Statistical Analysis Plan

1 TITLE

Study title: A preoperative "window-opportunity", multicenter, pharmacokinetic-pharmacodynamic study to evaluate the inhibitory effect of AZD2281 (Olaparib), in patients with localized endometrial carcinoma.

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

Sponsor: MedSIR

Protocol number: MedOPP044

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2 VERSION HISTORY

Version	Date	Status
Final version	11-Dec-2017	Final version

3 INTRODUCTION

3.1 Analysis summary and proposal

The main objective of the present study proposal is to assess the biological consequences of PARP inhibition in type I primary ECs, in patients who receive treatment with AZD2281 during the period of time between diagnosis and surgery. This is a phase 0 trial or "Exploratory Investigational New Drug" study, a type of trial that involves a limited number of patients under drug therapy and has the objective of anti-tumor biological efficacy. The purpose of the phase 0 studies is to assist in the go versus no-go decision-making process of a drug's fate earlier in the development process, using relevant human models instead of relying on sometimes inconsistent animal data, thus helping to confirm endpoints such as mechanism of action, pharmacology, bioavailability and pharmacodynamics.

In our proposal, the biologic effects will be assessed by comparing the expression of several targets of PARP inhibitors between the initial biopsy and tumor tissue at surgery, after PARP inhibition. The biomarkers that have been chosen are well known targets of PARP, which play a role in important cellular function: 1) Apoptosis (cleaved-caspase 3, NFkB), 2) DNA repair (Histone 2Ax phosphorylation), 3) cell proliferation (Ki-67, cyclin D1), 4) Mitosis (phosphohistone H3), 5) angiogenesis (VEGF, and HIF1alpha). Moreover, the possible predictive role of several pathological and molecular features (PTEN loss, Microsatellite instability (MSI), PARP expression) will be assessed. Therefore, changes in the expression of these markers would allow assessment of the effect of PARP inhibitors in these tumors.

4 OBJECTIVES AND ENDPOINTS

4.1 Study objectives

Primary Objective: The primary objective of this study is to identify anti-tumor biological efficacy by measuring, in human tumor samples, biomarker changes associated with short exposure to AZD2281 as potential predictors of activity in endometrial carcinoma (EC). This is an exploratory study with a biological primary endpoint.

Secondary objectives:

- To estimate the tolerability to AZD2281 throughout the study and up to 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 predictive potential with regard to the following biomarkers (immunostaining for PTEN (phosphatase and tensin homolog), MLH-1 (mutL homolog 1), MSH-2 (mutS homolog 2), MSH-6 (mutS homolog 6), PMS-2 (Postmeiotic Segregation Increased S. Cerevisiae. 2).

- To estimate the potential predictive role of microsatellite instability (MSI) 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 modeling (PBMC modeling) as surrogate pharmacodynamic marker of AZD2281 activity in endometrial tumors. - To establish a pharmacokinetic-dynamic modeling, based on the status of the variables of time (t), concentration (C) in blood, and molecular effect (E). PK-PD analysis will be performed based on the plasma concentration - PARP inhibition % in the tissue.

Secondary initial objectives that were dismissed:

- To quantify AZD2281 levels in human tissues after the oral administration of the drug.
- To explore the correlation between intratumoral AZD2281 concentrations with plasma PK parameters and molecular alterations in EC after AZD2281 treatment.
- To compare intratumoral AZD2281 concentrations with those present in healthy tissues.
- To establish a pharmacokinetic-pharmacodynamic modeling, based on the status of the variables of time (t) and concentration (C) in the tissue.

4.2 Variables

(ICH E9; 2.2.2)

4.2.1 Primary endpoint

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 treatment. The histological score will be obtained by applying the following formula:

Hscore= 1x(%light staining) + 2x(%moderate staining) + 3x(%strong staining).

4.2.2 Secondary endpoints:

Secondary endpoints:

- To measure the correlation between PARP inhibitor effect and other changes in tumor-tissue:
    - DNA repair: PARP, PARP-1, pHistone 2AX
    - Mitosis: pHistone 2AX
    - Angiogenesis (VEGF, HIF-1alpha)
    - Apoptosis (NFkB p65, p50)
    - Mutations and deletions
    - Microsatellite instability (MSI).
- AZD2281 blood levels on days 1, 7, 14, 21, the last day (28 +/-5 days) of treatment and day of surgery.
- Drug levels in tumor tissue on the day of surgery.

- Drug levels in healthy tissue on the day of surgery.

4.2.3 Safety variables

- To test the tolerability for all AZD2281-treated patients measured as per Common Terminology Criteria for Adverse Events (CTCAE v.4).

5 STUDY DESIGN

5.1 Study design

(ICH E3;9.)

This is an open-label, non-randomized, uncontrolled, multicenter phase 0 study that will enroll approximately 36 patients. No efficacy objectives are included in this study. Randomization, blinding or control group are not required in this study design. The schedule of the assessments and the procedures performed in the patient is described in Tables 1 and 2.

Table 1. Study Schedule

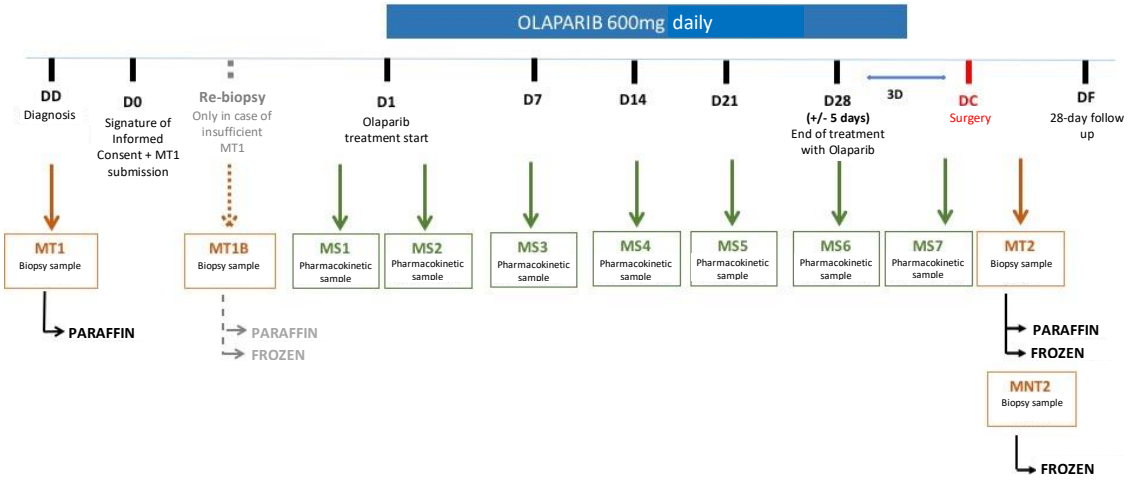


Table 2. Study Procedure Schedule

Study procedures	SCREENING From Day (-14) to Day 0	START From Day (-7) to Day 0	TREATMENT PERIOD From Day 1 to Day 28 (+/- 5 days)	SURGERY or CT-biopsy Day 29	FOLLOW UP 28 days after the last dose of the drug
Signed informed consent		X			
Anamnesis and physical examination		X			
Concomitant medication record		X	D7-D14-D21-D28		
Performance status (WHO) and vital signs		X	D7-D14-D21-D28		X
Safety assessment (CTCAE v 4.1)		X	D7-D14-D21-D28		X
Imaging evaluations		X			
Standard laboratory procedures					
Pregnancy test		X			
Hematology/biochemistry values		X	D7-D14-D21-D28	X	X
Experimental laboratory (sample collection)					
Blood sample BS1 BS2 BS3 BS4 BS5 BS6 BS7			D1 (Before the first dose) D1 (After the first dose) D7 D14 D21 D28	D29 (Prior to surgery)	
Formalin-fixed, paraffin embedded (FFPE) tumor tissue	X			X	
Frozen tumor tissue	X(1)			X	
Tumor tissue samples will be obtained as follows:					

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

5.2 Study population

(ICH E3;9.3. ICH E9;2.2.1)

5.3 Target study population

This study will enroll patients with histologically confirmed type I primary endometrial carcinoma (EC).

5.3.1 Inclusion criteria

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are enrolled in the study.
Patients are eligible for inclusion into the study only if they meet ALL of the following criteria:
1. Patients must have histologically confirmed type 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 tumor cellularity/stroma is inadequate, one re-biopsy with adequate tumor 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 >10 g/dL
5. Adequate liver function as shown by:
    - o Serum bilirubin ≤ 1.5 x ULN
    - o INR < 1.3 (or < 3 on anticoagulants)
    - o ALT and AST ≤ 2.5 x 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 enrolled 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.

5.3.2 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, hormone therapy 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 have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
    - o Symptomatic congestive heart failure of New York Heart Association Class III or IV.
    - o Unstable angina pectoris, myocardial infarction within 6 months of start of study drug, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease
    - o Severely impaired lung function
    - o Uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN.
    - o Active (acute or chronic) or uncontrolled severe infections
    - o Liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis
    - o A known history of HIV seropositivity.
7. Patients with an active, bleeding diathesis.
8. Female patients who are pregnant or breast feeding, or adults of child-bearing potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the trial by both sexes. Hormonal contraceptives are acceptable as a sole method of contraception. (Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to administration of AZD2281).
9. History of noncompliance to medical regimens.
10. Patients unwilling to or unable to comply with the protocol.

5.4 Sample size calculation

(ICH E3; 9.7.2. ICH E9; 3.5)

The primary objective is to identify, in human tumor samples, biomarker changes associated with short exposure to AZD2281 as potential predictors of activity in Endometrial Carcinoma (EC). The primary endpoint is the difference between pre and post treatment immunostaining of cyclin D1, Ki67 and active caspase 3 on endometrial tumor tissue, after four weeks of treatment. Therefore, the primary analysis will be based on comparing pre and post treatment immunostaining on target biomarkers. The histological

score will be obtained by applying the following formula: Hscore= 1x(%light staining) + 2x(%moderate staining) + 3x(%strong staining). Although a preliminary power analysis has been performed, in agreement with the exploratory nature of phase 0 studies, the sample size has been limited to 36 patients (It is expected that each participating site includes an average of about 6-10 patients) for clinical and practical considerations, rather than statistical ones (Kummar et al 2009).

Analysis will be performed in accordance with a statistical evaluation scheme specifically developed for Phase 0 trials (Rubinstein et al 2010). In the analysis we will define response at the patient level (patients with significant inhibition of biomarkers), before analyzing the number of responding patients in the study sample.

Definition of response at the patient level:

Significant inhibition of biomarker activity is defined as the reduction in biomarker levels after four weeks treatment exposure (compared to baseline) that should satisfy two criteria: reduction is at least 50 % (biological), and reduction is sufficient when compared to the variation among the baseline values, to yield 95 % statistical confidence that it is not due to chance variations.

Variability will be measured on log-transformed values. The standard deviation (SD) will be the square root of baseline inter-patient variance. Pre- and post-treatment difference of log Plk1 values will be compared to the threshold of 1.6448 SD (normal distribution is used because number of samples is higher than 30), to establish statistically significant reduction at the one-sided 0.05 level.

Definition of a significant effect at study sample:

Significant inhibition of biomarker activity will be declared if 5 of 36 patients have significant inhibition at patient level. Based on these assumptions, there is a 95% power to detect a true 35% rate of significant inhibition with an overall alpha error below 10%. As we consider three biomarkers in the primary analysis (cyclin D1, Ki67 and active caspase 3), the type I error was divided into 3,3% (<5%) for each analysis. Power and type I error has been derived from the binomial distribution (Rubinstein et al 2010), according to (A'Hern 2001).

Study dropouts

We assume the loss of patients between recruitment and end of study. Study dropouts will be analyzed as patients not displaying significant inhibition of the biomarker activity.

5.5 Randomization and blinding.

(ICH E3; 9.4.3, 9.4.6. ICH E9; 2.3.1, 2.3.2)

The randomization or blinding was not planned in this study.

6 ANALYSIS SEQUENCE

6.1 Interim analysis

Prior to the completion of the study, an interim analysis with a cut-off dated 08-May-2018 will be performed in case the study was not completed up to that date. The results will be presented at the ASCO annual meeting 2018. The results will include patient characteristics in the different analysis populations. Primary and secondary biomarker analyses of the samples available up to that date and safety analyses.

6.2 Final analysis

The final analysis will report all the analyses planned for the study.

7 STATISTICAL METHODS

7.1 General considerations

The demographic and baseline numeric variables will be summarized by the number of patients, the number of valid patients, mean, standard deviation, median, quartiles, maximum and minimum. The frequency and percentages based on the total of patients in the analysis set will be reported for the categorical variables. Quantitative variables will be summarized by the number of patients, mean, median, 95% confidence interval, standard deviation, quartiles, minimum and maximum, as appropriate. Qualitative variables will be summarized by the frequency, the percentage and the confidence interval of the odds ratio, where appropriate.

Time-to-event variables will be summarized by showing the number of events, percentage, median survival with its 95% confidence interval, and will be analyzed through the Kaplan-Meyer method.

The evolution of quantitative variables will be analyzed through the Wilcoxon's non-parametric test, mean difference, medians and their 95% confidence intervals.

The evolution of qualitative variables will be analyzed through the McNemar test.

No inferential statistics will be performed for baseline variables or safety variables, unless otherwise specified.

7.2 Populations for analysis

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 5.2)

Full analysis set

This set will include all the patients who have received the treatment. This set will also be the safety analysis set.

Per protocol set

This set will include all the patients of the full analysis set that do not have major protocol violations that may affect the assessment of treatment in the primary variable (e.g., non-evaluable patients for

biomarkers). The definition of these deviations is described in section 9.1. For the analysis of secondary variables, the number of evaluable patients for a certain biomarker analysis set will be considered.

Sensitivity analysis

The primary biomarker analysis (significant inhibition of cyclin D1, Ki67 and active caspase-3) and the secondary analyses will be performed in the full analysis set and the per protocol population.

The safety analyses will be performed in the full analysis set.

PKD population

We propose to analyze and model pharmacokinetics (PK), pharmacokinetics-pharmacodynamic (PBMC) and AZD2281 concentration, considering all patients with a complete treatment concentration-time profile.

Analyses will not be repeated between different analysis populations if they only differ by 10% patients. The largest analysis population will be used for the analyses.

7.3 Covariate and subset analysis

(ICH E3; 9.7.1, 11.4.2.1. ICH E9; 5.7. CPMP 2002; 4. CPMP 2003.)

In the covariate and subset analysis, the pre-treatment and post-treatment biomarker levels and the differences between these two periods will be analyzed. For the subset analysis, biomarker levels will be compared through the Mann-Whitney U test. When comparing qualitative variables between different subsets, the Chi-square test or Fisher's exact test will be used. The correlation between different quantitative variables or discrete variables will be performed through Spearman's correlation, and their corresponding 95% confidence intervals will be presented. The subset analysis will include the difference of the biomarker level depending on the different molecular (p53, MSI, POLE…) and clinical (days since surgery, administration breach [>3 days, >6 days, ≥14 days]) classifications.

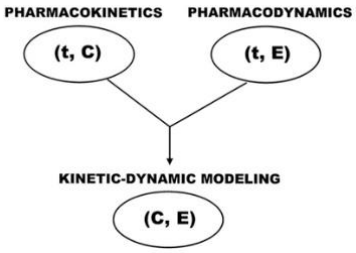
7.4 Pharmacokinetic analysis

Plasma samples for pharmacokinetic evaluation will be analyzed for each patient on days 1 (before first dose of olaparib and 1 to 4 hours after the first dose), day 7 (1 to 4 hours after olaparib dose), day 14 (1 to 4 hours after olaparib dose), day 21 (1 to 4 hours after olaparib dose), the last day of treatment (1 to 4 hours after olaparib dose) and the day of surgery (preferably 1 to 4 hours before, or within 24h prior to surgery).

All samples will be analyzed to determine olaparib level and the plasma concentration versus time data, together with information about dosing and patient characteristics will be pooled and analyzed using a population pharmacokinetic analysis approach to obtain *post-hoc* estimates of steady-state area under the concentration-time curve of AZD2281.

7.5 Pharmacokinetic-pharmacodynamic modeling (PBMC modeling)

The pharmacokinetic-pharmacodynamic modeling, in which the variable of time is incorporated into the relationship of drug effect and both plasma and tissue concentration will be described.



As a model PK/PD the relationship established between PARP inhibition in patient PBMCs after administration of olaparib, expressed as a mean percentage of PARP activity before administration of olaparib over time vs. plasma exposure using a simple E_{max} model, will be used.

The estimate of the existing correlation between mean plasma levels and the differences from baseline activity in PARP, HIF1, GLUT1 and CICLIND1 activity will be performed. MS1 levels will be dismissed because there is no drug, MS2 levels, because C_{max} is reached after the first dose, and MS7 levels, because of the end of treatment. This same analysis will look for the correlation between the levels and the final activity of biomarkers. Based on the time-concentration curve, the existing correlation between drug exposure and biomarker activity will be estimated.

Finally, mean plasma levels and mean exposure between the sets of patients with and without significant biomarker inhibition will be compared. The definition of the response level defined in the protocol (page 11/20 section Definition of the Response Level) will be applied here.

7.6 Missing data imputation

(ICH E3; 9.7.1, 11.4.2.2. ICH E9; 5.3. EMA Guideline on Missing Data in Confirmatory Clinical Trials)
Patients without quantitative biomarker values at the baseline visit will be assigned the mean of the patients at that visit. Patients without quantitative values at the follow-up visits will be assigned the same value as in the baseline visit. This imputation is intended to be conservative and go against the study objective (to detect a significant evolution between pre- and post-treatment biomarker values). In the case of qualitative variables, the lack of mutation or the characteristic analyzed will be assumed.

The different study populations where the different analyses will be performed will help to assess the imputation on the results. The analyses are only considered positive if the result is equivalent in all the analysis populations used.

7.7 Analysis of the specific effects of each site.

(ICH E3; 9.7.1, 11.4.2.4. ICH E9; 3.2)

The number of patients enrolled in each site will be described. Considering the small sample size, no analyses are expected to adjust the results by the site effect.

7.8 Alpha error correction through multiple analyses

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 2.2.5)

The type-I error for primary biomarker analysis is 10%. As we analyze the inhibition of three biomarkers as primary variable (cyclin D1, Ki67 and active caspase 3), the type I error was divided into 3,3% (<5%) for each analysis.

Prior to the completion of the study, an interim analysis with a cut-off dated 08-May-2018 will be performed in case the study was not completed up to that date. The results will be presented at the ASCO annual meeting 2018. In order to correct the alpha error associated with multiple primary analyses, it was considered that only statistically significant biomarker differences could be declared when the analysis showed p-values <3.3% in the interim and the final analyses for both analysis populations (full analysis set and per protocol set).

For secondary analyses (analysis of the difference and correlation between the levels of different biomarkers), multiple analyses were corrected through Benjamini-Hochberg's procedure "false Discovery rate (FDR)" of 10%. This procedure lists the analyses performed from lowest to highest p-value. A difference is considered statistically relevant in an analysis if the p-value obtained is equal or lower than the range assigned in that analysis, divided into the number of analyses and multiplying by 10%.

7.9 Interim analysis and data monitoring

(ICH E3; 9.7.1, 11.4.2.3. ICH E9; 4.1, FDA Feb 2010 "Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics")

Prior to the completion of the study, an interim analysis with a cut-off date on 08-May-2018 will be performed in case the study was not completed up to that date. The results will be presented at the ASCO annual meeting 2018. The results will include patient characteristics in the different analysis populations. Primary and secondary biomarker analyses and safety analyses.

Alpha error correction methods for primary and secondary variables were described in the corresponding section.

7.10 Statistical report conventions

7.10.1 Conventions to report data

All the tables, figures and lists will be presented in a vertical orientation, unless the horizontal orientation is required to view the information better. Legends will be used to describe the methods and results of these tables.

7.10.2 Statistical conventions

These tables will show the total patients in the sample of each analysis set or population in the headers of the columns (N=xxx). The total patients may also be presented in the table (n=xxx).
The summary of categorical variables will include the categories where the patients responded and the categories with missing values. All the summaries of continuous variables will include: N, mean and SD. Other summaries will be used (e.g., mean, quartiles, 5%, 95% intervals, CV or % CV), as appropriate. All percentages should be rounded up and only one decimal point should be reported (xx.x%). If percentages are reported as whole, percentages above 0% but <1% will be reported as <1%, whereas percentages above 99% but <100% will be reported as > 99%. A 100% percentage will be reported as 100%. 0% values should not be reported. Any percentage calculation resulting in 0% should be reported as a blank space. P-values will be reported with three decimal points after an initial zero value (0.001). p-values <0.001 will be reported as <0.001.

8 PROTOCOL DEVIATIONS

Description	Category	Does the deviation exclude the analysis population?			
		Full analysis and safety set	Per protocol set	Biomarker analysis subset	PKD population
Unsigned Informed Consent (main and sample).	Inclusion/Exclusion	Yes	Yes	Yes	Yes
Signed an outdated version.	Inclusion/Exclusion	Case by case	Case by case	Case by case	Case by case
The investigational product was not provided.	Treatment	Yes	Yes	Yes	Yes
Treatment was discontinued early, but the patient has received at least one administration.	Treatment.	No	Case by case	Case by case	Case by case
Patients with missing or non-evaluable pre-treatment and post-treatment biomarker/PK values.	Biomarker analysis	No	Case by case	Case by case	Yes
Patients who do not have type I primary endometrial carcinoma (EC) (see	Inclusion/Exclusion	No	Case by case	Case by case	Case by case

UICC-FIGO Classification [Stage]).					
Age < 18 years.	Inclusion/Exclusion	No	Case by case	No	No
ECOG>2.	Inclusion/Exclusion	No	No	No	No
Inappropriate organic function: ANC < 1.5 x 10^9/L Platelets < 100 x 109/L Hb ≤ 10g/dL Serum bilirubin > 1.5 x ULN INR ≥ 1.3 (o ≥ 3) ALT and AST > 2.5 x ULN Serum creatinine > 1.5 x mg/dL Serum cholesterol > 300 mg/dL or > 7.75 mmol/L Triglycerides > 2.5 x ULN	Inclusion/Exclusion	No	No	No	Case by case (PK-PD Modeling)
Prior anti-cancer treatments for current endometrial cancer.	Inclusion/Exclusion	No	Case by case	Case by case	Case by case
Major surgery or significant injury within the four weeks prior to start of the study drug.	Inclusion/Exclusion	No	Case by case	No	No
Side effects of any major surgery or major surgery throughout the study.	Inclusion/Exclusion	No	No	No	No
Serious and/or uncontrolled condition.	Inclusion/Exclusion	No	Case by case	Case by case	Case by case
Prior prohibited medication	Inclusion/Exclusion	No	Case by case	Case by case	Case by case
Pregnant or nursing (lactating) women.	Inclusion/Exclusion	No	No	No	No
Urine or serum pregnancy	Inclusion/Exclusion	No	No	No	No

test with positive result within 7 days before first dose administration.					
History of non-compliance with medical regimens.	Inclusion/Exclusion	No	Case by case	Case by case	Case by case
Patients unwilling to or unable to comply with the protocol.	Inclusion/Exclusion	No	Case by case	Case by case	Case by case
The study treatment was not administered according to the protocol: < 23 days or > 33 days	Treatment	No	Case by case	Case by case	Case by case
The study treatment was not administered according to the protocol: dose > 600 mg/day	Treatment	No	Case by case	Case by case	Case by case
The study treatment was not administered according to the protocol: Patients did not comply with the administration up to 3 days prior according to the protocol (>3 days for any reason).	Treatment	No	Case by case	Case by case	Case by case
The study treatment was not administered according to the protocol: Patients did not comply with the minimum 50% (14 days) drug administration.	Treatment	No	Case by case	Case by case	Case by case
The study treatment was not administered according to the protocol: Patients did not comply with the administration margin >6 days (3+3) for any reason.	Treatment	No	Case by case	Case by case	Case by case
Toxicities not managed according to the protocol	Treatment Safety	No	Case by case	Case by case	Case by case

(dose interruption/reduction, study treatment discontinuation/withdrawal not performed according to the protocol, toxicities not followed up 28 days post-treatment).					
The pre-treatment biopsy (MT1) was not collected.	Treatment	No	No	Case by case	No
The pre-treatment biopsy (MT1) was not performed according to the protocol (biopsy date > 14 days prior to treatment start).	Biomarker analysis	No	Case by case	Case by case	Case by case
The post-treatment surgery/biopsy was not performed according to the protocol (it was not performed +4 days upon end of treatment or any of the samples [MT2 paraffin/frozen, MNT2 frozen] was not collected).	Biomarker analysis	No	Case by case	Case by case	Case by case
Pre-treatment blood sample was not collected according to the protocol (MS1 not collected or not collected before the first dose).	Biomarker analysis	No	Case by case	Case by case	Case by case
Post-treatment blood sample in post-treatment was not collected according to the protocol (some of MS2 to MS7 samples were not collected, MS2 to MS6 samples were not collected 1-4 hours after	Biomarker analysis	No	Case by case	Case by case	Case by case

the dose and/or MS7 sample was not collected 24 hours before the surgery).					
The patient was withdrawn from the study.	Safety	No	Case by case	Case by case	Case by case
Serious concomitant diseases, including diseases that may interfere with drug absorption.	Safety	No	Case by case	Case by case	Case by case
Visits performed outside of the window (Screening > 14 days, visits D7 to D28 > 7 ± 3 working days or follow-up visit > 35 days after the last dose).	Procedures	No	Case by case	Case by case	Case by case
Screening assessments performed > 28 days prior to treatment start.	Procedures	No	Case by case	Case by case	Case by case
D1 test performed > 3 days prior to treatment start date or not performed.	Procedures Safety	No	No	No	No
D7 to D28 tests, surgery and follow-up not performed one day prior or on the same day as the date of the visit or not performed.	Procedures Safety	No	No	No	No
Any test value not performed.	Procedures	No	No	No	Case by case (PK-PD Modeling)

9 STATISTICAL REPORT SECTIONS

9.1 Summary of analysis.

This analysis will show the following tables and figures:

Figure 1. Patients enrolled and included in the study.

Table 1. Description of the analysis population. Descriptive statistics. All patients enrolled.

Table 2. Patient baseline characteristics. Descriptive statistics. Full analysis and per-protocol set.

Table 3. Patients who achieve a significant inhibition in the histological score between the post-treatment and pre-treatment period. Inferential statistics. Full analysis and per-protocol set.

Figure 2. Difference between the baseline and post-treatment levels of biomarkers (cyclin D1, Ki67, active caspase 3 and PARP1). Inferential statistics. Full analysis and per-protocol set.

Figure 3. Correlation between the levels of biomarkers with significant inhibition and PARP1. Inferential statistics. Full analysis and per-protocol set.

Figure 4. Change between baseline biomarker levels (PARP1 and with significant inhibition) depending on the mutation or deficiency identified (including MSI). Inferential statistics. Full analysis and per-protocol set.

Table 4. Adverse events observed in the study, occurred at least in 10% of patients. Descriptive statistics. Safety analysis.

Table 5.- Plasma concentrations of the drug for each patient by time.
Figure 5.- Mean plasma level curve of the drug by time.

9.2 Study full analysis.

9.2.1 Patients recruited, enrolled and disposition of patients in the study.

9.2.2 Patient baseline characteristics

9.2.3 Biomarker analysis

9.2.3.1 Primary analysis

9.2.3.2 Secondary analyses

9.2.3.3 Subset and covariate analysis

9.2.3.4 Pharmacokinetic/pharmacodynamic analysis

9.2.3.5 Pharmacokinetic-pharmacodynamic modeling (PBMC modeling)

9.2.4 Safety analysis

9.2.4.1 Treatment exposure analysis

(Treatment delays, reductions and discontinuations, duration in days and strength of the dose received).

9.2.4.2 Analysis of adverse effects

(All serious related adverse effects, discontinuations, deaths and other relevant events).

9.2.4.3 Analysis of concomitant medication received

9.2.4.4 Analysis of the physical examination and other safety-related remarks