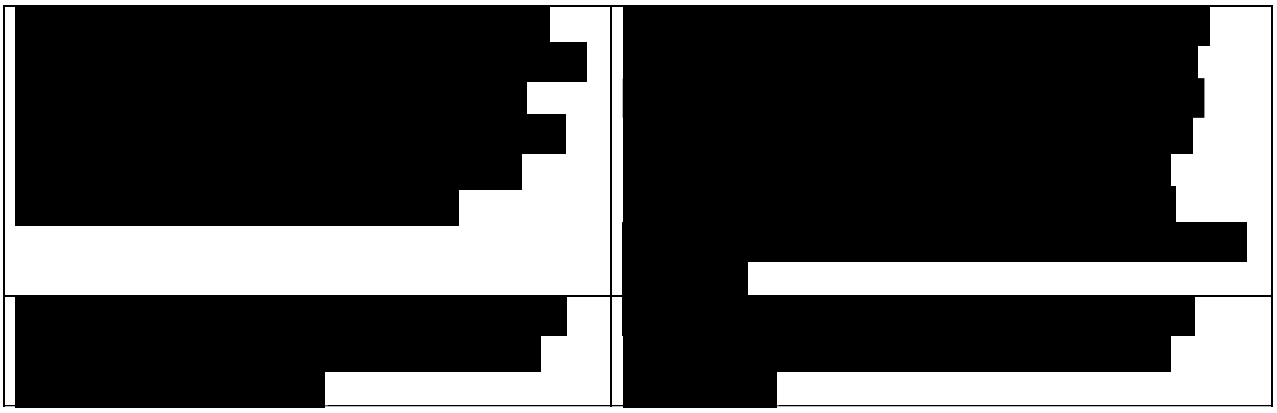
Protocol Full Title:	Phase 1 Trial of the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Clinical Activity of RP-3467 Alone and in Combination with Olaparib in Participants with Advanced Solid Tumors (POLAR Trial)
Sponsor Confidentiality Statement:	This document is confidential. It contains proprietary information of Repare Therapeutics (Sponsor). Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this trial.
GCP Statement	This trial is to be performed in full compliance with International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use and all applicable local Good Clinical Practice (GCP) guidelines and regulations. All required trial documentation will be archived as required by regulatory authorities.
Protocol Number:	RP-3467-01
Version:	2.0
Amendment Number:	1
Amendment Scope:	To accommodate requests from the Food and Drug Administration (FDA)
Compound Number(s):	RP-3467, olaparib
Trial Phase:	Phase 1
Acronym:	**POLAR**
Short Title:	Phase 1 Trial of RP-3467 Alone and in Combination with Olaparib in Participants with Advanced Solid Tumors
Sponsor Name and Address:	Repare Therapeutics 7171 Frederick-Banting Building 2 St-Laurent, Quebec, H4S 1Z9 Canada
Regulatory Agency Identifier Number(s):	IND: 170556
Sponsor Approval Date:	17 July 2024

1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

Objectives and Endpoints

Primary Objectives	Primary Endpoints
To assess the safety and tolerability of RP-3467 alone and in combination with olaparib in participants with eligible advanced solid tumors and to define the maximum tolerated dose (MTD) or maximum administered dose (MAD) for RP-3467 monotherapy	Dose-limiting toxicities (DLTs), incidence and severity of treatment-emergent adverse events (TEAEs)
[redacted]	[redacted]



Overall Design

Several key aspects of the trial design are summarized below.

Intervention Model:	N/A	**Population Type:**	Adult participants
Control:	None	**Population Diagnosis or Condition:**	Advanced solid tumors
Active Comparator:	N/A	**Population Age:**	Minimum: 18 years Maximum: N/A
Trial Intervention Assignment Method:	N/A	**Site Distribution:**	Multi-site and multi-regional

Number of Arms: 2

Blinding: Not applicable (no blinding)

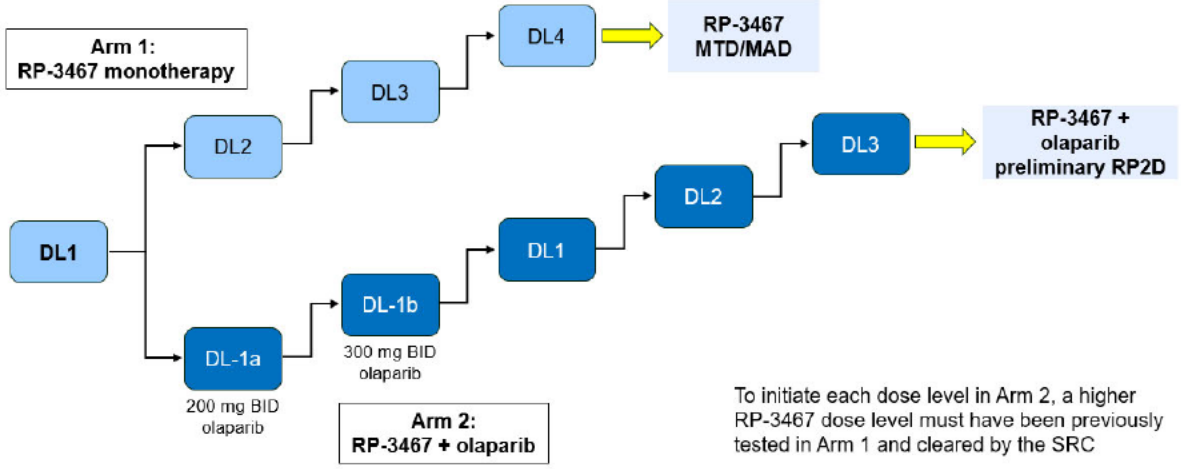
Number of Participants: Approximately 52 evaluable participants

Trial Duration: Approximately 24 months

This is a multicenter, open-label Phase 1 trial to investigate the safety and preliminary efficacy of the Polθ inhibitor RP-3467 alone or in combination with the poly-ADP ribose polymerase (PARP) inhibitor (PARPi) olaparib in adults with molecularly selected advanced solid tumors.

This trial will enroll participants with breast, ovarian, prostate, or pancreatic cancers that harbor a deleterious alteration in *BRCA1/2, PALB2, RAD51B/C/D* or that have homologous recombination deficiency (HRD+). The estimated sample size for this trial will be approximately 52 evaluable participants , including an estimated 36 participants in dose escalation and an estimated 16 participants in backfill cohorts. Dose finding will follow Bayesian Optimal Interval (BOIN) decision criteria for both the monotherapy (Arm 1) and combination (Arm 2) arms, which will occur in parallel, starting

with Arm 1, as per the below schematic. [redacted]



BID = twice daily; DL = dose level; MAD = maximum administered dose; MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose; SRC = Safety Review Committee

In Arm 1, eligible participants will be treated with escalating doses of RP-3467 monotherapy, preceded by a 2-day PK run-in, to evaluate the safety and tolerability, PK, and pharmacodynamics of RP-3467 monotherapy. The cycle length will be 21 days. Evaluation of escalating doses of RP-3467 in combination with olaparib in Arm 2 will occur in parallel with Arm 1. The starting RP-3467 dose for the combination in Arm 2 will be at least one dose level lower (DL-1) than the highest monotherapy dose level evaluated and considered tolerated/safe by the Safety Review Committee (SRC). [redacted] Following disease progression, participants in the monotherapy arm will have the opportunity to receive the combination of RP-3467 and olaparib at the highest previously evaluated dose level of the combination deemed safe and tolerable (or at the preliminary RP2D if previously determined), provided they meet all required eligibility criteria, have not had Grade >2 drug-related toxicities at their current monotherapy dose, and following discussion with and approval by the Medical Monitor.

A starting Arm 1 dose level of 160 mg once daily (QD) for RP-3467 monotherapy was chosen based on preclinical Good Laboratory Practice (GLP) safety data. *In vitro* data suggest RP-3467 may be a weak cytochrome P450 (CYP) 3A inhibitor and inducer; thus, due to an unclear potential for drug-drug interactions (DDI) and confounding toxicities from olaparib alone, a starting dose of 200 mg twice daily (BID) olaparib, a lower dose than the United States Prescribing Information (USPI) recommended dose of 300 mg BID, will initially be evaluated in Arm 2 (DL-1a). Once safety and tolerability of the combination is confirmed and PK data reviewed from the initial Arm 2 cohort(s), the olaparib dose may be increased to 300 mg BID for subsequent cohorts (e.g., DL-1b).

Dose escalation and de-escalation decisions will be based on BOIN criteria. The decision to escalate either RP-3467 or olaparib following the first dose level of Arm 2 will be based on [redacted] safety data and agreed upon by the SRC. The exposure of olaparib and RP-3467 from the first combination cohort in Arm 2 will be evaluated and used to inform the dose selection of the next combination dose level. Specifically, the RP-3467 dose will be escalated to a level that is not expected to exceed the exposure of the dose of RP-3467 monotherapy which has been cleared by the SRC. [redacted] During the dose escalation phase, initially up to 3 participants will be treated at each monotherapy dose level in Arm 1, and 3 participants will be treated at each combination dose level in Arm 2. In addition to satisfying BOIN criteria, to initiate each dose level in Arm 2, a higher RP-3467 dose level must have been previously tested in Arm 1 and cleared by the SRC.

In Arm 1, RP-3467 may be escalated in increments of 100% until dose level N is reached, defined as follows:

- Any Grade ≥3 hematological toxicity, or
- >50% decrease in platelets or neutrophils from the first dose, or
- >2 g/dL decrease in hemoglobin from the first dose, or
- Any ≥ Grade 2 drug-related non-hematological toxicity lasting >5 days or requiring clinical intervention, except Grade 2 fatigue, nausea, vomiting, diarrhea, or constipation, or
- Adverse event (AE) of any grade limiting tolerability as assessed by the SRC.

After dose level N is reached, subsequent dose levels will evaluate RP-3467 dose increases of up to 75%, as determined by the SRC, which based on the safety profile observed, may be guided by a modified Fibonacci sequence (up to 67%, 50%, and 33%) in consecutive cohorts per SRC discretion.

Dose escalations of RP-3467 in Arm 2 will be guided by the dose levels established in Arm 1. The same triggers as for Dose level N in Arm 1 will trigger reduced dose escalation increments in Arm 2 if the events occur during the DLT evaluation period (from the start of first dose through the end of Cycle 1). Thus, in the setting of combination-specific toxicities, the RP-3467 dose in Arm 2 may be lower than at the corresponding dose level in Arm 1. Intermediate dose levels of RP-3467 can be evaluated if recommended by the SRC.

Dose Level	**Arm 1**	**Arm 2**	
	RP-3467 Daily (mg)[a] or % of previous dose	**RP-3467 Daily (mg)[a]**	**Olaparib (mg, BID)**
-1a	NA	80	200
-1b[b]			300[b]
1	160		300

Dose Level	Arm 1	Arm 2	
	RP-3467 Daily (mg)[a] or % of previous dose	RP-3467 Daily (mg)[a]	Olaparib (mg, BID)
2	Up to 100% increase until level N	RP-3467 dose no higher than corresponding Arm 1 DL	300
N+1	≤75% increase (per SRC, guided by modified Fibonacci)		300

BID = twice daily; DL = dose level; NA = not applicable; PK = pharmacodynamics; QD= daily; SRC = safety review committee

[a] Initially, a QD regimen will be evaluated for RP-3467. [redacted]

[b] Per review of safety/PK data and discussion with SRC, 160 mg RP-3467 may alternatively be evaluated in combination with 200 mg BID olaparib as the 2nd dose cohort (DL1a). [redacted]

Once a dose level has been identified that results in RP-3467 exposure predicted to be maximally efficacious in the combination setting based on available preclinical data, this dose level may be expanded (as long as BOIN de-escalation criteria are not met) in Arm 2 to at least 6 participants to better assess safety/tolerability and RP-3467 exposure relative to the target exposure for optimal efficacy based on preclinical studies.

Lower dose levels of RP-3467 (below the starting dose) may also be evaluated in Arm 1 or 2 if instructed per BOIN rules (where the decision is to de-escalate at the first RP-3467 dose level) and as agreed upon by the SRC.

Monotherapy dose-escalation may be stopped before a monotherapy MTD is established if:

[redacted]

- MTD is exceeded in the combination dose-escalation arm.

Intraparticipant dose escalations of RP-3467 (and olaparib escalation to 300 mg BID for participants starting at 200 mg BID) may be allowed at the discretion of the Investigator and with Sponsor approval. A participant may be considered for dose escalation only if they have completed at least 1 cycle of treatment and did not experience Grade >2 or significant, unacceptable, or irreversible toxicities considered related to the trial intervention(s) and have not required any dose reductions. All available safety [redacted] data will be used to determine intraparticipant dose escalations. The RP-3467 dose for an individual participant may only be escalated to a dose level that has been declared safe and tolerable by the SRC.

Evaluation of the [redacted] safety results at any time may trigger adjustment of the RP-3467 dosing schedule to be more frequent (e.g., BID) in subsequent cohorts. Any decision to switch from QD to BID dosing during the trial may be made after agreement with the SRC.

[redacted]

[redacted]

For all participants, treatment will continue until radiographic disease progression, intolerability to trial intervention, risk to participant (including clinical progression) as determined by the Investigator and/or Sponsor, consent withdrawal, start of a non-trial anticancer treatment, major protocol noncompliance that would jeopardize participant safety and/or data interpretation as determined by the Sponsor, pregnancy, or death. For participants with progression based on tumor markers per GCIG or PCWG3 criteria, evidence of radiographic and/or other signs of clinical progression should be used in determining treatment decisions. Participants requiring more than 3 continuous weeks off planned trial treatment for any reason will be discontinued unless the Investigator in agreement with the Sponsor believes that the participant would derive clinical benefit with continued treatment.

Participants are allowed to continue treatment after disease progression if the Investigator deems that it is in the participant's best interest. Participants in Arm 1 will have the opportunity to continue treatment post-progression with the combination of RP-3467 and olaparib (up to the highest dose level of the combination deemed safe and tolerable and cleared by the SRC, but dependent on the participant's overall tolerability of RP-3467 monotherapy). In all cases of treatment post-progression, the participant will be required to provide signed written consent agreeing to treatment after disease progression. [redacted]

Eligibility Criteria

Inclusion Criteria:

To be eligible to participate in this trial, an individual must meet all the following criteria:

1. Written informed consent, according to local guidelines, signed and dated by the participant or legal guardian prior to the performance of any trial-specific procedures, sampling, or analyses. Participants with impaired decision-making capacity must have a close caregiver or legally authorized representative (LAR) present.

2. Male or female participants ≥18 years of age at the time of signing the informed consent

3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

4. Participant must have one of the following that has progressed or was non-responsive to prior systemic therapy and for which no standard or available known therapeutic option exists:

a. locally advanced or metastatic epithelial ovarian cancer (including fallopian tube or primary peritoneal), or

b. metastatic breast cancer, or

c. metastatic castration-resistant prostate cancer (mCRPC), or

d. pancreatic adenocarcinoma

Participants are also eligible if the treating physician determines the participant is not a candidate for or would be unlikely to tolerate or derive significant clinical benefit from standard of care therapy, or if the participant declines standard-of-care therapy. Documented counselling by center Investigator on benefits/risks of standard-of-care therapy is required for enrolled participants who decline standard-of-care therapy.

PARPi-naïve participants that would be eligible to receive a monotherapy PARPi per USPI label will also be eligible for treatment in Arm 2 after a safe and tolerable combination dose level (with 300 mg BID olaparib) has been established and agreed upon by the SRC.

5. Measurable disease per RECIST v1.1

   Exception: Participants with non-measurable but evaluable disease (e.g., nontarget lesions only per RECIST v1.1 and/or elevated tumor markers for participants with prostate or ovarian cancer) and evidence of locally advanced or metastatic disease on imaging obtained during Screening, may be eligible if agreed upon by the Sponsor and Investigator.

6. Existing biomarker profile reported from a local test obtained in a College of Pathology (CAP)/Clinical Laboratory Improvement Amendments (CLIA) certified lab (International Organization for Standardization [ISO] or equivalent):

   a. Pathogenic or likely pathogenic somatic or germline alteration in at least 1 of the following genes: *BRCA1, BRCA2, PALB2, RAD51B/C/D*

      And/or

   b. HRD+ (by Myriad MyChoice®CDx or FoundationOne®CDx tests)

   For all participants, an anonymized/redacted Molecular Pathology report should be submitted to the central annotation group during Pre-screening to confirm eligibility. For details on the pre-screening eligibility process, see the Molecular Eligibility Manual.

7. Provision of archival tumor tissue, or if adequate archival tumor tissue is not available, provision of a fresh biopsy if there is a lesion that can be safely biopsied

Note: If adequate archived tumor tissue is not available and/or a fresh biopsy cannot be safely performed, the participant may still be eligible with prior Sponsor approval.

8. Acceptable organ function at Screening, as evidenced by the following laboratory data:

    a. Creatinine clearance ≥ 60 mL/min calculated using Cockcroft-Gault equation or measured by 24-hour urine collection

    b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 × upper limit of normal (ULN) or ≤ 5.0 × ULN if liver metastases present

    c. Total bilirubin ≤ 1.5 × ULN or < 3.0 × ULN if known Gilbert's disease

    d. Albumin ≥ 2.5 g/dL

9. Acceptable hematologic function at Screening:

    a. No red blood cell (RBC) or platelet transfusions or growth factors within 14 days of the first dose

    b. Absolute neutrophil count ≥ 1500/μL

    c. Hemoglobin ≥ 10.0 g/dL

    d. Platelets ≥ 120,000/μL

10. Negative pregnancy test (serum) for women of childbearing potential (WOCBP) at Screening.

    a. WOCBP is defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. WOCBP, who are sexually active, and their partners must agree to use a highly effective form of contraception [redacted] throughout their participation in the trial and for 6 months after the last dose of trial intervention. Female participants must refrain from donating eggs during their participation in the trial and for 6 months following last dose of trial intervention.

    b. Women are considered post-menopausal and not of childbearing potential if they have had no menses for 12 months without an alternative, potentially reversible medical cause or permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

11. Male participants with female partners of childbearing potential must follow a contraception method at least as conservative as Clinical Trial Facilitation Group (CTFG) recommendations [redacted] during their participation in the trial for 3 months following last dose of trial intervention. Male participants must also refrain from donating sperm during their participation in the trial and for 3 months following last dose of trial intervention.

12. Ability to comply with the protocol and trial procedures detailed in the Schedule of Activities

13. Ability to swallow and retain whole, intact oral medications, without crushing or chewing

14. Life expectancy ≥12 weeks after the start of the treatment according to the Investigator's judgment

Exclusion Criteria:

An individual who meets any of the following criteria will be excluded from participation in this trial:

1. History or current condition (such as transfusion-dependent anemia, thrombocytopenia, or chronic neutropenia) or laboratory abnormality that in the opinion of the Investigator or Sponsor might pose a significant risk to participant safety, confound the trial results, or interfere with participation for the full duration of the trial treatment

2. Life-threatening illness, medical condition, active uncontrolled infection, or organ system dysfunction (such as coagulopathy or encephalopathy), or other reasons which, in the Investigator's opinion, could compromise the participant's safety, or interfere with or compromise the integrity of the trial outcomes

3. Uncontrolled, symptomatic brain metastases. Participants with previously treated brain metastases may participate provided the metastases are stable (without evidence of progression by imaging within 4 weeks prior to the first dose of trial intervention and any neurologic symptoms are controlled and stable), they have no evidence of new or enlarged brain metastases, and they are clinically stable and off steroids for at least 7 days prior to trial treatment. Participants with leptomeningeal disease are excluded without exception.

4. Presence of other known second malignancy with the exception of any cancer that has been in complete remission for ≥ 2 years, International Society of Urological Pathology (ISUP) Grade group 1 prostate cancer on active surveillance, non-muscle invasive bladder cancer, any carcinoma in-situ, or completely resected squamous and basal cell carcinomas of the skin

5. Major surgical procedures ≤28 days prior to trial treatment initiation. Participants must have recovered from any of the effects of any major surgery. No waiting period is

required following central venous access placement, biopsy collection, or minor surgeries as long as the Investigator assesses the impact on trial participation.

6. Active, uncontrolled bacterial, fungal, or viral infection, including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness. In equivocal cases, participants with a negative viral load may be eligible. Eligibility criteria for HIV positive participants currently on highly active antiretroviral therapy should be evaluated and discussed with the Medical Monitor and will be based on current and past CD4 and T cell counts, history (if any) of AIDS-defining conditions (e.g., opportunistic infections), and status of HIV treatment. Participants with previously treated HBV and HCV with negative viral load are eligible.

7. Clinically significant vascular (both arterial and venous) and nonvascular cardiac conditions, active or within 6 months prior to enrollment, including:

    a. Arterial disease such as cerebral vascular accident/stroke (including transient ischemic attack), myocardial infarction, and unstable angina

    b. Venous diseases such as deep vein thrombosis and/or pulmonary embolism, central venous thrombosis (active or within 3 months prior to enrollment)

    c. Nonvascular cardiac disease such as congestive heart failure (New York Heart Association Classification Class ≥2)

    d. Conduction abnormality not controlled with pacemaker or medication

    e. Significant ventricular or supraventricular arrhythmias, including history of Torsades de pointes (TdP) unless all risk factors that contributed to TdP have been corrected. Participants with chronic rate-controlled atrial fibrillation/flutter in the absence of other cardiac abnormalities are eligible.

    f. Family history of sudden unexplained death or long electrocardiogram (ECG) interval measured from the onset of the QRS complex to the end of the T wave (QT syndrome)

    g. History of risk factors for QT prolongation or TdP (e.g., organic heart disease, congestive heart failure, hypokalemia, hypocalcemia, hypomagnesemia, congenital long QT syndrome, myocardial ischemia, or infarction)

8. Mean resting QT interval corrected for heart rate (QTc) using the Fridericia formula (QTcF) >470 msec (as calculated per institutional standards) demonstrated by at least 2 ECGs ≥1 minute apart at trial entry

9. Uncontrolled hypertension (systolic blood pressure [BP] ≥160 mmHg; diastolic BP ≥100 mmHg) despite adequate treatment prior to first dose of treatment. Optimization of anti-hypertensive regimen and re-Screening are permissible.

10. Persistent Grade >1 non-hematological toxicity from prior cancer therapy (except alopecia, anorexia, or toxicity that is stable and poses no significant risk to the participant). Grade 2 peripheral neuropathy after documented treatment with anti-cancer therapies known to induce neuropathy is allowed.

11. Participants with either previous or current myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or features suggestive of MDS/AML

12. Chemotherapy, small molecule, or biologic antineoplastic agent given within 21 days or < 5 half-lives, whichever is shorter, and monoclonal antibodies given within 28 days or <5 half-lives, whichever is shorter, prior to first dose of trial intervention. For compounds for which 5 half-lives is ≤ 21 days, a minimum of 10 days between termination of the prior treatment and administration of trial intervention is required.

13. Other anticancer therapy (chemotherapy, immunotherapy, hormonal anticancer therapy, biological therapy, lanreotide/octreotide for neuroendocrine tumors (NETs)/neuroendocrine carcinomas (NECs), or other novel agent) administered while the participant is receiving trial intervention. For participants with breast or prostate cancer, continuation of long-term luteinizing hormone-releasing hormone (LHRH)/gonadotrophin-releasing hormone (GnRH) analogs are allowed if these medications were prescribed for at least 4 months before trial entry. Participants with prostate cancer without history of bilateral orchiectomy are required to be maintained on LHRH/GnRH analog and have serum testosterone < 50 ng/dL documented during Screening.

14. Previously prescribed receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor and bisphosphonates must be prescribed at least 28 days prior to enrollment.

15. Prior therapy with a Polθ inhibitor other than RP-3467

16. *For Arm 2 participants only*: Discontinued treatment with any prior full-dose monotherapy PARPi regimen due to poor tolerability or has a history of intolerability to full dose PARPi (when given as monotherapy).

17. Use of radiotherapy (except for palliative reasons) within 14 days prior to trial treatment initiation unless approved by Sponsor

18. Current treatment with medications that are known to prolong the QT interval [redacted]

19. Participants who are receiving moderate or strong CYP3A inhibitors or inducers and P-gp inhibitors within 14 days or 5 half-lives (whichever is longer) prior to first dose of trial intervention

20. Gastrointestinal abnormalities which may significantly impact absorption of trial intervention(s), including: requirement for intravenous alimentation, prior surgical procedures affecting absorption including gastric resection/bypass or lap band, active inflammatory gastrointestinal disease, treatment for active peptic ulcer disease in the past 6 months, and malabsorption syndromes

21. Any known hypersensitivity or contraindication to the components of the trial interventions RP-3467 and/or olaparib (as applicable per Arm)

22. Participants who are breastfeeding at Screening or planning to become pregnant (self or partner) at any time during trial participation

23. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the trial protocol and/or follow-up procedures outlined in the protocol

Trial Interventions

RP-3467 will be administered as immediate-release solid dosage form for oral self-administration. Olaparib will be administered as immediate-release tablets for oral administration.

Committees

Independent Committees: SRC