(ln(HR_{overall})) = w_1^2 var(ln(HR_{ATM\ negative})) + w_2^2 var(ln(HR_{ATM\ positive}))$$

PFS will be analysed in the ATM-positive population using a Cox proportional hazards model, using the same methodology as described below for the ATM-negative population.

The overall hazard ratio (HR; olaparib in combination with paclitaxel: matching placebo in combination with paclitaxel) for treatment will be estimated together with its 80% confidence interval and one-sided p-value (a HR less than 1 will favour olaparib in combination with paclitaxel). A Kaplan-Meier plot of PFS and estimates of median PFS will be presented by treatment group and ATM subgroup.

12.2.1.2 PFS in the ATM-negative population

PFS will be analysed using a Cox proportional hazards model. The model will allow for the effect of treatment and will include terms for gastrectomy (full, partial, none). The model will include these effects regardless of whether the inclusion of effects significantly improves the fit of the model.

The model will be fitted using PROC PHREG (in SAS Version 8.1) with the EFRON method to control for ties.

The hazard ratio (HR; olaparib in combination with paclitaxel: matching placebo in combination with paclitaxel) for treatment will be estimated together with its 80% confidence interval and one-sided p-value (a HR less than 1 will favour olaparib in combination with paclitaxel). A Kaplan-Meier plot of PFS and estimates of median PFS will be presented by treatment group.

The assumption of proportionality will be assessed using plots of complementary log-log event times versus log time. If the assumptions of proportional hazards are shown not to hold

for some of the baseline covariates then this will be explored but no action will be taken in the model fitting.

If there is a substantial departure in the proportional hazards assumption for treatment then the nature of non-proportionality will be explored and reported in the Clinical Study Report with the findings from the model. This information will be then used to aid the planning of the future direction of the olaparib program.

12.2.2 Overall Survival

The methodology for analysing OS in the overall population and ATM-negative population will be the same as that described for the analyses of PFS in Section 12.2.1.

Whilst OS will initially be assessed at the time of the primary analysis of PFS, a further survival analysis may be performed when approximately 90 deaths have occurred, depending on the PFS results.

No adjustment for multiplicity will be made in the overall survival analyses.

12.2.3 Objective Response Rate

12.2.3.1 ORR in the overall population

A log odds ratio for the overall population will be derived using a weighted estimate of the log odds ratio in the ATM-negative population and log odds ratio in the ATM-positive population.

ORR will be analysed in the ATM-positive population using the same methodology as described below for the ATM-negative population.

12.2.3.2 ORR in the ATM-negative population

The ORR will be compared between olaparib in combination with paclitaxel vs. paclitaxel alone using a multivariate logistic regression model and using the same covariates as used in the PFS analyses, provided there are enough responses for a meaningful analysis. The results of the analysis will be presented in terms of an odds ratio together with its associated 80% confidence interval and one-sided p-value.

The variable used in the analysis will be the objective programmed assessment of response and not the investigators overall opinion. Any differences between the two will be highlighted and discussed in the CSR.

12.2.4 Percentage change in tumour size at Week 8

Before any analyses are carried out, the distribution of the percentage change in tumour size data will be looked at and if necessary, an appropriate transformation or non-parametric technique will be used.

12.2.4.1 Percentage change in tumour size at Week 8 in the overall population

Assuming no transformation, the effect of olaparib in combination with paclitaxel on percentage changes in tumour size will be estimated from an analysis of covariance (ANCOVA) model including terms for treatment (olaparib in combination with paclitaxel or matching placebo in combination with paclitaxel) as well as a covariate for baseline tumour size, a covariate for the treatment*ATM interaction and the same covariates as used in the PFS analyses. The percentage change in tumour size at Week 8 in the overall population will be estimated from a single model by including a treatment * mutation interaction and weighting the parameter estimates accordingly. An estimate of the treatment effect (difference1; olaparib in combination with paclitaxel minus matching placebo in combination with paclitaxel) will be calculated together with its 2-sided 80% confidence interval.

Assumptions will be explored to validate the results of the main analysis.

Frequencies of non-target lesion progressions and new lesions at Week 8 will be presented together with the change in tumour size at 8 weeks results in order to put the change in tumour size results in perspective.

12.2.4.2 Percentage change in tumour size at Week 8 in the ATM-negative population

Assuming no transformation, the effect of olaparib in combination with paclitaxel on percentage changes in tumour size will be estimated from an analysis of covariance (ANCOVA) model including terms for treatment (olaparib in combination with paclitacel or matching placebo in combination with paclitaxel) as well as a covariate for baseline tumour size and the same covariates as used in the PFS analyses. The results of the analysis will be presented in terms of adjusted means (least square means [lsmeans]) for each treatment, together with their two-sided 80% confidence intervals. An estimate of the treatment effect (difference of the lsmeans; olaparib in combination with paclitaxel minus matching placebo in combination with paclitaxel) will be calculated together with its two-sided 80% confidence interval.

Assumptions will be explored to validate the results of the main analysis.

Frequencies of non-target lesion progressions and new lesions at Week 8 will be presented together with the percentage change in tumour size at Week 8 results in order to put the change in tumour size results in perspective.

12.2.5 Health Related Quality of Life

Numerical (standardised) score data for the 2-item global QoL scale and the 5 disease related multi-item symptom subscales (dysphagia, eating restriction, stomach pain, reflux, anxiety) will be summarised and descriptive statistics (mean, median, SD, minimum, maximum) will be calculated by visit and the mean change from baseline over time presented graphically by treatment group.

Time to deterioration of Global QoL (the 2-item global QoL scale), and each of the 5 disease related multi-item symptom subscales (dysphagia, eating restriction, stomach pain, reflux,

anxiety) will be summarised and presented by treatment group. Patients who have not deteriorated at the time of analysis will be censored at the time of their last evaluable assessment relating to the outcome variable in question. Kaplan Meier plots of Time to deterioration by treatment group will be presented for each of the six endpoints.

12.2.6 Summaries of additional endpoints

No formal statistical analyses of BOR or DoR will be performed.

Summaries of BOR by ATM status and treatment arm will be produced.

Descriptive data will be provided for the DoR in responding patients by ATM status and treatment arm will be produced, including the associated Kaplan Meier curves (without any formal comparison or p-value attached).

12.2.7 Safety evaluation

No formal statistical analyses will be carried out on the safety data. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

12.2.8 Interim analyses

Analyses of the secondary outcome variable OS will be performed at the time of the analyses of the primary outcome variable PFS. A further analysis may be performed when approximately 90 deaths have occurred. No adjustment for multiplicity will be made in the OS analyses, however it will be taken into account when interpreting the data.

12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

This trial is designed with two co-primary analysis populations: the first will comprise all patients; the second will comprise those patients in the ATM-negative subgroup as it is expected that patients who are ATM-negative, assumed to be approximately 25% of total population (AstraZeneca, unpublished), will show a greater response to AZD2281 in combination with paclitaxel compared with paclitaxel alone than patients who are ATM-positive.

This trial is designed as a randomised screening trial to quantify the level of risk entailed for further development. Thus the Type I and Type II error have been adjusted to be less constrained, so that the targeted treatment benefit may be appropriate while the sample size remains reasonable (Rubinstein et al 2005). The trial is of sufficient size to show that if olaparib in combination with paclitaxel is truly active, there is a high probability that it will demonstrate an effect sufficiently promising that it would warrant a follow up assessment in PIII.

The primary endpoint will be PFS for both co-primary analysis populations and the PFS analyses will be performed when approximately 104 progression events have occurred (and approximately 50 events in the HRD-selected population). If the true HR is 0.55 (likely to correspond to an 80% prolongation of PFS) in the ATM-negative population, this analysis will have approximately 80% power to demonstrate a statistically significant difference for PFS, assuming a 10% one-sided significance level. Assuming a true prevalence of 25% for the ATM-negative group, if the true HR in the ATM-positive group is 0.65, then this study will have 80% power to detect a weighted overall HR of 0.62 (likely to correspond to a 61% prolongation of PFS), assuming a 10% one-sided significance level.

This trial has been sized using one-sided 10% significance levels as it is a Phase II study looking for a signal of improved efficacy. If a one-sided $p<0.1$ is observed for the comparison of PFS between the olaparib + paclitaxel vs. paclitaxel alone in either of the co-primary populations, the results will be regarded as promising (but not definitive) in the relevant population as there is less than 1 in 5 probability that such a result could have been detected if there was truly no treatment effect.

Assuming 50 events in the HRD selected population occur, an observed HR of < 0.69 will achieve a one-sided p-value <0.1 within the trial. Similarly, assuming 104 events overall and a 25% prevalence of ATM-negative (to be assessed from screening log), an observed weighted HR of <0.75 will achieve a p-value of <0.1 within the trial.

Assuming non-uniform recruitment and a median PFS of 3 months (Emi et al 2008) in the control group, if approximately 120 patients (60 per arm) are recruited over 15 months it is expected that 104 events will occur approximately 6 months following recruitment of the last patient.

Patients will continue to be followed for survival. Whilst overall survival will initially be assessed at the time of the primary analysis of PFS, a further survival analysis may be performed when approximately 90 deaths have occurred, depending on the PFS results.

No adjustments will be made for multiplicity in sizing the study, however it will be taken into account when interpreting the data.

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

12.4 Data monitoring committee

No formal data monitoring committee will be set up during this Phase II study.

AstraZeneca will routinely monitor the safety data, and if any emerging clinically important events related to olaparib are identified then investigators will be informed in accordance with ICH guidelines.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal investigator 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 6.4.4**

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 AstraZeneca Research and Development site shown below.

[redacted]

13.2 Overdose

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

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, i.e. 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 AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study olaparib or matching placebo should be discontinued immediately.

The outcome of any conception occurring from the date of the first dose until three months after the last dose should be followed up and documented.

Pregnancy itself is not regarded as an adverse event 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, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was withdrawn from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel must inform appropriate AstraZeneca representatives **within one day** i.e. 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 AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies

The same timelines apply when outcome information is available.

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

13.3.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for three months following the last dose.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until three months after the last dose should be followed up and documented.

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Clinical Study Protocol Appendix B

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00039
[redacted]	

Appendix B
Additional Safety Information

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

Outpatient 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.

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.

Clinical Study Protocol Appendix C

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00039
[redacted]	

Appendix C
International Airline Transportation Association (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. Category 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. Category 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 Category 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.

AstraZeneca

Clinical Study Protocol Appendix D

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00039
[redacted]	

Appendix D
Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

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LIST OF TABLES

1. INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D0810C00039 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

Patients with at least one lesion (measurable and/or non-measurable) that can be accurately assessed by imaging (CT/MRI) at baseline and follow up visits should be included in this study.

Measurable: A lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Non-measurable: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline*).

Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.

Previously irradiated lesions**

Skin lesions assessed by clinical examination

Brain metastasis

* Nodes with <10mm short axis are considered non-pathological and should not be recorded or followed as NTL.

**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.

Special Cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions.

Target lesions: A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline.

Non-Target lesions: All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

3. METHODS OF ASSESSMENT

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

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	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest x-ray	X-ray, Chest x-ray
		Ultrasound
		Bone Scan

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 identification of any new lesions.

In the D0810C00039 study it is recommended that CT examinations of the chest, abdomen and pelvis will be used to assess tumour burden at baseline and follow-up visits. 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 D0810C00039 study, clinical examination will not be used for assessment of 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.

3.3 X-ray

3.3.1 Chest X-ray

In the D0810C00039 study, chest x-ray assessment will not be used for assessment of 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 D0810C00039 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 D0810C00039 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

In the D0810C00039 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

3.6 Tumour markers

In the D0810C00039 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

3.7 Cytology and histology

In the D0810C00039 study histology will not be used as part of the tumour response assessment as per RECIST 1.1.

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 (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline 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.

In the D0810C00039 study isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

3.9 FDG-PET scan

In the D0810C00039 study FDG-PET scans will not be used for assessment of tumour response as FDG-PET evaluations do not form part of the RECIST framework.

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days (see Study Schedule from Study Protocol) before the date of randomization. Follow-up assessments will be performed every 8 weeks (+/- 1 week) after randomisation, up to week 40, then every 16 weeks (+/- 1 week) (see Study Schedule from Study Protocol) until objective disease progression as defined by RECIST v1.1. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. 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 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- 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.

Table 2 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
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 diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response

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 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 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL
Progression (PD)	Unequivocal progression of existing non-target lesions. 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.

Table 3 Evaluation of Non-Target Lesions

Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

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.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

4.6 Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 4.

[redacted]

Table 4 Overall Visit Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/Non PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if three are no TL/NTLs at baseline).

5. CONFIRMATION OF RESPONSE

In the D0810C00039 study, imaging for confirmation of response (CR or PR) should be performed at the next scheduled RECIST assessment.

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 chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. **Anatomic coverage:** Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of

imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. **IV contrast administration**: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

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.

c. Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

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 has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be

measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

7. REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247

Clinical Study Protocol Appendix E

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00039
[redacted]	

Appendix E
Acceptable Birth Control Methods

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.

Appendix F
Example of Performance Status (ECOG/Karnofsky Scale)

EXAMPLE OF PERFORMANCE STATUS (ECOG/KARNOFSKY SCALE)

Table 1 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 ie, 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.

Clinical Study Protocol: Appendix G

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00039

[redacted]

Appendix G
Pharmacogenetics Research

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
LIMS	Laboratory information management system
PGx	Pharmacogenetics

1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the olaparib clinical development programme to explore how genetic variations may affect the clinical parameters associated with olaparib and/or agents used in combination or as comparators. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

It is emphasised that AstraZeneca will only look for markers within genes relevant to the mode of action of, and response to olaparib and/or agents used in combination or as comparators, and gastric cancer under study within the current Clinical Study Protocol. No other research will be performed on the samples.

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to olaparib and/or agents used in combination and/or as comparators and/or susceptibility to or prognosis of cancer.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

3.1.2 Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant

- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

3.1.4 Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at or after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at visit 1, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 7.1 of the Clinical Study Protocol.

3.3 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 25 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

4.1 Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

4.2 Subject data protection

AstraZeneca will not provide individual genotype results to subjects, 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 subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal

statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

7. LIST OF REFERENCES

None.

Clinical Study Protocol Appendix H

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00039
[redacted]	

Appendix H
EORTC QLQ-30 + -STO22 Health Related Quality of Life Questionnaire Samples

[redacted]

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ – STO22

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had problems eating solid foods?	1	2	3	4
32. Have you had problems eating liquidised or soft foods?	1	2	3	4
33. Have you had problems drinking liquids?	1	2	3	4
34. Have you had discomfort when eating?	1	2	3	4
35. Have you had pain in your stomach area?	1	2	3	4
36. Have you had discomfort in your stomach area?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
39. Have you had acid indigestion or heartburn?	1	2	3	4
40. Have you had trouble with belching?	1	2	3	4
41. Have you felt full up too quickly after beginning to eat?	1	2	3	4
42. Have you had trouble enjoying your meals?	1	2	3	4
43. Has it taken you a long time to complete your meals?	1	2	3	4
44. Have you had a dry mouth?	1	2	3	4
45. Did food and drink taste different from usual?	1	2	3	4
46. Have you had trouble with eating in front of other people?	1	2	3	4
47. Have you been thinking about your illness?	1	2	3	4
48. Have you worried about your weight being too low?	1	2	3	4
49. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4
51. Have you lost any hair?	1	2	3	4
52. Answer this question only if you lost any hair: If so, were you upset by the loss of your hair?	1	2	3	4

Clinical Study Protocol Amendment	
Amendment Number	5
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00039
[redacted]	

A randomized, double-blinded, multicentre phase II study to assess the efficacy of olaparib (AZD2281, KU-0059436) in combination with paclitaxel versus paclitaxel in patients with recurrent or metastatic gastric cancer who progress following first-line therapy

Sponsor:

[redacted]

Centres affected by the Amendment:

All participating sites.

The protocol for the study is to be amended as follows:

To amend the statistical analyses of the overall population to use an un-weighted analysis.

This change also results in amendment of the sample size determination.

Reason for amendment:

The percentage of ATM-negative patients recruited has been smaller than originally anticipated, thus reducing the statistical power of the analyses.

The impact of these changes on the relevant sections of the protocol is described below.

Persons who initiated the Amendment:

Global product statistician

Section of protocol affected:

Protocol synopsis

Previous text:

Statistical methods

It is assumed that patients who are ATM-negative will show a greater response to olaparib than patients who are ATM-positive. As the prevalence of ATM-negative patients is assumed to be approximately 25% of the overall population (AstraZeneca, unpublished) and this study population will have a 50% prevalence, analyses of endpoints in the overall population will be calculated using weighted estimates of the ATM-negative and ATM-positive patients. Weights w_1 and w_2 (proportion of ATM-negative patients and ATM-positive patients respectively) will be estimated from the screening records (up until the ATM-positive group is closed to recruitment). For calculation of Confidence Intervals, the variance will take into account the variance of both groups.

The PFS analyses will be performed when approximately 104 progression events have occurred (and approximately 50 events in the ATM-negative population). If the true HR is 0.55 (likely to correspond to an 80% prolongation of PFS) in the ATM-negative population, this analysis will have approximately 80% power to demonstrate a statistically significant difference for PFS, assuming a 10% one-sided significance level. Assuming a true prevalence of 25% for the ATM-negative group, if the true HR in the ATM-positive group is 0.65, then this study will have 80% power to detect a weighted overall HR of 0.62 (likely to correspond to a 61% prolongation of PFS), assuming a 10% one-sided significance level. This trial has been sized using one-sided 10% significance levels as it is a Phase II study looking for a signal of improved efficacy. If a one-sided p-value <0.1 is observed for the comparison of PFS between the paclitaxel + olaparib vs. paclitaxel + matching placebo in either of the co-primary populations, the results will be regarded as promising (but not definitive) in the relevant population as there is less than 1 in 5 probability that such a result could have been detected if there was truly no treatment effect. Assuming 50 events in the ATM-positive population occur, an observed HR of <0.69 will achieve a one-sided p-value <0.1. Similarly, assuming 104 events overall and a 25% prevalence of HRD-negative (to be assessed from screening log), an observed weighted HR of <0.75 will achieve a p-value of <0.1.

Assuming non-uniform recruitment and a median PFS of 3 months (Emi et al 2008) in the control group, if approximately 120 patients (60 per arm) are recruited over 15 months it is expected that 104 events will occur approximately 6 months following recruitment of the last patient.

Revised text:

Statistical methods

The PFS analyses will be performed when approximately 99 progression events have occurred. If the true HR is 0.65, this analysis will have approximately 80% power to demonstrate a statistically significant difference for PFS, assuming a 10% one-sided

significance level. In addition, it is expected that there will be approximately 50 events in the ATM-negative population at the time of the PFS analysis. If the true HR in the ATM-negative population is 0.55, the analysis will have approximately 80% power to demonstrate a statistically significant difference for PFS, assuming a 10% one-sided significance level. This trial has been sized using one-sided 10% significance level, as it is a Phase II study looking for a signal of improved efficacy.

Assuming non-uniform recruitment and a median PFS of 3 months (Emi et al 2008) in the control group, if approximately 120 patients (60 per arm) are recruited over 15 months it is expected that 99 events will occur approximately 6 months following recruitment of the last patient.

Section of protocol affected:

12.2 Methods of statistical analyses

Previous text:

It is assumed that patients who are ATM-negative will show a greater response to olaparib than patients who are ATM-positive. As the prevalence of ATM-negative patients is assumed to be approximately 25% of the overall population (AstraZeneca, unpublished) and this study population will have a 50% prevalence, analyses of endpoints in the overall population will be calculated using weighted estimates of the ATM-negative and ATM-positive patients. Weights w_1 and w_2 (proportion of ATM-negative patients and ATM-positive patients respectively) will be estimated from the screening records (up until the ATM-positive group is closed to recruitment). For calculation of Confidence Intervals, the variance will take into account the variance of both groups.

No adjustments for multiplicity have been made in sizing the study but this will be taken into account when interpreting the data.

Confidence intervals for the treatment effects will be critical in interpretation of results from this trial. Results of secondary outcome variables need to be broadly consistent with primary outcomes.

Revised text:

Confidence intervals for the treatment effects will be critical in interpretation of results from this trial. Results of secondary outcome variables need to be broadly consistent with primary outcomes.

Section of protocol affected:

12.2.1 Progression-free Survival

Previous text:

12.2.1.1 PFS in the overall population

To achieve an estimated HR that is representative of the overall population, a weighted estimate of the overall HR ('$HR_{overall}$') will be calculated using the estimated HR in the ATM-negative population ('$HR_{ATM\ negative}$') and the estimated HR in the ATM-positive population ('$HR_{ATM\ positive}$'):

$$ln(HR_{overall}) = w_1 ln(HR_{ATM\ negative}) + w_2 ln(HR_{ATM\ positive})$$

where weights w_1 and w_2 (proportion of ATM-negative patients and ATM-positive patients respectively) will be estimated from the screening records (up until the ATM-positive group is closed to recruitment).

For calculation of Confidence Intervals, the overall variance (log scale) will take into account the variance of both groups (that are independent), and thus be calculated as:

$$var(ln(HR_{overall})) = w_1^2 var(ln(HR_{ATM\ negative})) + w_2^2 var(ln(HR_{ATM\ positive}))$$

PFS will be analysed in the ATM-positive population using a Cox proportional hazards model, using the same methodology as described below for the ATM-negative population.

The overall hazard ratio (HR; olaparib in combination with paclitaxel: matching placebo in combination with paclitaxel) for treatment will be estimated together with its 80% confidence interval and one-sided p-value (a HR less than 1 will favour olaparib in combination with paclitaxel). A Kaplan-Meier plot of PFS and estimates of median PFS will be presented by treatment group and ATM subgroup.

12.2.1.2 PFS in the ATM-negative population

PFS will be analysed using a Cox proportional hazards model. The model will allow for the effect of treatment and will include terms for gastrectomy (full, partial, none). The model will include these effects regardless of whether the inclusion of effects significantly improves the fit of the model.

The model will be fitted using PROC PHREG (in SAS Version 8.1 or greater) with the EFRON method to control for ties.

The hazard ratio (HR; olaparib in combination with paclitaxel: matching placebo in combination with paclitaxel) for treatment will be estimated together with its 80% confidence interval and one-sided p-value (a HR less than 1 will favour olaparib in combination with paclitaxel). A Kaplan-Meier plot of PFS and estimates of median PFS will be presented by treatment group.

The assumption of proportionality will be assessed using plots of complementary log-log event times versus log time. If the assumptions of proportional hazards are shown not to hold

for some of the baseline covariates then this will be explored but no action will be taken in the model fitting.

If there is a substantial departure in the proportional hazards assumption for treatment then the nature of non-proportionality will be explored and reported in the Clinical Study Report with the findings from the model. This information will be then used to aid the planning of the future direction of the olaparib program.

Revised text:

PFS will be analysed using a Cox proportional hazards model with covariates gastrectomy status (full, partial, none) and ATM group (positive, negative). The model will include these effects regardless of whether the inclusion of effects significantly improves the fit of the model.

The model will be fitted using PROC PHREG (in Version 8.1 or greater) with the EFRON method to control for ties.

The hazard ratio (HR; olaparib in combination with paclitaxel: matching placebo in combination with paclitaxel) for treatment will be estimated together with its 80% confidence interval and one-sided p-value (a HR less than 1 will favour olaparib in combination with paclitaxel). A Kaplan-Meier plot of PFS and estimates of median PFS will be presented by treatment group.

The assumption of proportionality will be assessed using plots of complementary log-log event times versus log time. If the assumptions of proportional hazards are shown not to hold for some of the baseline covariates then this will be explored but no action will be taken in the model fitting.

If there is a substantial departure in the proportional hazards assumption for treatment then the nature of non-proportionality will be explored and reported in the Clinical Study Report with the findings from the model. This information will be then used to aid the planning of the future direction of the olaparib program.

A subgroup analysis of PFS will be carried out to investigate the treatment effect within ATM groups and gastrectomy status groups using a Cox proportional hazards model.

A supportive analysis of PFS will be carried out in which a weighted estimate of the overall HR ('$HR_{overall}$') will be calculated using the estimated HR in the ATM-negative population ('$HR_{ATM\ negative}$') and the estimated HR in the ATM-positive population ('$HR_{ATM\ positive}$'):

$$ln(HR_{overall}) = w_1 ln(HR_{ATM\ negative}) + w_2 ln(HR_{ATM\ positive})$$

where weights w_1 and w_2 (proportion of ATM-negative patients and ATM-positive patients respectively) will be estimated from the screening records (up until the ATM-positive group is closed to recruitment).

For calculation of Confidence Intervals, the overall variance (log scale) will take into account the variance of both groups (that are independent), and thus be calculated as:

$$var(ln(HR_{overall})) = w_1^2 var(ln(HR_{ATM\ negative})) + w_2^2 var(ln(HR_{ATM\ positive})).$$

Section of protocol affected:

12.2.2 Overall Survival

Previous text:

The methodology for analysing OS in the overall population and ATM-negative population will be the same as that described for the analyses of PFS in Section 12.2.1.

Revised text:

OS will be analysed using a Cox proportional hazards model including covariates gastrectomy status and ATM group. The model will be fitted using PROC PHREG (in SAS Version 8.1 or greater) with the EFRON method to control for ties.

The hazard ratio for treatment will be estimated together with its 80% confidence interval and one-sided p-value. A Kaplan-Meier plot of OS and estimates of median OS will be presented by treatment group.

OS will be analysed in the overall population as well as the ATM-negative population.

Section of protocol affected:

12.2.3 Objective Response Rate

Previous text:

12.2.3.1 ORR in the overall population

A log odds ratio for the overall population will be derived using a weighted estimate of the log odds ratio in the ATM-negative population and log odds ratio in the ATM-positive population.

ORR will be analysed in the ATM-positive population using the same methodology as described below for the ATM-negative population.

12.2.3.2 ORR in the ATM-negative population

The ORR will be compared between olaparib in combination with paclitaxel vs. paclitaxel alone using a multivariate logistic regression model and using the same covariates as used in the PFS analyses, provided there are enough responses for a meaningful analysis. The results

of the analysis will be presented in terms of an odds ratio together with its associated 80% confidence interval and one-sided p-value.

The variable used in the analysis will be the objective programmed assessment of response and not the investigators overall opinion. Any differences between the two will be highlighted and discussed in the CSR.

Revised text:

The ORR will be compared between olaparib in combination with paclitaxel vs. paclitaxel alone using a logistic regression model including the same covariates as used in the PFS analysis, provided there are enough responses for a meaningful analysis. The results of the analysis will be presented in terms of an odds ratio together with its associated 80% confidence interval and one-sided p-value.

The variable used in the analysis will be the objective programmed assessment of response and not the investigators overall opinion. Any differences between the two will be highlighted and discussed in the CSR.

ORR will be analysed in the overall population and the ATM-negative population.

Section of protocol affected:

12.2.4 Percentage change in tumour size at Week 8

Previous text:

12.2.4.1 Percentage change in tumour size at Week 8 in the overall population

Assuming no transformation, the effect of olaparib in combination with paclitaxel on percentage changes in tumour size will be estimated from an analysis of covariance (ANCOVA) model including terms for treatment (olaparib in combination with paclitaxel or matching placebo in combination with paclitaxel) as well as a covariate for baseline tumour size, a covariate for the treatment*ATM interaction and the same covariates as used in the PFS analyses. The percentage change in tumour size at Week 8 in the overall population will be estimated from a single model by including a treatment * mutation interaction and weighting the parameter estimates accordingly. An estimate of the treatment effect (difference1; olaparib in combination with paclitaxel minus matching placebo in combination with paclitaxel) will be calculated together with its 2-sided 80% confidence interval.

Assumptions will be explored to validate the results of the main analysis.

Frequencies of non-target lesion progressions and new lesions at Week 8 will be presented together with the change in tumour size at 8 weeks results in order to put the change in tumour size results in perspective.

12.2.4.2 Percentage change in tumour size at Week 8 in the ATM-negative population

Assuming no transformation, the effect of olaparib in combination with paclitaxel on percentage changes in tumour size will be estimated from an analysis of covariance (ANCOVA) model including terms for treatment (olaparib in combination with paclitacel or matching placebo in combination with paclitaxel) as well as a covariate for baseline tumour size and the same covariates as used in the PFS analyses. The results of the analysis will be presented in terms of adjusted means (least square means [lsmeans]) for each treatment, together with their two-sided 80% confidence intervals. An estimate of the treatment effect (difference of the lsmeans; olaparib in combination with paclitaxel minus matching placebo in combination with paclitaxel) will be calculated together with its two-sided 80% confidence interval.

Assumptions will be explored to validate the results of the main analysis.

Frequencies of non-target lesion progressions and new lesions at Week 8 will be presented together with the percentage change in tumour size at Week 8 results in order to put the change in tumour size results in perspective.

Revised text:

Assuming no transformation, the effect of olaparib in combination with paclitaxel on percentage change in tumour size will be estimated from an analysis of covariance (ANCOVA) model including covariates for baseline tumour size, gastrectomy status and ATM group. The results of the analysis will be presented in terms of adjusted means (least square means [lsmeans]) for each treatment, together with their two-sided 80% confidence intervals. An estimate of the treatment effect (difference of the lsmeans; olaparib in combination with paclitaxel minus matching placebo in combination with paclitaxel) will be calculated together with its two-sided 80% confidence interval.

Percentage change in tumour size at Week 8 will be analysed in the overall population and the ATM-negative population.

Assumptions will be explored to validate the results of the main analysis.

Frequencies of non-target lesion progressions and new lesions at Week 8 will be presented together with the percentage change in tumour size at Week 8 results in order to put the change in tumour size results in perspective.

Section of protocol affected:

12.2.6 Summaries of additional endpoints

Previous text:

No formal statistical analyses of BOR or DoR will be performed.

Summaries of BOR by ATM status and treatment arm will be produced.

Descriptive data will be provided for the DoR in responding patients by ATM status and treatment arm will be produced, including the associated Kaplan Meier curves (without any formal comparison or p-value attached).

Revised text:

No formal statistical analyses of BOR or DoR will be performed.

Summaries of BOR by treatment arm will be produced.

Descriptive data will be provided for the DoR in responding patients by treatment arm will be produced, including the associated Kaplan Meier curves (without any formal comparison or p-value attached).

Section of protocol affected:

12.3 Determination of sample Size

Previous text:

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

This trial is designed with two co-primary analysis populations: the first will comprise all patients; the second will comprise those patients in the ATM-negative subgroup as it is expected that patients who are ATM-negative, assumed to be approximately 25% of total population (AstraZeneca, unpublished), will show a greater response to AZD2281 in combination with paclitaxel compared with paclitaxel alone than patients who are ATM-positive.

This trial is designed as a randomised screening trial to quantify the level of risk entailed for further development. Thus the Type I and Type II error have been adjusted to be less constrained, so that the targeted treatment benefit may be appropriate while the sample size remains reasonable (Rubinstein et al 2005). The trial is of sufficient size to show that if olaparib in combination with paclitaxel is truly active, there is a high probability that it will demonstrate an effect sufficiently promising that it would warrant a follow up assessment in PIII.

The primary endpoint will be PFS for both co-primary analysis populations and the PFS analyses will be performed when approximately 104 progression events have occurred (and approximately 50 events in the HRD-selected population). If the true HR is 0.55 (likely to correspond to an 80% prolongation of PFS) in the ATM-negative population, this analysis will have approximately 80% power to demonstrate a statistically significant difference for PFS, assuming a 10% one-sided significance level. Assuming a true prevalence of 25% for the

ATM-negative group, if the true HR in the ATM-positive group is 0.65, then this study will have 80% power to detect a weighted overall HR of 0.62 (likely to correspond to a 61% prolongation of PFS), assuming a 10% one-sided significance level.

This trial has been sized using one-sided 10% significance levels as it is a Phase II study looking for a signal of improved efficacy. If a one-sided $p<0.1$ is observed for the comparison of PFS between the olaparib + paclitaxel vs. paclitaxel alone in either of the co-primary populations, the results will be regarded as promising (but not definitive) in the relevant population as there is less than 1 in 5 probability that such a result could have been detected if there was truly no treatment effect.

Assuming 50 events in the HRD selected population occur, an observed HR of < 0.69 will achieve a one-sided p-value <0.1 within the trial. Similarly, assuming 104 events overall and a 25% prevalence of ATM-negative (to be assessed from screening log), an observed weighted HR of <0.75 will achieve a p-value of <0.1 within the trial.

Assuming non-uniform recruitment and a median PFS of 3 months (Emi et al 2008) in the control group, if approximately 120 patients (60 per arm) are recruited over 15 months it is expected that 104 events will occur approximately 6 months following recruitment of the last patient.

Patients will continue to be followed for survival. Whilst overall survival will initially be assessed at the time of the primary analysis of PFS, a further survival analysis may be performed when approximately 90 deaths have occurred, depending on the PFS results.

No adjustments will be made for multiplicity in sizing the study, however it will be taken into account when interpreting the data.

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate

Revised text:

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

This trial is designed as a randomised trial to quantify the level of risk entailed for further development. Thus the Type I and Type II error have been adjusted to be less constrained, so that the targeted treatment benefit may be appropriate while the sample size remains reasonable (Rubinstein et al 2005). The trial is of sufficient size to show that if olaparib in combination with paclitaxel is truly active, there is a high probability that it will demonstrate an effect sufficiently promising that it would warrant a follow up assessment in PIII.

The primary endpoint will be PFS and the PFS analysis will be performed when approximately 99 progression events have occurred. If the true HR is 0.65, this analysis will

have approximately 80% power to demonstrate a statistically significant difference for PFS, assuming a 10% one-sided significance level. The PFS of ATM-negative patients is a co-primary objective and it is estimated that there will be approximately 50 events in the ATM-negative population at the time of the PFS analysis. If the true HR in the ATM-negative population is 0.55, the analysis will have approximately 80% power to demonstrate a statistically significant difference for PFS, assuming a 10% one-sided significance level. This trial has been sized using one-sided 10% significance level, as it is a Phase II study looking for a signal of improved efficacy.

Assuming non-uniform recruitment and a median PFS of 3 months (Emi et al 2008) in the control group, if approximately 120 patients (60 per arm) are recruited over 15 months it is expected that 99 events will occur approximately 6 months following recruitment of the last patient.

Patients will continue to be followed for survival. Whilst overall survival will initially be assessed at the time of the primary analysis of PFS, a further survival analysis may be performed when approximately 90 deaths have occurred, depending on the PFS results.

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

Clinical Study Protocol Amendment No 5
Appendix A

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00039
Edition Number	5.0

[redacted]

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A randomized, double-blinded, multicentre phase II study to assess the efficacy of olaparib (AZD2281, KU-0059436) in combination with paclitaxel versus paclitaxel in patients with recurrent or metastatic gastric cancer who progress following first-line therapy

This Clinical Study Protocol Amendment 5 has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol amendment.

AstraZeneca Research and Development site representative

[redacted]

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

[redacted]

ASTRAZENECA SIGNATURE(S)

A randomized, double-blinded, multicentre phase II study to assess the efficacy of olaparib (AZD2281, KU-0059436) in combination with paclitaxel versus paclitaxel in patients with recurrent or metastatic gastric cancer who progress following first-line therapy

This Clinical Study Protocol Amendment 5 has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol amendment.

AstraZeneca Research and Developme
site representative

[redacted]

[redacted]

ASTRAZENECA SIGNATURE(S)

A randomized, double-blinded, multicentre phase II study to assess the efficacy of olaparib (AZD2281, KU-0059436) in combination with paclitaxel versus paclitaxel in patients with recurrent or metastatic gastric cancer who progress following first-line therapy

This Clinical Study Protocol Amendment 5 has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol amendment.

AstraZeneca Research and Development site representative

[redacted]

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

[redacted]

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A randomized, double-blinded, multicentre phase II study to assess the efficacy of olaparib (AZD2281, KU-0059436) in combination with paclitaxel versus paclitaxel in patients with recurrent or metastatic gastric cancer who progress following first-line therapy

This Clinical Study Protocol Amendment 5 has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol amendment. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations, and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

Centre No.:

Signature: [redacted]

Clinical Study Protocol Amendment

Amendment Number	6
Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00039

[redacted]

A randomized, double-blinded, multicentre phase II study to assess the efficacy of olaparib (AZD2281, KU-0059436) in combination with paclitaxel versus paclitaxel in patients with recurrent or metastatic gastric cancer who progress following first-line therapy

Sponsor:

[redacted]

Centres affected by the Amendment:

All participating sites.

The protocol for the study is to be amended as follows:

- To update estimated date of last patient completed and number of centres
- To incorporate procedures for the management of patients still receiving study treatment following final analysis.
- To clarify to the definition of the timeline of SAE reporting when SAE reports are received outside of normal hours
- After the final analysis, we have reached the end of study as defined per protocol and no further data management activities are necessary.

Section of protocol affected:

PROTOCOL SYNOPSIS, Study centre(s) and number of patients planned

[redacted]

Previous text:

Approximately 6-8 centres will be required for this study. Approximately 240 patients will be enrolled in this study to achieve 120 patients randomized.

Study period		Phase of development
Estimated date of first patient enrolled	1Q2010	II
Estimated date of last patient completed	4Q2011	II

Revised text:

Approximately 13 centres will be required for this study. Approximately 240 patients will be enrolled in this study to achieve 120 patients randomized.

Study period		Phase of development
Estimated date of first patient enrolled	1Q2010	II
Estimated date of last patient completed	2Q2012	II

Reason for Amendment:

To update estimated date of last patient completed and number of centres

Persons who initiated the Amendment:

Study leader

Section of protocol affected:

PROTOCOL SYNOPSIS, Duration of treatment, 4th paragraph

Previous text:

After the combination treatment including paclitaxel is stopped, patients will continue with olaparib or matching placebo monotherapy until objective progression as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. The olaparib or matching placebo dose will be increased to the recommended monotherapy dose of 200 mg bd, or matched placebo commencing on the day following the scheduled completion of the last cycle of chemotherapy (i.e. 28 days after the first of the three pacliatxel doses in this cycle) as long as the specified criteria for bone marrow, hepatic and renal function are met (see Section 4.1) otherwise the tablet dose (100 mg or matched placebo bd) will be maintained until these criteria are met at a subsequent scheduled visit, at which time the olaparib or matching placebo dose should be increased to 200 mg bd or placebo to match, until objective disease progression by RECIST v1.1 as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. Once patients receiving olaparib or matching placebo have been discontinued from study treatment, other treatment options will be at the discretion of the Investigator. Patients will be unblinded after the final analysis. No cross over to olaparib is permitted.

Revised text:

After the combination treatment including paclitaxel is stopped, patients will continue with olaparib or matching placebo monotherapy until objective progression as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. The olaparib or matching placebo dose will be increased to the recommended monotherapy dose of 200 mg bd, or matched placebo commencing on the day following the scheduled completion of the last cycle of chemotherapy (i.e. 28 days after the first of the three pacliatxel doses in this cycle) as long as the specified criteria for bone marrow, hepatic and renal function are met (see Section 4.1) otherwise the tablet dose (100 mg or matched placebo bd) will be maintained until these criteria are met at a subsequent scheduled visit, at which time the olaparib or matching placebo dose should be increased to 200 mg bd or placebo to match, until objective disease progression by RECIST v1.1 as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. Once patients receiving olaparib or matching placebo have been discontinued from study treatment, other treatment options will be at the discretion of the Investigator. Patients will be unblinded after the final analysis. No cross over to olaparib is permitted. For the end of study procedures and management of patients following final analysis, refer to Appendix I.

Reason for Amendment:

To incorporate procedures for the management of patients still receiving study treatment following final planned data analyses.

Persons who initiated the Amendment:

Study leader

Section of protocol affected:

Table of contents, List of Appendices & Supplements

Previous text:

NA

Revised text:

Appendix I End of Study Procedures – Management of Patients Following final analysis

Reason for Amendment:

To incorporate procedures for the management of patients still receiving study treatment following final planned data analyses.

Persons who initiated the Amendment:

Study leader

Section of protocol affected:

5.4.2 Methods for unblinding the study, 3rd paragraph

Previous text:

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

Revised text:

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented. For the end of study procedures and management of patients following final analysis, refer to Appendix I.

Reason for Amendment:

To incorporate procedures for the management of patients still receiving study treatment following final planned data analyses.

Persons who initiated the Amendment:

Study leader

Section of protocol affected:

5.5.2 Doses and treatment regimens, final paragraph

Previous text:

Patients will be unblinded after the final analysis. No cross over to olaparib is permitted.

Revised text:

Patients will be unblinded after the final analysis. No cross over to olaparib is permitted. For the end of study unblinding procedures for the patients who are receiving study treatment following final analysis, refer to Appendix I.

Reason for Amendment:

To incorporate procedures for the management of patients still receiving study treatment following final planned data analyses.

Persons who initiated the Amendment:

Study leader

Section of protocol affected:

6.4.3 Recording of adverse events, Post Follow-up adverse events, 2nd parhagraph

Previous text:

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and / or post study completion then as a minimum all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe (section 6.4.4).

Revised text:

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and / or post study completion then as a minimum all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe (section 6.4.4). For the end of study SAE reporting procedures for the patients who are receiving study treatment following final analysis, refer to Appendix I.

Reason for Amendment:

To incorporate procedures for the management of patients still receiving study treatment following final planned data analyses.

Persons who initiated the Amendment:

Study leader

Section of protocol affected:

6.4.4 Reporting of serious adverse events

Previous text:

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives within one day i.e. 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 the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigator(s) or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e. immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site personnel

reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site personnel how to proceed.

Revised text:

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

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 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigator(s) or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site personnel how to proceed.

Reason for Amendment:

To clarify to the definition of the timeline of SAE reporting when SAE reports are received outside of normal hours

Persons who initiated the Amendment:

Study leader

Section of protocol affected:

9.5 Study timetable and end of study, 1st and 2nd paragraph

Previous text:

The end of this study is defined as the date when all patients receiving olaparib or placebo have been followed for a minimum period of 6 months since start of treatment or the date of

the final analysis of the data, whichever is the later. At this time point, the clinical study database will close to new data. Patients are however permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the investigator, they are continuing to receive benefit from treatment with olaparib.

[redacted]

Revised text:

The end of this study is defined as the date when all patients receiving olaparib or placebo have been followed for a minimum period of 6 months since start of treatment or the date of the final analysis of the data, whichever is the later. At this time point, the clinical study database will close to new data. Patients are however permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the investigator, they are continuing to receive benefit from treatment with their current study treatments (e.g., paclitaxel + olaparib or paclitaxel + matching placebo or olaparib as monotherapy. No cross over to olaparib is permitted. The patients still taking randomized treatment will continue to follow the scheduled assessment until Ethics Committee approval of Appendix I and the notification from AstraZeneca. Investigators should fully document the findings of these visits in the patients' medical records.

[redacted]

Patients are no longer following the protocol but routine clinical practice and that the only data collection will be SAEs via fax to patient safety/TCS as the clinical database will be closed. Refer to Appendix I for end of study open label treatment procedures for patients currently receiving study treatment following final analysis.

Reason for Amendment:

To incorporate procedures for the management of patients still receiving study treatment following final planned data analyses.

After the final analysis, we have reached the end of study as defined per protocol and no further data management activities are necessary.

Persons who initiated the Amendment:

Study leader

Section of protocol affected:

13.2 Overdose

Previous text:

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, i.e. immediately but no later than **the end of the next business day** of when he or

she becomes aware of it.

Revised text:

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately but **no later than 24 hours** of when he or she becomes aware of it.

Reason for Amendment:

To clarify to the definition of the timeline of SAE reporting when SAE reports are received outside of normal hours

Persons who initiated the Amendment:

Study leader

Section of protocol affected:

13.3.1 Maternal exposure

Previous text:

If any pregnancy occurs in the course of the study, then investigators or other site personnel must inform appropriate AstraZeneca representatives **within one day** i.e. immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

Revised text:

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 24 hours** of when he or she becomes aware of it.

Reason for Amendment:

To clarify to the definition of the timeline of SAE reporting when SAE reports are received outside of normal hours

Persons who initiated the Amendment:

Study leader

Clinical Study Protocol Amendment No 6 Appendix A

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00039
Edition Number	1.0

[redacted]

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A randomized, double-blinded, multicentre phase II study to assess the efficacy of olaparib (AZD2281, KU-0059436) in combination with paclitaxel versus paclitaxel in patients with recurrent or metastatic gastric cancer who progress following first-line therapy

This Clinical Study Protocol Amendment 6 has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol amendment.

AstraZeneca Research and Developr
site representative

[redacted]

ASTRAZENECA SIGNATURE(S)

A randomized, double-blinded, multicentre phase II study to assess the efficacy of olaparib (AZD2281, KU-0059436) in combination with paclitaxel versus paclitaxel in patients with recurrent or metastatic gastric cancer who progress following first-line therapy

This Clinical Study Protocol Amendment 6 has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol amendment.

AstraZeneca Research and Develop
site representative

[redacted]

ASTRAZENECA SIGNATURE(S)

A randomized, double-blinded, multicentre phase II study to assess the efficacy of olaparib (AZD2281, KU-0059436) in combination with paclitaxel versus paclitaxel in patients with recurrent or metastatic gastric cancer who progress following first-line therapy

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This Clinical Study Protocol Amendment 6 has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol amendment.

AstraZeneca Research and Development site representative [redacted]

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A randomized, double-blinded, multicentre phase II study to assess the efficacy of olaparib (AZD2281, KU-0059436) in combination with paclitaxel versus paclitaxel in patients with recurrent or metastatic gastric cancer who progress following first-line therapy

This Clinical Study Protocol Amendment 6 has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations, and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

Centre No.: [redacted]

Signature: