SANDOZ

Study Protocol

Sandoz Global Clinical Development

Protocol Number: 21-VIN-0166

Protocol Title: A Randomized, Open Label, Multi-centre, Two-treatment, Two-period, Two-sequence, Two-stage, Multiple Dose, Steady-state, Crossover, Bioequivalence Study of Olaparib Tablets, 150 mg (Lek Pharmaceuticals d.d.) and Lynparza® (Olaparib) Tablets 150 mg (AstraZeneca Pharmaceuticals LP), in Patients With BRCA Mutated Ovarian Cancer, Recurrent Ovarian Cancer or Metastatic Breast Cancer Under Fasting Condition

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Confidential

PROJECT NO. [redacted]

Protocol Number	[redacted]
Study Sites	Investigator sites
Protocol Title	A randomized, open label, multi-centre, two-treatment, two-period, two-sequence, two-stage, multiple dose, steady-state, crossover, bioequivalence study of Olaparib tablets, 150 mg [redacted] and Lynparza® (olaparib) tablets 150 mg [redacted] in patients with BRCA mutated ovarian cancer, recurrent ovarian cancer or metastatic breast cancer under fasting condition.
Version Number	[redacted]
Protocol Date	[redacted]
Sponsor	[redacted]
Contract Research Organization (CRO)	[redacted]

Confidentiality Statement

The information contained in this document is trade secrets and commercial information that are privileged or confidential, especially unpublished data, and is the property of the [redacted] (or under its control), and therefore provided to you in confidence as an Investigator or consultant, for review by you, your staff and an applicable Institutional Ethics Committee. By accepting this document, you agree that this information will not be disclosed to others without written authorization from [redacted] unless such disclosure is required by applicable law or regulations or to the extent necessary to obtain informed consent from those persons (including their legally acceptable representatives as applicable) to whom the drug may be administered. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

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[redacted]

1.0 AUTHORIZATION OF PROTOCOL

1.1 Protocol Preparation and Authorization

I, the undersigned, have read and understood this protocol and hereby agree to conduct the study in accordance with this protocol and to comply with all the pertinent requirements of the Ethical guidelines for biomedical research on human participants (ICMR) 2017, New Drugs and Clinical Trials Rules (2019) of India, US FDA regulations, rules and guidelines, cGCP guideline(s), ICH (Step 5) 'Guidance on Good Clinical Practice' ICH Guidance E6 (R2), Declaration of Helsinki (Brazil, 2013), Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46) and with procedures oriented to Good Laboratory Practice and applicable regulatory guidelines.

I agree to comply with all relevant SOPs required for the conduct of this study. I further agree to ensure that all associates assisting in the conduct of this study are informed regarding their obligations.

[redacted]

[redacted]

[redacted]

1.2 Quality Assurance Statement

The contents of the protocol were reviewed for compliance with the applicable VIN SOPs, pertinent requirements of the Ethical guidelines for biomedical research on human participants (ICMR) 2017, New Drugs and Clinical Trials Rules (2019) of India, USFDA regulations, rules and guidelines, cGCP guideline(s), ICH (Step 5) 'Guidance on Good Clinical Practice' ICH Guidance E6 (R2), Declaration of Helsinki (Brazil, 2013)), Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46) and with procedures oriented to Good Laboratory Practice and applicable regulatory guidelines.

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1.3 Sponsor's Review and Approval

I, the undersigned, have read, understood and approve this protocol. We agree to comply with all requirements of the Ethical guidelines for biomedical research on human participants (ICMR) 2017, New Drugs and Clinical Trials Rules (2019) of India, USFDA regulations, rules and guidelines, cGCP guideline(s), ICH (Step 5) 'Guidance on Good Clinical Practice' ICH Guidance E6 (R2), Declaration of Helsinki (Brazil, 2013), Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46) and with procedures oriented to Good Laboratory Practice and applicable regulatory guidelines.

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2.0 LIST OF ABBREVIATIONS

ß HCG	:	Human chorionic gonadotropin
AE	:	Adverse Event
ALT	:	Alanine Aminotransferase
AML	:	Acute Myeloid Leukemia
ANC	:	Absolute Neutrophil Count
ANOVA	:	Analysis of Variance
AST	:	Aspartate Aminotransferase
AUC	:	Area Under Curve
BE	:	Bioequivalence
BP	:	Blood Pressure
BSA	:	Body surface area
C_{max}	:	Maximum Measured Plasma Concentration
CBC	:	Complete Blood Count
COA	:	Certificates of Analysis
CRF	:	Case Record Form
CRO	:	Contract/Clinical Research Organization
CTC	:	Common toxicity criteria
CTCAE	:	Common Terminology Criteria for Adverse Event
CV	:	Coefficient of Variation
DCGI	:	Drugs Controller General of India
DLT	:	Dose Limiting Toxicity
ECG	:	Electrocardiogram
ECHO	:	Echocardiogram
ECOG	:	Eastern Cooperative Oncology Group
eCTD	:	Electronic Common Technical Document
FCBP		Female of child bearing potential
GCP	:	Good Clinical Practice
GRAS	:	Generally Recognized As Safe
HBsAg	:	Hepatitis B surface Antigen
HCV	:	Hepatitis C Virus
HIV	:	Human Immunodeficiency Virus
ICF	:	Informed Consent Form
ICH	:	International Council for Harmonization
ICMR	:	Indian Council of Medical Research
IEC	:	Institutional Ethics Committee
IMP	:	Investigational medicinal product

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IRB	:	Institutional Review Board
K3EDTA		Tripotassium ethylenediaminetetraacetic acid
LC-MS/MS	:	Liquid Chromatography –Tandem Mass Spectrometry
LLOQ	:	Lower Limit of Quantification
MedDRA	:	Medical Dictionary for Regulatory Activities
Mg	:	Milligram
ml /mL	:	Millilitre
mm Hg	:	Millimetre of Mercury
NA	:	Not Applicable
NCI	:	National Cancer Institute
NCS	:	Not Clinically Significant
PI	:	Principal Investigator
PIS	:	Patient Information Sheet
PK	:	Pharmacokinetic
RBC	:	Red Blood Cell
REMS	:	Risk Evaluation and Mitigation Strategy
Rpm	:	Revolutions per minute
RS	:	Respiratory System
SAS	:	Statistical Analysis System
SAE	:	Serious Adverse Event
SDV	:	Source Data Verification
SGOT	:	Serum Glutamic-Oxaloacetic Transaminase
SGPT	:	Serum Glutamic Pyruvic Transaminase
SOP	:	Standard Operating Procedure
T_{maxss}	:	Time of the Maximum Measured Plasma Concentration over the steady state dosing interval
ULN	:	Upper Limit of Normal
USFDA	:	United States Food and Drug Administration

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3.0 SYNOPSIS

Name of Sponsor	[redacted]
Name of Investigational Medicinal Product	Test Product: Olaparib tablets, 150 mg of [redacted] Reference Product: Lynparza® (olaparib) tablets 150 mg Manufactured for: [redacted]
Title of Study	A randomized, open label, multi-centre, two-treatment, two-period, two-sequence, two-stage, multiple dose, steady-state, crossover, bioequivalence study of Olaparib tablets, 150 mg [redacted] and Lynparza® (olaparib) tablets 150 mg [redacted] in patients with BRCA mutated ovarian cancer, recurrent ovarian cancer or metastatic breast cancer under fasting condition.
Clinical Study Centre(s)	Clinical facilities will be the hospitals at different investigators' sites in India
Central Laboratory study centre(s)	[redacted]
BRCA Test Laboratory study centre(s)	[redacted]
Bio-analytical Study Centre(s)	[redacted]
Statistical Centre	[redacted]

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	[redacted]
Objectives	• Primary Objective: To assess the pharmacokinetics and establish bioequivalence of the Test Product (Olaparib tablets, 150 mg) relative to that of Reference Product (Lynparza® (olaparib) tablets 150 mg) in patients with BRCA mutated ovarian cancer, recurrent ovarian cancer or metastatic breast cancer. • Secondary Objective: To monitor the adverse events of patients and to assess safety of each of the two formulations.
Methodology	This is a two-way crossover bioequivalence study between test and reference product in patients diagnosed with BRCA mutated ovarian cancer, recurrent ovarian cancer or metastatic breast cancer that are receiving Lynparza® (olaparib) tablets (2*150 mg twice daily) or are eligible to receive Lynparza® (olaparib) tablets (2*150 mg twice daily). The study will be conducted in 2 stages, in the Stage 1 sufficient number of patients will be enrolled to achieve 56 evaluable patients and Stage 2 (if needed) sample size will be decided on the basis of data obtained after the completion of Stage 1. Patients will be enrolled after providing written informed consent and treatments will be allocated to patient by carrying out randomization using statistical techniques. The patients will undergo screening for a maximum period of 40 days (up to 30 days for patients that are already receiving a stable dose of Lynparza® (olaparib) tablets), which will include a Dose Stabilization period of 10 days (only applicable for patients not yet on a stable dose of Lynparza® (olaparib) tablets). The patients found eligible for participation in the study, but not yet on a stable dose of Lynparza® (olaparib) tablets, will be enrolled in the Dose Stabilization period. Dose Stabilization period will be applicable for patients that are not on a stable dose of Lynparza® (olaparib) tablets 2*150 mg (for at least 10 days). Following this, patients will be randomized to participate in the study. Patients that do not tolerate the mentioned dose or require dose modifications for any reason will be considered as screen failure. Patients who miss 2 or more consecutive doses or more than 3 non-consecutive doses in the Dose Stabilization period will be considered screen failure. Patients that are already on a stable dose of Lynparza® (olaparib) tablets (2*150 mg twice daily) for at least 10 days and have met the eligibility criteria will be directly

[redacted]

	randomized for participation in the study. After randomization patients will receive either test or reference product in a crossover manner based on the randomization schedule. Patients will receive the dose of 300 mg twice daily for 16 days in a crossover design. In period-I (Day 1 to Day 8), patients will receive either Test product or Reference product for 8 days based on the randomization schedule. In period-II (Day 9 to Day 16), patients will be switched to the other product for a second period of 8 days. Blood samples for pharmacokinetic assessment will be collected on Days 1, 6, 7 and 8 and on Days 14, 15 and 16. After the study is completed (after last Pharmacokinetic (PK) sample collection on Day 16), patients may be continued on their established dose of Olaparib using an approved Olaparib product as prescribed by their clinicians. Plasma concentration of Olaparib will be quantified using a validated analytical method. Statistical Analysis of pharmacokinetic parameters of test and reference formulations will be performed to assess bioequivalence.
Number of Patients	A sufficient number of patients will be enrolled to have 56 evaluable patients in Stage 1 (about, but not limited to, 70 enrolled patients). Stage 2 sample size (if needed) will be decided on the basis of data (observed CV) obtained after the completion of Stage 1. Maximum sample size (Stage 1 + Stage 2) is expected, but not limited to, approximately 120 enrolled patients. This is a 2-stage design according to Potvin C method[1]. Enrollment will be continued until at least 56 evaluable patients will complete Stage 1. If additional patients are recruited, those patients will continue the study until completion/withdrawal and be included in the pharmacokinetic and statistical analyses as applicable.
Inclusion Criteria	To be eligible for the study, patients must meet all the following inclusion criteria: 1. **First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer** maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian,

[redacted]

	fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients based on a diagnostic test for BRCA mutation by NGS – Next Generation Sequencing method. OR **Maintenance Treatment of Recurrent Ovarian Cancer** maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy. OR **Advanced Germline BRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy** treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients based on a diagnostic test for BRCA mutation by NGS – Next Generation Sequencing method. OR **Germline BRCA-mutated HER2-negative Metastatic Breast Cancer** treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients based on a diagnostic test for BRCA mutation by NGS – Next Generation Sequencing method. 2. Non-smoking, non-pregnant, non-lactating female patient ≥18 years of age with a body mass index (BMI) in the range of 18.50 to 30.00 kg/m^2 (both inclusive). 3. Able to give written informed consent for participation in the trial and willing to adhere to protocol requirements. 4. Patients that are already receiving a stable dose of Lynparza® (olaparib) tablets (2*150 mg tablets) 300 mg twice daily for at least 10 days. OR Patients requiring Olaparib in the dose of 300 mg (2*150 mg tablets) twice daily as per the discretion of the Investigators; these patients will be stabilized on

[redacted]

Olaparib as a part of study and those patients that tolerate Olaparib in the dose of 300 mg twice daily for 10 days will be randomized in the study. Patients that do not tolerate the mentioned dose or require dose modifications for any reason will be considered as screen failure. Patients who miss 2 or more consecutive doses or more than 3 non-consecutive doses in the Dose Stabilization period will be considered screen failure.

5. Patient having an estimated survival of at least 3 months.
6. Adequate organ and bone marrow function based upon the following laboratory criteria at the time of eligibility assessment prior to dosing in period 1:

Body system	**Parameters**
Bone marrow function	a) Hemoglobin ≥9.0 g/dL b) Absolute neutrophil count ≥1500/uL c) Platelet count ≥100,000/uL d) WBC count > 3000/mm^3
enal function	Creatinine Clearance > 50 mL/min (calculated based on Cockcroft-Gault formula)

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
8. Absence of blood transfusion in the 28 days prior to randomization.
9. **Women of non child bearing potential** with documented evidence of hysterectomy / bilateral salpingectomy / bilateral oophorectomy at least 6 months prior to IMP administration) or postmenopausal for at least 12 consecutive months.

   OR

   Women of child bearing potential must have negative pregnancy test at screening visit and before randomization and must agree to use an effective method of avoiding pregnancy (including oral, transdermal or implanted contraceptives [any hormonal method in conjunction with a secondary method], intrauterine device, female condom with spermicide, diaphragm with spermicide, absolute sexual abstinence, use of condom with spermicide by sexual partner or sterile [at least 6 months prior to IMP administration] sexual partner) for at least 4 weeks prior to IMP administration, during the study and up to 6 months after the last dose of IMP. Cessation of birth control after this point should be discussed with a responsible physician.

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Exclusion Criteria	Patients who meet any of the following criteria at screening will not be enrolled in the study: 1. History of known hypersensitivity to olaparib or its components which, in the opinion of the Investigator, would compromise the safety of the patient or the results of the study. 2. Patients found positive for HIV, Syphilis, Hepatitis B surface antigen or Hepatitis C antibody at screening. 3. Have ongoing clinically significant adverse event(s) due to prior treatments administered, as determined by the investigator. 4. Patients with Pneumonitis 5. Patients with severe hepatic impairment (Child Pugh classification category C) 6. Patients who received any chemotherapy, radiotherapy, or any other anti-cancer therapy within 4 weeks from the last dose prior to first dosing in period 01 (or a longer period depending on the defined characteristics of the agents used). 7. History or presence of any active infection or uncontrolled systemic disease (e.g. cardiovascular disease, hypertension, diabetes mellitus etc.) or any clinically significant disease, condition, disorder or abnormal laboratory finding that, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or influence the study results or the patient's ability to participate in the study. 8. Patient had major surgery within 4 weeks prior to first dosing in Period 01, or who have not recovered from prior major surgery. 9. In the opinion of the Investigator, the patient will not be compliant with the requirements of the study procedures. 10. Blood loss (1 unit or 350 ml) within 90 days prior to first dosing in Period 01 for the current study. 11. Receipt of an investigational medicinal product or participation in another drug research study involving IMP administration within 30 days (or 5 half-lives, whichever is longer) prior to first dosing in Period 01 for the current study. Note: Elimination half-life of the study drug should be taken into consideration for inclusion of the patient in the study. 12. Usage of strong and moderate CYP3A4 inhibitors (e.g., cimetidine, ciprofloxacin,

	grapefruit juice) or strong and moderate CYP3A4 inducers (e.g., carbamazepine, phenytoin, St. John's Wort, rifampicin) within 30 days prior to first dosing in Period 01 (refer annexure IV for a full list of prohibited medications). 13. History of difficulty in accessibility of veins or intolerance to direct venipuncture. 14. Pregnant or lactating females. 15. Patient positive on Breath alcohol analyzer test at the time of baseline/randomization visit. 16. Positive on urine test for drugs of abuse (including amphetamines, barbiturates, benzodiazepines, marijuana, cocaine, and morphine) prior to receiving the first dose of investigational medicinal product in the study. 17. History or presence of alcoholism or drug abuse. 18. Patients with psychiatric illness/social situations that would limit compliance with study requirements. 19. Difficulty in swallowing tablets. 20. Problems with fasting. 21. History or presence of clinically significant lactose, galactose, or fructose intolerance.
Mode of Administration for Test and Reference product	Patients will be dosed or advised to take the investigational medicinal product (2*150 mg twice daily) (allocated as per randomization schedule) orally in sitting posture with approximately 240 (±5 mL) of drinking water at ambient temperature which must be completely consumed. Patients will be instructed not to chew, crush, touch or divide the tablet but to swallow as a whole. On days of housing, dosing will be followed by thorough hand and mouth check for assessing compliance. Dosing time on Day 1 morning will be considered as reference time for dosing in the entire study. Evening dose will be administered 12 hours after the morning dose. All the patients will be required to consume the investigational medicinal product preferably at the same time each day. Window period of within 1 hour will be allowed if the patient misses the scheduled time of dosing. If a patient misses a dose, the dose should be taken as soon as possible, if this can be done within 1 hour of the scheduled time. The next dose should be taken at its scheduled time. If a patient misses a dose for more than 1 hour, they should take the next dose at its scheduled time.

	In period I: On Day 0, patient will be asked to reach the site at least 12 hours prior to scheduled dosing on Day 1 and will be housed for 12 hours after morning dose of Day 1. Patient will be administered two tablets (2*150 mg tablets) of investigational medicinal product in morning and evening as per randomization schedule under supervision of trained study personnel at clinical facility. Dosing on Day 1 (morning as well as evening) would be done at site. Patients will be discharged after administration of evening dose of Day 1 at site. Dosing from Day 2 to Day 5 morning can be done at home by patients. The patient will be provided with sufficient investigational medicinal product for dosing at their home from Day 2 to Day 4 (for morning and evening daily dosing at 12-hours interval) and Day 5 morning dosing. Day 5 evening dose will be done at site. Patient will also be provided with a patient diary card to enter the details of study drug consumption and details of AE (if any) at their home. Patient and their attendant will be provided with adequate instructions to complete the patient diary card at their home. Patient will be requested to come to the clinical facility for evening dose on Day 5 (at least 12 hours prior to scheduled morning dosing on Day 6) for housing in the clinical facility. During the patients stay in the clinical facility on Day 6, Day 7 and Day 8 patients will be administered the investigational medicinal product at the scheduled time of dosing in morning and evening daily at 12-hours interval under supervision of trained study personnel. In period II: Patient will be crossed over to the other investigational medicinal product (allocated as per randomization schedule) on Day 9 morning dose. Dosing on Day 9 (morning as well as evening) would be done at site. Patient will be discharged after administration of evening dose of Day 9 at site. Dosing from Day 10 to Day 13 morning can be done at home by patients. The patient will be provided with sufficient investigational medicinal product for dosing at their home from Day 10 to Day 12 (for morning and evening daily dosing at 12-hours interval) and Day 13 morning dosing. Day 13 evening dose will be done at site.

[redacted]

	Patient will also be provided with a patient diary card to enter the details of study drug consumption and details of AE (if any) at their home. Patient and their attendant will be provided with adequate instructions to complete the patient diary card at their home. Patient will be requested to come to the clinical facility for evening dose on Day 13 (at least 12 hours prior to scheduled morning dosing on Day 14) for housing in the clinical facility. During the patients stay in the clinical facility on Day 14, Day 15 and Day 16 patients will be administered the investigational medicinal product at the scheduled time of dosing in morning and evening daily at 12-hours interval under supervision of trained study personnel. Note: • In the Dose Stabilization period, patients will receive approved marketed version of Olaparib, details of the same will be included in IMP plan. • After the study is completed (after last PK sample collection on Day 16), patients may be continued on their current dose of Olaparib using an approved Olaparib product as prescribed by their clinicians.
Posture restrictions	Patients will be advised to remain awake and in semi-reclined position for the first 4 hours after morning dosing on Day 1, Day 8 and Day 16. They will be asked to rise only with assistance during this period of time and at the first rising when this period is over. After 4 hours after dosing, the patients will be allowed to engage in normal activities while avoiding strenuous physical exertion.
Dietary and Water restrictions	On housing days, patients will be required to do an overnight fast of at least 8 hours before their scheduled time for dosing and for 4 hours after dosing for the morning dose, and 2 hours before their scheduled time for dosing and 2 hours after dosing for the evening dose. For dosing at home, all patients will be required to remain in fasting condition of at least 2 hours before their scheduled time for dosing and 2 hours after dosing for morning and evening dose. On housing days, patients will receive standard meals (lunch, snacks and dinner) with

	the same quantity and same menu will be used (on housing days) for both periods. There will not be any pre-dose and post-dose water restriction during dosing at home. On housing days, water will not be allowed for 1 hour before and 1 hour after morning dose and evening dose drug administration, when no liquid should be permitted other than that 240 mL (±5 mL) for drug dosing.
Housing	Patients will be housed in the clinical facility at least 12 hours prior to morning dose on Day 1 and will be confined for at least 12 hours after morning dose on Day 1. The patients will also be housed in the clinic at least 12 hours before morning dose on Day 6 until 12 hours post morning dose on Day 9. The patients will also be housed in the clinic at least 12 hours before morning dose on Day 14 until 12 hours post morning dose on Day 16. *Note: In addition to above requirements, the patients may be housed in the clinical facility (hospital) for the entire duration of the study or a definite duration in the study, if in the opinion of the Investigator, it facilitates the study procedures or for social reasons (like difficulty in travelling etc.). The Investigator will be required to document this decision in the patient source document (like patient hospital records). Hospitalizations performed for these reasons will not be considered as SAE. However, if the patient is hospitalised for reasons related to safety or adverse events, the hospitalization will be considered as SAE.*
Duration of Study	Total expected study duration will be approximately 64 days consisting of: • Screening period including 10-day Dose Stabilization period: 40 days • Treatment Period: 16 days • End of Study: on Day 16 • Safety follow-up visit: On Day 24 ± 2 days; 8 ± 2 days after End of Study For patients who are already receiving a stable dose of Lynparza® (olaparib) tablets (2*150 mg twice daily) for at least 10 days before screening visit, the duration of screening period will be 30 days. Expected study duration will be approximately 54 days.
Blood Collection Times	A total of 43 blood samples each of 03 mL will be collected from each patient for PK assessment during the study. The venous blood samples will be withdrawn from each patient in each period at the

[redacted]

	following timepoints: [redacted] The post dose blood samples will be collected with an allowable deviation of ± 2 minutes. In all instances, however, the exact time of dosing and of each sample collection must be recorded. Samples collected outside the scheduled time will be considered as protocol deviations. Note: • [redacted] blood sample must be collected prior to next drug administration. • Blood sample collection (PK samples) will be collected first if other activities are coinciding.
Clinical and safety assessment	It is the responsibility of the PI to ensure that adequate medical supervision and care is available for the study patients during housing and during the study duration to ensure the utmost safety and well-being of the study patients. At study sites, medical personnel will be available 24 hours a day and physician in charge will remain at the clinical site for at least the first 4 hours following drug administration. On PK sampling days (Day 8 and 16), investigator will remain at the clinical site for at least the first 4 hours following morning drug administration. In addition, if necessary, investigators will be available on-call at all times. **Medical and Medication history and Review of Inclusion and Exclusion Criteria**: Screening and at the time of randomization. **HER2 Testing (Only applicable for breast cancer patients):** Screening (If the report is not available with the patients at the time of screening). **Germline or Somatic BRCA1 and BRCA2 diagnostic test for olaparib by NGS – Next Generation Sequencing method:** Screening (the details for applicable patients and type of sample as per the section 5.6) Note: The Germline or Somatic BRCA1 and BRCA2 test need not be repeated in those patients who have been started on olaparib post BRCA testing done by NGS – Next Generation Sequencing method.

[redacted]

	Physical examination: Screening, Day 0, Day 5, Day 13 and end of study (Day 16), Safety follow up (on day 24±2). **Demographics:** Age, gender, ethnicity and race will be noted at screening visit. **Vital signs and body measurements**: ➢ Body height: Screening visit ➢ Body weight: Screening, End of Study ➢ Body temperature, Blood pressure, Heart rate and Respiratory rate: o Screening o Day 0, Day 5 and Day 13 o Before morning dose on Day 1, Day 6 to Day 9 and on Day 14 to Day 16 o At 3 hour after morning dose on Day 6 to Day 9 and on Day 14 to Day 16 o End of study (Day 16) o Safety follow up (On day 24±2) o Note: Blood pressure, pulse rate, respiratory rate and body temperature prior to IMP administration will be measured within 60 minutes prior to dosing and after administration of the IMP will be measured within ± 30 minutes of the scheduled time. Additional vital examinations may be performed at any time during the study as per Investigator's judgment; all results must be documented appropriately. **HIV, HCV, HbSAg, and VDRL or RPR (for syphilis):** Screening **12-Lead ECG:** Screening, Day 5, Day 13 and End of Study (Day 16) **2D-ECHO**: Screening **Urine drug Screen (benzodiazepines, opioids, amphetamines, cannabinoids, cocaine and barbiturates) and Alcohol Breath Test:** Day 0, Day 5 and Day 13. Note: Separate mouthpiece will be used in breath test for every patient in the study. **Pregnancy test:** Screening visit (Serum), Day 0, Day 5, Day 13 (Urine), and at End of Study Visit (Serum) for FCBP only. **X-ray (chest)**: To be performed based on Investigator's discretion.

	Hematology, Blood chemistry and Urinalysis: Screening, and at the end of the study (Day 16) **CBC, Creatinine Clearance, S Bilirubin, SGPT and SGOT:** Prior to dosing in period 1 (Day -2 to 0) and period 2 (can be performed after evening dose on Day 8) (can be done at local laboratory) In addition to protocol-specific laboratory tests and/or clinical examinations at scheduled time points, additional tests/clinical examination may be conducted to evaluate patient safety at any time during the study, at the discretion of the Investigator (can be done in local laboratory or nearby clinic/hospital/institution). **Note**: It is recommended that general precautions should be taken by the staff with respect to ongoing COVID-19 pandemic situation during the trial.
Concomitant Medications	Prohibited Medications: Moderate or strong CYP 3A4 inhibitors or inducers (refer annexure IV) Patients should be instructed to avoid grapefruit, grapefruit juice, Seville oranges, Seville orange juice, starfruit and pomelo. Any drug therapy taken by a patient should be the same for both periods. If a change in concomitant medications is necessary or if drug therapy (prescription or over-the-counter) other than that specified in the protocol is required prior to or during the study, decisions shall be taken by the Investigator and sponsor to continue or discontinue the patient based on the following: • The pharmacology and pharmacokinetics of the non-study medication. • The likelihood of a drug–drug interaction, thereby affecting the pharmacokinetic comparison of study medicine. • The likelihood of a drug–drug LC-MS/MS cross-interaction, thereby affecting the determination of olaparib concentration in patient plasma. • The time and duration of administration of the non-study medicine. If it is necessary for the patient's safety to add any medication that interferes or changes the PK of olaparib, the patient should be withdrawn from the study. Before prescribing any drug it is mandatory to refer Prescribing Information of Lynparza® including but not limited to interaction with other medicinal products and

[redacted]

	other forms of interaction, contraindications, special warnings and precautions for use, undesirable side effects, etc. The Investigator should ask the patient to notify the study site of any new medications they take after the start of the study. All instances of concomitant drug administration will be recorded and reported in the CRF and final report. **Medication taken prior to first dosing**: All prescription medications and over-the-counter drugs (including vitamins and herbal remedies) taken within 30 days prior to screening must be recorded in the CRF. **Concomitant medications:** All the medications ongoing at the time of consent and medications consumed until the end of the study safety assessments will be recorded in prior/concomitant medications section of the CRF.
Drug Analysis	The concentration of Olaparib in plasma samples will be quantified at [redacted] using a validated LC-MS/MS method. Please refer latest version of Bio-analytical plan for details.
Pharmacokinetic and Statistical Methods	Pharmacokinetic and statistical analysis will be performed at [redacted] Using the concentration time profile of Olaparib, the following pharmacokinetic parameters will be computed and reported: Primary variables: C_{maxSS} and $AUC_{(0-\tau)ss}$ Secondary variables: C_{minSS}, T_{maxSS}, C_{avSS}, swing and percentage of fluctuation. ANOVA, least squares means for test and reference formulations, difference between test and reference formulations, intra-subject variability and power will be calculated for ln-transformed pharmacokinetic parameters C_{maxSS} and $AUC_{(0-\tau)ss}$. Geometric least squares means of test and reference formulations, T/R ratio, 90% confidence interval for geometric least squares means ratio and Two One-Sided Tests for 90% confidence interval limits will be calculated for pharmacokinetic parameters C_{maxSS} and $AUC_{(0-\tau)ss}$. [redacted] By considering the three day's morning pre-dose concentrations in a given period,

[redacted]

	steady state analysis will be performed for each subject in each period by using the linear regression analysis to obtain the p-values. The above analyses will be done using procedure PROC REG in SAS, version 9.4 or higher. For achieving the steady state following procedure should be assessed: Step 1: For each subject in each period the P-values should be statistically insignificant at 5% level of significance. If, P-values are found statistically insignificant, those patients are considered to achieve steady state. If, P-values are found significant for particular subject then go for the second step. Go for second step for patients who have missing pre-dose sample for Day 6 or Day 14. Step 2: Ratio of the pre-dose concentrations of last two pre-dose should be $\geq$ 80.00% or should be $\leq$ 120.00%. In case ratio of last two pre-dose concentrations is found to be $\geq$ 80.00% or $\leq$ 120.00% patients will be considered to achieve steady state. If two pre-dose concentrations is found to be less than 80.00% or greater than 120.00%, patients will not be considered to achieve steady state and will be removed from bioequivalence evaluation. Two stage design according to Potvin C: Evaluate the power at stage 1 using the variance estimate from stage 1 and an α level of 0.05. If the power is greater than or equal to 80%, evaluate BE at stage 1 using an α level of 0.05 and stop whether BE is met or not. If the power is less than 80%, evaluate BE using an α of 0.0294. If the BE criterion is met, stop. If the BE criterion is not met, calculate the sample size based on the variance estimated at stage 1 and an α level of 0.0294 and continue to stage 2. If the ratio is outside 80.00%-125.00% then study will not proceed for stage 2. Evaluate BE at stage 2 using data from both stages and an α level of 0.0294. Stop here whether BE is met or not and regardless of the power achieved.
Bioequivalence criteria	For Stage 1 with Power $\geq$ 80%: Based on the statistical results of 90% confidence intervals for the geometric least squares means ratio for the log-transformed pharmacokinetic parameters C_{maxSS} and $AUC_{(0-\tau)SS}$ for Olaparib the conclusions will be drawn whether test formulation is bioequivalent to reference formulation under Fasting condition. Acceptance range for bioequivalence is 80.00%-125.00% for 90% confidence intervals of the geometric

	least square means ratio of C_{maxSS} and $AUC_{(0-\tau)SS}$. For Stage 1 with Power < 80% and for Stage 2, if required: Based on the statistical results of 94.12% confidence intervals for the geometric least squares means ratio for the log-transformed pharmacokinetic parameters C_{maxSS} and $AUC_{(0-\tau)SS}$ for Olaparib the conclusions will be drawn whether test formulation is bioequivalent to reference formulation under Fasting condition. Acceptance range for bioequivalence is 80.00%-125.00% for 94.12% confidence intervals of the geometric least square means ratio of C_{maxSS} and $AUC_{(0-\tau)SS}$.
Ethical Issue	The study will commence only after a written approval is obtained from the Institutional Ethics Committee and applicable regulatory authorities. The study will be conducted as per the biomedical research on human participants (ICMR) 2017 guidelines, New Drugs and Clinical Trial Rules (2019) of India, USFDA regulations, rules and guidelines, ICH (Step 5) 'Guidance on Good Clinical Practice' ICH Guidance E6 (R2), Declaration of Helsinki (Brazil, 2013) and with procedures oriented to Good Laboratory Practice and applicable regulatory guidelines.

[redacted]

[redacted]

4.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

4.1 Clinical Facilities

Investigator's Sites

4.2 Bio-analytical, Pharmacokinetics and Biostatistics Services and Quality Assurance

[redacted]

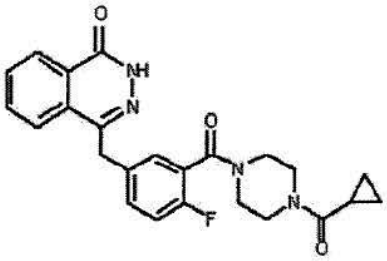
4.3 Medical Experts

[redacted]

5.0 BACKGROUND INFORMATION

5.1 Introduction[2]

Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor. It has the following chemical structure:



Olaparib is a crystalline solid, is non-chiral and shows pH-independent low solubility across the physiological pH range.

Olaparib tablets for oral use contain 100 mg or 150 mg of olaparib, however only the 150 mg tablet strength will be used in this study.

5.2 Pharmacology[2]

Mechanism of Action

Olaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular functions, such as DNA transcription and DNA repair.

Pharmacodynamics

Cardiac Electrophysiology

The effect of olaparib on cardiac repolarization was assessed in 119 patients following a single dose of 300 mg and in 109 patients following multiple dosing of 300 mg twice daily. No clinically relevant effect of olaparib on QT interval was observed.

Pharmacokinetics

The area under the curve (AUC) of olaparib increases approximately proportionally following administration of single doses of 25 mg to 450 mg (0.08 to 1.5 times the recommended dose) and maximal concentrations (Cmax) increased slightly less than proportionally for the same dose range. Olaparib showed time-dependent pharmacokinetics and an AUC mean accumulation ratio of 1.8 is observed at steady state following a dose of 300 mg twice daily.

The mean (CV%) olaparib Cmax is 5.4 µg/mL (32%) and AUC is 39.2 µg*h/mL (44%) following a single 300 mg dose. The mean steady state olaparib Cmax and AUC is 7.6 µg/mL (35%) and 49.2 µg*h/mL (44%),

following a dose of 300 mg twice daily.

Absorption

Following oral administration of olaparib, the median time to peak plasma concentration is 1.5 hours.

Effect of Food

Co-administration of a high fat and high calorie meal (800-1000 kcal, 50% of the calorie content made up from fat) with olaparib slowed the rate (tmax delayed by 2.5 hours) of absorption, but did not significantly alter the extent of olaparib absorption (mean AUC increased by approximately 8%).

Distribution

The mean (± standard deviation) apparent volume of distribution of olaparib is 158 ± 136 L following a single 300 mg dose of Olaparib. The protein binding of olaparib is approximately 82% in vitro.

Elimination

The mean (± standard deviation) terminal plasma half-life of olaparib is 14.9 ± 8.2 hours and the apparent plasma clearance is 7.4 ± 3.9 L/h following a single 300 mg dose of Olaparib.

Metabolism

Olaparib is metabolized by cytochrome P450 (CYP) 3A in vitro.

Following an oral dose of radiolabeled olaparib to female patients, unchanged olaparib accounted for 70% of the circulating radioactivity in plasma. It was extensively metabolized with unchanged drug accounting for 15% and 6% of radioactivity in urine and feces, respectively. The majority of the metabolism is attributable to oxidation reactions with a number of the components produced undergoing subsequent glucuronide or sulfate conjugation.

Excretion

Following a single dose of radiolabeled olaparib, 86% of the dosed radioactivity was recovered within a 7-day collection period, 44% via the urine and 42% via the feces. The majority of the material was excreted as metabolites.

Specific Populations

Patients with Renal Impairment

In a renal impairment trial, the mean AUC increased by 24% and Cmax by 15%, when olaparib was dosed in patients with mild renal impairment (CLcr=51-80 mL/min defined by the Cockcroft-Gault equation; n=13) and by 44% and 26%, respectively, when olaparib was dosed in patients with moderate renal impairment (CLcr=31-50 mL/min; n=13), compared to those with normal renal function (CLcr ≥81 mL/min; n=12). There was no evidence of a relationship between the extent of plasma protein binding of olaparib and creatinine clearance. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

[redacted]

Patients with Hepatic Impairment

In a hepatic impairment trial, the mean AUC increased by 15% and the mean Cmax increased by 13% when olaparib was dosed in patients with mild hepatic impairment (Child-Pugh classification A; n=10) and the mean AUC increased by 8% and the mean Cmax decreased by 13% when olaparib was dosed in patients with moderate hepatic impairment (Child-Pugh classification B; n=8), compared to patients with normal hepatic function (n=13). Hepatic impairment has no effect on the protein binding of olaparib and, therefore, total plasma exposure was representative of free drug. There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

Drug Interaction Studies

Clinical Studies

CYP3A Inhibitors: Concomitant use of itraconazole (strong CYP3A inhibitor) increased olaparib Cmax by 42% and AUC by 170%. Concomitant use of fluconazole (moderate CYP3A inhibitor) is predicted to increase olaparib Cmax by 14% and AUC by 121%.

CYP3A Inducers: Concomitant use of rifampicin (strong CYP3A inducer) decreased olaparib Cmax by 71% and AUC by 87%. Concomitant use of efavirenz (moderate CYP3A inducer) is predicted to decrease olaparib Cmax by 31% and AUC by 60%.

In vitro Studies

CYP Enzymes: Olaparib is both an inhibitor and inducer of CYP3A and an inducer of CYP2B6. Olaparib is predicted to be a weak CYP3A inhibitor in humans.

UGT Enzymes: Olaparib is an inhibitor of UGT1A1.

Transporters: Olaparib is an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1, and MATE2K. Olaparib is a substrate and inhibitor of the efflux transporter P-gp. The potential for olaparib to induce P-gp has not been evaluated.

5.3 Adverse Reactions[2]

Adverse Reactions from Clinical Studies

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the "Warnings and precautions" section of Prescribing information[2] reflect exposure to olaparib as a single agent in 2901 patients; 2135 patients with exposure to 300 mg twice daily tablet dose including five controlled, randomized, trials (SOLO-1, SOLO-2, OlympiAD, POLO, and PROfound) and to 400 mg twice daily capsule dose in 766 patients in other trials that were pooled to conduct safety analyses. In

these trials, 56% of patients were exposed for 6 months or longer and 28% were exposed for greater than one year in the Olaparib group.

In this pooled safety population, the most common adverse reactions in ≥10% of patients were nausea (60%), fatigue (55%), anemia (36%), vomiting (32%), diarrhea (24%), decreased appetite (22%), headache (16%), dysgeusia (15%), cough (15%), neutropenia (14%), dyspnea (14%), dizziness (12%), dyspepsia (12%), leukopenia (11%), and thrombocytopenia (10%).

First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer

SOLO-1

The safety of Olaparib for the maintenance treatment of patients with BRCA-mutated advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was investigated in SOLO-1. Patients received Olaparib tablets 300 mg orally twice daily (n=260) or placebo (n=130) until disease progression or unacceptable toxicity. The median duration of study treatment was 25 months for patients who received Olaparib and 14 months for patients who received placebo. Among patients who received Olaparib, dose interruptions due to an adverse reaction of any grade occurred in 52% and dose reductions due to an adverse reaction occurred in 28%. The most frequent adverse reactions leading to dose interruption or reduction of Olaparib were anemia (23%), nausea (14%), and vomiting (10%). Discontinuation due to adverse reactions occurred in 12% of patients receiving Olaparib. The most frequent adverse reactions that led to discontinuation of Olaparib were fatigue (3.1%), anemia (2.3%), and nausea (2.3%).

Table: Adverse Reactions Occurring in SOLO-1 (≥10% of Patients Who Received Olaparib)

Adverse Reaction	Olaparib tablets n=260		Placebo n=130	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Gastrointestinal Disorders				
Nausea	77	1	38	0
Abdominal pain[†]	45	2	35	1
Vomiting	40	0	15	1
Diarrhea[‡]	37	3	26	0
Constipation	28	0	19	0
Dyspepsia	17	0	12	0
Stomatitis[§]	11	0	2	0
General Disorders and Administration Site Conditions				
Fatigue[¶]	67	4	42	2

Blood and Lymphatic System Disorders				
Anemia	38	21	9	2
Neutropenia[#]	17	6	7	3
Leukopenia[Þ]	13	3	8	0
Thrombocytopenia[ß]	11	1	4	2
Infections and Infestations				
Upper respiratory tract infection/ influenza/nasopharyngitis/bronchitis	28	0	23	0
UTI[à]	13	1	7	0
Nervous System Disorders				
Dysgeusia	26	0	4	0
Dizziness	20	0	15	1
Metabolism and Nutrition Disorders				
Decreased appetite	20	0	10	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea[è]	15	0	6	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.
† Includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal distension, abdominal discomfort, and abdominal tenderness.
‡Includes colitis, diarrhea, and gastroenteritis.
§Includes stomatitis, aphthous ulcer; and mouth ulceration.
¶ Includes asthenia, fatigue, lethargy, and malaise.
# Includes neutropenia, and febrile neutropenia.
Þ Includes leukopenia, and white blood cell count decreased.
ß Includes platelet count decreased, and thrombocytopenia.
à Includes urosepsis, urinary tract infection, urinary tract pain, and pyuria
è Includes dyspnea, and dyspnea exertional.

In addition, the adverse reactions observed in SOLO-1 that occurred in <10% of patients receiving Olaparib were increased blood creatinine (8%), lymphopenia (6%), hypersensitivity (2%), MDS/AML (1%), dermatitis (1%), and increased mean cell volume (0.4%).

Table 3 Laboratory Abnormalities Reported in ≥25% of Patients in SOLO-1

Laboratory Parameter*	**Olaparib tablets n†=260**	**Placebo n†=130**

	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	87	19	63	2
Increase in mean corpuscular volume	87	-	43	-
Decrease in leukocytes	70	7	52	1
Decrease in lymphocytes	67	14	29	5
Decrease in absolute neutrophil count	51	9	38	6
Decrease in platelets	35	1	20	2
Increase in serum creatinine	34	0	18	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluablepatients for each laboratory parameter.

Maintenance Treatment of Recurrent Ovarian Cancer

SOLO-2

The safety of Olaparib for the maintenance treatment of patients with platinum sensitive g*BRCA*m ovarian cancer was investigated in SOLO-2. Patients received Olaparib tablets 300 mg orally twice daily (n=195) or placebo (n=99) until disease progression or unacceptable toxicity. The median duration of study treatment was 19.4 months for patients who received Olaparib and 5.6 months for patients who received placebo.

Among patients who received Olaparib, dose interruptions due to an adverse reaction of any grade occurred in 45% and dose reductions due to an adverse reaction occurred in 27%. The most frequent adverse reactions leading to dose interruption or reduction of Olaparib were anemia (22%), neutropenia (9%), and fatigue/asthenia (8%). Discontinuation due to an adverse reaction occurred in 11% of patients receiving Olaparib.

Below tables summarize adverse reactions and laboratory abnormalities in SOLO-2.

Table: Adverse Reactions* in SOLO-2 (≥20% of Patients Who Received Olaparib)

Adverse Reaction	Olaparib tablets n=195		Placebo n=99	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	76	3	33	0
Vomiting	37	3	19	1
Diarrhea	33	2	22	0
Stomatitis†	20	1	16	0

General Disorders and Administration Site Conditions				
Fatigue including asthenia	66	4	39	2
Blood and Lymphatic Disorders				
Anemia‡	44	20	9	2
Infections and Infestations				
Nasopharyngitis/URI/sinusitis/ rhinitis/influenza	36	0	29	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/myalgia	30	0	28	0
Nervous System Disorders				
Dysgeusia	27	0	7	0
Headache	26	1	14	0
Metabolism and Nutrition Disorders				
Decreased appetite	22	0	11	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version4.0.

† Represents grouped term consisting of abscess oral, aphthous ulcer, gingival abscess, gingival disorder, gingival pain, gingivitis, mouth ulceration, mucosal infection, mucosal inflammation, oral candidiasis, oral discomfort, oral herpes, oralinfection, oral mucosal erythema, oral pain, oropharyngeal discomfort, and oropharyngeal pain.

‡ Represents grouped term consisting of anemia, hematocrit decreased, hemoglobin decreased, iron deficiency, mean cell volume increased and red blood cell count decreased.

In addition, the adverse reactions observed in SOLO-2 that occurred in <20% of patients receiving Olaparib were neutropenia (19%), cough (18%), leukopenia (16%), hypomagnesemia (14%), thrombocytopenia (14%), dizziness (13%), dyspepsia (11%), increased creatinine (11%), MDS/AML (8%), edema (8%), rash (6%), and lymphopenia (1%).

Table: Laboratory Abnormalities Reported in ≥25% of Patients in SOLO-2

Laboratory Parameter*	**Olaparib tablets n†=195**		**Placebo n†=99**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Increase in mean corpuscular volume‡	89	-	52	-
Decrease in hemoglobin	83	17	69	0
Decrease in leukocytes	69	5	48	1
Decrease in lymphocytes	67	11	37	1
Decrease in absolute neutrophil count	51	7	34	3

Increase in serum creatinine	44	0	29	0
Decrease in platelets	42	2	22	1

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluablepatients for each laboratory parameter.

‡ Represents the proportion of subjects whose mean corpuscular volume was > upper limit of normal (ULN).

Study 19

The safety of Olaparib as maintenance monotherapy was evaluated in patients with platinum sensitive ovarian cancer who had received 2 or more previous platinum containing regimens in Study 19. Patients received Olaparib capsules 400 mg orally twice daily (n=136) or placebo (n=128). At the time of final analysis, the median duration of exposure was 8.7 months in patients who received Olaparib and 4.6 months in patients who received placebo.

Adverse reactions led to dose interruptions in 35% of patients receiving Olaparib; dose reductions in 26% and discontinuation in 6% of patients receiving Olaparib.

Below tables summarize adverse reactions and laboratory abnormalities in Study 19.

Table: Adverse Reactions* in Study 19 (≥20% of Patients Who Received Olaparib)

Adverse Reaction	Olaparib capsules n=136		Placebo n=128	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	71	2	36	0
Vomiting	35	2	14	1
Diarrhea	28	2	25	2
Constipation	22	1	12	0
Dyspepsia	20	0	9	0
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	63	9	46	3
Blood and Lymphatic Disorders				
Anemia†	23	7	7	1
Infections and Infestations				
Respiratory tract infection	22	2	11	0
Metabolism and Nutrition Disorders				

Decreased appetite	21	0	13	0
Nervous System Disorders				
Headache	21	0	13	1

* Graded according to NCI CTCAE v4.0.

† Represents grouped terms of related terms that reflect the medical concept of the adverse reaction.

In addition, the adverse reactions in Study 19 that occurred in <20% of patients receiving Olaparib were dysgeusia (16%), dizziness (15%), dyspnea (13%), pyrexia (10%), stomatitis (9%), edema (9%), increase in creatinine (7%), neutropenia (5%), thrombocytopenia (4%), leukopenia (2%), MDS/AML (1%) and lymphopenia (1%).

Table: Laboratory Abnormalities Reported in ≥25% of Patients in Study 19

Laboratory Parameter*	**Olaparib capsules n†=136**		**Placebo n†=129**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Decrease in hemoglobin	82	8	58	1
Increase in mean corpuscular volume‡	82	-	51	-
Decrease in leukocytes	58	4	37	2
Decrease in lymphocytes	52	10	32	3
Decrease in absolute neutrophil count	47	7	40	2
Increase in serum creatinine	45	0	14	0
Decrease in platelets	36	4	18	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluablepatients for each laboratory parameter.

‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

Advanced Germline *BRCA*-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy

Pooled Data

The safety of Olaparib was investigated in 223 patients (pooled from 6 studies) with g*BRCA*m advanced ovarian cancer who had received 3 or more prior lines of chemotherapy. Patients received Olaparib capsules 400 mg orally twice daily until disease progression or unacceptable tolerability. The median exposure to Olaparib in these patients was 5.2 months.

There were 8 (4%) patients with adverse reactions leading to death, two were attributed to acute leukemia, and one each was attributed to COPD, cerebrovascular accident, intestinal perforation, pulmonary embolism, sepsis, and suture rupture. Adverse reactions led to dose interruption in 40% of patients, dose reduction in 4%, and discontinuation in 7%.

Below tables summarize the adverse reactions and laboratory abnormalities from the pooled studies.

Table: Adverse Reactions Reported in Pooled Data (≥20% of Patients Who Received Olaparib)

Adverse Reaction	Olaparib capsules n=223	
	Grades 1-4 (%)	Grades 3-4 (%)
General Disorders		
Fatigue/asthenia	66	8
Gastrointestinal Disorders		
Nausea	64	3
Vomiting	43	4
Diarrhea	31	1
Dyspepsia	25	0
Decreased appetite	22	1
Blood and Lymphatic Disorders		
Anemia	34	18
Infections and Infestations		
Nasopharyngitis/URI	26	0
Musculoskeletal and Connective Tissue Disorders		
Arthralgia/musculoskeletal pain	21	0
Myalgia	22	0

Table: Laboratory Abnormalities Reported in ≥25% of Patients in Pooled Data

Laboratory Parameter*	Olaparib capsules n†=223	
	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	90	15
Mean corpuscular volume elevation	57	-
Decrease in lymphocytes	56	17

Decrease in platelets	30	3
Increase in creatinine	30	2
Decrease in absolute neutrophil count	25	7

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluablepatients for each laboratory parameter

The following adverse reactions and laboratory abnormalities have been identified in ≥10 to <20% of the 223 patients receiving Olaparib and not included in the table: cough (16%), constipation (16%), dysgeusia (16%), headache (15%), peripheral edema (14%), back pain (14%), urinary tract infection (14%), dyspnea (13%), and dizziness (11%).

The following adverse reactions and laboratory abnormalities have been identified in <10% of the 223 patients receiving Olaparib and not included in the table: leukopenia (9%), pyrexia (8%), peripheral neuropathy (5%), hypomagnesemia (5%), rash (5%), stomatitis (4%), MDS/AML (1.8%), and venous thrombosis (including pulmonary embolism) (1%).

Germline *BRCA*-mutated HER2-negative Metastatic Breast Cancer

OlympiAD

The safety of Olaparib was evaluated in g*BRCA*m patients with HER2-negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease in OlympiAD. Patients received either Olaparib tablets 300 mg orally twice daily (n=205) or a chemotherapy (capecitabine, eribulin, or vinorelbine) of the healthcare provider's choice (n=91) until disease progression or unacceptable toxicity. The median duration of study treatment was 8.2 months in patients who received Olaparib and 3.4 months in patients who received chemotherapy.

Among patients who received Olaparib, dose interruptions due to an adverse reaction of any grade occurred in 35% and dose reductions due to an adverse reaction occurred in 25%. Discontinuation due to an adverse reaction occurred in 5% of patients receiving Olaparib.

Below tables summarize the adverse reactions and laboratory abnormalities in OlympiAD.

Table: Adverse Reactions* in OlympiAD (≥20% of Patients Who Received Olaparib)

Adverse Reaction	Olaparib tablets n=205		Chemotherapy n=91	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				

Nausea	58	0	35	1
Vomiting	30	0	15	1
Diarrhea	21	1	22	0
Blood and Lymphatic Disorders				
Anemia†	40	16	26	4
Neutropenia‡	27	9	50	26
Leukopenia§	25	5	31	13
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	37	4	36	1
Infections and Infestations				
Respiratory tract infection‖	27	1	22	0
Nervous System Disorders				
Headache	20	1	15	2

* Graded according to NCI CTCAE v4.0.

† Represents grouped terms consisting of anemia (anemia erythropenia, hematocrit decreased, hemoglobin decreased and redblood cell count decreased).

‡Represents grouped terms consisting of neutropenia (febrile neutropenia, granulocyte count decreased, granulocytopenia,neutropenia, neutropenic infection, neutropenic sepsis, and neutrophil count decreased).

§ Represents grouped terms consisting of leukopenia (leukopenia and white blood cell count decreased).

‖ Represents grouped terms consisting of bronchitis, influenza, lower respiratory tract infection, nasopharyngitis, pharyngitis,respiratory tract infection, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.

In addition, adverse reactions in OlympiAD that occurred in <20% of patients receiving Olaparib were cough (18%), decreased appetite (16%), thrombocytopenia (11%), dysgeusia (9%), lymphopenia (8%), dyspepsia (8%), dizziness (7%), stomatitis (7%), upper abdominal pain (7%), rash (5%), increase in serum creatinine (3%), and dermatitis (1%).

Table: Laboratory Abnormalities Reported in ≥25% of Patients in OlympiAD

Laboratory Parameter*	Olaparib tablets n†= 205		Chemotherapy n†= 91	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	82	17	66	3
Decrease in lymphocytes	73	21	63	3
Decrease in leukocytes	71	8	70	23
Increase in mean corpuscular volume‡	71	-	33	-
Decrease in absolute neutrophil count	46	11	65	38

[redacted]

Decrease in platelets	33	3	28	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluablepatients for each laboratory parameter.

‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

Postmarketing Experience[2]

The following adverse reactions have been identified during post approval use of Olaparib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Immune System Disorders: Hypersensitivity including angioedema.
- Skin and subcutaneous tissue disorders: Erythema nodosum, rash, dermatitis.

5.4 Warnings and precautions[2]

Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic syndrome (MDS)/Acute Myeloid Leukemia (AML) has occurred in patients treated with Olaparib and some cases were fatal.

In clinical studies enrolling 2901 patients with various cancers who received Olaparib as a single agent, the cumulative incidence of MDS/AML was approximately 1.5% (43/2901). Of these, 51% (22/43) had a fatal outcome. The median duration of therapy with Olaparib in patients who developed MDS/AML was 2 years (range: < 6 months to > 10 years). All of these patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.

Do not start Olaparib until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt Olaparib and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Olaparib.

Pneumonitis

In clinical studies enrolling 2901 patients with various cancers who received Olaparib as a single agent, the incidence of pneumonitis, including fatal cases, was 0.8% (24/2901). If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological abnormality occurs, interrupt Olaparib treatment and promptly assess the source of the symptoms. If pneumonitis is confirmed,

[redacted]

discontinue Olaparib treatment and treat the patient appropriately.

Embryo-Fetal Toxicity

Olaparib can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. In an animal reproduction study, administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily. Apprise pregnant women of the potential hazard to a fetus and the potential risk for loss of the pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Olaparib.

Venous Thromboembolic Events

Venous thromboembolic events, including pulmonary embolism, occurred in 7% of patients with metastatic castration resistant prostate cancer who received Olaparib plus androgen deprivation therapy (ADT) compared to 3.1% of patients receiving enzalutamide or abiraterone plus ADT in the PROfound study. Patients receiving Olaparib and ADT had a 6% incidence of pulmonary embolism compared to 0.8% of patients treated with ADT plus either enzalutamide or abiraterone. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

5.5 Indications and usage[2,3]

First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer

Olaparib is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Patients must have confirmation of deleterious or suspected deleterious germline and/or somatic mutations in the BRCA 1 or 2 using a validated test.

Maintenance Treatment of Recurrent Ovarian Cancer

Olaparib is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy. There is no requirement for BRCA1/2 testing.

Advanced Germline BRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy

Olaparib is indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Patients must have confirmation of a deleterious or suspected deleterious gBRCA1/2 mutation

[redacted]

before treatment. gBRCA1/2 mutation status should be determined by a validated test.

Germline BRCA-mutated HER2-negative Metastatic Breast Cancer

Olaparib is indicated for the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Patients must have confirmation of a deleterious or suspected deleterious gBRCA1/2 mutation before treatment. gBRCA1/2 mutation status should be determined by a validated test method.

5.6 Therapeutic Dosage[2]

DOSAGE AND ADMINISTRATION

Patient Selection

Patients for treatment with Olaparib should be selected based on the presence of deleterious or suspected deleterious BRCA mutations, or genomic instability based on the indication, biomarker, and sample type as indicated in the table below.

Table: Biomarker Testing for Patient Selection for indications included in the study

Indication	Biomarker	Sample Type	
		Tumor	Blood
First-line maintenance treatment of germline or somatic *BRCA*m advanced ovarian cancer	*BRCA1*m, *BRCA2*m	X	X
Maintenance treatment of recurrent ovarian cancer	No requirement for biomarker testing		
Advanced g*BRCA*m ovarian cancer	*gBRCA1*m, *gBRCA2*m		X
g*BRCA*m HER2-negative metastatic breast cancer	*gBRCA1*m, *gBRCA2*m		X

[redacted]

5.7 Contraindication[3]

Hypersensitivity to the active substance or to any of the excipients of olaparib. Breast-feeding during treatment and for 1 month after the last dose.

5.8 Drug Interaction[2]

Use with Anticancer Agents

Clinical studies of Olaparib with other myelosuppressive anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

Effect of Other Drugs on Olaparib

Strong and Moderate CYP3A Inhibitors

Coadministration of CYP3A inhibitors can increase olaparib concentrations, which may increase the risk for adverse reactions. Strong and Moderate CYP3A Inhibitors are prohibited during the study (refer annexure IV).

Strong and Moderate CYP3A Inducers

Concomitant use with a strong or moderate CYP3A inducer decreased olaparib exposure, which may reduce Olaparib efficacy. Strong and Moderate CYP3A Inducers are prohibited during the study (refer annexure IV).

5.9 Use in specific populations[2]

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, Olaparib can cause fetal harm when administered to a pregnant woman. There are no available data on Olaparib use in pregnant women to inform the drug-associated risk. In an animal reproduction study, the administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily. Apprise pregnant women of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. The estimated background risk in the U.S. general population of major birth defects is 2-4%; and the risk for spontaneous abortion is approximately 15-20% in clinically recognized pregnancies.

Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing for females of reproductive potential is required prior to initiating treatment with Olaparib.

Contraception

Olaparib can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with Olaparib and for at least 6 months following the last dose.

Renal Impairment

No dosage modification is recommended in patients with mild renal impairment (CLcr 51 to 80 mL/min estimated by Cockcroft-Gault). Patients with moderate (CLcr 31 to 50 mL/min) and severe (CLcr ≤30 mL/min) renal impairment are not eligible for the study. Olaparib dosage should be reduced to 200 mg twice daily in patients with moderate renal impairment (CLcr 31 to 50 mL/min). There are no data in patients with severe renal impairment or end-stage disease (CLcr ≤30 mL/min) If dose reduction is needed, the patient should be withdrawn from the study.

Hepatic Impairment

No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

6.0 OBJECTIVE

- Primary Objective: To assess the pharmacokinetics and establish bioequivalence of the Test Product (Olaparib tablets, 150 mg) relative to that of Reference Product (Lynparza® (olaparib) tablets 150 mg) in patients with BRCA mutated ovarian cancer, recurrent ovarian cancer or metastatic breast cancer.

- Secondary Objective: To monitor the adverse events of patients and to assess safety of each of the two formulations.

7.0 STUDY DESIGN

A randomized, open label, multi-centre, two-treatment, two-period, two-sequence, two-stage, multiple dose, steady-state, crossover, bioequivalence study of Olaparib tablets, 150 mg [redacted] and Lynparza® (olaparib) tablets 150 mg [redacted] in patients with BRCA mutated ovarian cancer, recurrent ovarian cancer or metastatic breast cancer under fasting condition.

Rationale:

The sponsor has developed a generic alternative to the reference-listed brand of olaparib 150 mg tablets.

Therefore, this study is being conducted to evaluate the bioequivalence of the test product Olaparib tablets, 150 mg [redacted] with Lynparza® (olaparib) tablets 150 mg [redacted] in patients with BRCA mutated ovarian cancer, recurrent ovarian cancer or metastatic breast cancer under fasting condition. Current study is randomized, open label, multi-center, two-treatment, two-period, two-sequence, two-stage, multiple dose, steady-state, bioequivalence study. The study design and endpoints are based on the FDA product specific guidance of Olaparib tablet 150 mg[4].

Rationale for selection of two-stage design:

Bioequivalence studies are generally conducted in healthy subjects and therefore organized in a way that all study subjects are dosed at the same time. Consequently, all the superseding procedures (blood draws, meals, safety checks, bioanalytics) are done for all subjects in parallel. In contrast, if a bioequivalence study is done in patients, these are being recruited for the study as they come to the doctor's office, meaning that they are included in the study one by one. In such instances it therefore makes sense to have an interim check to assess whether adequate study power was already achieved, and recruitment can be stopped. When the CV is relatively high and not enough data are known, a two-stage adaptive design is ideal since it allows to measure the observed variability from the actual patients participating in the trial and make adjustments as required and as planned in the methodology (approved by the regulators). In addition, adaptive designs are encouraged also due to COVID-19 Pandemic, as indicated by the FDA public note[5]. For these reasons, two-stage design is proposed for this bioequivalence study.

7.1 Number of Patients

Considering a maximum expected intra-patient variability of 35% based on available literature estimates, a true ratio (T/R) of 0.95, 56 evaluable patients are adequate to achieve at least 81% power at 5% level of significance to meet the bioequivalence limit of 80.00% to 125.00% at Stage 1.

Sufficient number of patients will be enrolled to have 56 evaluable patients in the Stage 1 (about, but not limited to, 70 enrolled patients) and Stage 2 sample size (if needed) will be decided on the basis of data (observed CV) obtained after the completion of Stage 1. Maximum sample size (Stage 1 + Stage 2) is expected, but not limited to, approximately 120 enrolled patients. This is a 2-stage design according to Potvin C method[1]. Overall expected power is 86%.

Enrollment will be continued until at least 56 evaluable patients will complete the Stage 1. In case additional patients are recruited, those patients will continue the study until completion/withdrawal and be included in the pharmacokinetic and statistical analyses as applicable.

Note: Patients enrolled in Stage 1 will not be eligible for Stage 2.

7.2 Randomization Method

Randomization will be carried out using SAS® (SAS Institute Inc., USA) version 9.4 or higher.

[redacted]

Randomization will be done in blocks using PROC PLAN such that the design is balanced. The order of receiving reference and test formulations for each patient during two-periods of study will be determined according to the randomization schedule for Stage 1 and Stage 2 (as applicable). Randomization will be generated separately for each stage.

	Period 1	Period 2
Sequence 1	Test (T)	Reference (R)
Sequence 2	Reference (R)	Test (T)

Screening and Randomization Numbering

Each patient will be assigned a unique number that will serve to identify laboratory specimens and all documents and will be used throughout the study. If a patient fails to qualify for allocation to the study i.e. is a screen failure, his/her number must not be reused for another patient.

The screening number will be a combination of the center number, the project number and the patient number. The center number will be assigned by [redacted] to the investigative site (e.g., A, B, C, D) and subsequent sites are assigned consecutive alphabet numbers. Upon signing the informed consent form, the patient will be assigned a screening number by the Investigator. At each site, the first patient consented is assigned screening number e.g., [redacted], and subsequent patients are assigned consecutive numbers (e.g., the second patient consented is assigned screening number [redacted], the third patient is assigned screening number [redacted]). Once a screening number assigned to a patient, that number will not be reused for any other patient.

If the patient is deemed eligible for enrollment into the study and will commence dosing with IMP in Period 1, then a randomization number will be assigned. The randomization number will be assigned by a combination of Site ID and Dosing sequence (e.g., A-01 where A is Site ID and 01 is number of first patient dosed, A-02 where A is site ID and 02 is number of second patient dosed). Patient will be randomized on first come first serve basis and will be given a randomization number accordingly irrespective of their screening number.

There should be a source document maintained at the site which links the screening number to the randomization assignment number (once assigned) and this information will also be reflected in screening and enrollment log of site investigator file.

[redacted]

7.3 Blinding

This is an open label study. However, the bio-analyst at [redacted] will be blinded to the randomization sequence of study drug administration to each of the patient. Samples that are shipped to the analytical laboratory will not contain treatment information on the sample label.

7.4 Duration of Study

Total expected study duration will be approximately 64 days consisting of:

- Screening period including 10-day Dose Stabilization period: 40 days
- Treatment Period: 16 days
- End of Study: on Day 16
- Safety follow-up visit: On Day 24 ± 2 days; 8 ± 2 days after End of Study

For patients who are already receiving a stable dose of Lynparza® (olaparib) tablets (2*150 mg twice daily) for at least 10 days before screening visit, the duration of screening period will be 30 days. Expected study duration will be approximately 54 days.

7.5 Washout

There will be no Washout period between study periods.

7.6 Premature Termination of the Study

The sponsor reserves the right to discontinue the participation of either an individual site or the whole study at any time, for any reason, including, but not limited to the following:

- Determination of unexpected, significant, or unacceptable risk to participants;
- Patient enrolment is unsatisfactory;
- The Investigator has received from the sponsor all investigational medicinal products, means and information necessary to perform the clinical study and has not included any patient after a reasonable period of time mutually agreed upon;
- Non-compliance of the investigator, delegated staff with any provision of the clinical study protocol, and/or breach of the applicable laws and regulations or breach of the ICH GCP.

The investigator or the CRO reserves the right to discontinue the study for safety reasons at any time. The Ethics Committee (EC) or Regulatory Authority may ask to terminate the study, if there are major violations of ethical considerations or due to any serious adverse event(s). In all cases sponsor needs to be notified prior to study termination. Reasons for termination of study will be provided to patients. In case sponsor/PI

[redacted]

decides to terminate the study, the reason(s) for the termination will be notified to the EC and/or Regulatory Authority as applicable within 30 working days.

In the case that the study is discontinued prematurely for any reason including lack of commercial interest in pursuing the new drug application, a summary report will be submitted within 3 months. The summary report should provide a brief description of the study, the number of patients exposed to the drug, dose and duration of exposure, details of adverse drug reactions, if any, and the reason(s) for discontinuation of the study.

8.0 INVESTIGATIONAL MEDICINAL PRODUCTS

Test Product (T)	:	Olaparib tablets, 150 mg [redacted]
Reference Product (R)	:	Lynparza® (olaparib) tablets 150 mg Manufactured for: [redacted]

8.1 Procurement, Storage and Accountability Procedures for Investigational Medicinal Products

8.1.1 Receipt and storage of Investigational Medicinal Products

Adequate supplies of investigational medicinal products (IMPs) for dose administration and sample retention purpose will be received by Pharmacy custodian at clinical facility of [redacted] from sponsor. Test and reference products will be received in their respective pack as supplied by sponsor or as per the storage container / label information provided. After receipt of IMPs, they will be transferred to the pharmacy. IMPs will be stored in a secure area with restricted access, under controlled storage conditions described in the product package labelling, unless otherwise instructed per protocol or IMP management plan. Certificates of analysis (COA) with the details of the product will be received from sponsor.

IMPs sufficient for dosing and retention shall be distributed to sites by [redacted] These IMPs shall be distributed to sites in containers labeled with the details of Product name, Product Type (Test/Reference), Strength, No. of dosage units, Manufacturer, Batch or Lot No., Expiry date and Storage conditions. IMP management plan will be prepared to describe the IMP handling, storage, distribution/dispensing in detail.

The Investigator has overall responsibility for ensuring that IMPs are stored in a safe, limited access location, according to the conditions noted on the label. All IMPs are to be stored at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F), unless otherwise specified in the label. In case of temperature excursion (storage outside the labeled storage conditions) of IMP, the monitor must be contacted without delay. And in such case the investigator will be instructed by [redacted] (in consultation with sponsor) to either go ahead with the use of IMP or quarantine the IMP.

8.1.2 Accountability of Investigational Medicinal Products

[redacted]

Accountability for each unit of the IMPs will be documented in the respective logs at [redacted] and at the individual investigator sites. The inventory log of IMP shipments will be maintained at [redacted]

8.2 Dispensing

Dispensing will be done by the delegated site personnel for the IMPs received from [redacted] Only the Investigator and his/ her team will be responsible for the dispensing/administration/dosing of IMPs at the sites. Only patients randomized in the study will receive IMPs. The IMPs will be issued to the patient(s) according to the randomization schedule. Treatments for individual patients will be dispensed at the study sites. Patient will be given adequate IMPs for dosing at home for Days 2 to 4 (morning and evening), Day 5 (morning), Days 10 to 12 (for morning and evening) and Day 13 (morning). Patients will be reminded to store the IMPs in the original package at 20°C to 25°C (68°F to 77°F) and to return all unused IMPs to the study staff.

The Investigator team will be responsible for the accountability of administered/dosed IMPs at the study site. The drug accountability log for recording the receipt, issuance to the patients, and return of the IMPs will be maintained by the Investigator or authorized personnel. Limited responsibility may be delegated to a pharmacy representative if the investigator chooses to use a hospital or clinical pharmacy for the dispensing of the IMPs. However, this delegation must be documented.

Reconciliation between the amounts of IMPs supplied, dispensed and unused must be performed by the CRA / monitor / designee and any discrepancies in the reconciliation of the IMPs should have necessary clarification.

8.3 Handling of Unused Investigational Medicinal Products

IMPs that have not been dispensed to the patient will be retained in their original containers by the Investigator under controlled temperature unless otherwise advise by the [redacted] IMPs that are dispensed but un-dosed (e.g., due to the patient being unwell or withdrawal from study etc.) including unused IMPs returned by the patients will be labeled as "Not For Use", and should be retained at site along with the unused samples. This product will be maintained, under controlled temperature conditions, on site until further instruction is obtained from the [redacted] post study completion.

8.4 Maintenance of Randomization Code and Dispensing Record

Randomization code and IMP dispensing record will be kept under controlled access. Personnel involved in dispensing of IMPs (dispensing pharmacist), and the Investigator will be accountable for ensuring the compliance to randomization schedule and the monitor will confirm compliance during the monitoring visit.

Note: Details of IMP handling, dispensing, preparation and administration will be as per the latest version of IMP Plan.

[redacted]

8.5 Retention samples

Investigator site shall retain the reserve samples as provided by [redacted] These samples must be stored in sealed original container under conditions described in section 8.1.1 to preserve the original characteristics of the products for at least 5 years after obtaining the marketing approval or for 5 years after completion of the trial, if not approved for marketing.

Respective clinical site should be responsible for the use of IMPs for conduct of the study and for retention of reserve samples. Site will randomly select the samples from the supplied IMPs for retention as reserve samples in a sealed original container and use the remaining IMPs for study purpose. Each clinical site will be responsible for the appropriate storage of IMPs and to maintain temperature records for the entire duration, until the retention quantities are handed-over to the regulatory agency or until expiration of the 5 year retention period and sponsor's confirmation.

If the investigator is unable to retain the reserve samples at site, a third party may be used for retention of reserve samples after completion of the study.

Retention of IMPs will be as per the applicable regulatory requirements, details of which will be provided in the IMP plan.

Note: Separate study-specific IMP plan will be prepared. The storage, receipt, handling, dispensing and retention of IMPs will be handled as per latest version of the IMP plan.

8.6 IMP Non-Conformances

1. **Definitions**

   Non-conformances to the investigational medicinal product (test and reference product) or medical device can include:

   1) Complaints connected to the quality of the product such as

   - any fault of quality and/or effectiveness e.g. change of visual appearance, change of amount, damaged tablets/capsules, presence of foreign matter.
   - any fault of the containers and outer packages e.g. surface imperfection, container leakage, broken syringe/plunger, missing contents, device malfunction.
   - any fault of the labeling e.g. missing or illegible label.
   - any falsification of the medicinal product or medical device e.g. suspected product mix-up, tampering or counterfeiting.

   2) Deviations connected to the transport of the product, such as damaged transport carton and/or damaged secondary package upon receipt of the shipment, missing drugs from the shipment package, unsuitable transport conditions.

2. **Process**

   In case any of the non-conformances listed above are detected or information about these nonconformances has been received, the completed Non-conformance Report must be sent to the sponsor study manager within 24 hours. In parallel local monitor or CRA of the respective study must be informed about the non-conformance. If possible, a photo of affected material should be attached to the report. Affected material should be retained and stored according to the storage conditions label and/or returned to sponsor if requested by the sponsor.

9.0 SELECTION AND WITHDRAWAL OF PATIENTS

All patients will undergo screening procedure up to 40 days prior to Day 1 (up to 30 days prior to Day 1 for patients that are already receiving a stable dose of Lynparza® (olaparib) tablets). The patients will be selected based on the following inclusion and exclusion criteria.

9.1 Inclusion Criteria

To be eligible for the study, patients must meet all the following inclusion criteria:

1. **First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer** maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients based on a diagnostic test for BRCA mutation by NGS – Next Generation Sequencing method.

   OR

   Maintenance Treatment of Recurrent Ovarian Cancer maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.

   OR

   Advanced Germline BRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients based on a diagnostic test for BRCA mutation by NGS – Next Generation Sequencing method.

   OR

   Germline BRCA-mutated HER2-negative Metastatic Breast Cancer treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy

or be considered inappropriate for endocrine therapy. Select patients based on a diagnostic test for BRCA mutation by NGS – Next Generation Sequencing method.

2. Non-smoking, non-pregnant, non-lactating female patient ≥18 years of age with a body mass index (BMI) in the range of 18.50 to 30.00 kg/m^2 (both inclusive).
3. Able to give written informed consent for participation in the trial and willing to adhere to protocol requirements.
4. Patients that are already receiving a stable dose of Lynparza® (olaparib) tablets (2*150 mg tablets) 300 mg twice daily for at least 10 days.

   OR

   Patients requiring Olaparib in the dose of 300 mg (2*150 mg tablets) twice daily as per the discretion of the Investigators; these patients will be stabilized on Olaparib as a part of study and those patients that tolerate Olaparib in the dose of 300mg twice daily will be randomized in the study. Patients that do not tolerate the mentioned dose or require dose modifications for any reason will be considered as screen failure. Patients who miss 2 or more consecutive doses or more than 3 non-consecutive doses in the Dose Stabilization period will be considered screen failure.
5. Patient having an estimated survival of at least 3 months.
6. Adequate organ and bone marrow function based upon the following laboratory criteria at the time of eligibility assessment prior to dosing in period 1:

Body system	**Parameters**
Bone marrow function	a) Hemoglobin ≥9.0 g/dL b) Absolute neutrophil count ≥1500/uL c) Platelet count ≥100,000/uL d) WBC count > 3000/mm^3
Renal function	Creatinine Clearance > 50 mL/min (calculated based on Cockcroft-Gault formula)

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
8. Absence of blood transfusion in the 28 days prior to randomization.
9. **Women of non child bearing potential** with documented evidence of hysterectomy / bilateral salpingectomy / bilateral oophorectomy at least 6 months prior to IMP administration) or postmenopausal for at least 12 consecutive months.

   OR

[redacted]

Women of child bearing potential must have negative pregnancy test at screening visit and before randomization and must agree to use an effective method of avoiding pregnancy (including oral, transdermal or implanted contraceptives [any hormonal method in conjunction with a secondary method], intrauterine device, female condom with spermicide, diaphragm with spermicide, absolute sexual abstinence, use of condom with spermicide by sexual partner or sterile [at least 6 months prior to IMP administration] sexual partner) for at least 4 weeks prior to IMP administration, during the study and up to 6 months after the last dose of IMP. Cessation of birth control after this point should be discussed with a responsible physician.

9.2 Exclusion Criteria

Patients who meet any of the following criteria at screening will not be enrolled in the study:

1. History of known hypersensitivity to olaparib or its components which, in the opinion of the Investigator, would compromise the safety of the patient or the results of the study.
2. Patients found positive for HIV, Syphilis, Hepatitis B surface antigen or Hepatitis C antibody at screening.
3. Have ongoing clinically significant adverse event(s) due to prior treatments administered, as determined by the investigator.
4. Patients with Pneumonitis.
5. Patients with severe hepatic impairment (Child Pugh classification category C)
6. Patients who received any chemotherapy, radiotherapy, or any other anti-cancer therapy within 4 weeks from the last dose prior to first dosing in Period 01 (or a longer period depending on the defined characteristics of the agents used).
7. History or presence of any active infection or uncontrolled systemic disease (e.g. cardiovascular disease, hypertension, diabetes mellitus etc.) or any clinically significant disease, condition, disorder or abnormal laboratory finding that, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or influence the study results or the patient's ability to participate in the study.
8. Patient had major surgery within 4 weeks prior to first dosing in Period 01, or who have not recovered from prior major surgery.
9. In the opinion of the Investigator, the patient will not be compliant with the requirements of the study procedures.
10. Blood loss (1 unit or 350 ml) within 90 days prior to first dosing in Period 01 for the current study.
11. Receipt of an investigational medicinal product or participation in another drug research study involving IMP administration within 30 days (or 5 half-lives, whichever is longer) prior to first dosing in Period 01 for the current study.

[redacted]

Note: Elimination half-life of the study drug should be taken in consideration for inclusion of the patient in the study.

12. Usage of strong and moderate CYP3A4 inhibitors (e.g., cimetidine, ciprofloxacin, grapefruit juice) or strong and moderate CYP3A4 inducers (e.g., carbamazepine, phenytoin, St. John's Wort, rifampicin) within 30 days prior to first dosing in Period 01 (refer annexure IV for full list of prohibited medications).
13. History of difficulty in accessibility of veins or intolerance to direct venipuncture.
14. Pregnant or lactating females.
15. Patient positive on Breath alcohol analyzer test at the time of baseline/randomization visit.
16. Positive on urine test for drugs of abuse (including amphetamines, barbiturates, benzodiazepines, marijuana, cocaine, and morphine) prior to receiving the first dose of investigational medicinal product in the study.
17. History or presence of alcoholism or drug abuse.
18. Patients with psychiatric illness/social situations that would limit compliance with study requirements.
19. Difficulty in swallowing tablets.
20. Problems with fasting.
21. History or presence of clinically significant lactose, galactose, or fructose intolerance.

9.3 Withdrawal Criteria

An investigator may withdraw a patient from the study for any of the following:

1. The patient may be withdrawn from the trial at the discretion of the investigator and/or the sponsor if judged to be non-compliant with protocol/trial procedures.
2. Any major/significant deviation from the protocol that in the opinion of the investigator/sponsor may impact the patient's safety and/or the scientific integrity of the trial.
3. Any major safety concern such as (but not limited to) serious, life-threatening, or intolerable AEs that, in the opinion of the investigator and/or sponsor requires withdrawal from the study.
4. Patients who experience emesis within two times of Tmax value (i.e. 3 hours) on Day 8 or Day 16. Patients who experience emesis at any other time during the study will be evaluated for their continued participation in the study based on the investigator's and sponsor's assessment.
5. Patients who experience diarrhea (defined as three or more episodes of loose stools during a 24 hour interval) at any time during the study will be evaluated by the investigator and sponsor and a decision for continued participation in the study will be made based on the potential impact of the event on the integrity of the study results and patient's safety.

[redacted]

6. If a patient found positive for Coronavirus infection (COVID-19) during the study.
7. If patient requires dose modification (i.e. change from 300 mg twice daily) or dose interruption during study participation.
8. Any patient who requires the use of unacceptable concomitant medicines.
9. If a patient becomes pregnant or develops hypersensitivity to Olaparib or to any of the excipients during the course of the trial.
10. Significant inter-current illness and/or surgery that in the opinion of the investigator and/or sponsor requires withdrawal from the study.
11. Disease exacerbation/progression that in the opinion of the investigator requires interruption and/or change in therapeutic modality.
12. If the patient requires any concomitant medication, which as per judgment of the investigator may significantly interfere with the pharmacokinetic property of the study IMP.
13. If it is felt in the investigator's opinion that it is not in the patient's best interest to continue.
14. If the patient on their own, wishes to withdraw consent.
15. Missing sample(s) or incidence of AEs that affect the pharmacokinetics of the analyte, thus preventing a planned statistical comparison.
16. Patients who miss 2 or more consecutive IMP doses or more than 3 non-consecutive doses in a given period.

Any patient withdrawal during the study along with the reason thereof shall be documented in the CRF and reported to sponsor.

The planned sample size accounts for withdrawal among the randomized patients, so withdrawn patients will not be replaced.

Irrespective of the reason of withdrawal, the patient will be requested to complete all procedures/activities required for End of Study safety assessment as far as possible.

10.0 TREATMENT OF PATIENTS

10.1 Housing

Patients will be housed in the clinical facility at least 12 hours prior to morning dose on Day 1 and will be confined for at least 12 hours after morning dose on Day 1.

The patients will also be housed in the clinic at least 12 hours before morning dose on Day 6 until 12 hours post morning dose on Day 9. The patients will also be housed in the clinic at least 12 hours before morning dose on Day 14 until 12 hours post morning dose on Day 16.

[redacted]

Note: In addition to above requirements, the patients may be housed in the clinical facility (hospital) for the entire duration of the study or a definite duration in the study, if in the opinion of the Investigator, it facilitates the study procedures or for social reasons (like difficulty in travelling etc.). The Investigator will be required to document this decision in the patient source document (like patient hospital records). Hospitalizations performed for these reasons will not be considered as SAE. However, if the patient is hospitalised for reasons related to safety or adverse events, the hospitalization will be considered as SAE.

10.2 Dosing

Stabilization Phase:

The patients found eligible for participation in the study, but not yet on a stable dose of Lynparza® (olaparib) tablets, will be enrolled in the Dose Stabilization period. Dose Stabilization period will be applicable for patients that are not on a stable dose of Lynparza® (olaparib) tablets 2*150 mg (for at least 10 days). Following this, patients will be randomized to participate in the study. Patients that do not tolerate the mentioned dose or require dose modifications for any reason will be considered as screen failure. Patients who miss 2 or more consecutive doses or more than 3 non-consecutive doses in the Dose Stabilization period will be considered screen failure.

Patients that are already on a stable dose of Lynparza® (olaparib) tablets (2*150 mg twice daily) for at least 10 days and have met the eligibility criteria will be directly randomized for participation in the study.

Periods I and II:

Patients will be dosed or advised to take the investigational medicinal product (2*150 mg twice daily) (allocated as per randomization schedule) orally in sitting posture with approximately 240 (±5 mL) of drinking water at ambient temperature which must be completely consumed. Patients will be instructed not to chew, crush, touch or divide the tablet but to swallow as a whole. On days of housing, dosing will be followed by thorough hand and mouth check for assessing compliance.

Dosing time on Day 1 morning will be considered as reference time for dosing in the entire study. Evening dose will be administered 12 hours after the morning dose. All the patients will be required to consume the investigational medicinal product preferably at the same time each day.

Window period of within 1 hour will be allowed if the patient misses the scheduled time of dosing. If a patient misses a dose, the dose should be taken as soon as possible, if this can be done within 1 hour of the scheduled time. The next dose should be taken at its scheduled time. If a patient misses a dose for more than 1 hour, they should take the next dose at its scheduled time.

In period I:

On day 0, patient will be asked to reach the site at least 12 hours prior to scheduled dosing on Day 1 and will be housed for 12 hours after morning dose of Day 1. Patient will be administered two tablets (2*150 mg

[redacted]

tablets) of investigational medicinal product in morning and evening as per randomization schedule under supervision of trained study personnel at clinical facility.

Dosing on Day 1 (morning as well as evening) would be done at site. Patients will be discharged after administration of evening dose of Day 1 at site. Dosing from Day 2 to Day 5 can be done at home by patients. The patient will be provided with sufficient Investigational medicinal product for dosing at their home for Day 2 and Day 4 (for morning and evening daily dosing at 12-hours interval) and Day 5 morning dosing). Day 5 evening dose will be done at site.

Patient will also be provided with a patient diary card to enter the details of study drug consumption and details of AE (if any) at their home. Patient and their attendant will be provided with adequate instructions to complete the patient diary card at their home.

Patient will be requested to come to the clinical facility for evening dose on Day 5 (at least 12 hours prior to scheduled morning dosing on Day 6) for housing in the clinical facility.

During the patients stay in the clinical facility on Day 6, Day 7 and Day 8, patients will be administered the investigational medicinal product at the scheduled time of dosing in morning and evening daily at 12-hours interval under supervision of trained study personnel.

In period II:

Patient will be crossed over to the other investigational medicinal product (allocated as per randomization schedule) on Day 9 morning dose. Dosing on Day 9 (morning as well as evening) would be done at site. Patient will be discharged after administration of evening dose of Day 9 at site. Dosing from Day 10 to Day 13 morning can be done at home by patients. The patient will be provided with sufficient investigational medicinal product for dosing at their home from Day 10 to Day 12 (for morning and evening daily dosing at 12-hours interval) and Day 13 morning dosing. Day 13 evening dose will be done at site.

Patient will also be provided with a patient diary card to enter the details of study drug consumption and details of AE (if any) at their home. Patient and their attendant will be provided with adequate instructions to complete the patient diary card at their home.

Patient will be requested to come to the clinical facility for evening dose on Day 13 (at least 12 hours prior to scheduled morning dosing on Day 14) for housing in the clinical facility.

During the patients stay in the clinical facility on Day 14, Day 15 and Day 16 patients will be administered the investigational medicinal product at the scheduled time of dosing in morning and evening daily at 12-hours interval under supervision of trained study personnel.

Note:

[redacted]

- In the Dose Stabilization period, patients will receive approved marketed version of Olaparib, details of the same will be included in IMP plan.
- After the study is completed (after last PK sample collection on Day 16), patients may be continued on their current dose of Olaparib using an approved Olaparib product as prescribed by their clinicians.

10.3 Dosing Compliance

Compliance for dosing will be assessed by checking the patient's diary for IMP consumption at home, pasting the duplicate label of dispensed container on the 'Dosing' section of individual source data form and a thorough check of the oral cavity using torch immediately after dosing when the dosing will be done in clinical facility. In addition to this the study coordinator will remind the patient on daily basis for consumption of IMP and a telephone log will be generated for the same.

Missing dose

Window period of within 1 hour will be allowed if the patient misses the scheduled time of dosing. If a patient misses a dose, the dose should be taken as soon as possible, if this can be done within 1 hour of the scheduled time. The next dose should be taken at its scheduled time. If a patient misses a dose for more than 1 hour, they should take the next dose at its scheduled time. Patients who miss 2 or more consecutive doses or more than 3 non-consecutive IMP doses in a given period will be discontinued from the study.

10.4 Sampling Schedule

A total of 43 blood samples each of 03 mL will be collected from each patient for PK assessment during the study.

The venous blood samples will be withdrawn from each patient in each period at the following timepoints:

[redacted]

The post dose blood samples will be collected with an allowable deviation of ± 2 minutes. In all instances, however, the exact time of dosing and of each sample collection must be recorded. Samples collected outside the scheduled time will be considered as protocol deviations.

Note:

1. 12.00 hours blood sample must be collected prior to next drug administration.
2. Blood sample collection (PK samples) will be collected first if other activities are coinciding.

[redacted]

[redacted]

10.5 Sample Collection Procedure

Blood samples will be collected through an indwelling intravenous cannula placed preferably in the forearm vein of the patients. Heparin-lock technique, injecting 0.5 mL of 5 IU/mL of heparin in normal saline solution, will be used to prevent clotting of blood in the indwelling cannula. While sampling through the cannula, blood samples will be collected after discarding the first 0.5 mL of heparinized blood from the cannula. If insertion of cannula is not possible, alternatively blood samples may be drawn by a fresh vein puncture or in case of blockade in an existing cannula, extra saline will be injected to stimulate the cannula and later blood samples will be collected after discarding the first 0.5 mL of blood. If required, blood samples may also be collected through a fresh vein puncture.

Blood samples will be withdrawn using syringe / adaptor and transferred into pre-labeled (Project No., Patient No., Period, Sampling time point and Sample code) vacutainer containing K3EDTA as anticoagulant.

10.6 Blood Volume

Total blood loss will not exceed 187 mL for each patient.

For each patient, a total of 43 PK samples each of 03 mL will be collected during the study and the total volume of blood drawn including 0.5 mL of discarded blood prior to each sample collected through cannula, up to 10 mL of blood drawn for screening prior to the study, up to 10 mL of blood drawn for CBC, Creatinine Clearance, S Bilirubin, SGPT and SGOT prior to dosing in periods 1 and 2 and up to 10 mL of blood drawn for post-study safety assessment will not exceed 177 + 10.0 mL (if required in case of sample hemolyzed, sample clotted, spillage or lost or any other reason) for each Patient.

	PK assessment (43 PK samples x 03 mL each)	=	129 mL
+	36 x 0.5 mL discarded blood	=	18 mL
+	For Screening prior to the study	=	10 mL
+	For CBC, Creatinine Clearance, S Bilirubin, SGPT and SGOT prior to dosing in period 1 and 2	=	10 mL
+	Blood withdrawn for post study safety assessment	=	10 mL
Blood Loss including 10 mL in case if blood recollection is required		=	**177 mL + 10 mL = 187 mL**

11.0 RESTRICTIONS

11.1 Posture restriction

Patients will be advised to remain awake and in semi-reclined position for the first 4 hours after morning dosing on Day 1, Day 8 and Day 16. They will be asked to rise only with assistance during this period of time and at the first rising when this period is over.

After 4 hours after dosing, the patients will be allowed to engage in normal activities while avoiding strenuous physical exertion.

11.2 Dietary and water restriction

On housing days, patients will be required to do an overnight fast of at least 8 hours before their scheduled time for dosing and for 4 hours after dosing for the morning dose, and 2 hours before their scheduled time for dosing and 2 hours after dosing for the evening dose.

For dosing at home, all patients will be required to remain in fasting condition of at least 2 hours before their scheduled time for dosing and 2 hours after dosing for morning and evening dose.

On housing days patients will receive standard meals (lunch, snacks and dinner) with the same quantity and same menu will be used (on housing day) for both periods.

There will not be any pre-dose and post-dose water restriction during dosing at home.

On housing days, water will not be allowed for 1 hour before and 1 hour after morning dose and evening dose drug administration, when no liquid should be permitted other than that 240 mL (±5 mL) for drug dosing.

11.3 Concomitant Medications

Prohibited Medications: Moderate or strong CYP 3A4 inhibitors and inducers (refer annexure IV). Patients should be instructed to avoid grapefruit, grapefruit juice, Seville oranges, Seville orange juice, starfruit and pomelo.

Any drug therapy taken by a patient should be the same for both periods. If a change in concomitant medications is necessary or if drug therapy (prescription or over-the-counter) other than that specified in the protocol is required prior to or during the study, decision shall be taken by the Investigator and sponsor to continue or discontinue the patient based on the following:

- The pharmacology and pharmacokinetics of the non-study medication.
- The likelihood of a drug–drug interaction, thereby affecting the pharmacokinetic comparison of study medicine.

[redacted]

- The likelihood of a drug–drug LC-MS/MS cross-interaction, thereby affecting the determination of olaparib concentration in patient plasma.
- The time and duration of administration of the non-study medicine.

If it is necessary for the patient's safety to add any medication that interferes or changes the PK of olaparib, the patient should be withdrawn from the study.

Before prescribing any drug it is mandatory to refer Prescribing Information of Lynparza® including but not limited to interaction with other medicinal products and other forms of interaction, contraindications, special warnings and precautions for use, undesirable side effects, etc.

The Investigator should ask the patient to notify to the study site about any new medications they take after the start of the study. All instances of concomitant drug administration will be recorded and reported in the CRF and final report.

Medication taken prior to first dosing: All prescription medications and over-the-counter drugs (including vitamins and herbal remedies) taken within 30 days prior to screening must be recorded in the CRF.

Concomitant medications: All the medications ongoing at the time of consent and mediations consumed until the end of the study safety assessments will be recorded in prior/ concomitant medications section of the CRF.

11.4 Others

Patients will be instructed during screening to refrain from smoking, chewing tobacco, pan or pan masala, gutkha, masala (containing betel nut and tobacco) and from consuming any alcoholic products, Xanthine-containing items (i.e., tea, coffee, cola drinks, or chocolate/coca etc.) from 48 hours prior to IMP administration on Day 1 until the last PK blood sample collection of study. All patients will also be instructed to abstain from grapefruit, pomelo, starfruit or Seville orange containing food/juice, recreational drugs (cocaine, amphetamines, barbiturates, benzodiazepines, cannabinoids and morphine) 28 days prior to randomization until the last PK blood sample collection of study. Patients should refrain from strenuous exercise for 24 hours before each check-in day.

12.0 CLINICAL AND SAFETY ASSESSMENT

It is the responsibility of the PI to ensure that adequate medical supervision and care is available for the study patients during housing and during the study duration to ensure the utmost safety and well-being of the study patients. At study sites, medical personnel will be available 24 hours a day and physician in charge will remain at the clinical site for at least the first 4 hours following drug administration. On PK sampling days (Day 8 and 16), Investigator will remain at the clinical site for at least the first 4 hours following morning drug administration. In addition, if necessary, Investigators will be available on-call at all times.

[redacted]

Medical and Medication history and Review of Inclusion and Exclusion Criteria: Screening and at the time of randomization.

HER2 Testing (Only applicable for breast cancer patients): Screening (If the report is not available with the patients at the time of screening).

Germline or Somatic BRCA1 and BRCA2 diagnostic test for olaparib by NGS – Next Generation Sequencing method: Screening (the details for applicable patients and type of sample as per the section 5.6).

Note: The Germline or Somatic BRCA1 and BRCA2 test need not be repeated in those patients who have been started on olaparib post BRCA testing done by NGS – Next Generation Sequencing method.

Physical examination: Screening, Day 0, Day 5 and Day 13 and End of Study (Day 16), Safety follow up (on day 24±2).

Demographics: Age, gender, ethnicity and race will be noted at screening visit.

[redacted]

Additional vital examinations may be performed at any time during the study as per Investigator's judgement; all results must be documented appropriately.

HIV, HCV, HbSAg, and VDRL or RPR (for syphilis): Screening

[redacted]

[redacted]

12-Lead ECG: Screening, Day 5, Day 13 and End of Study (Day 16)

2D-ECHO: Screening

Urine drug Screen (benzodiazepines, opioids, amphetamines, cannabinoids, cocaine and barbiturates) and Alcohol Breath Test: Day 0, Day 5 and Day 13

Note: Separate mouthpiece will be used in breath test for every patient in the study

Pregnancy test: Screening visit (Serum), Day 0, Day 5, Day 13 (Urine), and at End of Study visit (Serum) for FCBP only.

X-ray (chest): To be performed based on Investigator's discretion.

Hematology, Blood chemistry and Urinalysis: Screening, and at the end of the study (Day 16).

CBC, Creatinine Clearance, S Billirubin, SGPT and SGOT: Prior to dosing in period 1 (Day -2 to 0) and period 2 (can be performed after evening dose on Day 8) (can be done at local laboratory).

In addition to protocol-specific laboratory tests and/or clinical examinations at scheduled time points, additional tests/clinical examination may be conducted to evaluate patient safety at any time during the study, at the discretion of the Investigator (can be done in local laboratory or nearby clinic/hospital/institution).

Note: It is recommended that general precautions are taken by the staff with respect to ongoing COVID-19 pandemic situation during the trial.

12.1 Clinical Examination

Relevant medical history/ Current medical conditions

Relevant medical history and current medical conditions occurring until provision of written informed consent will be reported in the Relevant Medical History and current medical conditions section of the CRF.

Physical examination

This evaluation will include an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and nervous system evaluation. Information about the physical examination must be present in the source documentation at the study site. Clinically significant findings that are present at the time of screening will be included in the relevant medical history and Current medical conditions section of the CRF. Clinically significant findings or worsening of any pre-existing conditions/diseases after providing written informed consent (after screening) must be recorded in the Adverse Event section of CRF.

ECG evaluations

Standard 12-lead ECGs will be performed. The patient identifiers, the date and actual time of the tracing must appear on each page of the tracing. Tracings will be dated and signed by the person who makes the interpretation.

[redacted]

Chest X-ray

Chest X-ray will be performed based on Investigator's discretion.

Standard clinical laboratory evaluations

The Investigator will evaluate the clinical significance of each laboratory value outside of the reference range. This decision shall be based upon the nature and degree of the observed abnormality. Values which are considered clinically significant will be noted in the Notes field of the CRF. The investigator may choose to repeat any abnormal result ONCE, in order to rule out laboratory error. "NCS" will be entered on the original laboratory sheet which are outside the reference range but are judged "not clinically significant" and archived with the source documents. The physician making these assessments shall date and sign or initial each laboratory report. Clinically relevant deviations of laboratory test results (see section 12.2.1) occurring during or at completion of the study must be reported as adverse events.

12.2 Safety monitoring and reporting

12.2.1 Adverse Events

12.2.1.1 Definition of adverse events and reporting requirements

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written study-specific informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. The investigator has the responsibility for managing the safety of individual subject and identifying adverse events. The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Any AE (non-serious and serious) occurring after the subject has provided study-specific informed consent and until the last study visit of the subject, has to be recorded on the AE pages of the Case Report Form (CRF).

Medical conditions/diseases present before providing written informed consent are only considered AEs if they worsen after enrolment.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms;
- they are considered clinically significant;
- they require therapy.

[redacted]

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about already known adverse drug reactions for the Investigational Medicinal Product drug can be found in the Reference Safety Information (e.g. Prescribing information).

Each adverse event should be evaluated to determine the following:

A. Severity of AEs

Adverse events should be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade refers to the severity of the AE. The CTCAE version 5.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

*Instrumental ADL (Activities of Daily Living) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

B. Relationship to IMP

Adverse event's relationship to the study treatment should be determined (suspected/not suspected). Causality assessments are critical and must be provided for each unique AE in relation to each IMP, non-investigational medicinal product (NIMP) or other concomitant medication, if applicable. Missing causality assessments will be handled as suspected to IMP by the sponsor. The causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject.

C. Evaluation of AEs (duration, action taken, outcome)

The duration (start and end dates) of adverse event should be recorded. Determine whether AE constitutes a serious adverse event (see Section 12.2.2 for definition of SAE) and which seriousness criteria have been met.

Actions taken with respect to investigation medicinal product should be documented as per the below given tabulation using CDISC STDM terminology.

Adverse Event Variable Label	CDISC STDM Terms
Action Taken with the IMP	• Dose increased; • Dose not changed; • Dose rate reduced; • Dose reduced; • Drug interrupted; • Drug withdrawn; • Not applicable; • Not known

The outcome of the adverse should be documented and assigned to one of the following categories:

Adverse Event Variable Label	CDISC STDM Terms
Outcome of event	• Not recovered/not resolved; • Recovered/resolved; • Recovered/resolved with sequelae; • Recovering/resolving; • Fatal; or • Unknown.

All AEs must be treated appropriately. The treatment of the AE should be documented in the CRF. Concomitant medication, other non-IMP treatments or changes in the administration of the IMP should be specified and documented. Treatment may include one or more of the following:

- No action taken (i.e. further observation only);

[redacted]

- IMP dosage adjusted/temporarily interrupted;
- IMP permanently discontinued due to this AE;
- Concomitant medication given;
- Non-drug therapy given, patient hospitalized / patient's hospitalization prolonged.

Adverse events should be recorded in the CRF under the signs, symptoms or diagnosis associated with them.

All AEs including both volunteered and the ones considered clinically relevant and reportable as AE by investigator will be recorded in the CRF and in the patient's medical records, irrespective of its association with study medications. Independent /Institutional Ethics Committee (IEC) will be informed regarding AEs as necessary.

12.2.1.2 The Most Common Adverse Events Associated with Study Medication

- Patients should be carefully monitored for adverse events/toxicity. To manage adverse events such as Myelodysplastic syndrome/Acute myeloid leukemia, Haematological toxicity, Pneumonitis, or Venous Thromboembolic Events, the dose may be reduced or interrupt the treatment.
- To manage adverse reactions, consider interruption of treatment or dose reduction. The recommended dose reduction is 250 mg taken twice daily. If a further dose reduction is required, then reduce to 200 mg taken twice daily.
- Dose adjustment is to be done by the Investigator as per the approved Summary of Product Characteristics, Prescribing Information of Lynparza® and the protocol.
- Refer Summary of Product Characteristics and Prescribing Information of Lynparza® for further information on management of AEs.

NOTE: If patient requires dose modification (i.e., change from 300 mg twice daily) or dose interruption during study participation, the patient should be withdrawn from the study.

12.2.2 Serious Adverse Events (SAE)

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)] which meets any one of the following criteria:

- results in death
- is life-threatening: Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition

- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the study specific informed consent
- General care, not associated with any deterioration in condition
- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- is medically significant: Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICHE2D Guidelines). All malignant neoplasms will be assessed as serious under "medically significant", if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction. All reports of intentional misuse and abuse of the product are also considered serious adverse events irrespective if a clinical event has occurred.

A **(Serious) Adverse Drug Reaction ((S)ADR) is** any (S)AE for which the investigator or sponsor assess a reasonable possibility for a causal relationship to a medicinal product.

A (Serious) Unexpected Adverse Reactions is defined as a (serious) adverse drug reaction, which is not consistent with the Reference Safety Information (e.g. Summary of Product Characteristics (SmPC), Product Monograph, Investigator's Brochure). Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events. The term 'severity' is used here to describe the intensity of a specific event. This has to be distinguished from the term 'serious'.

12.2.2.1 SAE reporting

It is **vitally important that the investigator reports immediately**, i.e., no later than 24 hours after awareness, any SAEs, or updates to previously reported SAEs, even if the investigator does not consider the AE to be drug-related.

The investigator should send SAE reports on the "Serious Adverse Event Report Form" (Novartis form), as initial or follow-up reports, via fax or email to the Country Organization Patient Safety Team, and in copy to the responsible Study Manager (Sponsor / CRO) as well as to the Indian Health Authority DCGI, to the addresses provided in the table below.

[redacted]

The investigator should also send all updates / new information on a new SAE Report Form as a follow-up to the previously reported SAE. The follow-up information should describe whether the event has resolved or continues, if a diagnosis is available, if and how it was treated, and whether the subject continued or withdrew from study participation.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs.

An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Any queries from the Country Organization Patient Safety Team, to Contract Research Organization (CRO) or sponsor regarding SAE reports should be answered by the investigator within 24 hours.

For more detailed information refer to the "Quick Reference Guide for Completing the SAE Form" and the Manual for Completing the Novartis SAE Form for Clinical Trials" (Novartis documents).

The investigator should retain a delivery confirmation of the SAE reports for all recipients in the investigator study file.

If a patient dies during participation in the study and an autopsy is performed, a copy of the report must be submitted.

The investigator will send a full/detailed report of SAE, after due analysis within 14 days of SAE to the Sponsor/Sponsor's representative, Central Licensing Authority, chairman of Ethics Committee, and the Head of the institution where the trial is being conducted.

Note: the initial SAE report must be sent within 24 hours of awareness.

In case investigator fails to report any SAE within stipulated period, the investigator shall have to furnish the reason for the delay to the satisfaction of licensing authority along with the report of SAE.

Ongoing serious adverse events at the time of last visit

For any SAEs still ongoing at the time of last visit, the investigator should continue to follow-up until the SAE has resolved or has stabilized or is judged permanent for SAEs considered to be related to IMP (SADRs), and for up to 30 days after the last dosing of subject for non-related SAEs. The investigator should send SAE follow-up reports to recipients as described in the preceding paragraphs. Where appropriate, medical tests and examinations will be performed to document resolution of event(s). The investigator should send SAE follow-up reports including all relevant new or reassessed information (e.g., concomitant treatment, medical history) obtained on the SAE /pregnancy as described in the preceding paragraphs.

Serious adverse events occurring after the last visit

Any SAEs experienced within the 30 day period following the last administration of study treatment has to be reported to sponsor. In case a compound with a long half-life is investigated, the 30-day period will be extended accordingly.

[redacted]

After this period, events should only be reported to sponsor if the investigator suspects a causal relationship to study treatment. The investigator must report the SADR to recipients as described in the preceding paragraphs.

[redacted]

[redacted]

12.2.3 Investigator Notification and 6 monthly line listings

If a SADR is not listed in the Reference Safety Information (e.g. Prescribing information), the sponsor may urgently require further information from the investigator for Health Authority reporting.

The sponsor may, if applicable, issue Investigator Notifications and 6 monthly line listings of Suspected Unexpected Serious Adverse Reactions (SUSARs) to all investigators concerned with any study with the same IMP.

The submission of these Investigator Notifications and 6-monthly line listings, if applicable, to local IRBs / Ethics Committees is the responsibility of the investigator or the CRO as stipulated in the study contract. The submission of Investigator Notifications and 6-monthly line listings to national Ethics Committee is the responsibility of the CRO, if applicable.

[redacted]

[redacted]

12.2.4 Health authority reporting

The sponsor will submit all reportable cases within the requested timelines to all concerned health authorities.

12.2.5 Pregnancy Reporting

The investigator must report any cases of pregnancy of subjects in the course of a study **immediately (within 24 hours)** of awareness to the Country Organization Patient Safety Team and in copy to the Study Manager (Sponsor / CRO). Pregnancies are only reported from the time of first IMP dose.

The investigator should immediately withdraw the subject from the study, and should follow-up each case of pregnancy, and report the outcome, including spontaneous or voluntary termination, details of the birth, and any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Cases of pregnancy are reported on a "Drug Exposure in Pregnancy Form" (Novartis form). Pregnancy follow-up are reported on the same form and should include an assessment of the relatedness of any untoward pregnancy outcome to the IMP.

Any SAE during pregnancy of a subject must be reported on the SAE Report Form and reported as described.

The investigator should retain a delivery confirmation of the "Drug Exposure in Pregnancy Form" for all recipients in the investigator study file.

For more detailed information refer to the "Quick Reference Guide for Completing the Drug Exposure in Pregnancy Form" (Novartis document).

12.2.6 Special case scenarios

Special case scenarios can be serious or non-serious (see table below), and they should be reported like AE cases as described in section 12.2.2 and 12.2.3, even if no (other) AEs are associated with their occurrence.

Special case scenario	Reportable within 24 hours from investigator to Country Organization Patient Safety Team
Drug exposure during breastfeeding	x
Intentional Overdose by patient (including suicide attempts, suicide attempt is always serious)	Only if associated with SAE
Drug / drug interactions	Only if associated with SAE
Withdrawal syndrome/ reaction	Only if associated with SAE
Drug dependence, misuse, abuse or addiction (always serious)	x

[redacted]

[redacted]

Special case scenario	Reportable within 24 hours from investigator to Country Organization Patient Safety Team
Suspected Transmission of infectious agents (always serious)	x
Death (incl. without other event, always serious)	x

12.2.7 IMP related complaints

In case of quality complaints related to the IMP, the investigator within 24 hours of learning of its occurrence informs the sponsor as described in section 8.6. Any AE associated with a quality complaint needs to be documented and reported in addition by the investigator as described in sections 12.2.1, 12.2.2 and 12.2.3.

12.2.8 Reconciliation

Reconciliation between the safety database of the sponsor and the clinical database at the CRO will be done periodically as described in Safety Management Plan by comparing line listings from the safety database with the data in the clinical database.

The Monitor will review the CRFs / the clinical database for potentially unreported cases. For any reportable case, the following parameters need to match exactly between the clinical and the safety database: trial number, site number, subject/patient number, randomization number, investigational drug, seriousness, date of death (if applicable) and investigator causality. All other parameters only need to be plausibly and medically consistent.

For any reportable case assessed as suspected or for other events of special interest (if applicable), a more detailed reconciliation should be conducted, including also treatment dates, outcome, medical history and concomitant therapy.

12.2.9 Investigator Training

By his/her signature of the study protocol, the principal investigator certifies that he/she has been trained in the Sponsor AE/SAE and pregnancy reporting obligations by the CRO as defined in the study protocol.

Note: All the activities will be performed as per the latest version of Safety Management Plan.

13.0 SAMPLE PROCESSING AND TRANSFER PROCEDURES

Clinical Laboratory Samples:

All clinical laboratory blood and urine samples will be transferred to the central laboratory/local laboratory in controlled temperature and in pre validated laboratory kits which will be supplied to all the sites by the central laboratory. In case of emergency, samples can be sent to local laboratory for safety assessment at the discretion of the Investigator.

[redacted]

Pharmacokinetic samples:

After collection of blood samples from patients at each time point, they will be centrifuged at 4000 revolutions per minute (RPM) for 10 minutes under ambient conditions or at 2-8°C temperature as per method requirement to separate plasma. After centrifugation, the plasma will be aspirated and transferred into 2 clear polypropylene aliquots. A minimum of 0.5 mL plasma will be transferred to the first aliquot and remaining mL of plasma will be transfer in to aliquot 2. Aliquots will be pre-labeled with at least the following information: Blood sampling time point, Protocol Number, Study Period, Aliquot Number and Subject/patient (terms may be used interchangeably) Number. The plasma samples will be stored at -20±5°C in a freezer until shipment to the Bioanalytical facility of [redacted] India and then stored at -78±8°C until analysis.

After completion of analysis aliquot 1 will be discarded after confirmation with sponsor and aliquot 2 will be stored at -78±8°C.

Throughout sample collection and following centrifugation, the samples will be kept in wet ice-bath until stored in the freezer. Entire sample processing should be completed within 2 hours of sample collection.

Sample Shipment

After completion of clinical phase/each period of the study, the plasma samples will be transferred from the clinical site to the bioanalytical research facility of [redacted] All plasma samples will be transported to [redacted] in at least two shipments, with each set of aliquots in separate shipments. Once the analytical site confirms the receipt of the first shipment the second set of aliquots will be sent based on the request from the analytical site. During transfer, all samples will be packed with sufficient dry ice for maintaining the integrity of samples and to prevent thermal degradation. Data logger(s) will be placed in each shipment to monitor the temperature during shipment.

Note: Please refer latest version of Laboratory Manual and Bio-analytical plan for details.

14.0 BIOANALYTICAL PROCEDURES

The concentration of Olaparib in plasma samples will be quantified at [redacted] using validated LC-MS/MS method.

14.1 Method Validation

Bioanalytical method will be validated at [redacted] which is in accordance with the current regulatory guidelines on validation of bioanalytical methods.

Method validation of Olaparib in human plasma will be carried out by using analytical method developed at [redacted] This analytical method will be validated for the sensitivity, specificity, matrix effect, linearity, ruggedness, accuracy and precision (repeatability and reproducibility), percent recovery and stability of samples (freeze-thaw stability, bench-top stability, autosampler stability, short-term and long-term stability of stock solution and internal standard).

[redacted]

14.2 Assay of Samples

The plasma sample will be quantified for Olaparib using a validated method. Plasma samples of patients included in the PK dataset (defined in section 15) will be analyzed.

Pharmacokinetic repeats will not be performed for this study.

The analysis of patient's samples will be done using calibration curve with quality control samples, distributed throughout each batch. The details for the preparation of the calibration curve and quality control samples and the analytical batch acceptance criteria will be discussed in the respective in-house procedure. The analyst will not have access to the randomization schedule until analysis is completed.

Incurred Study Sample Re-analysis

Incurred Study sample analysis will be performed to ensure method reproducibility as per [redacted]

Note: All the activities will be performed as per the latest /updated version of bioanalytical plan for the study.

15.0 PHARMACOKINETICS AND STATISTICAL ANALYSIS

Pharmacokinetic and statistical analyses for plasma concentration versus time profile of Olaparib will be performed on the data obtained from patients included in the PK dataset.

PK dataset

Data from the following patients will be included in the PK dataset:

- Patients who have completed both periods and have missed samples in any period that may not affect the estimation of the $C_{max,ss}$ and/or AUC parameters and have been predetermined prior to the bioanalytical analysis to not significantly impact the overall outcome of the study;
- Patients who complied with all protocol requirements, or encountered protocol deviations that do not impact the estimation of the PK parameters.

Patients withdrawn prior to sample analysis for pharmacokinetic reasons (i.e., an event that could result in an inadequately characterized pharmacokinetic profile for olaparib) will not be included in the PK and statistical analysis.

Any decision for excluding data from the final data set will be provided with a detailed explanation and will be properly recorded and dated.

PK dataset will be defined in consultation with the sponsor at different study stages for different sets of patients, prior to initiation of sample analysis for each set of patients. This dataset will be reassessed, if

[redacted]

required (e.g., missing concentration value due to analytical reason), upon completion of the sample analysis. The PK dataset will be finally confirmed by the sponsor prior to database lock.

Safety Dataset

The safety dataset will include randomized patients who receive at least one dose of IMP. Data from subjects in this dataset will be used for the assessment of safety.

15.1 Pharmacokinetic Parameters

Pharmacokinetic parameters C_{maxSS}, C_{minSS}, $AUC_{(0-\tau)SS}$, C_{avSS}, T_{maxSS}, Swing, percentage of fluctuation will be calculated using plasma concentration vs time profile (Actual time of sample collection) data of both investigational medicinal products in individual patients using Phoenix®WinNonlin® Software Version 8.2 or higher (Pharsight Corporation, USA).

Primary parameters:	
C_{maxSS}	Maximum plasma concentration during the dosing interval at steady state
$AUC_{(0-\tau)SS}$	Area under the plasma concentration versus time curve for one dosing interval at steady state

Secondary Parameters:	
C_{minSS}	Concentration at the end of a dosing interval
C_{avSS}	Average plasma concentration over the steady state dosing interval
T_{maxSS}	Time of maximum measured plasma concentration over the steady state dosing interval
Swing	$[C_{maxSS}–C_{minSS}/ C_{minSS}]*100$
Percentage of fluctuation	$[C_{maxSS}–C_{minSS}/C_{avSS}]*100$

Pharmacokinetic parameters will be calculated by non-compartmental analysis using Phoenix®WinNonlin® software Version 8.2 or higher (Pharsight Corporation, USA). All pharmacokinetic parameters will be estimated from the Plasma concentration time profile data.

All concentration values below the Limit of Quantification (LOQ) will be set to "zero" for all pharmacokinetic and statistical calculations. Any missing sample will be reported as "Missing" and will not be included for pharmacokinetic and statistical analysis.

[redacted]

Data from patients with missing concentration values (missed blood draws, lost samples, samples unable to be quantified) may be used if pharmacokinetic parameters can be estimated using the remaining data points. Otherwise, concentration data from these subjects will be excluded from the final analysis.

In case of sample collection deviations, the actual time point of sample collection will be used for the computation of pharmacokinetic parameters.

Missing plasma samples will be handled as per [redacted]

15.2 Statistical Analysis

SAS® Software, Version 9.4 or higher will be used for statistical analysis of pharmacokinetic parameters C_{maxSS} and $AUC_{(0-\tau)SS}$.

By considering the three day's morning pre-dose concentrations in a given period, steady state analysis will be performed for each subject in each period by using the linear regression analysis to obtain the p-values. The above analyses will be done using procedure PROC REG in SAS, version 9.4 or higher.

For achieving the steady state following procedure should be assessed:

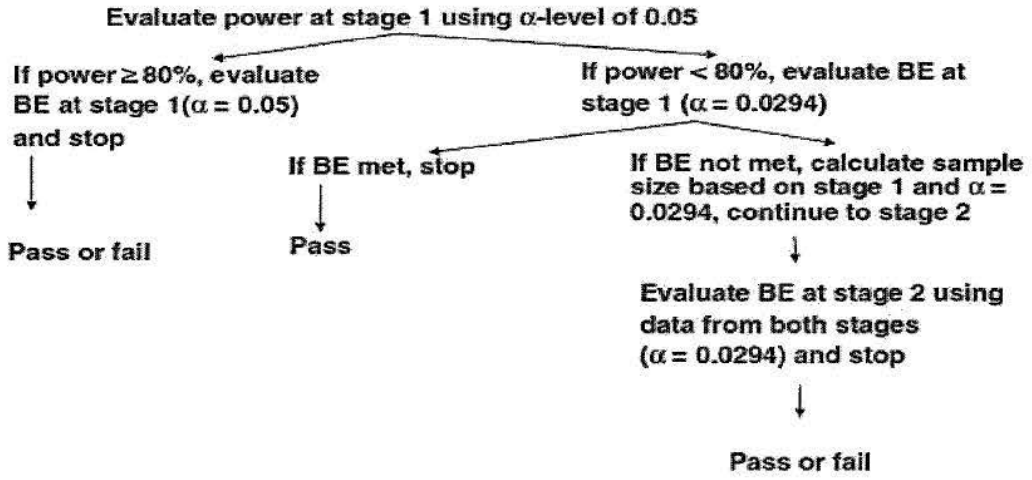
Step 1: For each subject in each period the P-values should be statistically insignificant at 5% level of significance.

If, P-values are found statistically insignificant, those patients are considered to achieve steady state. If, P-values are found significant for particular subject then go for the second step. Go for second step for patients who have missing pre-dose sample for Day 6 or Day 14.

Step 2: Ratio of the pre-dose concentrations of last two pre-dose should be $\geq$ 80% or should be $\leq$ 120.00%.

In case ratio of last two pre-dose concentrations is found to be $\geq$ 80% or $\leq$ 120.00% patients will be considered to achieve steady state. If two pre-dose concentrations is found to be less than 80% or greater than 120%, patients will not be considered to achieve steady state and will be removed from bioequivalence evaluation.

Two stage design according to Potvin C: Evaluate the power at stage 1 using the variance estimate from stage 1 and an α level of 0.05. If the power is greater than or equal to 80% (calculated by observed variability and GMR=0.95), evaluate BE at stage 1 using an α level of 0.05 and stop whether BE is met or not. If the power is less than 80%, evaluate BE using an α of 0.0294. If the BE criterion is met, stop. If the BE criterion is not met, calculate the sample size based on the variance estimated at stage 1, GMR=0.95 and an α level of 0.0294 and continue to stage 2. If the ratio is outside 80.00%-125.00% then study will not proceed for stage 2. Evaluate BE at stage 2 using data from both stages and an α level of 0.0294. Stop here whether BE is met or not and regardless of the power achieved.



For outlier identification, appropriate statistical tests could be performed. Outliers are defined as subjects having discordant values of one or more pharmacokinetic parameters when compared with other values, e.g., a subject differs notably from the rest of the subjects for the test product response versus the reference product response. Outlier test will be performed using appropriate statistical method as per [redacted] for "Detection of Outliers". Subject data will not be removed from the statistical analysis solely based on the results of statistical outlier tests. Outlier data may only be removed from the statistical analysis if there is a real-time documentation demonstrating a protocol violation during the clinical and/or analytical phase of the BE study.

15.2.1 Analysis of variance

For Stage 1:

The ln-transformed pharmacokinetic parameters (C_{maxSS} and $AUC_{(0-\tau)SS}$) will be analyzed using ANOVA model with the main effects of Center, Treatment, Period (Center), Sequence, Sequence*Center as fixed effects and Patient (Within Sequence*Center) as random effect.

The sequence effect will be tested at the 0.10 level of significance using the Patient (within Sequence*Center) mean square from the ANOVA as the error term. All other main effects will be tested at the 0.05 level of significance against the residual error (mean square error/MSE) from the ANOVA as the error term.

[redacted]

Each analysis of variance will include calculation of least-squares means, the difference between the adjusted formulation means and the standard error associated with the difference. The above analyses will be done using procedure PROC GLM in SAS, version 9.4 or higher.

For Stage 2:

The ln-transformed pharmacokinetic parameters (C_{maxSS} and $AUC_{(0-\tau)ss}$) will be analyzed using ANOVA model with the main effects of Center, Stage, Treatment, Period (Center*Stage), Sequence, Sequence*Center, Center*Stage, Sequence*Center*Stage, as fixed effects and Patient (Within Sequence*Center*Stage) as random effect.

The Sequence, Stage and Center effects will be tested using the Patient (within Sequence*Center*Stage) effect as the error term.

The sequence effect will be tested at the 0.10 level of significance using the Patient (within Sequence*Center*Stage) mean square from the ANOVA as the error term. All other main effects will be tested at the 0.05 level of significance against the residual error (mean square error/MSE) from the ANOVA as the error term.

Each analysis of variance will include calculation of least-squares means, the difference between the adjusted formulation means and the standard error associated with the difference. The above analyses will be done using procedure PROC GLM in SAS, version 9.4 or higher

Note: Prior to ANOVA analysis for assessment of center effect, data from all the centers will be arranged in ascending order based on the number of evaluable patients available per center. This shall lead to center with least number of evaluable patients followed by center which has more number of evaluable patients in increasing order. This will lead to center with maximum number of evaluable patients as last center and center with least number of patients as first center. In case any center has less than five evaluable patients, data from this center will be pooled with subsequent center as per the center arrangement done as mentioned above. If there are more than one center with less than five patients in each center, the data of all this centers will be combined until five or more than five patients are available and this will be treated as separate center for further data analysis. After combining centers as mentioned above, further assessment will be done for treatment sequence available for combined center data. After combining two or more centers, at least one patient should be having TR and RT sequence each. In case same is true, centers combined will be used further for data analysis. Incase same is not observed, data combining will be continued for subsequent center as per the center arrangement done as mentioned above. This shall be continued until at least one patient for each treatment sequence TR and RT is available.

Note: Analysis of study will be performed as per latest/updated Statistical Analysis Plan (SAP).

15.2.2 Intra- patient Variability

[redacted]

Intra-subject variability will be calculated using mean square error of ANOVA for ln-transformed analysis of C_{maxSS} and $AUC_{(0-\tau)SS}$ for Olaparib.

15.2.3 Two one-sided tests for bioequivalence

90% (if power is more than 80% at stage 1) & 94.12% (as applicable, if the power is less than 80% at stage 1 and stage 2) confidence intervals for the difference between least squares means of test and reference formulations will be calculated using mean square error, obtained in ANOVA, for ln-transformed C_{maxSS} and $AUC_{(0-\tau)SS}$. 90% (if power is more than 80% at stage 1) & 94.12% (as applicable, if the power is less than 80% at stage 1 and stage 2) confidence interval for the geometric least squares means ratio will be obtained by taking the exponent of lower and upper limits of 90% (if power is more than 80% at stage 1) & 94.12% (as applicable, if the power is less than 80% at stage 1 and stage 2) confidence interval, obtained for the least squares means difference.

Two one-sided test, namely Schuirmann's test, will be employed at 5% level of significance for the lower and upper limits of 90% (if power is more than 80% at stage 1) & 94.12% (as applicable, if the power is less than 80% at stage 1 and stage 2) confidence interval to check whether the 90% (if power is more than 80% at stage 1) & 94.12 (as applicable, if the power is less than 80% at stage 1 and stage 2) confidence interval for C_{maxSS} and $AUC_{(0-\tau)SS}$ will be entirely within the bioequivalence limits of 80.00% to 125.00%.

15.2.4 Ratio analysis

Geometric least squares means for test and reference formulations will be obtained by taking the exponent of least squares means of test and reference formulations for ln-transformed C_{maxSS} and $AUC_{(0-\tau)SS}$. Ratio will be obtained by taking the exponent of difference of least squares means of test to reference formulations for ln-transformed C_{maxSS} and $AUC_{(0-\tau)SS}$. The comparisons of interest are T vs. R, so the ratios determined will be of the form T/R, where T = Test formulation and R = Reference formulation.

15.2.5 Power

Power of test to detect at least 20% mean difference between formulations will be reported for $C_{max,ss}$ and $AUC_{(0-\tau)SS}$.

15.2.6 Bioequivalence criteria

For Stage 1 with Power $\geq$ 80%:

Based on the statistical results of 90% confidence intervals for the geometric least squares means ratio for the ln-pharmacokinetic parameters C_{maxSS} and $AUC_{(0-\tau)SS}$ for Olaparib the conclusions will be drawn whether test formulation is bioequivalent to reference formulation under Fasting condition. Acceptance range for bioequivalence is 80.00%-125.00% for 90% confidence intervals of the geometric least squares means ratio of C_{maxSS} and $AUC_{(0-\tau)SS}$.

For Stage 1 with Power < 80% and for Stage 2, if required:

Based on the statistical results of 94.12% confidence intervals for the geometric least squares means ratio for

the log-transformed pharmacokinetic parameters C_{maxSS} and $AUC_{(0-\tau)ss}$ for Olaparib the conclusions will be drawn whether test formulation is bioequivalent to reference formulation under Fasting condition. Acceptance range for bioequivalence is 80.00%-125.00% for 94.12% confidence intervals of the geometric least square means ratio of C_{maxSS} and $AUC_{(0-\tau)ss}$.

15.2.7 Safety data

All randomized patients who have received a dose of IMP will be included in safety evaluation. Results obtained when evaluating safety and tolerability (adverse events, vital signs, and clinical laboratory tests) will be listed in the report. AEs occurring prior to first IMP administration will be presented in a separate listing within study report. All AEs will be classified by System Organ Class, Preferred Term (using the Medical Dictionary for Regulatory Activities (MedDRA), version 20.0 or higher), and Severity with respect to treatment received.

16.0 AMENDMENT AND PROTOCOL DEVIATION IN REGARDS TO THE PROTOCOL

16.1 Amendment to protocol

Any significant change in study procedure or study design will only be in effect upon mutual agreement with Sponsor, and after obtaining approval or a favorable opinion from Ethics Committee (EC). All such changes will be documented in amended version of protocol and a list of changes with reference to previous version will be generated. The Investigator will not implement any changes to the protocol and/or ICF without consent of sponsor and without issuing an amendment except when necessary to eliminate an immediate hazard to subject.

16.2 Protocol deviation definition and reporting

A protocol deviation is an unintended excursion from the approved protocol.

A major protocol deviation is a protocol deviation that may, as evaluated by the investigator, or person designated by the investigator, lead to withdrawal of a subject from the study or to exclusion from the bioanalytical and/or statistical part. Deviations not classified as major are considered as minor protocol deviations.

Major protocol deviations should be reported to the sponsor by the CRO and monitor (if present on site) at the earliest possible time. The sponsor can propose to re-classify a protocol deviation (minor to major or vice versa) upon evaluation. In such case, the classification made by the sponsor prevails and will be communicated to the CRO together with a written justification.

The sponsor must be informed of minor protocol deviations within 10 working days, but before start of the following clinical study period or before start of the bio-analytic phase/ statistical phase.

The exceptions are minor protocol deviation which can be reported with the draft study report:

[redacted]

- logistic deviations (time deviations from scheduled time for blood sampling; follow up visits that occurred outside the protocol required time frame because of the participant's schedule etc.)
- administrative deviations (e.g. change of names)

Protocol deviation notification and reports are submitted to HA and/or relevant IRB according to applicable requirements/guidelines/law.

Procedure for documenting protocol deviations

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol. The notification of protocol deviation to sponsor can be in exceptional cases communicated by verbal means (if immediate action/notification is needed) and must be followed-up with written documentation (e.g. by e-mail; period update). All protocol deviations must be described in the final study report.

17.0 SOURCE DATA ACCESSIBILITY

Quality Assurance (QA) auditors and Quality Monitors of [redacted] as well as sponsor's monitors and auditors, IEC and Regulatory agency(ies) will have access to all documents related to the study, including the subject's medical records, source documents, drug accountability records and study drugs during study monitoring, inspection and audits.

18.0 QUALITY CONTROL AND QUALITY ASSURANCE

The raw data generated during the course of the study as well as reports will undergo a thorough quality control check and random quality assurance process for conformance to this protocol and all the governing SOPs by the Monitors and the auditors from Quality Assurance department of [redacted] respectively. The final report will contain a statement of quality assurance duly signed by the Head, Quality Assurance department.

19.0 ETHICS

19.1 Ethics Committee

This protocol, corresponding Informed Consent Document (ICD) (containing information about the study to be given to patients) to be used to obtain written informed consent of study patients and other relevant essential documents will be reviewed by IEC and patients will not be enrolled into the study until IEC approves the protocol and ICD.

Study will be conducted as per the ICMR Guidelines for Biomedical Research on Human Subjects, New drug and clinical trials rules (2019) of India, ICH-GCP Guidelines and in accordance with the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, revised by the WMA General Assembly, Brazil 2013).

[redacted]

[redacted]

19.2 Written Informed Consent

The Investigator or designated study personnel before initiation of any study related procedure will inform the patient (in English or in a language best understood by the patient) through an oral presentation regarding the purpose, procedures to be carried out, information on the investigational medicinal products, potential hazards, benefits and rights of the study patients. Patients will be encouraged to ask questions and clarify their doubts regarding any aspect of the study and the same would be documented in the source notes with sign and date. Ample time will be given to the patients after completion of ICD discussion to think and take an informed and voluntary decision. The Investigator will ensure that the entire process of informed consent is followed as per local regulatory requirement for each patient at the respective site maintaining the confidentiality of patient's personal information and all relevant records will be maintained in the source file. The responsibility for taking informed consent must remain with a medically qualified person and cannot be delegated to a non-medically qualified person. The Investigator/designee will also ensure that the entire informed consent process is documented in the source notes of the patient.

If the patient is unable to give informed consent, then the patient's legally acceptable representative (LAR) should be present during the entire informed consent process and will also append his/her signature on the ICD to confirm that the study information was presented to and understood by the patient. If the patient's legally acceptable representative is unable to read/write, an impartial witness should be present during the entire informed consent process, and will append his/her signature on the ICD with sign/thumb impression of LAR. In both cases, the patient will be required to sign the ICD, or, if unable to do so, give a thumb impression on the ICD. Only those patients who are able to understand the ICD and to adequately communicate with the study personnel will be enrolled in the study.

In case a patient cannot read/write, then the patient will be required to give a thumb impression and an impartial witness should be present during the entire informed consent process, and will append his/her signature on the ICD to confirm that the study information was presented to and understood by the patient.

The ICD will also be signed by the Investigator or his/her designate.

If any new information becomes available during the course of the study that may be relevant to the patient's willingness to continue participating in the trial, the Investigator must inform the patient in a timely manner, and a revised written ICD must be obtained.

The Investigator will ensure that all the patients are given a copy of the signed and dated ICD immediately after the informed consent process is completed.

19.2.1 Patient Participation Fee

Patients will be paid an adequate participation fee, approved by Institutional / Independent Ethics Committee (IEC), on account of their participation in the study. In case of withdrawal of a patient before completion of the study, patients will be paid a pro-rated participation depending upon the extent of participation and any controversy pertaining to this will be forwarded to Institutional Ethics Committee (IEC) and the decision of Institutional / Independent Ethics Committee (IEC) will be final as well as binding on both the patients and

[redacted]

[redacted]

19.2.2 Post-trial access

Based on the Investigator discretion, patients who complete the study in its entirety may receive Olaparib tablet 150 mg on compassionate basis. If patient who completed the study does not have access to Olaparib treatment (e.g., Olaparib reimbursement is not possible), Olaparib 150 mg tablets may be offered for a period of up to 9 months, provided that the patient is deriving benefit (no disease progression as assessed by the physician), and the benefit outweighs the risk for the patient.

20.0 DATA HANDLING AND RECORD KEEPING

All clinical data generated during the conduct of the study will be entered in the source notes and will be transcribed in the respective CRF. The computer-generated randomization schedule will also be treated as raw data. All raw data and transcribed data forms compiled by the study personnel assisting in the study will be checked for completeness. All data related to the project will be in the custody of the Investigator or Project Manager until transferred to archives.

All bioanalytical raw data generated during the conduct of the project compiled by the study personnel assisting in the study will be checked for completeness. All analytical data generated through analytical system will be exported and transferred electronically through intranet to Pharmacokinetic Biostatistics (PB) department for further evaluation. The PB department, after receipt of the raw data, will perform a statistical analysis and the statistical data will be generated which will be further sent for compilation of the final clinical study report.

21.0 STUDY REPORTS AND SUPPLEMENTARY DOCUMENTS

The final report will be compiled and sent as per eCTD (Module 5) format. All copies of supplementary documents such as approved final version of Protocol along with all appendices, IEC approval letter, List of IEC members, CVs of investigators, all patient CRFs, adverse event form (if any), IMP Accountability records, Randomization list, Summary report of pharmacokinetic and statistical Analysis, Protocol deviations, Demographics and Baseline Characteristics, Sampling deviations and Safety data will be submitted to sponsor with the final study report.

22.0 ARCHIVING

All raw data generated in connection with this study, together with a copy of this protocol, signed ICDs and the final report will be archived at least 25 years as per sponsor requirements, according to the ICH guideline for good clinical practice and as per applicable regulatory requirements.

The investigator must notify the Sponsor prior to destroying any study essential documents following the clinical study completion or discontinuation.

If the investigator's situation is such that archiving can no longer be ensured by him/her, the investigator shall inform the sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

[redacted]

Sponsor should be contacted for further instructions, when agreed storage period of study samples expires.

In case of sample destruction, Certificate of Destruction is provided to Sponsor.

23.0 INSURANCE POLICY

[redacted] on behalf of sponsor has a clinical trial insurance policy to cover the risks to patients and/or any other eventualities pertaining to study.

24.0 CONFIDENTIALITY OF DATA

The data identifying each patient by name will be kept confidential and will be accessible to the study personnel (involved in check-in procedure and Monitors) and if necessary, to the QA auditors, IEC, Sponsor representative and Regulatory agency(ies).

25.0 PUBLICATION POLICY

The results of the study including all data obtained will be the property of sponsor of this study. [redacted] encourages the scientific publication of data from clinical research trials. However, Investigators must not present or publish partial or complete study results individually.

The Investigators and [redacted] may propose appropriate scientific manuscripts or abstracts from the study data. All proposed publications must be reviewed by [redacted] before submission for publication.

26.0 REFERENCES

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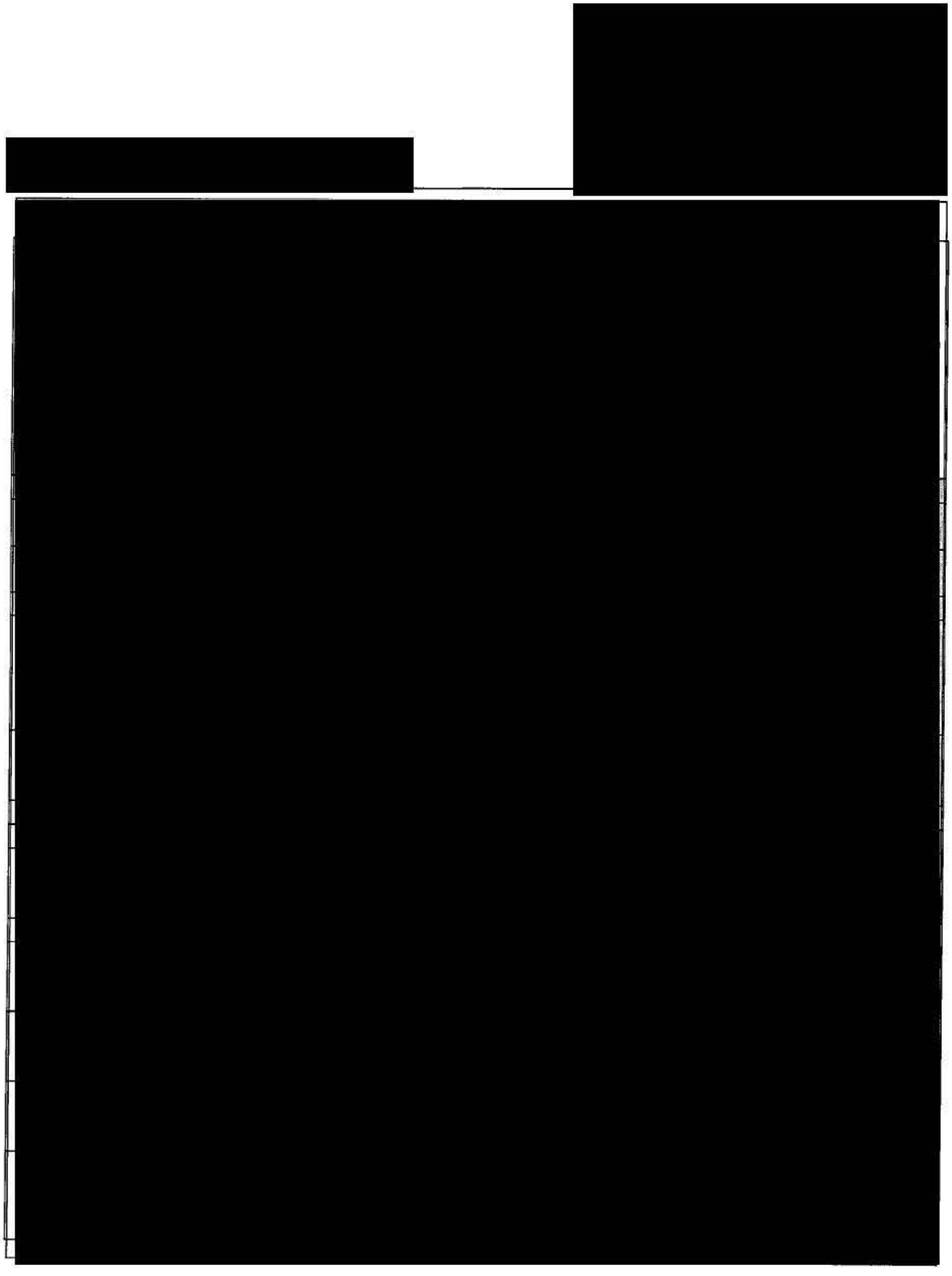
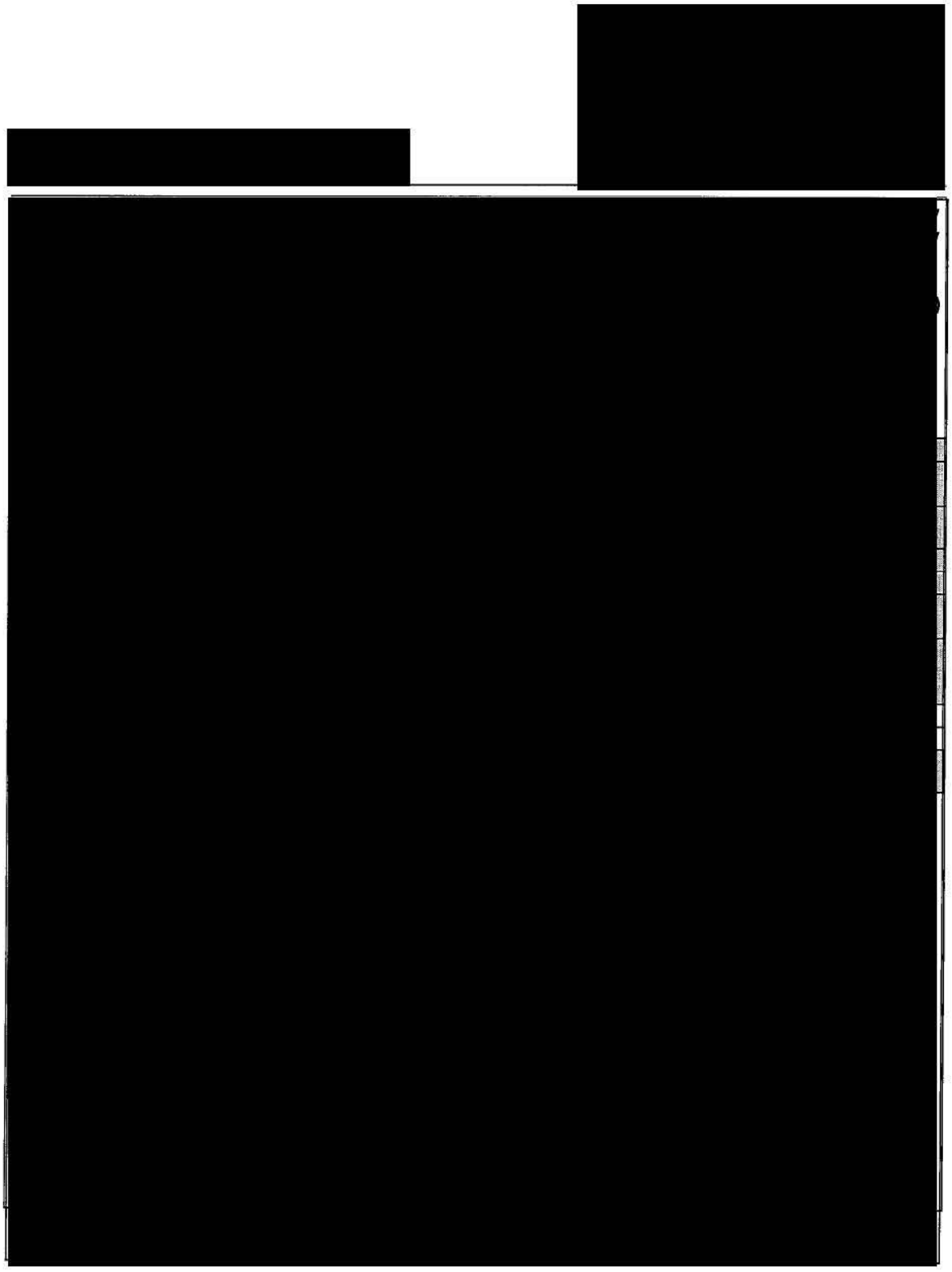
27.0 LIST OF ANNEXURES

- I Schedule of Events
- II Laboratory parameters
- III ECOG Performance Status
- IV List of Prohibited drugs during the study
- V Signature(s) of Investigator(s)





[redacted]

[redacted]

27.2 ANNEXURE II: LABORATORY PARAMETERS

HEMATOLOGY	
Haemoglobin	Neutrophils
WBC Count	Lymphocytes
Platelet Count	Eosinophils
Absolute Neutrophil Count	Basophils
	Monocytes
BIOCHEMICAL PARAMETERS	
SGOT (AST)	Blood Sugar
SGPT (ALT)	Total Protein
Gamma GT (GGT)	Serum Albumin
Alkaline Phosphatase (ALP)	Serum Cholesterol
Total Bilirubin	Serum Triglyceride
Direct Bilirubin	Serum Creatinine
Indirect Bilirubin	eGFR evaluation (MDRD)
Serum Uric acid	Blood Urea Nitrogen/Urea

SEROLOGY			
HIV (1 & 2) antibodies	HbsAg (Hepatitis B surface antigen)	HCV antibodies	Syphilis (VDRL or RPR)

URINE ANALYSIS				
Color	Glucose	WBC	pH	Nitrite
Odor	Bilirubin	Epithelial Cells	Protein	Leucocyte
Clarity	Blood	RBC	Bacteria	Crystals
Volume	Ketones	Casts	Specific gravity	Urobilinogen

[redacted]

[redacted]

27.3 ANNEXURE III: ECOG Performance Status[13]

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hrs
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hrs.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

27.4 ANNEXURE IV: List of Prohibited drugs during the study[14]

CYP3A4 inhibitors	Aprepitant, Amiodarone, Amprenavir, Atazanavir, Atomoxetine, Boceprivir, Cimetidine, Ciprofloxacin, Cilostazol, Clarithromycin, Chloramphenicol, Chlorzoxazone, Clarithromycin, Clotrimazole, Cobicistat, Conivaptan,Crizotinib, Cyclosporine, Danoprevir , Darunavir, Dasabuvir Diltiazem, Delaviridine, Diethyl dithiocarbamate, Dronedarone, Erythromycin, Elvitegravir ,Esomeprazole, Fluconazole, Fluoxamine, Fosaprepitant , Fosumprenavir, Grapefruit, Gestodene, Idelalisib, Imatinib, Indinavir, Itraconazole, Ivacaftor, Ketoconazole, Lesinurad, Lopinavir , Lomitapide, Mibefradil, Mifepristone, Nefazodone, Nelfinavir, Norfluoxetine, Diltiazem, Netupitant/Palonosetron, Norfloxacin, Ombitasvir , Omeprazole, Paritaprevir Posaconazole, Pantoprazole, Ranitidine, Ranolazine, Ritonavir, Regorafenib, Ribociclib, Starfruit, Pomelo, Seville orange, Saquinavir, Starfruit, Telaprevir, Telithromycin, Tipranavir, Ticagrelor, Tofisopam, Troleandomycin ,Verapamil, Voriconazole
CYP3A4 inducers	Apalutamide, Armodafinil, Barbiturates, Brigatinib, Bosentan, Carbamazepine, Efavirenz, Enzalutamide, Etravirine, Glucocorticoids, Mitotane, Modafinil, Nafcillin, Nevirapine, Oxcarbazepine, Phenytoin, Pioglitazone, Phenobarbital, Primidone, Rifampin, Rifabutin, Rufinamide, St. John's wort, Troglitazone

Note: This list of drugs is not exhaustive. However, any drug which is not mentioned above and having a possible effect on Olaparib pharmacokinetics, should be confirmed with Medical Monitor/Medical Expert.

[redacted]

[redacted]

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[redacted]

Protocol Number: [redacted]

Errata No. 02 in Protocol Version 01 [redacted]

A randomized, open label, multi-centre, two-treatment, two-period, two-sequence, two-stage, multiple dose, steady-state, crossover, bioequivalence study of Olaparib tablets, 150 mg [redacted] and Lynparza® (olaparib) tablets 150 mg [redacted] LP), in patients with BRCA mutated ovarian cancer, recurrent ovarian cancer or metastatic breast cancer under fasting condition.

Sr. No.	Section	Typed as	It should be read as	Reason for change
1	Section 3.0 Synopsis and Section 9.1 Inclusion criteria. Annexure I: Schedule of Events (And Wherever applicable throughout the protocol)	6. Adequate organ and bone marrow function based upon the following laboratory criteria at the time of eligibility assessment prior to dosing in period 1: Enal function	6. Adequate organ and bone marrow function based upon the following laboratory criteria at the time of eligibility assessment **at screening and** prior to dosing in period 1: Renal function	To rectify the error and provide better clarity with respect to clinical test
2	Section 3.0 Synopsis and Section 12 Clinical and Safety assessment. Annexure I: Schedule of Events (And Wherever applicable throughout the protocol)	CBC, Creatinine Clearance, S Bilirubin, SGPT and SGOT: Prior to dosing in period 1 (Day -2 to 0) and period 2 (can be performed after evening dose on Day 8) (can be done at local laboratory)	CBC, Creatinine Clearance, S Bilirubin, SGPT and SGOT: **Screening,** Prior to dosing in period 1 (Day -2 to 0) and period 2 (can be performed after **Morning** dose on Day 8) (can be done at local laboratory)	To rectify the error and provide better clarity with respect to clinical test

[redacted]

[redacted]

[redacted]

Sr. No.	Section	Typed as	It should be read as	Reason for change
3	Section 13 sample processing and transfer procedures	The plasma samples will be stored at **-20±5°C** in a freezer until shipment to the Bioanalytical facility of [redacted] and then stored at -78±8°C until analysis.	The plasma samples will be stored at **-15° C or colder** in a freezer until shipment to the Bioanalytical facility of [redacted] and then stored at -78±8°C until analysis.	To rectify the error and provide better clarity with respect to storage condition of PK samples at site.
4	Section 19.2.2 Post trial access	Based on the Investigator discretion, patients who complete the study in its entirety may receive Olaparib tablet 150 mg on compassionate basis.	Based on the Investigator discretion, patients who complete the study in its entirety may receive Olaparib tablet 150 mg **and/or Olaparib tablet 100 mg** on compassionate basis. **Dose modification/reduction of olaparib can be done based on discretion of investigator after completion of study.**	As per the suggestion of principal investigator

[redacted]

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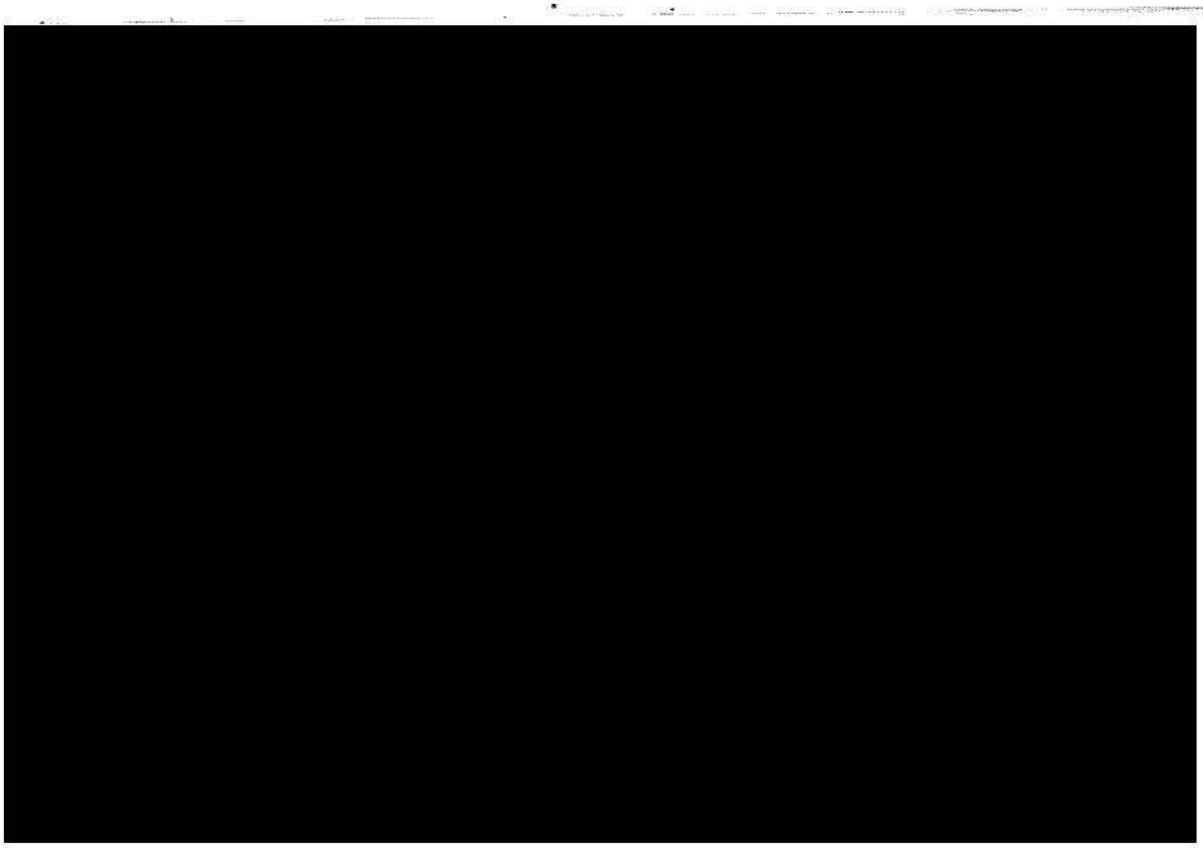
[redacted]



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[redacted]

Protocol Number: [redacted]

Errata No. 01 in Protocol Version 01 Dated [redacted]

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Sr. No.	Section	Typed as	It should be read as	Reason for change
1	Annexure I: Schedule of Events (And Wherever applicable throughout the protocol)	Procedure: Check in day i.e. Day 0, day 5 and day 13 Study drug administration: X Procedure: Day 1, day 6,day 7,day 8,day 14,day 15 and day 16 PK sampling: X	Procedure: Check in day i.e. Day 0, day 5 and day 13 Study drug administration: **X (on Day 5 and Day 13)** Procedure: Day 1, **Day 9,** day 6,day 7,day 8,day 14,day 15 and day 16 PK sampling: **X (except on day 9)**	To rectify the error and provide better clarity.
2	Section 3.0 Synopsis, and Section 12 Clinical and Safety	Urine drug Screen (benzodiazepines, opioids, amphetamines, cannabinoids, cocaine and barbiturates) : Day 0, Day 5	Urine drug Screen (amphetamines, barbiturates, benzodiazepines, **marijuana(THC),** cocaine, and **morphine**) : Day 0, Day	To rectify the error and provide better clarity with respect to clinical test

[redacted]

[redacted]

Sr. No.	Section	Typed as	It should be read as	Reason for change
	assessment.	and Day 13	5 and Day 13	

Note: Above mentioned changes are applicable to all the relevant section of protocol.

[redacted]

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