Clinical Study Protocol	
Drug Substance	Olaparib
Study Code	D0816R00025
Version	Version 2.0
Date	19/10/2019

A Prospective, Multicentre, Phase-IV Clinical Trial of Olaparib in Indian Patients with Platinum Sensitive Relapsed Ovarian Cancer who are in Complete or Partial Response Following Platinum Based Chemotherapy and Metastatic Breast Cancer with Germline BRCA1/2 Mutation (SOLI Study)

Sponsor:

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VERSION HISTORY

Version 1.0, Date 17 Dec 2018
Initial Document Creation
Version 2.0, Date 19 October 2019
Section 1.1 Schedule of Activities: Window Period Added for visit 3 -9 **Section 1.2 Synopsis: Study timelines (Table 2) and No of Subjects updated** **Section 4: Patient Numbers updated and window period of +/- 3 days added** **Section 9.2 Sample Size determination: Updated to reflect 200 patients as mandated by the Indian HA**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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Screening Phase (Visit 1)

Subjects, or their legally acceptable representative, will provide written informed consent before any trial-specific procedures are performed. During the Screening Phase, eligibility criteria will be reviewed, and a complete clinical evaluation will be performed as specified in the Time and Events Schedule. Screening procedures will be performed within 7 days before Day 1 of therapy with olaparib. All baseline disease characteristics will be captured based on the evaluations as performed as a part of routine clinical practice in the enrolment hospital. The documented tests that are required before consideration of subject for olaparib treatment based on the local prescribing information by investigator must have been performed within 7 days before Day 1.

Treatment Phase (Visit 2-7)

The Treatment Phase will extend from Day 1 to Day 182; or until study drug discontinuation due to either disease progression or unacceptable toxicity; or other reasons whichever occurs first, as listed in the Drug Discontinuation Section. Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedule. Subjects will be closely monitored for AEs and other safety evaluations including laboratory investigations and concomitant medications. If disease progression is diagnosed before Day 182, then the subject will discontinue study drug with completion of the End-of-Treatment Visit on the day of progression and will enter the Follow-up Phase. For visit 3 – 7, a window of ± 3 days will be allowed per visit.

End-Of–Treatment Visit (EOT; Visit 8)

An End-of-Treatment Visit is to be scheduled on Day 182 of the study drug administration. In a case where subject discontinues the study treatment for any reason listed in Drug Discontinuation Section before Day 182, the last visit of the subject will be considered as End-of-treatment Visit. Every effort should be made to conduct the telephonic End-of-Study Visit before the subject starts subsequent treatment. For end – of – treatment visit, a window of ± 3 days will be allowed.

Follow - Up Phase (End – Of – Study; Visit 9)

Only subjects who discontinue treatment with olaparib before end of Treatment Phase on study will be followed for 28 days after discontinuation of study drug or until the start of alternate treatment intervention, whichever is earlier. A telephone follow-up will be conducted 28 days after the EOT Visit. This will be considered as End-of-Study visit. Every effort should be made to conduct the telephone End-of-Study Visit before the subject starts subsequent treatment. For Follow – Up Phase visit, a window of ± 3 days will be allowed.

Table 1 Study of Assessments

Study Phase	Screening Phase[0]	Treatment Phase					Follow-up Phase
Cycle		On Treatment				EOT	EOS
Visit No.	1	2	3	4	5- 7	8	9
Study Days	-6 to 0	1	15 (± 3 days)	29 (± 3 days)	57, 85 & 141 (± 3 days)	182 (± 3 days)	28 days post-EOT (± 3 days)
Screening/Enrolment visit							
Informed consent[b]	Subjects must sign the informed consent form before any study-specific procedures are performed.						
Eligibility criteria	X						
Demographics/ Review medical history (including all treatments for ovarian cancer/breast cancer)	X						
WHO Performance Status	X			X	X	X	X
General physical examination	X	Targeted physical exam (based on symptoms)					
Prior concomitant medication recording	Continuous from time of ICF until 28 days after last olaparib dose in treatment phase.						
Study drug administration							
Olaparib dosing		The recommended dose is 300 mg (150 mg X 2 tablets) twice a day					
Disease evaluations (disease characteristics will be performed as per routine clinical practice)							
Disease characteristics assessment	X			X	X		
Tumor imaging	X					X	

Study Phase	Screening Phase[0]	Treatment Phase					Follow-up Phase
Cycle		On Treatment				EOT	EOS
Visit No.	1	2	3	4	5- 7	8	9
Study Days	-6 to 0	1	15 (± 3 days)	29 (± 3 days)	57, 85 & 141 (± 3 days)	182 (± 3 days)	28 days post-EOT (± 3 days)
Safety evaluations							
Physical examination	X	Symptom-directed physical examination only					
Vital sign parameters	X	X			X	X	
ECG	X	Performed if clinically indicated					
Adverse event monitoring	Continuous from time of ICF until 28 days after last olaparib dose in Treatment Phase and Follow-up Phase if eligible.						
Haematology & Biochemistry[c]	X	X	X	X	X	X	X
Hepatitis B and C	X						
Pregnancy Test	X	X	X	X	X	X	X
PT/INR	X	X	X	X	X	X	X
Comprehensive serum chemistry panel	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X

Footnotes:
EOT = End-of-Treatment. EOS = End-of-Study. ICF = informed consent form.

a. The Screening Phase begins when the first screening procedure is conducted. Screening tests should be performed within 7 days of Day 1 except for disease evaluations (performed as routine clinical practice).
b. Must be signed before first study-related activity.
c. Haematology and biochemistry as described in the Safety Evaluations section

1.2 Synopsis

National Co-ordinating Investigator

Name: PPD

Title: PPD

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Email PPD

Protocol Title: A Prospective, Multicentre, Phase-IV Clinical Trial of Olaparib in Indian Patients with Platinum Sensitive Relapsed Ovarian Cancer who are in Complete or Partial Response Following Platinum Based Chemotherapy and Metastatic Breast Cancer with Germline BRCA1/2 Mutation (SOLI Study)

Short Title: Phase IV Study of Olaparib in Indian Patients

Rationale:

Objectives and Endpoints

Primary objective:	Endpoint/variable:
To assess the safety of olaparib in Indian subjects with: • **platinum sensitive relapsed ovarian cancer who are in complete or partial response following platinum-based chemotherapy, and** • **HER – 2 negative metastatic breast cancer with germline BRCA1/2 mutation.**	Number, frequency and proportion of subjects with adverse events (AEs) and serious adverse events (SAEs). The safety variables to be analysed include AEs, clinical laboratory tests (haematology and chemistry), physical examination results, vital parameters, World Health Organization (WHO) performance status (PS), and deaths as observed by participating physician.

Overall design: This is a prospective, single - arm, multicentre, interventional phase – IV trial investigating the safety of olaparib in Indian adult subjects receiving olaparib as per the local approved prescribing information.

Study Period:

Table 2 Study Timelines

Total planned Study period	
Estimated date of first subject in	March 2020
Estimated date of last subject in	March 2021
Estimated date of last subject last visit	October 2021
Estimated date of data base lock	December 2021

Number of Subjects:

No. of total screened subjects: Approximately 225 (180 for Ovarian and 45 for Breast)

No. of total enrolled subjects: Approximately 200 (160 for Ovarian and 40 for Breast)

No. of study sites: 15

Treatments and treatment duration: Single arm study. Study Subjects will receive Olaparib tablets 300 mg (150 mg X 2) BD

Data Monitoring Committee: As constituted by the Principal Investigator/ National co – ordinating investigator.

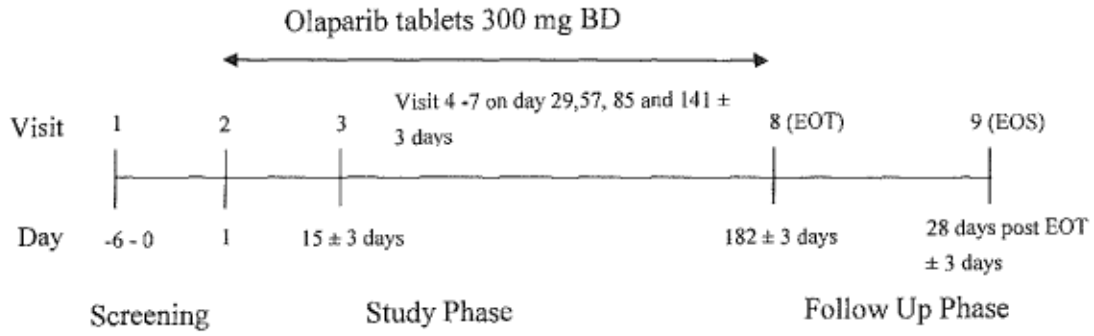
Statistical methods

There is no formal sample size calculation as this study is being conducted as a regulatory requirement for a phase IV study including Indian patients in the approved indications post marketing of olaparib.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



EOT: End of Treatment; EOS: End of Study

2. INTRODUCTION

2.1 Background and study rationale

In India, ovarian cancer is the third leading site cancer among women next to cervical and breast cancers. In India, incidence of ovarian cancer as reported in various population based registries ranges between 1.7 to 15.2 (age-adjusted incidence rate per 100,000 population) between 2012-14 (National Cancer Registry Programme, 2016a). Incidence of ovarian cancer is increasing from 1982 till date in India. Projected burden of ovarian cancer in India was 45,231 subjects in 2015 and is estimated to touch 59,000 subjects in 2020 (National Cancer Registry Programme, 2016b). Similarly, projected cases of ovarian cancer mortality in India during 2021 and 2026 is approximately 17000 and 20000, respectively (D'Souza et al., 2013). Ovarian cancer is therefore an important public health issue in India.

The prognosis of ovarian cancer is worst among all gynecological malignancies with the 5-year survival rate of 46% across all stages and 27% for advanced stages in USA (Siegel et al., 2017). Poorer outcomes are noted in other developing economies too. This is more evident in a country like India where the patients present in advanced stages and chances of optimal treatment are bleak. Due to detection in late stages of disease the recurrence is common and eventually death follows. The overall 5-year survival rate was 16 % during the period of 2010-14 in India (Allemani et al., 2018).

The proportion of breast cancer cases in India has been steadily increasing in the past few decades and in 2012, breast cancer dethroned cervical cancer as the commonest cause of cancer among women in India (Rangarajan et al., 2016). It is estimated that in 2015, 155,000 patients were affected with breast cancer in India (Rangarajan et al., 2016). While the presentation of breast cancers in India is similar to the western countries in early stages, there is a considerably higher number of Indian patients presenting with triple negative breast cancers in advanced stages (Sandhu et al., 2016). In India, 5-year survival rate for patients with breast cancer was 66 % during the period of 2010-14 (Allemani et al., 2018) compared to the western countries like USA which have a 5 – year survival rate of > 90 %. Also, it is imperative to note that stage IV (metastatic) breast cancers have a 5 – year survival of only 22 % in Indians (Agarwal and Ramakant, 2008). Approximately 5 % of the patients with breast cancer harbour germline BRCA mutations (gBRCAm) (Farmer et al., 2005; Murai et al., 2012). These mutations are more likely to be present in patients who are younger, with strong family history of breast cancer and those patients who are estrogen receptor (ER)/ progesterone receptor (PR) negative and human epidermal growth factor receptor – 2 (HER2) negative (triple negative) (Farmer et al., 2005; Murai et al., 2012).Olaparib (Lynparza®) is an inhibitor of the mammalian polyadenosine 5'-diphosphoribose polymerase (PARP) enzyme. When olaparib is bound to the active site of DNA associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair (Bryant et al., 2005). In replicating cells, this leads to DNA double strand breaks (DSBs) when replication forks meet the PARP DNA adduct. In normal cells, homologous recombination repair (HRR), which requires functional BRCA1 and 2 genes, is effective at repairing these DNA double strand breaks (Ashworth, 2008; Shin et al., 2004). In the absence of functional BRCA1 or 2, DNA DSBs cannot

be repaired via HRR. Instead, alternative and error-prone pathways are activated, such as the non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After many rounds of replication genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells have a high DNA damage load relative to normal cells (Ashworth, 2008; Farmer et al., 2005; Shin et al., 2004).

Lynparza® tablet is currently approved in USA for (A) maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy; (B) the treatment of adult patients with deleterious or suspected deleterious gBRCAm advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy; and (C) in 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 (USFDA, 2017).

The 69th meeting of the Oncology and Haematology Subject Expert Committee held in April 2018 has given positive recommendations for approval of olaparib as monotherapy with a condition to conduct phase IV clinical trial as per the requirements of Indian Good Clinical Practices (GCP) and schedule Y of Drugs and Cosmetics Rules, 1945 (Drug Controller General (India), 2018). Subsequently, the Drugs Controller General of India (DCGI) has provided market authorization for olaparib in the following indications: (A) for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy; (B)for the treatment of adult patients with deleterious or suspected deleterious gBRCAm advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy; and (C) in patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have previously 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 treatment (Drugs Controller General (India), 2018).

The approval for olaparib in ovarian cancer is based on Study 19 (n = 265), Study 42 (n = 137) and SOLO2 (n = 295). Study 19, a phase II study, which included patients irrespective of their BRCA status, showed a significant progression free survival (PFS) benefit (8.4 vs 4.8 months) over placebo with a hazard ratio of 0.35, p <0.0001 (Ledermann et al., 2012). There is now long term safety and efficacy data of the patients enrolled in Study 19 with 15 patients (11%) on the study drug for >6 years which included an equal proportion of gBRCAm as well as non – BRCA mutated patients (Gourley et al., 2017). In Study 19 (dose of olaparib used in the study was 400 mg BD in Capsule formulation), common grade 3 or worse adverse events in the olaparib group were fatigue (8%) and anaemia (6%). 22 % patients in the olaparib group reported serious adverse events.(Ledermann JA , et al, 2016) The phase III SOLO2 study which included only gBRCAm patients with ovarian cancer in the maintenance management of ovarian cancer, showed a significant PFS benefit over placebo (19.1 vs 5.5 months; HR of 0.30, p <0.0001) (Pujade-Lauraine et al., 2017). In the SOLO – 2 study (dose of olaparib used in the study was 300 mg BD in tablet formulation), serious adverse events were experienced by 18 % patients in the olaparib group compared to 8 % patients in the placebo group. The most common in the olaparib group were anaemia (4 % patients), abdominal pain (2% patients), and intestinal obstruction (2 % patients)

(Pujade-Lauraine et al., 2017). In the third-line or later treatment indication of olaparib, the approval is based on the results of the phase II study 42 (n = 137), which, in gBRCAm patients showed an ORR of 34% (Domchek et al., 2016; Matulonis et al., 2016). In Study 42, Grade ≥ 3 AE's were observed in 55 % of the patients with the commonest ones being anaemia (20 %), abdominal pain (8 %) and fatigue (7 %).(Domchek et al., 2016)

The approval of olaparib for patients with metastatic breast cancer was based on the OlympiAD trial (n=302) which showed a significantly better median PFS of 7 months compared to 4.2 months in the standard chemotherapy arm (capecitabine, eribulin mesylate or vinorelbine). This translates to a 42 % reduction in risk of progression or death in the olaparib arm (Robson et al., 2017). The PFS benefit with olaparib appeared to be more marked in patients with triple negative breast disease as compared to those with HER-2 negative and HR positive disease on prespecified subgroup analysis (Robson et al., 2017). In the OlympiAD study, grade 3 or higher adverse events were observed in 36.6 % in the olaparib group and 50.5% in the standard-therapy group, and the rate of treatment discontinuation due to adverse effects was 4.9 % and 7.7 %, respectively
As per recommendation from DCGI, the current phase-IV study is planned with the aim to assess the safety in Indian subjects receiving olaparib as per the approved label indications in India in accordance with the requirements of the Health Authorities of India. This study attempts to descriptively elucidate the safety of Olaparib in Indian subjects receiving olaparib as per the Indian regulatory approved indications in India. The data obtained from the present study will help to understand the safety profile of olaparib in Indian patients.

2.2 Benefit/risk assessment

This study attempts to capture and elucidate the safety of Olaparib in Indian Subjects. After due consideration to the facts that global clinical trials with Lynparza have not included subjects from India and also, to fulfil the regulatory requirement for the approval of Lynparza, this study's results will be one of the first reports of the safety of Olaparib in Indian patients. The common side effects of Olaparib include nausea, anaemia, fatigue and abdominal pain. However, considering the small sample size of this study and the fact that this study is not powered to compare the safety of this study population versus that see in the global clinical trials, it is possible that certain adverse events may be under or over – represented. No effort will be made to statistically compare the side effects observed in this study with that seen in the global clinical trials with Olaparib.

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Primary objective:	Endpoint/variable:
To assess the safety of olaparib in Indian subjects with: • **platinum sensitive relapsed ovarian cancer who are in complete or partial response following platinum-based chemotherapy, and** • **HER – 2 negative metastatic breast cancer with germline BRCA1/2 mutation.**	Number, frequency and proportion of subjects with adverse events (AEs) and serious adverse events (SAEs). The safety variables to be analysed include AEs, clinical laboratory tests (haematology and chemistry), physical examination results, vital parameters, World Health Organization (WHO) performance status (PS), and deaths as observed by participating physician.

4. STUDY DESIGN

4.1 Overall design

This is a prospective, single - arm, multicentre, interventional phase – IV trial investigating the safety of olaparib in Indian adult subjects receiving olaparib as per the local approved prescribing information. The investigator will be trained on the locally approved prescribing information before the enrolment of the first subject at their site to ensure compliant and proper dosing of the study drug.

The decision of subjects to participate in this study must not, in any way, impact upon the standard of care that they are receiving or any benefits to which they are otherwise entitled. Prior to data collection, all subjects must sign an informed consent form (ICF) allowing data collection and source data verification in accordance with local requirements and sponsor policy. Subjects who are prescribed olaparib by an independent clinical judgement of investigator in his/her routine practice based on locally approved prescribing information will be eligible for screening under this study. To enrol approximately 200 subjects (160 patients to be enrolled in the ovarian cancer indication and 40 from the breast cancer indication), it is expected that approximately 225 subjects (180 patients with ovarian and 45 patients with breast cancer) will be screened.

Subjects will be monitored throughout the study period for AEs of olaparib.

Subject participation will include a Screening/Enrolment Phase, a Treatment Phase, and a Follow-up Phase. The Screening/Enrolment Phase will be up to 7 days prior to Day 1. The Treatment Phase will extend from Day 1 to Day 182; or until study drug discontinuation due to either disease progression or unacceptable toxicity; or other reasons as listed in Drug Discontinuation Section, whichever occurs first. The Follow-up Phase will begin once a subject discontinues study drug during Treatment Phase, and will continue until 28 days after last dose, death, loss to follow - up, consent withdrawal for study participation, or study end, whichever occurs first (see section 7). Subjects who are observed to continue to receive clinical benefit from olaparib at end of Treatment

Phase (as defined in SoA) will continue treatment in Extension Phase (defined in section 6.7) as long-term clinical benefit is observed or until the investigator decides it is not in the best interest of the subject to continue olaparib treatment.

Safety will be evaluated throughout the evaluation phase and during the follow - up of subjects who discontinue treatment before end of Treatment Phase by physical exams including vital signs, AE/SAE monitoring, laboratory evaluations and recording of concomitant medications. The sponsor shall provide the laboratory investigations for safety evaluation including haematology and biochemistry as mentioned in the Time and Events Schedule to monitor the safety throughout the study period. A window period of +/- 3 days will be allowed for visits 3 – 9.

Screening Phase (Visit 1)

Subjects, or their legally acceptable representative, will provide written informed consent before any trial-specific procedures are performed. During the Screening Phase, eligibility criteria will be reviewed, and a complete clinical evaluation will be performed as specified in the Time and Events Schedule. Screening procedures will be performed within 7 days before Day 1 of therapy with olaparib. All baseline disease characteristics will be captured based on the evaluations as performed as a part of routine clinical practice in the enrolment hospital. The documented tests that are required before consideration of subject for olaparib treatment based on the local prescribing information by investigator must have been performed within 7 days before Day 1.

Treatment Phase (Visit 2-7)

The Treatment Phase will extend from Day 1 to Day 182; or until study drug discontinuation due to either disease progression or unacceptable toxicity; or other reasons whichever occurs first, as listed in the Drug Discontinuation Section. Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedule. Subjects will be closely monitored for AEs and other safety evaluations including laboratory investigations and concomitant medications. If disease progression is diagnosed before Day 182, then the subject will discontinue study drug with completion of the End-of-Treatment Visit on the day of progression and will enter the Follow-up Phase.

End-Of–Treatment Visit (EOT; Visit 8)

An End-of-Treatment Visit is to be scheduled on Day 182 of the study drug administration. In a case where subject discontinues the study treatment for any reason listed in Drug Discontinuation Section before Day 182, the last visit of the subject will be considered as End-of-treatment Visit. Every effort should be made to conduct the telephonic End-of-Study Visit before the subject starts subsequent treatment.

Follow - Up Phase (End – Of – Study; Visit 9)

Only subjects who discontinue treatment with olaparib before end of Treatment Phase on study will be followed for 28 days after discontinuation of study drug or until the start of alternate treatment intervention, whichever is earlier. A telephone follow-up will be conducted 28 days after the EOT Visit. This will be considered as End-of-Study visit. Every effort should be made to conduct the telephone End-of-Study Visit before the subject starts subsequent treatment.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

For details on what is included in the study endpoints, see Section 3 Objectives and Endpoints.

4.2 Scientific rationale for study design

This is a phase IV single arm study being conducted to fulfil the regulatory requirement for the conditional approval of Olaparib in India. The safety results need to be submitted to the health authorities within 2 years of the market authorization which makes it practically impossible to include data on efficacy considering the median PFS in SOLO – 2 was 19.1 months and 8.4 months for Study 19 (Ledermann JA , et al, 2016; Pujade-Lauraine et al., 2017).

4.3 Justification for dose

This study's Inclusion criteria specifies that patients fitting into the Indian Approved Prescribing information will be included.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last subject undergoing the study.

A subject is considered to have completed the study when he/she has completed his/her end of study visit as per the SoA in Section 1.1.

See Appendix A 6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each subject should meet all the inclusion criteria and none of the exclusion criteria for this study in order to assigned/randomised to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures, refer to section 5.4.

In this protocol, "enrolled" subjects are defined as those who sign informed consent.

For procedures for withdrawal of incorrectly enrolled subjects see Section 7.3.

5.1 Inclusion criteria

Subjects are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2. *Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses.*

The ICF process is described in Appendix A 3.

Age

3. *Subjects ≥ 18 years of age*

Type of subject and disease characteristics

4. *Subjects receiving olaparib for the following indications in ovarian cancer:*

   for the maintenance treatment of adult subjects with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy

5. *Subjects receiving olaparib for the following indication in breast cancer:*

   in subjects with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Subjects with HR-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment

Sex

6. *Only Females will be recruited*

Reproduction

7. *Negative pregnancy test (urine or serum) for female subjects of childbearing potential at least 72 hours prior to beginning treatment.*

8. *Female subjects of childbearing potential must be willing to use an adequate method of contraception for the course of the study and through 120 days after the last dose of trial treatment.*

Organ function

9. *Have adequate organ function as defined in Table X. Specimens must be collected within 10 days prior to the start of trial treatment.*

Table X Adequate Organ Function Laboratory Values

System	Laboratory value
Hematological	
Absolute neutrophil count (ANC)	*≥1500/μL*
Platelets	*≥100,000/μL*
Hemoglobin	*≥9.0 g/dL or ≥5.6 mmol/L*
Renal	
Creatinine OR Mesaured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	*≤1.5 x ULN OR ≥30 ml/min for subject with creatinine levels >1.5 x institutional ULN*
Hepatic	
Total bilirubin	*≤1.5 x ULN OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 x ULN*
AST (SGOT) and ALT (SGPT)	*≤2.5 x ULN OR ≤5 x ULN for subjects with liver metastases*
Coagulation	
International normalized ratio (INR) or prothrombin time (PT) *Activated partial thromboplastin time (aPTT)*	*≤1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants*

5.2 Exclusion criteria

Medical conditions

1. Subjects with either the history of hypersensitivity to excipients of the study drug or to drugs with a similar chemical structure or class to the study drug OR
2. pregnant and/or lactating women OR
3. Patients with a previously or currently diagnosed MDS/ AML or pneumonitis OR
4. Patients who have not recovered sufficiently from prior surgery or anticancer treatment OR
5. Patients who have known history of hepatitis B or hepatitis C OR
6. Patients with active infection such as TB

Prior/concurrent clinical study experience

7. Participation in another clinical study with a study drug administered in the last 3 months

Other exclusions

8. Judgment by the investigator that the subject should not participate in the study if the subject is unlikely to comply with study procedures, restrictions and requirements.
9. Previous enrolment in the present study.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

No specific dietary restrictions will be imposed on subjects recruited for this study. Co-administration with food slowed the rate of absorption but did not significantly affect the extent of absorption of olaparib. Consequently, patients should take Lynparza without regard to food.

5.3.2 Caffeine, alcohol, and tobacco

No specific restrictions will apply.

5.3.3 Activity

There are no specific restrictions that will apply.

5.4 Screen failures

Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the

Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) shall not be rescreened.

These subjects should have the reason for study withdrawal recorded in the eCRF.

6. STUDY TREATMENTS

Study treatment is defined as any study drug(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to Olaparib.

6.1 Treatments administered

6.1.1 Study Drug

Table 4 Study Drug particulars

	Study Treatment
Study treatment name:	Olaparib
Dosage formulation:	Tablets
Route of administration	Oral
Dosing instructions:	The recommended dose of olaparib is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction
Packaging and labelling	Study treatment will be provided in a bottle. Each bottle will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per Indian regulatory requirement.
Provider	AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply olaparib to the Investigator as green film-coated tablets.

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. The study treatment must be stored in a secure, environmentally controlled, and monitored area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

The Dispensing and retention of reserve samples of the study treatment will be performed in accordance with the local Indian regulations.

6.3 Measures to minimise bias: randomisation and blinding

If a subject withdraws from the study, then they will not be replaced.

The National co- ordinating investigator and any person appointed by him/her will have access to the patient level data. The appointed CRO shall help in the analysis but will not have access to the patient particulars. AstraZeneca employees shall not be in possession of patient level data at any time.

Open-label, single arm study. No blinding at site level	*This is an open-label study; potential bias will be reduced by the following steps:* *1) Consecutive subjects fitting into the inclusion criteria from the respective sites shall be enrolled in an effort to reduce selection bias in enrolment.*

6.4 Treatment compliance

Any change in the dosing schedule, dose interruptions, dose reductions or dose discontinuations should be recorded in the eCRF.

The investigator(s) shall be responsible for ensuring that the subject has returned all the unused study drug.

6.5 Concomitant therapy

Any medication or vaccine, including over the counter or prescription medications, vitamins and/or herbal supplements that the subject is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information

6.5.1 Other concomitant treatment

Any medication other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the case report form (CRF).

Medications that may NOT be administered

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement therapy (HRT) is acceptable), radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication.

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

Restricted concomitant medications

Strong or Moderate CYP3A inhibitors

Known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib.

If there is no suitable alternative concomitant medication, then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use.

• Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg bd for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards.

• Moderate CYP3A inhibitors - reduce the dose of olaparib to 150 mg bd for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards.

• After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

Strong or Moderate CYP3A inducers

Strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil) of CYP3A should not be taken with olaparib.

If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib.

If a patient requires use of a strong or moderate CYP3A inducer then they must be monitored carefully for any change in efficacy of olaparib.

P-gp inhibitors

It is possible that co-administration of P-gp inhibitors (eg amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be observed.

Effect of olaparib on other drugs

- Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K.
- Based on limited in vitro data, olaparib may reduce the exposure to substrates of CYP3A4, 2B6, 2C9, 2C19 and P-gp.
- The efficacy of hormonal contraceptives may be reduced if co administered with olaparib.
- Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered. Examples of substrates include:

  • CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine

  • CYP2B6 – bupropion, efavirenz

  • CYP2C9 – warfarin

  • CYP2C19 - lansoprazole, omeprazole, S-mephenytoin

  • P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine

  • OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan

  • OCT1, MATE1, MATE2K – metformin

  • OCT2 - serum creatinine

  • OAT3 -furosemide, methotrexate

Anticoagulant Therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.

Anti-emetics/Anti-diarrhoeals

From visit 2 onwards, should a patient develop nausea, vomiting and / or diarrhoea, then these symptoms should be reported as AEs (see section 8.3) and appropriate treatment of the event given.

Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Administration of other anti-cancer agents

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

Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the eCRF.

6.5.2 Rescue medication

The study site shall not supply rescue medication as a part of this study. In case of AE's, please refer to section 8.4.5 and 8.4.6 for the management of drug related toxicities.

6.6 Dose modification

This protocol allows for some alteration from the currently outlined dosing schedule, but the maximum daily dose shall not exceed 300 mg BD. Dose modifications are permitted in case of AE's as per section 8.4.6.

In case a dose reduction is necessary, the Study treatment will be administered as follows:

Table 5: Dose Reduction Schedule

Initial dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg twice daily	250 mg Twice daily	200 mg twice daily (lowest allowable dose level)

6.7 Treatment after the end of study (Post Trial Access to Olaparib)

Subjects receiving olaparib at the time of study completion (i.e. after completion of Treatment Phase) may continue to receive olaparib, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment or have not progressed clinically. These subjects shall receive the study drug free of cost under a separate compassionate use program and will not receive the medication via the clinical trial supply for this study. These subjects shall not be actively monitored for AE's and it will be the responsibility of the treating physician to ensure reporting of all SAE's, pregnancies, overdose and medication errors to the relevant authorities as per the standard practice in India.

DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

Subjects may be discontinued from olaparib in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study

- Disease Progression: Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the study drug is being studied. It may be an increase in the severity of the disease under study (DUS) and/or increases in the signs and symptoms of the cancer. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE (if the progression was 'as expected'). Events, which are unequivocally due to disease progression, should not be reported as an AE during the study. All the events occurring at the Indian sites that meet the criteria for seriousness will be reported expeditiously as SAEs per local regulatory requirements to the Indian regulatory authority and the concerned ethics committees. In this study, disease progression shall be determined by the investigator as per the guidelines currently being followed by the site for the indication in question. Progression of disease assessed radiographically should occur in comparison to baseline imaging obtained during screening.

- Adverse Event (including laboratory abnormality or intercurrent illness) which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- The subject (or the subject's legally acceptable representative) withdraws consent for administration of study drug
- ILD/Pneumonitis
- Acute myeloid leukemia/Myelodysplastic syndrome or other de novo malignancy requiring active treatment
- Pregnancy
- Any adverse event deemed to be related to olaparib that requires a dose hold of more than 21 days will result in permanent discontinuation of olaparib.
- Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks
- Severe non-compliance with the Clinical Study Protocol
- The patient has a confirmed positive serum pregnancy test

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Rechallenge

Rechallenge with Olaparib in this study is not allowed. Due to adverse events, the maximum dose can be reduced to 200 mg BD as per section 8.4.6. However, if drug discontinuation is necessary, the subject shall not be restarted on Olaparib subsequently.

7.1.2 Procedures for discontinuation of study treatment

The investigator should instruct the subject to contact the site before or at the time if Study treatment is stopped. A subject that decides to discontinue Study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of Study treatment should be documented in the eCRF. All Study treatment should be returned by the subject at their next on-site study visit or unscheduled visit. Subjects permanently discontinuing Study treatment should be given locally available standard of care therapy, at the discretion of the Investigator.

Discontinuation of Study treatment, for any reason, does not impact on the subject's participation in the study. The subject should continue attending subsequent study visits and data collection should continue according to the study protocol. If the subject does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the subject at 28 days post discontinuation

(End of Study Visit as described in SoA), a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A subject that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.2 Lost to follow-up

A subject will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject or next of kin by e.g. repeat telephone calls, certified letter to the subject's last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's medical record.
- Efforts to reach the subject should continue until the end of the study. Should the subject be unreachable at the end of the study, the subject should be considered to be lost to follow up with unknown vital status at end of study and censored at latest follow up contact.

7.3 Withdrawal from the study

A subject may withdraw from the study (e.g., withdraw consent), at any time (study drug **and** assessments) at his/her own request, without prejudice to further treatment.

A subject who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating physician, or information from medical records).

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up subjects as medically indicated.

AstraZeneca or its delegate will request investigators to collect information on subjects' vital status (dead or alive; date of death when applicable) at the EOS visit (Day 182 or 28 days from the date of withdrawal from the study) from publicly available sources, in accordance with local

regulations. Knowledge of the vital status at the EOS visit in all subject is crucial for the integrity of the study.

See SoA, Table 1, for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All Study treatment should be returned by the subject.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

The investigator will ensure that data are recorded on the electronic Case Report Forms

The investigator ensures the accuracy, completeness, for eCRFs include: legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue Study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 10 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

This study does not intend to assess any clinical efficacy outcomes as the study is being conducted as a part of the local regulatory requirement.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Clinical safety laboratory assessments

See Table 6 Laboratory safety variables for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA.

The Investigator should assess the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate CRF.

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Table 6 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
Urinalysis (dipstick)	S/P-Albumin
U-Hb/Erythrocytes/Blood	
U-Protein/Albumin	
U-Glucose	

NB. In case a subject shows an AST **or** ALT ≥3xULN together with total bilirubin ≥2xULN please refer to Appendix E 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

8.2.1.1 Coagulation

Activated partial thromboblastin time (APTT)will be performed at screening and if clinically indicated.

International normalised ratio (INR) will be performed at screening and if clinically indicated. Subjects taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

Each coagulation test result will be recorded in eCRF.

8.2.1.2 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for subjects with prolonged haematological toxicities as defined in Section 8.4.5.3

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Full reports must be provided by the investigator for documentation on the Patient Safety database. These data will be recorded in eCRF.

8.2.2 Physical examinations

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, lymph nodes and musculoskeletal system.

Physical examination will be performed at timelines as specified in the SoA, Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as adverse events, see Section 8.3.7 for details.

8.2.3 ECG

ECGs are required within 7 days prior to starting study treatment and when clinically indicated.

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

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the subject medical record as source data.

8.2.4 Vital signs

- Oral temperature, pulse rate, Respiratory rate and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

8.3 Collection of adverse events

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

The definitions of an AE or SAE can be found in Appendix B.

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.2 Time - period and frequency for collecting AE and SAE information

Adverse Events will be collected continuously from time of ICF until 28 days after last olaparib dose in Treatment Phase and Follow-up Phase.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject's last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAE's will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

'The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Intensity and change in intensity of the AE
- CTCAE grade and changes in the CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Study Drug (yes or no)
- Action taken with regard to Study Drug
- AE caused subject's withdrawal from study (yes or no)
- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death

- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication'

8.3.5 Causality collection

The Investigator will assess causal relationship between study drug and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study drug?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

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

8.3.6 Adverse events based on signs and symptoms

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

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs as in section 8.2 should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the study drug.

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

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see sections 8.3.9 and 8.3.10.

8.3.8 Hy's law

Cases where a subject shows elevation in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq$ 3xULN together with total bilirubin $\geq$ 2xULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.9 Disease-under study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of advanced ovarian or metastatic breast cancer. The symptoms include:

1) Abdominal bloating, indigestion or nausea.
2) Changes in appetite, such as a loss of appetite or feeling full sooner.
3) Pressure in the pelvis or lower back.
4) A more frequent or urgent need to urinate and/or constipation.
5) Changes in bowel movements.
6) Increased abdominal girth.
7) Tiredness or low energy.
8) Changes in menstruation.
9) constant back, bone, or joint pain.
10) numbness or weakness anywhere in your body.
11) a constant dry cough.
12) difficulty breathing.
13) shortness of breath.
14) chest pain.

Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the study drug. All the events occurring at the Indian sites that meet the criteria for seriousness will be reported expeditiously as SAEs per local regulatory requirements to the Indian regulatory authority and the concerned ethics committees.

8.3.10 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the study drug is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study. All the events occurring at the Indian sites that meet the

criteria for seriousness will be reported expeditiously as SAEs per local regulatory requirements to the Indian regulatory authority and the concerned ethics committees.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

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

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

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative.

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

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study subject has received any study drug

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

If a subject becomes pregnant during the course of the study, the study drug olaparib should be discontinued immediately.

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

If any pregnancy occurs during the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 9.2.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

<<When the CRF module is used include the following: The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.>>

8.4.3 Overdose

For this study, any dose of olaparib greater than 300 mg BD within 24 hours will be considered an overdose.

AstraZeneca does not recommend specific treatment for an overdose.

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening)or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.4.5 Management of study drug - related toxicities, dose interruptions and dose reductions

Toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed and study treatment should be discontinued.

Once dose is reduced, escalation is not permitted.

8.4.5.1 Management of haematological toxicity

Management of anaemia

Table 7 Management of Anaemia

Haemoglobin	Action to be Taken
Hb < 10 *but* ≥ 8 g/dl (CTCAE Grade 2)	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg transfusion) or interrupt dose for a maximum of 4 weeks. If repeat Hb< 10 but ≥ 8 g/dl, dose interrupt (for max of 4 weeks) until Hb ≥ 10 g/dl and upon recovery dose reduction to **250 mg twice**

	daily as a first step and to **200 mg twice daily** as a second step may be considered.
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks. until improved to Hb ≥ 10 g/dl. Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease

Common treatable causes of anaemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anaemia may require blood transfusions. For cases where subjects develop prolonged haematological toxicity (≥2-week interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence), refer to Section 8.4.5.3 for the management of this.

8.4.5.2 Management of neutropenia, leukopenia and thrombocytopenia

Table 8 Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a subject develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where subjects develop prolonged haematological toxicity (≥2 weeks interruption/delay in study treatment due to CTC grade 3 or worse), refer to Section 8.4.5.3.

8.4.5.3 Management of prolonged hematological toxicities while on study treatment

If a subject develops prolonged haematological toxicity such as:

- ≥2 weeks interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence
- ≥2 weeks interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 109/L)
- ≥2 weeks interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50 x 109/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the subject should be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Study treatment should be discontinued if blood counts do not recover to CTC gr 1 or better within 4 weeks of dose interruption.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to AstraZeneca Patient Safety. Olaparib treatment should be discontinued if subject's diagnosis of MDS and/or AML is confirmed.

8.4.6 Management of Non – hematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the study monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the subject should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 250 mg bd as a first step and to 200 mg bd as a second step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

8.4.6.1 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g., dyspnoea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high - resolution CT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

8.4.6.2 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients (Ledermann JA , et al, 2016). These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment. However, subjects should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (i.e., 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer subjects, generally a single agent antiemetic should be considered e.g. dopamine receptor antagonist, antihistamines or dexamethasone (National Comprehensive Cancer Network, 2018a, 2018b).

8.4.6.3 Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a subject cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with AZ study physician.

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

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a subject undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, subjects should be advised to use caution while driving or using machinery if these symptoms occur. For the dose reduction schedule, please refer to Table 5: Dose Reduction Schedule

8.5 Pharmacokinetics

PK parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6.1 Collection of samples

Pharmacodynamic samples will not be taken during the study

8.7 Genetics

No genetic tests will be performed as a part of this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

There is no formal sample size calculation as this study is being conducted as a regulatory requirement for a phase IV study including Indian subjects in the approved indications post marketing of olaparib. The primary endpoint is to demonstrate the safety profile of olaparib in routine clinical practice as assessed by the incidence of AEs (serious and non-serious) observed during trial.

9.2 Sample size determination

Based on the results of OlympiAD and SOLO – 2 trials of Olaparib tablets in platinum sensitive, relapsed ovarian cancer patients with BRCA1/2 mutation and in gBRCAm positive metastatic breast cancer, the incidence rate of the any adverse event (mentioned as part of the labelling information of Olaparib) of severity grade 3 or higher was observed to be approximately 40%. This value of the incidence rate of interest has been used for the sample size estimation in this study.(Pujade-Lauraine et al., 2017; Robson et al., 2017)

Assuming the true incidence rate of any adverse event (mentioned as part of the labelling information of Olaparib) of severity grade 3 or higher to be 40%, corresponding data from approximately 190 Indian adult patients satisfying the protocol specified eligibility criteria will be required in this study for estimating the sample (study based) incidence rate with 7% error margin and using 95% confidence interval. In this study, we expect to recruit 160 patients from platinum sensitive relapsed ovarian cancer and 40 patients from gBRCAm positive metastatic breast cancer as per the Indian HA approved indication to satisfy the Lynparza MA conditional approval.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All subjects who sign the ICF
Evaluable	All enrolled subjects
Safety analysis set	All subjects randomly assigned to Study treatment and who take at least 1 dose of study drug.

9.4 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan will be developed and finalised before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the clinical study report.

9.4.1 Efficacy analyses

No efficacy analyses will be performed on the subjects enrolled in this study.

9.4.2 Safety analyses

Safety analyses will be performed on the safety analysis set as described above in section 9.3.

Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate.

AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by subject. Any AE occurring before treatment with olaparib will be included in the data listings but will not be included in the summary tables of AEs.

Any AE occurring within 28 days of discontinuation of study drug (i.e., the last dose of olaparib) will be included in the AE summaries. Any events in this period that occur after a subject has received further therapy for cancer (following discontinuation of olaparib) will be flagged in the data listings.

9.4.3 Other analyses

PK, Pharmacodynamic and biomarker analysis will not be evaluated in this study.

9.4.4 Methods for multiplicity control

Not applicable for this study

9.5 Interim analyses

This study doesn't have a provision for internal analysis considering the fact that this study will not be evaluating any efficacy variables.

9.5.1 Data monitoring committee (DMC)

A data monitoring committee will be utilized for this study. Section A 5 in the appendix provides more details on the rationale for and the remit of the committee.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorised representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of the local regulations, ICH guidelines, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date and time the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative.

A 4 Data protection

Each subject will be assigned a unique identifier by the sponsor. Any subject records or data sets transferred to the sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com and http://ctri.nic.in/Clinicaltrials/login.php as will the summary of the study results when they are

available. The clinical trial and/or summary of the study results may also be available on other websites according to the locally prevalent regulations in India.

A 7 Data quality assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Results in a congenital abnormality or a birth defect
- Is an important medical event that may jeopardise the subject or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life threatening

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

B 4 Hospitalisation

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

B 5 Important medical event or medical treatment

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

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

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

B 6 Grading Scales for oncology studies:

The grading scales found in the revised National Cancer Institute CTCAE latest version will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When the investigator is assessing causality, consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug:

- Time Course. Exposure to suspect drug. Has the subject received at least one dose of the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

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

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

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

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

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

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

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

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

The Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until disposal.

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

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

C 2 Withdrawal of Informed Consent for donated biological samples

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

The Investigator:

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

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

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

This section is not applicable as no biological samples shall be transported out of the study sites during the course of this study.

Appendix D Genetics

This section is not applicable for this study as no genetic testing shall be performed on the study subjects.

Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 8.4.6 of the Clinical Study Protocol.

During the course of the study, the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the study drug.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 ×ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

E 3 Identification of potential Hy's Law cases

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN

- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

The Investigator will remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from local laboratory results the Investigator will without delay:

- Determine whether the subject meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the subject meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

E 4 Follow-up

E 4.1 Potential Hy's Law criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

Determine whether PHL criteria were met at any study visit prior to starting Study treatment (See Section 8.4 Safety Reporting)

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact, the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. << For studies using a central laboratory add: This includes deciding which the tests available in the Hy's law lab kit should be used>>
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

E 5 Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study drug. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions required when potential Hy's Law criteria are met before and after starting study treatment

This section is applicable to subjects who meet PHL criteria on Study treatment having previously met PHL criteria at a study visit prior to starting Study treatment.

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a significant change in the subjects' condition[#] compared with the last visit where PHL criteria were met.[#]

- If there is no significant change, no action is required
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Appendix B 5.
- A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 7 Actions required for repeat episodes of potential Hy's Law

This section is applicable when a subject meets PHL criteria on study treatment, and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (e.g., chronic or progressing malignant disease, severe infection or liver disease).

If **No**: Follow the process described in Appendix E 4.1.

If **Yes**: Determine if there has been a significant[#] change in the subject's condition compared with when PHL criteria were previously met.

If there is no significant change, no action is required.

If there is a significant change, follow the process described in Appendix E 4.

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

Appendix F Abbreviations

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukamia
APTT	Activated Partial Thromboplastin True
AST	Aspartate Aminotransferase
BD	Twice daily
BP	Blood pressure
BRCA	Breast cancer susceptibility gene
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CR	Complete response
CrCl	Creatinine clearance
eCRF	Electronic case report form
CSA	clinical study agreement
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Event
DAE	discontinuation of study drug due to adverse event
DNA	deoxyribonucleic acid
DOR	Duration of response
DSB	Double stranded breaks
EC	Ethics committee, synonymous to institutional review board (IRB) and independent ethics committee (IEC)
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FAS	Full analysis set
FSI	First subject in
gBRCAm	Germline BRCA mutation
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
Hb	Haemoglobin

Abbreviation or special term	Explanation
HR	Hazard ratio
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
HRR	Homologous Recombination Repair
MCV	Mean Cell Volume
MDS	Myelodysplastic syndrome
MBC	Metastatic Breast Cancer
NHEJ	Non – homologous end junction
OAE	Other significant adverse event
OC	Ovarian Cancer
PARP	Poly-adenosine 5'diphosphoribose (ADP) Polymerase
PD	Progression of disease
PFS	Progression free survival
PI	Principal investigator
p.o.	Administration by mouth
PR	Partial response
PSR	Platinum Sensitive Relapsed
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid tumours version 1.1.
SAE	serious adverse event
SAP	statistical analysis plan
SD	Stable disease
ULN	Upper limit of normal
US	United States of America
WBDC	Web based data capture

ASTRAZENECA SIGNATURE(S)

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This Clinical Study Protocol has been subjected to an internal AstraZeneca review

I agree to the terms of this Study protocol.

AstraZeneca representative

PPD

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