Clinical Trial Protocol

A preoperative "window-opportunity", multicenter, pharmacokinetic-pharmacodynamic study to evaluate the inhibitory effects of single agent AZD2281 (Olaparib), in patients with early-stage endometrial carcinoma.

Preoperative **OL**aparib **EN**dometrial Carcinoma Study (**POLEN**)

Study Drug(s):	Olaparib (AZD2281)
EudraCT#:	2015-001156-30
Clinical Trials.gov#:	NCT02506816
Protocol#:	MedOPP044
Protocol version:	Final amendment no. 4
Protocol date:	November 3, 2016

CLINICAL TRIAL PROTOCOL SYNOPSIS

Product:	Olaparib (AZD2281)
Protocol Number:	MedOPP044
EudraCT Number:	2015-001156-30
Protocol Title:	A preoperative "window-opportunity", multicenter, pharmacokinetic-pharmacodynamic study to evaluate the inhibitory effects of single agent AZD2281 (Olaparib), in patients with early-stage endometrial carcinoma.
Short title:	**P**reoperative **OL**aparib in **EN**dometrial carcinoma (**POLEN**)
Target disease:	Endometrial carcinoma (EC)
Subjects:	Patients diagnosed with endometrial carcinoma prior surgery
Number of patients:	36 patients
Selection criteria:	Patients are eligible for inclusion into the study only if they meet ALL of the following criteria: **Inclusion criteria** 1. Patients must have histologically confirmed type I primary endometrial carcinoma (EC). Diagnosis biopsy must contain 3-12 mg of tumor cellularity/stroma (Tumor: 5-20 mm) and this will be checked in the central laboratory for this trial. If tumour cellularity/stroma is inadequate, one re-biopsy with adequate tumour cellularity/stroma will be mandatory before study entry. 2. Age ≥ 18 years. 3. WHO performance status ≤ 2. 4. Adequate bone marrow function as shown by ANC ≥ 1.5 x 10^9/L, Platelets ≥ 100 x 10^9/L, Hb >10g/dL. 5. Adequate liver function as shown by: o serum bilirubin ≤ 1.5 x ULN

- INR < 1.3 (or < 3 on anticoagulants)
- ALT and AST ≤ 2.5x ULN

6. Adequate renal function: serum creatinine ≤ 1.5 x mg/dL.
7. Fasting serum cholesterol ≤300 mg/dL or ≤7.75 mmol/L and fasting triglycerides ≤ 2.5 x ULN.

   NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after normalization values with appropriate lipid lowering medication.

8. Signed informed consent, including consent to tissue collection and blood samples as specified by the protocol.

Exclusion criteria

Patients will be excluded from the study if they meet ANY of the following criteria:

1. Subjects who have received prior anticancer therapies for the current endometrial cancer (including chemotherapy, radiotherapy, antibody-based therapy, hormonotherapy or surgery).
2. Patients, who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study.
3. Prior treatment with any investigational drug within the preceding 4 weeks.
4. Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent, except corticosteroids with a daily dosage equivalent to prednisone ≤ 20 mg. However, patients receiving corticosteroids must have been on a stable dosage regimen for a minimum of 4 weeks prior the study entry. Topical or inhaled corticosteroids are allowed.
5. Patients who have received immunization with attenuated live vaccines within one week of study entry (note: during study period these kinds of vaccines are also not allowed).

6. Patients who need treatment with inhibitors or potent inductors of CYP3A4

7. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

   - Symptomatic congestive heart failure of New York heart Association Class III or IV
   - unstable angina pectoris, myocardial infarction within 6 months of start of study drug, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease
   - severely impaired lung function
   - uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN
   - active (acute or chronic) or uncontrolled severe infections
   - liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis
   - a known history of HIV seropositivity.

8. Patients with an active, bleeding diathesis.

9. Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods (e.g. total sexual abstinence*, doble barrier methods like condom + spermicide, or condom + diaphragm with spermicide , intra-uterine device (IUD) and condom, diaphragm with spermicide, or vasectomize partner with azoospermia confirmed. Hormonal contraceptives are acceptable as a sole method of contraception.

   Women able to conceive and using hormonal contraceptives have to be into the administration of a stable doses of the contraceptive at least 4 weeks before the first dose of drug study, during the whole study period and until 30 days after the study treatment will be retired. The women in fertile period must have a negative urine or serum pregnancy test within 7 days prior to administration of AZD2281.

   The only women exempt of this requirement are the postmenopausal (define by not having a menstrual period for 12

	consecutive months, from the corresponding group age, and without any other known or possible reason), the ones submitted to a chirurgic sterilization o can demonstrate sterility by other means (that is, chirurgic bilateral tubal ligation, and bilateral chirurgic hysterectomy or oophorectomy at least one month before the first dose of experimental drug administration. *Total sexual abstinence will be acceptable only in the case that is in consonance with the way of life of the patient. 10. History of noncompliance to medical regimens. 11. Patients unwilling to or unable to comply with the protocol.
Study objectives:	**Primary Objective:** The primary objective of this study is to identify, the antitumoral biological efficacy, by measuring, biomarker changes associated to short exposure to AZD2281 as potential predictors of activity in Endometrial Carcinoma (EC) in human tumor samples. This is an exploratory study with a biological primary endpoint. **Secondary Objectives** - To consider the tolerability to AZD2281 during the study and until 28 days after the last dose of AZD2281. - To correlate changes induced by AZD2281 with the different type of endometrial carcinoma and other tumor biomarkers (NFkBp65 and p50, PARP, PARP-1, pHistone 2AX, pHistoneH3, VEGF (Vascular Endothelial Growth Factor), HIF(Hypoxia inducible factor)-1alpha). - To estimate the potential predictive value of histological type: Endometrioid endometrial carcinoma (EEC) versus Non Endometrioid Endometrial Carcinoma (NEEC), and some biomarkers (immunostaining for PTEN (Phosphatase and tensin homolog), MLH-1 (mutL homolog 1), MSH-2 (mutS Homologue 2), MSH-6 (MutS homologue 6), PMS-2 (Postmeiotic Segregation Increased S. Cerevisiae. 2).

	- To estimate the potential predictive role of microsatellite instability and PTEN loss in clinical tumor changes and PARP inhibition. - To correlate clinical tumor changes with several targets of PARP inhibition. - To further explore the use of Pharmacokinetic-dynamic modelling (PBMC modelling) as surrogate pharmacodynamic marker of AZD2281 activity in endometrial tumors. - To quantify AZD2281 levels in human tissues after the oral administration of the drug - To explore the correlation between intra-tumoral AZD2281 concentrations with plasma PK parameters and molecular alterations in EC after AZD2281 treatment. - To compare intra-tumoral AZD2281 concentrations with those present in healthy tissues. - To establish a kinetic-dynamic modelling, based on the status of the variables of time (t), concentration (C) in blood and in tissue, and molecular effect (E). - To estimate the tolerability to AZD2281 throughout the study and up to 28 days after the last dose of AZD2281.
Type of study:	This is an open-label, non-randomized, non-controlled, multicenter phase 0 study that will enroll approximately 36 patients.
Therapy:	Eligible patients will receive 300mg of AZD2281 (two tablets of 150 mg of AZD2281) twice daily throughout 28 (+/- 5) days. Total daily dose will be 600 mg of AZD2281.
Evaluation Criteria:	**Primary Endpoint**: The primary endpoint for this study is to assess the histological score of the cell cycle-related proteins cyclin D1, ki67 and active caspase 3, directly on endometrial tumor tissue after 28 (+/-5) days of therapy. The histological score will be obtained by applying the following formula:

	Hscore= 1x(%light staining) + 2x(%moderate staining) + 3x(%strong staining). **Secondary Endpoint-Safety** - To measure the correlation between PARP inhibitor effect and other changes in tumor-tissue: o DNA repair: PARP, PARP-1, pHistone 2AX o Mitosis: pHistone 2AX o Angiogenesis (VEGF, HIF-1alpha) o Apoptosis (NFkB p65, p50) o Mutations and deletions o Microsatellite instability - AZD2281 blood levels on days 1, 7, 14, 21,28 of the therapy and day of surgery - Drug tumoral tissue levels on day 28 of the treatment. - Drug healthy tissue levels on day 28 of the treatment. - To test the tolerability for all AZD2281-treated patients measured by CTCAE v.4.
Study follow-up:	Inclusion period: 12 months. Follow-up period: 28 days

Appendix 1: Schedule of assessments and study procedures

Study Procedures	SCREENING Day (-14) -Day 0	BASELINE Day (-7) -Day 0	THERAPY PERIOD Day 1 – Day 28 (+/-5 days)	SURGERY or TC-biopsy Day 29	FOLLOW UP 28 days after last drug dose
Informed consent signed		X			
Anamnesis and Physical examination		X			
Concomitant medication record		X	D7-D14-D21-D28		
Functional status (WHO) and Vital signs		X	D7-D14-D21-D28		X
Safety assessment (CTCAE v 4.1)		X	D7-D14-D21-D28		X
Imaging assessment		X			
Standard laboratory procedures:					
Pregnancy test		X			
Hematology / Biochemistry values		X	D7-D14-D21-D28	X	X
Experimental laboratory (Sampling collection):					
Blood sample			D1 (before first dose), BS1 D1 (after first dose), BS2 D7, BS3, D14, BS4, D21, BS5 D28, BS6	D29 (before surgery), BS7	

Study Procedures	SCREENING Day (-14) -Day 0	BASELINE Day (-7) -Day 0	THERAPY PERIOD Day 1 – Day 28 (+/-5 days)	SURGERY or TC-biopsy Day 29	FOLLOW UP 28 days after last drug dose
Formalin-fixed, paraffin-embedded (FFPE) tumor tissue	X MT1			X MT2	
Frozen tumor tissue	X(1)			X	

Tumor tissue samples will obtained as follow:

- Biopsy: at least 1 paraffin-embedded biopsy will be obtained, prior to initiating therapy period. (1) It will be recommended to collect frozen tissue sample if possible.
- Surgical tumor section or biopsy samples will be obtained in the 24 hours following the last dose of therapy study. In case that surgical tumor sections are taken, 50% will be frozen and 50% paraffin embedded. In the case that biopsy samples are taken, at least 2 tumors will be obtained, 50% will be frozen and 50% paraffin embedded.