Title: A Phase 2, Randomized, Open-Label, 3-Arm Study of Relacorilant in Combination with Nab-Paclitaxel for Patients with Recurrent Platinum-Resistant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

NCT number: NCT03776812

Date: 23 October 2019

CLINICAL STUDY PROTOCOL
CORT125134-552

Title	A Phase 2, Randomized, Open-label, 3-arm Study of Relacorilant in Combination with Nab-Paclitaxel for Patients with Recurrent Platinum-Resistant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
Investigational Product	Relacorilant (CORT125134)
EudraCT Number	2018-004186-14
Medical Monitor	[redacted] Secondary Medical Monitor: [redacted]
Sponsor	Corcept Therapeutics Incorporated 149 Commonwealth Drive Menlo Park, California 94025 USA (650) 327-3270
Version	Amendment 2
Date	23 October 2019

Good Clinical Practice Statement

This study will be conducted in compliance with the protocol, International Council of Harmonisation Good Clinical Practice guidelines, and ethical principles contained in the Declaration of Helsinki (1989), or with the laws and regulations of the country in which the research is conducted, whichever provides greater protection of the human study participants. Compliance with these standards provides assurance that the rights, safety, and well-being of study participants are protected.

Confidentiality Statement

SPONSOR SIGNATURE PAGE

Protocol Title	A Phase 2, Randomized, Open-label, 3-arm Study of Relacorilant in Combination with Nab-Paclitaxel for Patients with Platinum-Resistant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
Protocol Number	CORT125134-552
Version	Amendment 2
Date	23 October 2019

APPROVAL STATEMENT

The undersigned has reviewed the format and content of the above protocol and approved for issuance.

[redacted]

10-23-2019

Date

SYNOPSIS

Name of Sponsor	**Name of Active Ingredient**	**Study Number**
Corcept Therapeutics	Relacorilant (CORT125134)	CORT125134-552

Title of Study

A Phase 2, Randomized, Open-label, 3-arm Study of Relacorilant in Combination with Nab-Paclitaxel for Patients with Recurrent Platinum-Resistant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study Centers

Approximately 36 sites in the United States and globally.

Phase of Development

Phase 2

Study Objectives

For all efficacy objectives and corresponding endpoints listed below, assessment for response and disease progression are according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by the Investigator or local radiologist, unless otherwise noted.

Primary:

To evaluate progression-free survival (PFS) in patients treated with intermittent or continuous regimens of relacorilant in combination with nab-paclitaxel compared with patients treated with nab-paclitaxel alone.

Secondary:

Efficacy

- To evaluate objective response rate (ORR) in patients with measurable disease at baseline treated with intermittent or continuous regimens of relacorilant in combination with nab-paclitaxel compared with patients treated with nab-paclitaxel alone.
- To evaluate duration of response (DoR) in patients treated with intermittent or continuous regimens of relacorilant in combination with nab-paclitaxel compared with patients treated with nab-paclitaxel alone.
- To assess response according to cancer antigen 125 (CA-125) using Gynecologic Cancer Intergroup (GCIG) criteria. A combined response endpoint based on both RECIST v1.1 and GCIG criteria will also be reported.
- To evaluate PFS rate at 6 and 12 months in patients treated with intermittent or continuous regimens of relacorilant in combination with nab-paclitaxel compared with patients treated with nab-paclitaxel alone.
- To evaluate overall survival (OS) in patients treated with intermittent or continuous regimens of relacorilant in combination with nab-paclitaxel compared with patients treated with nab-paclitaxel alone.
- To evaluate PFS, ORR, DoR and best overall response (BoR) in patients who receive continuous relacorilant in combination with nab-paclitaxel following progression on nab-paclitaxel (Crossover).
- To assess response according to CA-125 using GCIG criteria in those patients who crossover to continuous relacorilant + nab-paclitaxel. A combined response endpoint based on both RECIST v1.1 and GCIG criteria will also be reported for Crossover patients.

Safety

- To assess the safety of relacorilant treatment in combination with nab-paclitaxel.
- To model the exposure-toxicity and exposure-response of relacorilant and nab-paclitaxel in each treatment arm to recommend a dosing regimen of relacorilant in combination with nab-paclitaxel for further development.

Pharmacokinetics

- To assess the pharmacokinetics (PK) of relacorilant and nab-paclitaxel following intermittent or continuous treatment regimens of relacorilant in combination with nab-paclitaxel compared with nab-paclitaxel alone.

Exploratory

Pharmacodynamics/Biomarkers

- To assess the relationship between baseline characteristics of patients that respond to intermittent or continuous treatment regimens of relacorilant in combination with nab-paclitaxel and patients treated with nab-paclitaxel alone.
- To assess pharmacodynamic effects of intermittent or continuous treatment regimens of relacorilant in combination with nab-paclitaxel and patients treated with nab-paclitaxel alone.

Patient-Reported Outcomes and Quality of Life

- To describe changes from baseline of Patient-Reported Outcomes (PRO) and Quality of Life (QoL) scores in the study population and to describe differences across treatment arms.

Population

Women with recurrent ovarian, primary peritoneal, or fallopian tube cancer following at least one treatment and which is resistant and/or refractory to platinum-based chemotherapy, including the following histological subtypes:

- High grade serous carcinoma
- Carcinosarcoma
- Endometrioid carcinoma

Number of Patients Planned

A total of approximately 177 patients will be randomized in a 1:1:1 ratio to one of the 3 treatment arms (approximately 59 patients per arm).

Methodology

This is a Phase 2, open-label, randomized, 3-arm study to evaluate the efficacy, safety, PK, pharmacodynamics, PRO and QoL of continuous and intermittent dosing of relacorilant in combination with nab-paclitaxel compared with nab-paclitaxel alone.

Screening procedures will be performed within the 28 days prior to the first dose of study treatment.

Eligible patients will be randomized 1:1:1 to one of the following 3 treatment arms. Patient randomization will be stratified by treatment-free interval from most recent taxane (relapse within 6 months vs >6 months) and presence of ascites (yes vs no).

- Arm A (continuous relacorilant): relacorilant starting at 100 mg, administered orally, once daily every day in combination with nab-paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle.
- Arm B (intermittent relacorilant): relacorilant 150 mg, administered orally, once daily on the day before (excluding Cycle 1 Day -1), the day of, and the day after nab-paclitaxel, in combination with nab-paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle.

- Arm C (comparator): nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle.

Study treatment will start on Cycle 1 Day 1 in all treatment arms.

Tumor assessments will be conducted using computerized tomography (CT) with contrast or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis. A radiographic tumor assessment is required within 28 days prior to the first dose of study treatment and then every 8 weeks (±7 days) from Cycle 1 Day 1 until unequivocal PD is documented, including in patients who prematurely discontinue therapy. Tumor response will be assessed by the Investigator or local radiologist using RECIST v1.1. Radiographic scans will be quality checked, anonymized, and stored centrally.

CA-125 will be assessed within 14 days prior to the first dose of study treatment and then every 4 weeks from Cycle 1 Day 1 for the first 12 months of study treatment, and CA-125 response will be determined according to GCIG criteria.

Tumor response will be assessed by RECIST v1.1, as described above. A combined response endpoint incorporating RECIST v1.1 and GCIG criteria will also be reported.

Patients will remain on study treatment until unequivocal PD per RECIST 1.1 as determined by the Investigator, unmanageable toxicity, or patient refusal, or until meeting other criteria for discontinuation of study treatment. Patients will be seen approximately 30 days after the last dose of relacorilant or nab-paclitaxel, whichever is latest, for a 30-Day Follow-up Visit.

Patients who discontinue treatment at any time will continue to be followed for survival information (i.e., the date and cause of death) and subsequent treatment information (i.e., name[s] of subsequent therapy regimen[s], dates of initiation and completion, PD on subsequent therapy and response to subsequent therapy) during the Long-Term Follow-up.

- For patients who discontinue treatment before unequivocal PD, subsequent treatment information will be collected at the same time as radiographic tumor assessments (i.e., every 8 weeks) until unequivocal PD. After PD, they will be followed every 3 months for the remainder of the Long-Term Follow-up.
- For patients with PD, or for patients who decline further radiographic tumor assessments, survival and subsequent treatment information will be collected every 3 months after the last dose of study treatment. Long-Term Follow-up will continue until the end point of death, the patient is lost to follow-up, or other study exit criteria are met (Section 4.4.2).

Crossover: Patients in Arm C (comparator) who experience unequivocal PD per RECIST v1.1 will be given the opportunity to receive continuous relacorilant in combination with nab-paclitaxel after discussion with the Medical Monitor. Radiographic tumor assessments at the time of PD on nab-paclitaxel will be considered the final tumor assessment for comparator-only treatment and baseline for combination therapy. If more than 28 days have passed since the date of PD and Cycle 1 Day 1 of the Crossover, then a new baseline radiographic tumor assessment will need to be obtained prior to initiating crossover treatment. Tumor assessments will then be performed every 8 weeks (±7 days) from the first dose of relacorilant until PD. CA-125 will be assessed within 14 days prior to the first dose of relacorilant and assessed every 4 weeks for the first 12 months. Study procedures will be performed according to the schedule for the Treatment Phase; assessments for the Arm C End-of-Treatment Visit and the Crossover Cycle 1 Day 1 Visit may be combined into one visit for patients in Arm C who crossover from nab-paclitaxel to combination treatment (relacorilant 100 mg, administered orally, once daily every day starting on Cycle 1 Day 1; in combination with nab-paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle).

Pharmacodynamics/Biomarkers

Optional paired tumor biopsies will be obtained within 6 weeks prior to treatment initiation and at Cycle 2 Day 1. A minimum of 6 patients providing biopsies in each of the 3 treatment arms is required. If additional patients are enrolled to achieve this target, consent to provide biopsies will become

mandatory. Pharmacodynamic markers will include mRNA gene panel (blood and tumor expression profiles), cytokines, cancer antigens, tumor biomarker assays (tumor tissue), and other exploratory biomarkers. Additionally, the neutrophil-to-lymphocyte ratio will be evaluated as a pharmacodynamic marker from the hematology results.

Pharmacokinetics

Intensive PK sampling for relacorilant and nab-paclitaxel will take place on Cycle 1 Day 15.

Patient-Reported Outcomes and Quality of Life

Baseline PRO and QoL assessments must be collected prior to the first dose of study treatment (relacorilant or nab-paclitaxel, whichever is earliest). Post-baseline assessments will be collected every other cycle, at the End-of-Treatment Visit, and at the 30-Day Follow-up Visit.

A detailed description of the study visits and procedures are provided in the schedule of assessments (Table 10) and PK (Table 11) and pharmacodynamic (Table 12) schedules of assessments.

Duration of Treatment and Duration of Study

Patients will receive treatment until reaching a protocol-defined event of disease progression (PD), experiencing unmanageable toxicity, or until other treatment discontinuation criteria are met. All patients will be followed for progression, subsequent therapies (start and end date and response), and survival.

Independent Data Monitoring Committee

To ensure patient safety, an Independent Data Monitoring Committee (IDMC) will evaluate safety data (which will include all patients enrolled in the study) after approximately 40 patients have enrolled and met at least one of the following criteria:

- Received 2 cycles of treatment
- Reached an event of PD
- Discontinued treatment due to toxicity

Subsequent reviews will be based on recommendations from the IDMC, with a minimum frequency of approximately every 6 months. A separate IDMC charter will be prepared and agreed by the IDMC members.

Criteria for Inclusion

Inclusion Criteria

1. Signed and dated Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to study-specific screening procedures.
2. Female patients aged ≥18 years old at time of consent.
3. Histologic diagnosis of high grade serous or endometrioid epithelial ovarian, primary peritoneal, or fallopian tube cancer or ovarian carcinosarcoma. Clear cell, mucinous and borderline histologic subtypes are excluded.
4. Received at least one line of therapy with evidence of cancer progression within 6 months after the last dose of platinum-based therapy (i.e., having a platinum-free interval of ≤6 months [platinum resistant]), or progressive disease during or immediately after platinum-based therapy (i.e., platinum refractory). Patients with primary platinum resistance (progression within 6 months of the last dose of first-line platinum-containing chemotherapy) are considered eligible.

   Notes: For the calculation of the platinum-free interval, cancer progression must be defined by clear evidence of progression, such as radiographic progression per RECIST v1.1. Calculating the platinum-free interval on the basis of increased CA-125 is not allowed.

5. Measurable or non-measurable disease by RECIST v1.1:
   - Previously irradiated lesions are not allowed as measurable disease, unless there is documented evidence of progression in the lesions.
   - To be eligible with non-measurable disease, patients must have evaluable disease with CA-125 of at least twice the upper limit of the reference range (or CA-125 ≥70 U/mL), along with radiographically evaluable disease by CT/MRI.
6. Availability and consent to provide tumor tissue for biomarker assays (archival or recent biopsy).
7. No more than 4 prior chemotherapeutic or myelosuppressive regimens (not including maintenance therapy such as single-agent bevacizumab or poly (ADP-ribose) polymerase [PARP] inhibitor). Patients with platinum-refractory cancer cannot have had more than 2 prior lines of treatment for refractory disease.
8. Appropriate to treat with nab-paclitaxel, in the opinion of the Investigator.
9. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
10. Adequate organ and bone marrow function meeting the following criteria:
    - Absolute neutrophil count (ANC) ≥1,500 cells/mm^3.
    - Platelet count ≥100,000/mm^3.
    - Hemoglobin ≥9 g/dL.
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN) (or ≤5×ULN in the context of liver metastasis).
    - Total bilirubin ≤1.5×ULN.
    - Creatinine clearance ≥45 mL/min/1.73 m^2 (measured or estimated).
    - Albumin ≥3 g/dL (≥30 g/L).
11. If patient has undergone surgery of the gastrointestinal or hepatobiliary tract, adequate absorption as evidenced by albumin ≥3.0 g/dL, controlled pancreatic insufficiency (if present), and lack of malabsorption.
12. Able to swallow and retain oral medication and does not have uncontrolled emesis.
13. Able to comply with protocol requirements.
14. Negative pregnancy test for patients of childbearing potential. Patients of childbearing potential must use appropriate precautions to avoid pregnancy, defined as of nonchildbearing potential (i.e., postmenopausal or permanently sterilized) or using highly effective contraception with low user-dependency, for at least 3 months after the last dose of relacorilant, or per the duration indicated in the product label for nab-paclitaxel, whichever is latest. A woman is postmenopausal if it is more than 12 months since her last menstruation, without an alternative medical cause. Accepted methods of permanent sterilization methods are hysterectomy, bilateral salpingectomy and/or bilateral oophorectomy. Accepted methods of highly effective contraception with low user-dependency are:
    - An intrauterine device (IUD), provided that the patient has tolerated its use for at least 3 months before the first dose of study medication and undertakes not to have it removed for 1 month after the last dose.
    - Abstinence from heterosexual intercourse, when it is in line with the patient's preferred and usual lifestyle. Periodic abstinence and withdrawal are NOT acceptable.
    - Vasectomized partner provided that the partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success.
    - Oral hormonal contraceptives are NOT permitted.

Exclusion Criteria

1. Clinically relevant toxicity from prior systemic anticancer therapies or radiotherapy that in the opinion of the Investigator has not resolved to Grade 1 or less prior to randomization.
2. Any major surgery within 4 weeks prior to randomization. If patient received major surgery including (curative or palliative surgery), they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
3. Treatment with the following prior to randomization:
   - Concurrent treatment with other anticancer therapy including other chemotherapy, immunotherapy, radiotherapy, chemoembolization, targeted therapy, an investigational agent or the non-approved use of a drug or device within 28 days before the first dose of study drug.
   - Hormonal anticancer therapies within 7 days of the first dose of study drug.
   - Systemic, inhaled, or prescription strength topical corticosteroids within 21 days of the first dose of study drug. Short courses (≤5 days) for non-cancer-related reasons are allowed if clinically required (such as prophylaxis for CT).
4. Received radiation to more than 25% of marrow-bearing areas.
5. Toxicities of prior therapies (except alopecia) that have not resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 ≤ Grade 1.
6. Requirement for treatment with chronic or frequently used oral corticosteroids for medical conditions or illnesses (e.g., rheumatoid arthritis, immunosuppression after organ transplantation).
7. History of severe hypersensitivity or severe reaction to either study drug.
8. Peripheral neuropathy from any cause > Grade 1.
9. Pregnant or lactating patients or patients expecting to conceive children within the projected duration of the trial, starting with the Screening Visit through at least 3 months after the last dose of relacorilant, or per the duration indicated in the product label for nab-paclitaxel, whichever is latest.
10. Human immunodeficiency virus or current chronic/active infection with hepatitis C virus or hepatitis B virus, including:
    - Patients with chronic or active hepatitis B as diagnosed by serologic tests are excluded from the study. In equivocal cases, hepatitis B or C polymerase chain reaction may be performed and must be negative for enrollment.
11. Patient has a clinically significant uncontrolled condition(s) or which in the opinion of the Investigator may confound the results of the trial or interfere with the patient's participation, including but not limited to:
    - Unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction 6 months before study entry.
    - Uncontrolled hypertension (sustained systolic blood pressure >150 mmHg or diastolic pressure >100 mmHg despite optimal management). Patients will be considered eligible if hypertension is treated and controlled during screening.
    - Active infection that requires parenteral antibiotics.
    - Bowel obstruction or gastric outlet obstruction.
    - Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Untreated parenchymal central nervous system metastases.
13. Any other concurrent cancer or a history of another invasive malignancy within the last 3 years that has a likelihood of recurrence of >30% within the next 5 years. Adequately treated

non-melanoma skin cancers or non-muscle invasive urothelial cancer or other tumors curatively treated with no evidence of disease are permissible.

14. Are taking a concomitant medication that is a strong CYP3A inhibitor or inducer, or that is a substrate of CYP3A with a narrow therapeutic window (Appendix D).
15. Concurrent treatment with mifepristone or other glucocorticoid receptor (GR) antagonists.
16. Concurrent treatment on other investigational treatment studies for the treatment of ovarian, fallopian tube, or primary peritoneal cancer.
17. Has received a live vaccine within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

Investigational Treatment, Dose, and Mode of Administration

Study treatment (relacorilant and/or nab-paclitaxel) will be administered according to the assigned treatment arm, starting on Cycle 1 Day 1.

Relacorilant:

- Formulation: 100-mg yellow, softgel capsules, 50-mg white, hard gelatin capsules, and 25-mg brown, softgel capsules
- Dose and mode of administration:
  - Arm A and Crossover (continuous relacorilant dosing): 100 mg (with upward dose titration permitted up to 150 mg), administered orally, once daily every day
  - Arm B (intermittent relacorilant dosing): 150 mg, administered orally, once daily on the day before, the day of, and the day after nab-paclitaxel

Patients should be encouraged to take their relacorilant dose with food and room temperature water.

Nab-paclitaxel (Abraxane®):

- Formulation: commercially available and supplied in single dose vials, each containing 100 mg paclitaxel and approximately 900 mg of human albumin as stabilizer.
- Dose and mode of administration: The maximal body surface area used for dose calculations in all arms will be 2.0 m2. Nab-paclitaxel will be administered according to the treatment arm as follows:
  - Arm A and Crossover: 80 mg/m^2 intravenous (IV) infusion over 30–40 minutes on Days 1, 8, and 15 of each 28-day cycle
  - Arm B: 80 mg/m^2 IV infusion over 30–40 minutes on Days 1, 8, and 15 of each 28-day cycle
  - Arm C: 100 mg/m^2 IV infusion over 30–40 minutes on Days 1, 8, and 15 of each 28-day cycle

Additional Study Treatments

All patients in Arm A (continuous relacorilant), Arm B (intermittent relacorilant), and the Crossover will receive prophylactic granulocyte colony-stimulating factor (G-CSF) to reduce the risk of neutropenia. Prophylactic G-CSF will consist of at least 1 injection of G-CSF the day after the nab-paclitaxel infusion.

Patients in Arm C (comparator) will receive G-CSF as per the Investigator's standard practice. Mandatory prophylactic growth factors will be used for patients at high risk for severe neutropenia, including the following:

- Age ≥65 years old
- History of febrile neutropenia, previous requirement for G-CSF, or complications of neutropenia, or
- Low bone marrow reserve such as a history of extensive disease infiltrating the bone marrow or chronic cytopenia considered secondary to bone marrow infiltration.

Criteria for Evaluation

Primary Endpoint

Efficacy

- Progression free survival: the time from randomization until the date of first documented PD by RECIST v1.1 (as determined by the Investigator at the local site) or death due to any cause, whichever occurs first.

Secondary Endpoints

Efficacy

- ORR: proportion of patients with measurable disease at baseline who attain complete response (CR) or partial response (PR) by RECIST v1.1 (confirmation not required).
- DoR: time from when response (CR or PR) was first documented to first objectively documented PD or death (whichever occurs first).
- BoR: the best response recorded from the date of randomization until PD/recurrence (or death).
- CA-125 response will be assessed per GCIG criteria (Rustin 2011) defined as ≥50% reduction in CA-125 from a pre-treatment sample and maintained for ≥28 days in patients with a pretreatment sample that is at least twice the upper limit of the reference range within 2 weeks before starting the treatment. In addition, patients who have a CA-125 response and whose CA 125 level falls to within the reference range will be classified as CA-125 complete responders.
- Combined response according to RECIST v1.1 + GCIG criteria. Response will be reported separately and combined for RECIST 1.1 and CA-125/GCIG criteria.
- Progression-free rate (proportion of patients who have not progressed) at 6 and 12 months
- PFS, ORR, DoR, and BoR in patients who crossover to treatment with continuous relacorilant in combination with nab-paclitaxel from the time of PD (baseline for combination therapy) on nab-paclitaxel alone.
- Overall survival: time from randomization to death by any cause.

Safety

The safety of each treatment group will be assessed by evaluating:

- Study drug exposure
- Exposure-toxicity and exposure-response of relacorilant and nab-paclitaxel
- Incidence of adverse events (AEs), serious AEs (SAEs), treatment-related AEs, AEs by severity, and deaths
- Discontinuation of treatment and study withdrawal due to AEs
- Dose interruptions and reductions due to AEs
- Change from baseline in clinical laboratory tests
- Change from baseline in vital signs (including blood pressure, heart rate)
- Change from baseline in physical examination
- Use of growth factors

- Change from baseline in ECOG performance status

Pharmacokinetics

- Primary PK parameters of relacorilant and nab-paclitaxel estimated from intensive PK sampling on Cycle 1 Day 15

Exploratory Endpoints

Pharmacodynamics

Baseline assessment of:

- Tumor immunohistochemistry: GR and immune markers such as [redacted]
- Tumor somatic DNA mutation panel
- RNA analyses from circulating cells and tumor, where feasible
- Cancer antigens, such as CA-125, CA15-3, CA19-9 and/or carcinoembryonic antigen (CEA)
- Cytokines

Change from baseline of:

- Tumor immunohistochemistry: GR and immune markers such as [redacted]
- RNA analyses from circulating cells and tumor, where feasible
- Cancer antigens, such as CA-125, CA15-3, CA19-9 and/or CEA
- Cytokines

Patient-Reported Outcomes and Quality of Life

Changes from baseline of PRO and QoL assessments scores using the Functional Assessment of Cancer Therapy Ovarian Symptom Index-18 (FACT NFOSI-18) and EuroQoL 5 Dimensions, 5 Levels (EQ-5D-5L/VASc) scales and Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function-Short Form score.

Statistical Methods

Analysis Populations

- Intent-to-Treat (ITT): All randomized patients, analyzed according to the randomized treatment arm. This population will be used for analysis of the primary endpoint and all secondary efficacy endpoints.
- Safety Analysis Population (SAF): All randomized patients who received at least 1 dose of study treatment, analyzed according to the treatment actually received. This population will be used in all analyses of safety endpoints.
- Pharmacokinetics Analysis Population (PKA): All patients in SAF who have PK data collected and available for analysis.

Statistical Analyses

Time-to-event endpoints will be summarized using Kaplan-Meier estimates and plots. Event probabilities at 6-month and 12-month time point and the median time-to-event (if estimable) will be presented. The log-rank test, stratified by stratification variable(s) used at randomization, will be used to compare the treatment groups with respect to time-to-event variables. Primary estimates of the treatment differences will be obtained using the hazard ratios and 1-sided 95% confidence intervals from stratified Cox regression models that includes treatment as a covariate and is stratified by stratification variables used at randomization. Response rate endpoints will be summarized by providing the point and interval estimates.

The primary efficacy analysis will be performed on the ITT population. Additional sensitivity analyses will be performed to evaluate the robustness of the results.

Secondary endpoints will each be tested at a 1-sided 0.05 level of significance, without the adjustment for multiplicity of testing. P-values from secondary and exploratory tests will be considered descriptive.

An evaluation of OS will be performed at the time of the primary analysis after 135 PFS events have occurred. An additional OS analysis will be performed when at least 120 OS events have occurred, which will be used for the purposes of final OS reporting.

Sample Size

The assumed median PFS in the current study is 3.8 months in the nab-paclitaxel alone arm (Arm C) and 5.4 and 6.8 months, respectively, in Arm B and Arm A. For the comparison between Arm C and Arm A, 91 PFS events will provide approximately 79% power for a 1-sided log-rank test at a 0.05 significance level to detect a hazard ratio [HR]=0.56. Assuming an exponential distribution of PFS, this corresponds to an increase in median PFS from 3.8 months in Arm C to 6.8 months in Arm A. For the comparison between Arm C and Arm B, 92 PFS events will provide approximately 39% power for a 1-sided log-rank test at a 0.05 significance level to detect a HR=0.7. Assuming an exponential distribution of PFS, this corresponds to an increase in median PFS from 3.8 months in Arm C to 5.4 months in Arm B. A total of approximately 177 patients will need to be randomized (1:1:1 ratio), assuming approximately 10% drop-out in each study arm.

Interim Analysis

No interim efficacy analysis will be performed.

Patient-Reported Outcomes and Quality of Life

For the FACT NFOSI-18, 4 subscale scores will be constructed and analyzed: 1) disease-related symptoms (DRS) scores, 2) emotional well-being (DRS-E) score, 3) treatment side effect (TSE) score, and 4) a functional well-being (FWB) score. For the primary PRO and QoL analysis, the overall mean change from baseline for the disease-related symptom (DRS) scores between groups will be assessed, using a longitudinal repeated measures model that takes into account the DRS measured at each assessment point up to 6 months or PD, whichever is later. Additional analyses based upon PRO endpoints will be specified in the statistical analysis plan.

CONTENTS

List of Tables

List of Figures

LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BoR	Best overall response
CA-125	Cancer antigen 125
CEA	Carcinoembryonic antigen
CI	Confidence interval
CR	Complete response
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DoR	Duration of response
DRS	Disease-related symptom
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EQ-5D-5L/VASc	EuroQoL 5 Dimensions, 5 Levels
EU	European Union
FACT NFOSI-18	Functional Assessment of Cancer Therapy Ovarian Symptom Index-18
G-CSF	Granulocyte colony-stimulating factor
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
GR	Glucocorticoid receptor
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenously

Abbreviation	Definition
IVRS/IWRS	Interactive voice/web response system
MedDRA	Medical Dictionary for Regulatory Affairs
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PD	Disease progression (progressive disease per RECIST v1.1)
PFS	Progression-free survival
PK	Pharmacokinetics
PKA	Pharmacokinetic Analysis Population
PR	Partial response
PRO	Patient-reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PS	Performance status
PT	Prothrombin time
QC	Quality control
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RSI	Reference Safety Information
SAE	Serious adverse event
SAF	Safety analysis population
SAP	Statistical analysis plan
SD	Stable Disease
SOD	Sum of the diameters
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse events
ULN	Upper limit of normal

1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2 STUDY OBJECTIVES

For all efficacy objectives listed below, as well as the corresponding endpoints (see Section 3.2), assessment for response and disease progression are according to RECIST v1.1 as assessed by the Investigator or local radiologist, unless otherwise noted.

2.1 Primary Objective

To evaluate progression-free survival (PFS) in patients treated with intermittent or continuous regimens of relacorilant in combination with nab-paclitaxel compared with patients treated with nab-paclitaxel alone.

2.2 Secondary Objectives

2.2.1 Secondary Efficacy Objectives

- To evaluate objective response rate (ORR) in patients with measurable disease treated with intermittent or continuous regimens of relacorilant in combination with nab-paclitaxel compared with patients treated with nab-paclitaxel alone.
- To evaluate duration of response (DoR) in patients treated with intermittent or continuous regimens of relacorilant in combination with nab-paclitaxel compared with patients treated with nab-paclitaxel alone.
- To assess response according to cancer antigen 125 (CA-125) using GCIG criteria. A combined response endpoint based on both RECIST v1.1 and GCIG criteria will also be reported.
- To evaluate PFS rate at 6 and 12 months in patients treated with intermittent or continuous regimens of relacorilant in combination with nab-paclitaxel compared with patients treated with nab-paclitaxel alone.
- To evaluate overall survival (OS) in patients treated with intermittent or continuous regimens of relacorilant with nab-paclitaxel compared with patients treated with nab-paclitaxel alone.
- To evaluate PFS, ORR, DoR and best overall response (BoR) in patients who receive continuous relacorilant in combination with nab-paclitaxel following progression on nab-paclitaxel (Crossover).
- To assess response according to CA-125 using GCIG criteria in those patients who crossover to continuous relacorilant + nab-paclitaxel. A combined response endpoint based on both RECIST v1.1 and GCIG criteria will also be reported for Crossover patients.

2.2.2 Safety Objectives

- To assess the safety of relacorilant treatment in combination with nab-paclitaxel.
- To model the exposure-toxicity and exposure-response of relacorilant and nab-paclitaxel in each treatment arm to recommend a dosing regimen of relacorilant in combination with nab-paclitaxel for further development.

2.2.3 Pharmacokinetic Objectives

To assess the PK of relacorilant and nab-paclitaxel following intermittent or continuous regimens of relacorilant in combination with nab-paclitaxel compared with nab-paclitaxel alone.

2.3 Exploratory Objectives

2.3.1 Pharmacodynamics/Biomarkers Objectives

- To assess the relationship between baseline characteristics of patients that respond to intermittent or continuous treatment regimens of relacorilant in combination with nab-paclitaxel and patients treated with nab-paclitaxel alone.
- To assess pharmacodynamic effects of intermittent or continuous treatment regimens of relacorilant in combination with nab-paclitaxel and patients treated with nab-paclitaxel alone.

2.3.2 Patient-Reported Outcomes and Quality of Life Objective

To describe changes from baseline of PRO and QoL scores in the study population and to describe differences across treatment arms.

3 STUDY DESIGN

3.1 Overall Design

This is a Phase 2, open-label, randomized, 3-arm study to evaluate the efficacy, safety, PK, pharmacodynamics, PRO and QoL of continuous and intermittent dosing of relacorilant in combination with nab-paclitaxel compared with nab-paclitaxel alone.

Eligible patients will be randomized 1:1:1 to one of the following 3 treatment arms. Patient randomization will be stratified by treatment-free interval from most recent taxane (relapse within 6 months vs >6 months) and presence of ascites (yes vs no).

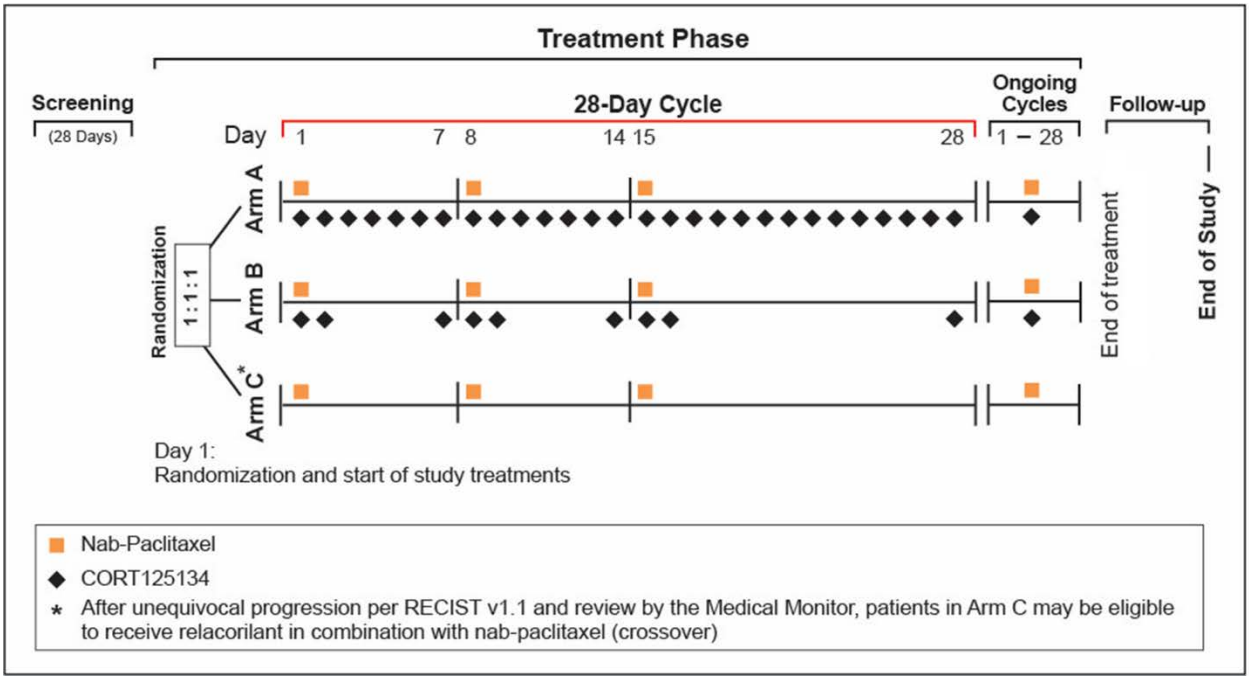
- **Arm A** (continuous relacorilant): relacorilant starting at 100 mg, administered orally, once daily every day, in combination with nab-paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle.
- **Arm B** (intermittent relacorilant): relacorilant 150 mg, administered orally, once daily on the day before (excluding Cycle 1 Day -1), the day of, and the day after nab-paclitaxel, in combination with nab-paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle.
- **Arm C** (comparator): nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle.

The study consists of the following phases:

- **Screening:** Patients will undergo screening procedures within 28 days prior to the first dose of study treatment (relacorilant or nab-paclitaxel, whichever is earliest).
- **Treatment Phase:** Study treatment will start on Cycle 1 Day 1 for all treatment arms and continue until disease progression, unacceptable toxicity, or other treatment discontinuation criteria are met. Patients in Arm C who experience unequivocal PD per RECIST v1.1 will be given the opportunity to crossover to the continuous regimen of relacorilant in combination with nab-paclitaxel after discussion with the Medical Monitor (Section 3.1.1).
- **30-Day Follow-up and Post-Treatment Follow-up:** Patients will return for a 30-Day Follow-up Visit approximately 30 days after the patient's final dose of study treatment. Patients who discontinue treatment prior to disease progression will continue radiographic tumor assessments every 8 weeks (±7 days) until unequivocal PD.
- **Long-Term Follow-up:** All patients will be followed after their final dose of study treatment to document survival as well as response/outcomes to subsequent anticancer treatment (Section 7.6).

See Figure 1 for an illustration of the study design.

Figure 1 CORT125134-552 Study Design



A detailed description of the study visits and procedures are provided in the schedule of assessments (Table 10) and PK (Table 11) and pharmacodynamic (Table 12) schedules of assessments.

All data will be recorded in an electronic case report form (eCRF).

Measures of Anticancer Activity

Tumor assessments will be conducted using computerized tomography (CT) with contrast or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis. A radiographic tumor assessment is required within 28 days prior to the first dose of study treatment and then every 8 weeks (±7 days) from Cycle 1 Day 1 until unequivocal PD is documented, including in patients who prematurely discontinue therapy. Tumor response will be assessed by the Investigator or local radiologist using RECIST v1.1. Radiographic scans will be quality checked, anonymized, and stored centrally.

CA-125 will be assessed within 14 days prior to the first dose of study treatment and then every 4 weeks from Cycle 1 Day 1 for the first 12 months of study treatment, and CA-125 response will be determined according to GCIG criteria.

Tumor response will be assessed by RECIST v1.1, as described above. A combined response endpoint incorporating RECIST v1.1 and GCIG criteria will also be reported.

Pharmacodynamics/Biomarkers

Optional paired tumor biopsies will be obtained in this study. For patients who consent to provide these, the first tumor biopsy will be collected within 6 weeks prior to treatment initiation (this can be the same pre-treatment biopsy used to meet eligibility criteria) and the second tumor

biopsy will be collected at Cycle 2 Day 1. In order to assess the study endpoints, paired biopsies from a minimum of 6 patients per treatment arm are needed. If additional patients have to be enrolled to achieve this target, consent to provide paired biopsies will become mandatory for enrollment in the study.

Pharmacodynamic markers will include mRNA gene panel (blood and tumor expression profiles), cytokines, cancer antigens, tumor biomarker assays (tumor tissue), and other exploratory biomarkers. Additionally, the neutrophil-to-lymphocyte ratio will be evaluated as a pharmacodynamic marker from the hematology results.

Intensive pharmacodynamic sampling (Table 12) will be performed on a subset of patients, comprising at least the first 20 patients enrolled in Arm A (Section 6.6.1). In order to achieve 20 pharmacodynamic-evaluable patients, additional patients in Arm A may undergo intensive pharmacodynamic sampling if some patients are not evaluable.

Pharmacokinetics

Intensive pharmacokinetic sampling for relacorilant and nab-paclitaxel will take place on Cycle 1 Day 15.

Patient-Reported Outcomes and Quality of Life

Baseline PRO and QoL assessments must be collected prior to the first dose of study treatment (relacorilant or nab-paclitaxel, whichever is earliest). Post-baseline assessments will be collected every other cycle, at the End-of-Treatment Visit, and at the 30-Day Follow-up Visit. To minimize bias, PRO and QoL assessments are to be completed prior to discussing the results of tumor assessments or disease-related clinical changes with the patient (Section 6.7).

3.1.1 Patient Crossover from Nab-Paclitaxel Treatment

Patients in Arm C (comparator) who experience unequivocal PD per RECIST v1.1 will be given the opportunity to receive the continuous regimen of relacorilant in combination with nab-paclitaxel after discussion with the Medical Monitor. Patients will receive relacorilant 100 mg, administered orally, once daily every day with nab-paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle. Radiographic tumor assessments at the time of PD on nab-paclitaxel will be considered the final tumor assessment for comparator-only treatment and baseline for combination therapy. If the most recent radiographic tumor assessment has occurred >28 days from Cycle 1 Day 1 of the Crossover, then a new baseline radiographic tumor assessment will need to be obtained prior to starting crossover treatment. Radiographic tumor assessments will then be performed every 8 weeks (±7 days) from the first dose of relacorilant until PD. CA-125 will be assessed within 14 days prior to the first dose of relacorilant and assessed every 4 weeks for the first 12 months. Study procedures will be performed according to the schedule for the Treatment Phase; assessments for the Arm C End-of-Treatment Visit and the Crossover Cycle 1 Day 1 Visit may be combined into 1 visit for patients in Arm C who crossover to combination treatment with continuous relacorilant and nab-paclitaxel.

3.2 Study Endpoints

3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be PFS, i.e., the time from the date of randomization until the date of first documented PD by RECIST v1.1 (as determined by the Investigator at the local site) or death from any cause, whichever occurs first.

3.2.2 Secondary Endpoints

3.2.2.1 Secondary Efficacy Endpoints

- Objective Response Rate (ORR): proportion of patients with measurable disease at baseline who attain CR or PR by RECIST v1.1 (confirmation not required).
- Duration of Response (DoR): time from when response (CR or PR) was first documented to first objectively documented PD or death (whichever occurs first).
- Best Overall Response (BoR): the best response recorded from the date of randomization until PD/recurrence (or death).
- CA-125 response will be assessed per GCIG criteria (Rustin et al. 2011) defined as ≥50% reduction in CA-125 from a pre-treatment sample and maintained for ≥28 days in patients with a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment. In addition, patients who have a CA-125 response and whose CA-125 level falls to within the reference range will be classified as CA-125 complete responders.
- Combined response according to RECIST v1.1 + GCIG criteria. Response will be reported separately and combined for RECIST v1.1 and CA-125/GCIG criteria.
- Progression-free rate (proportion of patients who have not progressed) at 6 and 12 months.
- PFS, ORR, DoR, and BoR in patients who crossover to the continuous treatment regimen of relacorilant in combination with nab-paclitaxel from the time of PD (baseline for combination therapy) on nab-paclitaxel alone.
- Overall survival: time from randomization to death by any cause.

3.2.2.2 Safety Endpoints

The safety of each treatment group will be assessed by evaluating:

- Study drug exposure
- Exposure-toxicity and exposure-response of relacorilant and nab-paclitaxel
- Incidence of AEs, serious AEs (SAEs), treatment-related AEs, AEs by severity, and deaths
- Discontinuation of treatment and study withdrawal due to AEs
- Dose interruptions and reductions due to AEs
- Change from baseline in clinical laboratory tests
- Change from baseline in vital signs (including blood pressure, heart rate)
- Change from baseline in physical examination
- Use of growth factors

- Change from baseline in Eastern Cooperative Oncology Group (ECOG) performance status (PS)

3.2.2.3 Pharmacokinetic Endpoints

Primary PK parameters of relacorilant and nab-paclitaxel estimated from intensive PK sampling on Cycle 1 Day 15 will be assessed.

3.2.3 Exploratory Endpoints

3.2.3.1 Pharmacodynamic Endpoints

Baseline assessment of:

- Tumor immunohistochemistry: GR and immune markers such as [redacted]
- Tumor somatic DNA mutation panel
- RNA analyses from circulating cells and tumor, where feasible
- Cancer antigens, such as CA-125, CA15-3, CA19-9 and/or CEA
- Cytokines

Change from baseline of:

- Tumor immunohistochemistry: GR and immune markers such as [redacted]
- RNA analyses from circulating cells and tumor, where feasible
- Cancer antigens, such as CA-125, CA15-3, CA19-9 and/or carcinoembryonic antigen (CEA)
- Cytokines

3.2.3.2 Patient-Reported Outcomes and Quality of Life Endpoints

Changes from baseline of PRO and QoL scores using the Functional Assessment of Cancer Therapy Ovarian Symptom Index-18 (FACT NFOSI-18) (Jensen et al. 2011) and EuroQoL 5 Dimensions, 5 Levels (EQ-5D-5L/VASc) scales (EuroQoL 1990) and Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function-Short Form score (Cella et al. 2007, Rose et al. 2008, Rose et al. 2014) will be assessed.

3.3 Number of Patients and Study Participation

3.3.1 Number of Patients

A total of approximately 177 patients will be randomized in a 1:1:1 ratio to one of the 3 treatment arms (approximately 59 patients per arm).

3.3.2 Patient Study Completion

Patients are considered to have completed the study if they have completed all phases of the study including the Long-Term Follow-up assessments (Section 7.6).

3.4 Definitions: End of Treatment, End of Study, and Study Duration

3.4.1 End of Treatment

Refer to Section 4.4 for reasons for treatment discontinuation.

The end of treatment is defined as the date on which the patient received her last treatment of relacorilant or nab-paclitaxel, whichever is latest.

3.4.2 End of Study

The end of study is defined as the date of last contact (visit, telephone, email) with the last study patient. Corcept will ensure that the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and the regulatory authority are notified that the study has finished according to Corcept's standard operating procedures (SOPs) and/or local or national regulations.

3.4.3 Study Duration

The assumed median PFS is 3.8 months in the comparator arm (Arm C), and 6.8 and 5.4 months, respectively, in Arm A and Arm B. Patients will receive treatment until reaching a protocol-defined event of PD, experiencing unmanageable toxicity, or until other treatment discontinuation criteria are met.

The total patient accrual duration is expected to be 24 months, with an overall expected study duration of 43 months.

All patients will be followed for progression, subsequent therapies (start and end date and response) and survival.

3.5 Independent Data Monitoring Committee

To ensure patient safety, an Independent Data Monitoring Committee (IDMC) will evaluate safety data (which will include all patients enrolled in the study) after approximately 40 patients have enrolled and met at least one of the following criteria:

- Received 2 cycles of treatment
- Reached an event of PD
- Discontinued treatment due to toxicity

Subsequent reviews will be based on recommendations from the IDMC, with a minimum frequency of approximately every 6 months. A separate IDMC charter will be prepared and agreed by the IDMC members.

4 STUDY POPULATION

4.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in the study:

1. Signed and dated IRB/IEC-approved informed consent form (ICF) prior to study-specific screening procedures. Note: standard of care assessments completed before the ICF is signed can be used for eligibility if done within the 28-day Screening Period.
2. Female patients aged ≥18 years old at time of consent.
3. Histologic diagnosis of high grade serous or endometrioid epithelial ovarian, primary peritoneal, or fallopian tube cancer or ovarian carcinosarcoma. Clear cell, mucinous and borderline histologic subtypes are excluded. Guidelines for identifying high grade serous carcinoma are provided in Appendix B.
4. Received at least one line of therapy with evidence of cancer progression within 6 months after the last dose of platinum-based therapy (i.e., having a platinum-free interval of ≤6 months [platinum resistant]), or progressive disease during or immediately after platinum-based therapy (i.e., platinum refractory). Patients with primary platinum resistance (progression within 6 months of the last dose of first-line platinum-containing chemotherapy) are considered eligible.

   Notes: For the calculation of the platinum-free interval, cancer progression must be defined by clear evidence of progression, such as radiographic progression per RECIST v1.1. Calculating the platinum-free interval on the basis of increased CA-125 is not allowed.
5. Measurable or non-measurable disease by RECIST v1.1:
   - Previously irradiated lesions are not allowed as measurable disease, unless there is documented evidence of progression in the lesions.
   - To be eligible with non-measurable disease, patients must have evaluable disease with CA-125 of at least twice the upper limit of the reference range (or CA-125 ≥70 U/mL), along with radiographically evaluable disease by CT/MRI.
6. Availability and consent to provide tumor tissue for biomarker assays (archival or recent biopsy).
7. No more than 4 prior chemotherapeutic or myelosuppressive regimens (not including maintenance therapy such as single-agent bevacizumab and poly (ADP-ribose) polymerase [PARP] inhibitors). Patients with platinum-refractory cancer cannot have had more than 2 prior lines of treatment for refractory disease. Guidance for counting prior lines of therapy are provided in Appendix G.
8. Appropriate to treat with nab-paclitaxel, in the opinion of the Investigator.
9. ECOG performance status 0 or 1.
10. Adequate organ and bone marrow function meeting the following criteria at the Screening Visit:
    - Absolute neutrophil count (ANC) ≥1,500 cells/mm^3.
    - Platelet count ≥100,000/mm^3.
    - Hemoglobin ≥9 g/dL.

- AST or alanine aminotransferase (ALT) ≤2.5× upper limit of normal (ULN) (or ≤5×ULN in the context of liver metastasis).
- Total bilirubin ≤1.5×ULN.
- Creatinine clearance ≥45 mL/min/1.73 m^2 (measured or estimated).
- Albumin ≥3 g/dL (≥30 g/L).

11. If patient has undergone surgery of the gastrointestinal or hepatobiliary tract, adequate absorption as evidenced by albumin ≥3.0 g/dL, controlled pancreatic insufficiency (if present), and lack of malabsorption.
12. Able to swallow and retain oral medication and does not have uncontrolled emesis.
13. Able to comply with protocol requirements.
14. Negative pregnancy test for patients of childbearing potential. Patients of childbearing potential must use appropriate precautions to avoid pregnancy, defined as of nonchildbearing potential (i.e., postmenopausal or permanently sterilized) or using highly effective contraception with low user-dependency, for at least 3 months after the last dose of relacorilant, or per the duration indicated in the product label for nab-paclitaxel, whichever is latest. A woman is postmenopausal if it is more than 12 months since her last menstruation, without an alternative medical cause. Accepted methods of permanent sterilization methods are hysterectomy, bilateral salpingectomy and/or bilateral oophorectomy. Accepted methods of highly effective contraception with low user-dependency are:
    - An intrauterine device (IUD), provided that the patient has tolerated its use for at least 3 months before the first dose of study medication and undertakes not to have it removed for 1 month after the last dose.
    - Abstinence from heterosexual intercourse, when it is in line with the patient's preferred and usual lifestyle. Periodic abstinence and withdrawal are NOT acceptable.
    - Vasectomized partner provided that the partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success.
    - Oral hormonal contraceptives are NOT permitted.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will not be permitted entry to the study:

1. Clinically relevant toxicity from prior systemic anticancer therapies or radiotherapy that in the opinion of the Investigator has not resolved to Grade 1 or less prior to randomization.
2. Any major surgery within 4 weeks prior to randomization. If the patient received major surgery including (curative or palliative surgery), they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
3. Treatment with the following prior to randomization:
    - Concurrent treatment with other anticancer therapy including other chemotherapy, immunotherapy, radiotherapy, chemoembolization, targeted therapy, an investigational agent, or the non-approved use of a drug or device within 28 days before the first dose of study drug.

- Hormonal anticancer therapies within 7 days of the first dose of study drug.
- Systemic, inhaled, or prescription strength topical corticosteroids within 21 days of the first dose of study drug. Short courses (≤5 days) for non-cancer-related reasons are allowed if clinically required (such as prophylaxis for CT).

4. Received radiation to more than 25% of marrow-bearing areas.
5. Toxicities of prior therapies (except alopecia) that have not resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0) ≤ Grade 1.
6. Requirement for treatment with chronic or frequently used oral corticosteroids for medical conditions or illnesses (e.g., rheumatoid arthritis, immunosuppression after organ transplantation).
7. History of severe hypersensitivity or severe reaction to either study drug.
8. Peripheral neuropathy from any cause > Grade 1.
9. Pregnant or lactating patients or patients expecting to conceive children within the projected duration of the trial, starting with the Screening Visit through at least 3 months after the last dose of relacorilant, or per the duration indicated in the product label for nab-paclitaxel, whichever is latest.
10. Human immunodeficiency virus (HIV) or current chronic/active infection with hepatitis C virus or hepatitis B virus including:
    - Patients with chronic or active hepatitis B as diagnosed by serologic tests are excluded from the study. In equivocal cases, hepatitis B or C polymerase chain reaction may be performed and must be negative for enrollment.
11. Patient has a clinically significant uncontrolled condition(s) or which in the opinion of the Investigator may confound the results of the trial or interfere with the patient's participation, including but not limited to:
    - Unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction 6 months before study entry.
    - Uncontrolled hypertension (sustained systolic blood pressure >150 mmHg or diastolic pressure >100 mmHg despite optimal management). Patients will be considered eligible if hypertension is treated and controlled during screening.
    - Active infection that requires parenteral antibiotics.
    - Bowel obstruction or gastric outlet obstruction.
    - Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Untreated parenchymal central nervous system metastases.
13. Any other concurrent cancer or a history of another invasive malignancy within the last 3 years that has a likelihood of recurrence of >30% within the next 5 years. Adequately treated non-melanoma skin cancers or non-muscle invasive urothelial cancer or other tumors curatively treated with no evidence of disease are permissible.
14. Are taking a concomitant medication that is a strong CYP3A inhibitor or inducer, or that is a substrate of CYP3A with a narrow therapeutic window (Appendix D).
15. Concurrent treatment with mifepristone or other GR antagonists.
16. Concurrent treatment on other investigational treatment studies for the treatment of ovarian, fallopian tube, or primary peritoneal cancer.

17. Has received a live vaccine within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

4.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized to study treatment.

A patient who has failed screening due to a reason that is temporary and expected to resolve (e.g., mild intercurrent infection) may be re-screened.

The reason for screen failure should be recorded.

4.4 Patient Discontinuation of Treatment or Study Completion/Withdrawal

In this study, patient "discontinuation" refers to discontinuation of study treatment. Patients who discontinue study treatment will continue to be followed for the study endpoints. This may include patients who have discontinued treatment due to disease progression, toxicity, Investigator decision, or personal decision. These patients will continue with the End-of-Treatment and 30-Day Follow-up Visits, radiographic tumor assessments (if disease progression has not occurred), and survival assessments. If a patient wishes to discontinue treatment and refuse further study procedures, the patient should be asked if she is willing to continue with survival assessments (which can be conducted over the telephone) (Section 7.6).

Patient study completion refers to completion of all study procedures and Long-Term Follow-up assessments (Section 3.3.2). Patient "withdrawal" refers to permanent withdrawal and cessation of all study treatments, procedures, and assessments without further follow-up (withdrawal of consent). If a patient wishes to withdraw consent to further participation in the study entirely, including Long-Term Follow-up, this should be clearly documented (1) in the patient's medical record and signed by the Investigator and (2) in the clinical study database (i.e., eCRF).

4.4.1 Patient Discontinuation of Study Treatment

Patients may discontinue treatment at any time at their own request, or they may have study treatment discontinued, at any time, at the discretion of the Investigator or Sponsor for safety or the inability of the patient to comply with the protocol-required schedule of assessments.

Reasons for study treatment discontinuation may include the following:

- Disease progression as defined by RECIST v1.1
- Unacceptable toxicity
- Adverse event
- Patient refuses further treatment (follow-up permitted by the patient)
- The Investigator decides it is in the patient's best interest to discontinue treatment and/or participation in the study. Reasons may include the following:
  - The patient requires prohibited medications, including a non-protocol-specified anticancer therapy
  - The patient is not compliant with protocol requirements

  - Global deterioration of health status requiring treatment discontinuation
- The patient is pregnant
- Any of the criteria listed in Section 4.4.2, as patients who withdraw/complete the study will also discontinue treatment

Patients who discontinue study treatment early should be encouraged to come to the clinic for an End-of-Treatment Visit, return for a 30-Day Follow-up Visit approximately 30 days after the patient's final dose of study treatment (Table 10), and should report any AEs, including SAEs, according to Section 8.1.2. For patients who elect to discontinue treatment, every effort should be made to determine whether the decision to discontinue treatment was related to an AE or a specific aspect of the study.

Patients who discontinue treatment before unequivocal PD will continue radiographic tumor assessments until unequivocal PD, and subsequent treatment information will be collected, every 8 weeks (±7 days) (Section 7.6). For patients with PD, or for patients who decline further radiographic tumor assessments, survival and subsequent treatment information will be collected every 3 months (±7 days) after the last dose of study treatment. Long-Term Follow-up will continue until the end point of death, the patient is lost to follow-up, or other study exit criteria are met (Section 4.4.2).

The date when the patient discontinues treatment and the reason for discontinuation must be recorded on the eCRF. The Investigator should notify the Sponsor within 48 hours if a patient discontinues study treatment.

For guidelines regarding temporary interruption of treatment or treatment modifications, see Section 5.3.

4.4.2 Patient Withdrawal from Study/Study Completion

Patients may withdraw voluntarily from the study at any time. As noted above, if a patient wishes to withdraw consent to further participation in the study entirely, including Long-Term Follow-up, this should be clearly documented (1) in the patient's medical record and signed by the Investigator and (2) in the clinical study database (eCRF). If the patient withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected.

Reasons for study exit may include the following medical or administrative reasons:

- Withdrawal of consent for further follow-up by the patient or legal guardian
- Completed study (Section 3.3.2)
- Adverse event
- Death
- Early termination of the study by the Sponsor
- Lost to follow-up

The date the patient is withdrawn from the study and the primary reason for withdrawal must be recorded on the eCRF.

The Investigator should notify the Sponsor within 48 hours if a patient withdraws from the study.

5 STUDY TREATMENTS AND MANAGEMENT

Study drug is defined as relacorilant. The comparator/co-administered drug is defined as nab-paclitaxel.

Study treatment is defined as the treatment administered according to randomization, and will begin on Cycle 1 Day 1:

- Arm A (continuous relacorilant): relacorilant 100 mg, administered orally, once daily every day in combination with nab-paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle. Upon the completion of Cycle 1 or 2, the dose of relacorilant may be increased in 25-mg increments per 28-day cycle to a maximum relacorilant dose of 150 mg once daily (see Section 5.1).
- Arm B (intermittent relacorilant): relacorilant 150 mg, administered orally, once daily on the day before (excluding Cycle 1 Day -1), the day of, and the day after nab-paclitaxel, in combination with nab-paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle
- Arm C (comparator): nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle

Patients in Arm C who experience unequivocal PD according to RECIST v1.1 will be given the opportunity to crossover, in consultation with the Medical Monitor, to treatment with relacorilant 100 mg, administered orally, once daily every day starting on Cycle 1 Day 1 (continuous regimen); and nab-paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle. See Section 3.1.1.

5.1 Study Drug (Relacorilant)

Relacorilant dose and regimen, formulation, packaging, and storage, are described in Table 1.

The current IB for relacorilant will be provided to Investigators.

Table 1 Relacorilant: Formulation, Administration, Packaging, and Storage

Specifications	Study Drug Relacorilant (CORT125134)
Description	For each capsule, relacorilant (CORT125134) is prepared as a 200 mg/g formulation [redacted].
Unit dose strength(s) and appearance	Relacorilant is presented as 100-mg yellow, softgel capsules, 50-mg white, hard gelatin capsules, and 25-mg brown, softgel capsules.
Administration	Orally, with 8 oz of room temperature water. Capsules are to be swallowed whole and should not be chewed, dissolved, or opened prior to swallowing.

Specifications	Study Drug Relacorilant (CORT125134)
Dose and regimen	**Arm A and Crossover (continuous relacorilant)**: relacorilant 100 mg (dose titration permitted up to 150 mg), administered orally, once daily every day **Arm B (intermittent relacorilant)**: relacorilant 150 mg, administered orally, once daily on the day before (excluding Cycle 1 Day -1), the day of, and the day after nab-paclitaxel **Arm C (comparator)**: no relacorilant Patients should make every effort to take their dose of relacorilant at the same time each day; however, a 6-hour window will be allowed. Patients should be encouraged to take their relacorilant dose with food, except on days when protocol-specified assessments require fasting, or if the patient is not able to tolerate food intake with the medication.
Restrictions	Medicines/foods known to strongly inhibit CYP3A or CYP2C8, and substrates of CYP3A with a narrow therapeutic window should be avoided. See Section 5.5.
Missed doses	If noticed >6 hours after scheduled dose, skip dose and take next scheduled dose.
Dispensing study treatment	Dispense to patients according to their visit schedule.
Packaging and labeling	Relacorilant 100-mg softgel capsules capsule will be provided in bottles containing 30 capsules each. Relacorilant 50-mg hard capsules will be provided in blister packaging with 7 capsules per blister pack and 2 blister packs per carton. Relacorilant 25-mg softgel capsules will be provided in bottles containing 30 capsules each. Each blister pack/carton and bottle will be labeled as required per country-specific requirements.
Storage	Store as follows: • In a secure location • At 20–25 °C (68–77 °F) • Out of reach and sight of children
Manufacturer	Corcept Therapeutics

Note: Procedures for inventory, reconciliation, and destruction or return of study drug are provided in Section 11.6.

5.1.1 Dose Titration

For patients receiving the continuous relacorilant regimen (Arm A and Crossover), the relacorilant dose will start at 100 mg daily on Cycle 1 Day 1.

Cycle 2 Day 1

If during the first cycle no intolerable Grade 2 nor any Grade 3 or 4 toxicities require dose reduction or omission of either relacorilant or nab-paclitaxel, then the relacorilant dose will be escalated to 125 mg once daily, beginning on Cycle 2 Day 1.

Cycle 3 Day 1

For patients who escalate the relacorilant dose to 125 mg, if no intolerable Grade 2 nor any Grade 3 or 4 toxicities require dose reduction or omission of either relacorilant or nab-paclitaxel in Cycle 2, then the relacorilant dose will be escalated to 150 mg once daily, beginning on Cycle 3 Day 1.

If the dose was not escalated at Cycle 1 or 2, then the dose should not be escalated in future cycles. For all cycles, dose delays and reductions will be managed according to Section 5.4.

5.2 Nab-Paclitaxel (Abraxane)

Nab-paclitaxel dose and regimen, formulation, packaging, and storage are described in Table 2.

Table 2 Nab-Paclitaxel: Formulation, Administration, Packaging, and Storage

Specifications	Nab-Paclitaxel (Abraxane)
Dosage formulation	The chemical name for paclitaxel is 5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. The empirical formula is $C_{47}H_{51}NO_{14}$.
Supplied	Single-use 50-mL vial
Unit dose strength(s)	Each 50-mL vial contains 100 mg paclitaxel and approximately 900 mg of human albumin as a stabilizer.
Appearance	White to off-white sterile lyophilized powder for reconstitution before use
Administration	Administer reconstituted formulation as an intravenous infusion over 30-40 minutes on Days 1, 8, and 15 of each 28-day cycle for all patients. Nab-paclitaxel infusions must be no less than 7 days apart.
Dose and regimen	**Arm A (continuous relacorilant), Arm B (intermittent relacorilant), and Crossover:** nab-paclitaxel, 80 mg/m^2 IV infusion over 30–40 minutes on Days 1, 8, and 15 of each 28-day cycle **Arm C (comparator):** nab-paclitaxel, 100 mg/m^2 intravenous infusion over 30–40 minutes on Days 1, 8, and 15 of each 28-day cycle The maximal body surface area used for dose calculations will be 2.0 m^2. Nab-paclitaxel infusions must be no less than 7 days apart.
Restrictions	Start of infusion must be within 15 minutes after relacorilant dose on Cycle 1 Day 15 (day for intensive pharmacokinetic sampling).
Missed doses	Refer to Appendix C and Section 5.4.
Dispensing study treatment	Nab-paclitaxel will be administered in the clinic.
Packaging and labeling	Refer to current prescribing information or Summary of Product Characteristics

Specifications	Nab-Paclitaxel (Abraxane)
Storage	• Store un-reconstituted nab-paclitaxel between 20–25 °C (68–77 °F) in its carton • Vials should be stored in their original cartons. Use reconstituted nab-paclitaxel immediately. If not used immediately, place the vial in its carton and store at 2–8 °C (36–46 °F) for a maximum of 8 hours • Store both forms in an area free of environmental extremes and accessible only to study personnel • Discard partially and completely used vials according to the site's guidelines Record disposition on the Study Drug Accountability Record Form
Manufacturer	Commercially available (Abraxis Biosciences, LLC, a wholly owned subsidiary of Celgene Corporation)

5.3 Additional Treatments

All patients in Arm A (continuous) and Arm B (intermittent), and patients participating in the Crossover, with the exception of patients with ANC >10,000/mm^3, will receive prophylactic G-CSF to reduce the risk of neutropenia. Prophylactic G-CSF will consist of at least 1 injection of G-CSF the day after the nab-paclitaxel infusion.

Patients in Arm C (comparator) will receive G-CSF as per standard practice, with mandatory prophylactic growth factors for patients at high risk for severe neutropenia, including the following:

- Age ≥65 years old,
- History of febrile neutropenia, previous requirement for G-CSF, or complications of neutropenia, or
- Low bone marrow reserve such as a history of extensive disease infiltrating the bone marrow or chronic cytopenia considered secondary to bone marrow infiltration.

Prophylactic treatment with filgrastim will be per protocol, as stated above. In addition, G-CSF treatment may be used to provide support for a patient with clinically meaningful neutropenia or to maintain dose intensity as consistent with the institutional guidelines and standard practice.

For patients receiving prophylactic G-CSF, filgrastim (5 µg/kg/day) will be administered at least 24 hours after completion of dosing with nab-paclitaxel with the last dose of filgrastim at least 24 hours prior to the next treatment with nab-paclitaxel.

Biosimilars of filgrastim and pegfilgrastim are permitted.

5.4 Dose Reductions or Delays

If a patient experiences an AE that results in a delay in starting a cycle or requires that study regimen is delayed or interrupted during a cycle (Table 3), the patient will complete the planned activities per the schedule of assessments (Table 10) until resuming treatment.

If study treatment is interrupted for >28 days with the approval of the Medical Monitor, clinical laboratory assessments may also be interrupted, if clinically significant laboratory abnormalities

have resolved to Grade 1 or to baseline. Tumor assessments (CT or MRI and CA-125) and PRO/QoL assessments should continue per the schedule of assessments (Table 10).

General chemotherapy dosing guidelines are provided in Appendix C.

Table 3 Dose Reductions or Delays Due to Adverse Events

Adverse Event	Nab-Paclitaxel Dose Modification	Relacorilant Dose Modification
Neutropenia: (ANC 1,000-1,499)	Cycle Day 1: • Delay Day 1 nab-paclitaxel until ANC is 1,500 or higher Cycle Day 8 or 15: • No change	• Withhold dose until ANC is 1,500 or higher • Reinitiate at same dose level
Neutropenia: (ANC <1,000)	Cycle Day 1: • Delay Day 1 nab-paclitaxel until ANC is 1,500 or higher. • Reduce 1 dose level Cycle Day 8 or 15: • Omit dose • Reduce 1 dose level	• Withhold dose until ANC is 1,500 or higher • Reinitiate at same dose level
Febrile neutropenia: Grade 3 or 4	• Withhold dose until fever resolves and ANC is 1,500 or higher. • Reduce 1 dose level	• Withhold dose until fever resolves and ANC is 1,500 or higher • Reinitiate at same dose level
Thrombocytopenia: (Platelets <100,000)	Cycle Day 1: • Delay Day 1 nab-paclitaxel until platelet is 100,000 or higher Cycle Day 8 or 15: • Platelets 50,000 to 99,000: No change • Platelets < 50,000 omit dose and then reduce nab-paclitaxel by 1 dose level	• No change
Peripheral neuropathy: Intolerable Grade 2	• Reduce 1 dose level	• No change
Peripheral neuropathy: Grade 3	• Delay dose until symptoms improve to Grade 2 or better • Reduce 1 dose level	• No change
Peripheral neuropathy: Grade 4	• Discontinue nab-paclitaxel	• Discontinue relacorilant
Cystoid macular edema	• Discontinue nab-paclitaxel	• Discontinue relacorilant

Adverse Event	Nab-Paclitaxel Dose Modification	Relacorilant Dose Modification
Cutaneous toxicity: Grade 3	• Withhold dose until improvement to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry • Reduce 1 dose level	• Withhold dose until improvement to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry • Reinitiate at same dose level
Cutaneous toxicity: Grade 4	• Discontinue nab-paclitaxel	• Discontinue relacorilant
Mucositis: Grade 3 or 4	• Withhold dose until improvement to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry • Reduce 1 dose level	• Withhold dose until improvement to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry • Reinitiate at same dose level
Diarrhea: Grade 3 or 4	• Withhold dose until improvement to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry • Reduce 1 dose level	• Withhold dose until improvement to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry • Reinitiate at same dose level
Other hematologic or non-hematologic adverse event: Grade 3 or 4	• Withhold dose until severity of adverse event improves to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry • Reduce 1 dose level	• For adverse events attributable only to nab-paclitaxel, continue relacorilant unchanged. • For adverse events attributable to relacorilant, withhold dose until severity of adverse event improves to Grade 1 or lower (or to baseline if Grade 2 toxicity was present at study entry) and reduce relacorilant by 1 dose level

Abbreviation: ANC, absolute neutrophil count

5.4.1 Dose Reductions or Delays for Nab-Paclitaxel

After Cycle 1 Day 1, if there is a delay in nab-paclitaxel administration for any reason, the following applies:

- If an infusion is delayed by >3 days, that dose may be skipped, and the patient may resume treatment with the next scheduled infusion if appropriate in the judgment of the Investigator. If treatment with nab-paclitaxel is delayed for >4 weeks (omission of nab-paclitaxel for >28 days), the Medical Monitor should be notified.

Nab-paclitaxel dose reductions (Table 4) should be made based on observed toxicities secondary to treatment, as indicated in Table 3. Sequential dose reductions may be made at the discretion of the Investigator. A maximum of 2 dose reductions are allowed. When a dose reduction is

required, no dose re-escalation will be permitted. If nab-paclitaxel is discontinued, then relacorilant will also be discontinued.

Table 4 Nab-Paclitaxel Dose Reductions

	Arms A and B, and Crossover	Arm C
Starting Dose	80 mg/m^2	100 mg/m^2
Dose Level -1	60 mg/m^2	80 mg/m^2
Dose Level -2	60 mg/m^2 biweekly (on Days 1 and 15 of each cycle)	60 mg/m^2

Note: Nab-paclitaxel administered on Days 1, 8, and 15 of each 28-day cycle unless otherwise noted.

For patients in Arm B, if a patient took relacorilant the day before and is not able to receive her scheduled nab-paclitaxel infusion, it is acceptable for the patient to receive up to 2 extra once-daily doses of relacorilant while awaiting her next infusion.

5.4.2 Dose Reductions or Delays for Relacorilant

See Section 5.1.1 for information on upward dose titration.

For any patient who experiences Grade 3 or 4 toxicity that is attributable to relacorilant but not nab-paclitaxel or the underlying disease, relacorilant will be interrupted until the toxicity resolves to ≤ Grade 1, or to baseline if Grade 2 toxicity was present at study entry. After recovery to ≤ Grade 1 toxicity, relacorilant will be resumed at 1 dose level lower than the current level (Table 5).

For toxicities that are known risks of nab-paclitaxel, nab-paclitaxel should be preferentially dose reduced and relacorilant continued at the current dose level.

A maximum of 3 dose reductions of relacorilant will be allowed. The minimum dose of relacorilant to be administered is 50 mg. In the event that relacorilant is discontinued, treatment with nab-paclitaxel will continue until disease progression, unmanageable toxicity, or other treatment discontinuation criteria are met.

Table 5 Relacorilant Dose Level Summary

	Relacorilant Dosing Regimen	
	Continuous	**Intermittent**
Dose Level -3	--	50 mg
Dose Level -2	50 mg	75 mg
Dose Level -1	75 mg	100 mg
Starting Dose	**100 mg**	**150 mg**
Dose Level +1 (Cycle 2 Day 1)	125 mg	--
Dose Level +2 (Cycle 3 Day 1)	150 mg	--

5.4.3 Management of Signs of Excessive Glucocorticoid Receptor Antagonism

For patients treated with relacorilant, signs or symptoms related to excessive GR antagonism may develop. If signs and/or symptoms of excessive GR antagonism such as malaise, fatigue, lethargy, weakness, anorexia, nausea, vomiting, abdominal pain, altered mental status, or hypoglycemia are present, particularly if coexistent, treatment with relacorilant should be interrupted and the Medical Monitor should be consulted to assist in evaluating whether treatment should continue. If excessive GR antagonism is suspected, standard supportive care (including fluid resuscitation as indicated) and medical therapy should be administered without delay. Systemic administration of corticosteroids should be considered (e.g., dexamethasone 4 mg daily for 3 days and then tapered by 1 mg per day, or as indicated based on clinical response). [redacted] In the event of significant trauma or surgery through 28 days after the last dose of relacorilant, supplemental glucocorticoids and appropriate medical care may be needed to prevent excessive GR antagonism that may arise due to increased cortisol requirements in the perioperative period.

5.5 Concomitant Medications and Procedures

5.5.1 Permitted Concomitant Medications

The best supportive care and treatment should be prescribed, as appropriate, to each patient to manage disease-related symptoms (e.g., anti-emetics, antibiotics, transfusions, nutritional support, and pain control) according to institutional guidelines or American Society of Clinical Oncology guidelines. Patients do not require and should not receive premedication with dexamethasone prior to nab-paclitaxel infusion, as hypersensitivity reactions are not expected. Initial anti-emetic prophylaxis is allowed with ondansetron or other therapies, as appropriate, but should not include dexamethasone.

Permitted treatments also include standard therapies for concurrent medical conditions.

Patients must be instructed to notify the investigational site about any new medications they take after the start of the study treatment. All medications (other than study treatments) administered within 30 days of study entry and during the study must be listed on the concomitant medications page in the eCRF.

Concurrent anticancer therapy with agents other than relacorilant and nab-paclitaxel is not allowed. See Section 5.5.3 for other prohibited concomitant medications.

5.5.2 Permitted and Not Recommended Concomitant Therapy Requiring Caution

Permitted medications to be used with caution from 1 week before first dose of study treatment (relacorilant or nab-paclitaxel, whichever is earliest) through the 30-Day Follow-up Visit are as follows:

- Warfarin, if its use cannot be avoided. If used, conduct additional international normalized ratio (INR) monitoring.
- Sulfonylureas. If used, conduct close glucose monitoring to assess for changes in diabetic control.

- Corticosteroids:
  - Systemic corticosteroids. Short courses of prednisone for non–cancer-related reasons are permitted if clinically required (e.g., as a premedication before CT/MRI contrast). Relacorilant treatment should be withheld during corticosteroid administration, and the Medical Monitor should be notified.
  - Potent (Group 3) topical corticosteroids should be used with caution due to the potential for systemic absorption, and the Medical Monitor should be contacted to discuss the treatment approach. Topical Kenalog® (triamcinolone) may be used sparingly for the treatment of oral mucositis.
- Medications that carry a possible risk for QT prolongation.
- Medical marijuana. Marijuana is metabolized by the liver and interacts with CYPs so should be used with caution with relacorilant.

[redacted]

The metabolism of nab-paclitaxel is catalyzed, in part, by CYP2C8. Caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to inhibit CYP2C8 (Abraxane USPI 2018; Abraxane SPC 2019). Administering nab-paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A is not recommended (refer to Section 5.5.3 for prohibited medications).

Due to potential drug-drug interactions, the following medications are permitted but must be used with caution from 1 week before the first relacorilant dose through the 30-Day Follow-up Visit:

- Sensitive substrates of CYP3A that do not have a narrow therapeutic index
- Moderate inhibitors of CYP3A and CYP2C8

Due to potential drug-drug interactions, inducers of CYP3A or CYP2C8 are not recommended from 1 week before first relacorilant dose through the 30-Day Follow-up Visit.

For examples of medications to be used with caution, see Appendix D.

5.5.3 Prohibited Medications and Foods

As the metabolism of both nab-paclitaxel and relacorilant are mediated in part by CYP3A, there is potential for CYP3A inhibitors to increase nab-paclitaxel and relacorilant exposure. Medicines and food known to strongly inhibit CYP3A should be avoided.

The following medications are prohibited in this study:

- St. John's wort
- Strong inhibitors or inducers of CYP3A
- Substrates of CYP3A with narrow therapeutic windows
- Other investigational and antineoplastic therapies
- Other GR antagonists (e.g., mifepristone)

Patients should be counseled to avoid consumption of grapefruit and Seville oranges (including marmalade and juices made from these fruits) from 14 days prior to the first dose of study treatment and until the last treatment cycle is completed.

Examples of medications, treatments, and foods that are prohibited or are to be used with caution are listed in Appendix D. It is not possible to produce an exhaustive list of medications that fall into the categories, so if in question, please refer to the appropriate product label. If the Investigator determines that such a medication is medically necessary, the Investigator will notify the Medical Monitor and discuss the Investigator's use of these medications and the Investigator's plans to medically monitor the patient.

5.5.4 Procedures

If a patient requires surgery during the study, then this needs to be discussed with the Medical Monitor. If surgery affects a target lesion, that patient will be considered nonevaluable for response of the resected area from that point forward and will continue to be followed for disease progression in all other target areas. The concomitant surgery should be noted on the corresponding eCRF.

Concomitant radiotherapy for the disease under study is not allowed. Radiotherapy for non-study-related lesions should be documented on the corresponding eCRF.

5.6 Method of Treatment Assignment and Randomization

All patients will be centrally assigned to randomized study treatment using an interactive voice/web response system (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

Once screening procedures are complete eligible patients will be randomized 1:1:1 to one of the 3 treatment arms. Patient randomization will be stratified by treatment-free interval from most recent taxane (relapse within 6 months vs >6 months) and presence of ascites (yes vs no).

Study treatment will be dispensed at the study visits summarized in the schedule of assessments (Table 10).

Returned study treatment should not be re-dispensed to patients.

5.7 Blinding

This is an open-label study; however, the specific treatment to be taken by a patient will be assigned using an IVRS/IWRS. The site will use the IVRS/IWRS to register the patient before the start of study treatment administration for each patient. The site will record the treatment assignment on the applicable eCRF, if required.

5.8 Dose Diary

A dose diary card will be provided to patients receiving relacorilant, and patients will be instructed to return all unused relacorilant and the dose diary card during the patient visits as indicated in the schedule of assessments (Table 10). Patients should complete an entry in the diary for each self-administered dose of relacorilant and note doses of any concomitant

medications taken. Entries will include the number of capsules as well as the date and time of relacorilant administration. On visit days when pre-dose samples are to be collected for PK (Table 11) or pharmacodynamics (Table 12), relacorilant should be taken in the clinic during the visit and after initial blood draws. Time and dose administered should be documented in the clinic charts.

5.9 Product Accountability and Treatment Compliance

Patients will be instructed to return all used and unused study drug containers at each study visit. Patient compliance with the dosing regimen will be assessed by reconciliation of the used and unused study drug. The quantity dispensed, returned, used, or lost must be recorded. Procedures for return and disposition of study drug by the clinical site are provided in Section 11.6.

6 DESCRIPTION OF STUDY ASSESSMENTS AND PROCEDURES AND APPROPRIATENESS OF MEASUREMENTS

Study procedures and their timing are summarized in the schedule of assessments (Table 10).

The Investigator and Sponsor will conduct the study in accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations. Adherence to the study design requirements, including those specified in the schedule of assessments, is essential and required for study conduct, and the Investigator must ensure that trial procedures are performed as described in the protocol. During the study, procedures and observations will be monitored to confirm that study requirements are being followed as outlined in the schedule of assessments.

6.1 Informed Consent and Screening

Written informed consent must be obtained in order for a patient to participate in this study. The ICF, which has been approved by the appropriate IRB/IEC, must be signed by the patient before any protocol-directed procedures are performed. The ICF must also be signed before any prohibited medications are withheld from patient in order for the patient to participate in the study.

Study patients must be notified of any changes that might affect their willingness to continue in the study in an update to the ICF and be given the opportunity to ask questions and/or withdraw consent. The patient's agreement must be documented in writing.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be used for screening purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the schedule of assessments (Table 10). Screening laboratory samples can be used for Cycle 1 Day 1 Visit if taken within 48 hours of the first dose of study treatment.

6.2 Medical and Oncology History

Medical history, including details regarding illnesses and allergies, date(s) of onset, and whether conditions are currently ongoing, and medication history will be collected on all patients during the Screening Period. Any new or clinically significant changes in the patient's medical or oncologic history between signing of the IRB/IEC-approved ICF and the first dose of study treatment will be recorded on the AE eCRF.

The following information will be collected:

- Complete medical history, including documentation of any clinically significant medical condition.
- History of tobacco and alcohol use.
- Presence and severity of any symptoms/conditions associated with ovarian cancer.
- Detailed oncology history, including but not limited to:
  - Date of primary cancer diagnosis
  - Pathology (histology or cytology) of primary tumor
  - Surgical history, including residual disease at the completion of surgery

- Anticancer and radiation treatments administered (including initiation and completion dates, type of modality, response, and reason for discontinuation and platinum-free interval, if applicable)
- Metastasis information (including the location and histological markers)
- Prior molecular testing/tumor profiling (including repeat biopsy from primary pathology, blood-based assays for molecular markers, and determinants of prognosis or drug sensitivity). The data collected will be the results of tumor molecular profiling or genetic testing relevant to cancer and may include testing for defects in homologous recombination (such as BRCA1 or BRCA2 mutation), TP53 mutation testing, and molecular profiling. Where possible, a comprehensive report would be preferred to a summary or notes on the results.
- Any new or clinically significant changes in the patient's medical or oncologic history between signing of the IRB/IEC-approved ICF and the first dose of study treatment will be recorded on the AE eCRF.

6.3 Safety Measures

Safety will be determined by evaluating study drug exposure, AEs, SAEs, all deaths, changes in laboratory determinations, and vital sign parameters. Vital signs, laboratory tests, and performance status assessment will be performed according the schedule of assessments (Table 10).

6.3.1 Physical Examination and Vital Signs

Physical examinations will be performed according to the schedule of assessments (Table 10).

A full physical examination will be performed at Screening, Day 1 of each cycle, at the End-of-Treatment Visit, and at the 30-Day Follow-up Visit. A targeted physical examination will be performed at Days 8 and 15 (or the day before) of each cycle. The performance of the physical examination will be recorded in the appropriate eCRF by the Investigator or designee.

Targeted physical examinations will include assessment of skin, heart, lungs, and abdomen, in addition to symptom-directed assessment of other organ systems. Note: all clinically significant abnormalities occurring before signature of informed consent should be recorded in the Medical History and/or Oncology History section of the eCRF; all abnormalities occurring or worsening after signature of informed consent should be recorded in the AE section of the eCRF.

Weight will be reported at each visit where a physical examination is performed. Height will be recorded at the Screening Visit only. Height and weight (without shoes) will be measured using an appropriate measuring device. Historical patient information and/or patient reports should not be used for either measurement.

Vital signs will be measured as noted in the schedule of assessments (Table 10) and include resting heart rate, blood pressure, respiratory rate, and body temperature. Systolic and diastolic blood pressure will be measured after patients have been at rest (seated) for at least 3 minutes. Blood pressure will be recorded in mmHg. Heart rate (beats per minute) will be measured after the patient has been in a resting state (seated) for at least 3 minutes. Heart rate should be recorded over 30 seconds or longer.

Unscheduled assessments of vital signs can be performed as necessary.

6.3.2 Pregnancy Test (in Women of Childbearing Potential)

For female patients of childbearing potential, a quantitative serum or urine pregnancy test will be performed to confirm that the patient meets eligibility requirements. A serum or urine pregnancy test will be obtained within 48 hours prior to the first dose of study treatment and reviewed prior to randomization. Pregnancy tests will be repeated every 12 weeks, or more frequently according to country requirements. Patients considered not of childbearing potential must be documented as being surgically sterile or postmenopausal (amenorrheic for at least 12 months).

If pregnancy test results are equivocal (e.g., false positive due to β-human chorionic gonadotropin being a tumor marker) in patients with evidence to support lack of pregnancy, the results should be discussed with the Medical Monitor and the Investigator's interpretation with supporting information documented in the source documents.

6.3.3 Triplicate 12-Lead Electrocardiogram

A resting 12-lead ECG will be performed in triplicate per the schedule of assessments (Table 10). Patients should be lying down for at least 10 minutes before each ECG evaluation.

The Investigator or qualified designee will indicate on the site's copy whether each ECG was normal, abnormal but not clinically significant, or abnormal and clinically significant and document this on the ECG eCRF. Any new or worsened abnormality noted as clinically significant will be reported as an AE. Each original ECG tracing or copy with physician's assessment will be retained in the patient's records at the study site.

6.3.4 ECOG Performance Status

ECOG performance status (Table 6) will be assessed at visits according to the schedule of assessments (Table 10).

Table 6 ECOG Performance Status

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

Abbreviation: ECOG, Eastern Cooperative Oncology Group
Source: Oken et al. 1982

6.3.5 Adverse Events

Details on definitions and reporting of AEs are provided in Section 8.

6.3.6 Clinical Laboratory Assessments

6.3.6.1 Laboratory Parameters

Blood samples will be collected for the analysis of safety in all patients at the times indicated in the schedule of assessments (Table 10). Laboratory samples will be analyzed at central or local laboratories as noted in Section 7.

A complete blood count and differential and blood chemistry will be obtained on Days 1, 8, and 15 of each cycle while the patient is on therapy, with other laboratory blood testing obtained prior to each 28-day treatment cycle.

Local laboratory data will be used for immediate treatment decisions and for safety assessment. Local laboratory CA-125 data will also be used to derive CA-125 response via GCIG criteria. The Investigator will review all local laboratory reports, evaluate the results, and sign/date the report.

Laboratory tests to be performed are listed in Table 7 and should be performed according to the schedule provided the schedule of assessments (Table 10).

Instructions for collection, preparation, and shipping of laboratory samples will be provided in the study laboratory manual.

Table 7 Clinical Laboratory Variables Evaluated During the Study

Hematology	Serum Chemistry	Urinalysis (dipstick)
Red blood cell count	Sodium	Bacteria
Hemoglobin	Potassium	Blood
Hematocrit	Calcium	Urobilinogen
Platelet count	Chloride	Nitrites
White blood cell count (WBC)	Phosphorus [a]	Color
WBC with 5-part differential:	Magnesium [a]	Clarity
Neutrophils	Serum creatinine	pH
Lymphocytes	Total bilirubin	Specific gravity
Monocytes	Albumin	Ketones
Eosinophils	Alkaline phosphatase	Protein
Basophils	Aspartate aminotransferase	Glucose
	Alanine aminotransferase	Bilirubin
Coagulation	Glucose, document whether fasting	Leukocyte esterase
International normalized ratio	or non-fasting	**Hormone**
Activated partial thromboplastin time	Blood urea nitrogen	Serum or urine human chorionic
Prothrombin time	Bicarbonate	gonadotropin, if applicable
Tumor Markers	Total protein	**Pharmacodynamic**
Cancer antigen 125	**Other [b]**	See Table 12 for details.
	HIV immunoassay [c]	
	Hepatitis B/C serology [d]	

[a] Magnesium and phosphorus at Screening and Day 1 of each cycle only.
[b] Must be confirmed as negative prior to randomization and first dose of study drug.
[c] 4th generation immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen.
[d] Serologic assays for hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis B surface antigen (anti-HBs), and anti-hepatitis C antibodies.

6.4 Measures of Anticancer Activity

Tumors will be assessed radiologically and response to treatment will be determined by using RECIST v1.1 (Eisenhauer 2009; Appendix E).

A CT or MRI scan of the chest, abdomen, and pelvis will be used to evaluate disease status per RECIST v1.1. A radiographic tumor assessment is required within 28 days prior to the first dose of study treatment and subsequent scans are required every 8 weeks (±7 days) from Cycle 1 Day 1 irrespective of treatment delays until unequivocal PD is documented, including in patients who discontinue treatment prematurely. At the End-of-Treatment Visit, a final radiographic tumor assessment will be done if ≥4 weeks have elapsed since the last radiographic tumor assessment, unless there is documented PD. The same method of assessment and the same

technique should be used at baseline and throughout the study. Radiographic scans will be quality checked, anonymized, and stored centrally.

CA-125 response will be assessed per GCIG criteria (Rustin et al. 2011; Appendix F). CA-125 will be assessed within 14 days prior to the first dose of study treatment and then every 4 weeks from Cycle 1 Day 1 for the first 12 months of study treatment. If Investigators collect CA-125 beyond 12 months as per their standard of care, this information will be documented in the eCRF. In addition, other tumor markers collected as standard practice (such as cancer antigens CA15-3 and CA19-9, and CEA) will be documented in the eCRF. Pharmacodynamic and biomarker collections are described in Section 6.6.

Patients who discontinue treatment at any time (Section 4.4.1) will continue to be followed for study endpoints (Section 7.6) after the last dose of study treatment until the endpoint of death, the patient is lost to follow-up, or until other study exit criteria are met (Section 4.4.2).

As described in Section 3.1.1, patients in Arm C (comparator) who experience unequivocal PD per RECIST v1.1 may be eligible to receive relacorilant in combination with nab-paclitaxel, after discussion with the Medical Monitor. Radiographic tumor assessments will be collected at the time of PD on nab-paclitaxel and be considered the final tumor assessment for comparator-only treatment and baseline for combination therapy. If more than 28 days have passed since the date of PD and Cycle 1 Day 1, then a new baseline radiographic tumor assessment will be obtained prior to initiating crossover treatment. Radiographic tumor assessments will then be performed every 8 weeks (±7 days) from the first dose of relacorilant until PD. CA-125 will be assessed within 14 days prior to the first dose of relacorilant and assessed every 4 weeks for the first 12 months. Study procedures will be performed according to the schedule for the Treatment Phase.

6.5 Pharmacokinetic Assessments

Intensive PK sampling for relacorilant and nab-paclitaxel will take place on Cycle 1 Day 15 and will consist of a total of 5 samples collected at the following time points: pre-dose (0 hour) and at 1, 2, 4, and 6 hours post-dose (Table 11).

Refer to Section 9.5.6 for a description of variables to be analyzed.

6.6 Pharmacodynamic/Biomarker Assessments

The development and improvement of therapies increasingly depends on insights gained from analysis of biomolecules. During this study and with the consent of patients (see Section 10.3.1), biological samples (e.g., blood, plasma, serum, or tumor tissue) will be obtained, either for analysis during the study or future analysis. These samples will be used to develop a better understanding of the mechanisms of both treatment response (predictive biomarkers) and disease processes (prognostic biomarkers) and ultimately to identify which patients have a high probability to benefit from treatment with relacorilant and those who do not.

The tests will be conducted via a central laboratory using a variety of techniques (e.g., immunohistochemistry and DNA/RNA analysis). Pharmacodynamic assays may be performed to correlate results of biomarker assessments to the physiological effects of relacorilant. A schedule of pharmacodynamic assessments, with timing and frequency of sample collections is provided in Table 12.

6.6.1 Blood Collection for GC-Related Pathways and Exploratory Biomarkers

Blood will be collected by venipuncture. Samples are to be obtained pre-dose, fasting, and between 7–9 am at the time points outlined (Table 12). On Cycle 1 Day 15, samples are to be collected in conjunction with the PK time point, if possible. The collection, processing and storage should be performed as described in the study-specific manual.

Intensive sampling is required from a subset of 20 patients (from Arm A only) for RNA analysis at additional time points: Cycle 1 Day 1 (4 hours post-dose), Cycle 1 Day 2, Cycle 1 Day 3, Cycle 1 Day 5, and Cycle 1 Day 10 (Table 12). At a minimum, the first 20 patients enrolled in Arm A will be included in this subset. In order to achieve 20 pharmacodynamic-evaluable patients, additional patients in Arm A may undergo intensive pharmacodynamic sampling if some patients are not evaluable. As this is a randomized study, it is unknown at the beginning of the study which sites will have patients who participate in the pharmacodynamic sampling. All sites/patients will be expected to participate until the Sponsor notifies the sites that the required number of patients has been reached.

6.6.2 Tumor Biopsy Tissue Collection

For patients enrolling in the study, consent and availability to archived tissue biopsy are required for eligibility. If archived tissue is not available, a fresh tumor biopsy should be obtained. Specimens obtained closest to the time of study enrollment are preferred, but not required. In addition, optional biopsies may be obtained if collected during standard-of-care procedures during the study or at the time of disease progression and with consent of the patient.

Optional paired pre- and post-treatment tumor biopsies will be collected within 6 weeks prior to treatment initiation and on Cycle 2 Day 1 (±7-day window) for determination of GR status and exploratory biomarkers. While these paired tumor biopsies are optional, a minimum of 6 patients per treatment arm are required to submit paired tumor biopsies. For these optional paired biopsies, archival biopsies collected >6 weeks prior to treatment initiation are not allowed to serve as the pre-treatment biopsy.

For patients in whom fresh tumor biopsy is mandatory for enrollment (because archival tissue is not available), patients must have at least 1 lesion accessible that is safely accessible for biopsy to be eligible for enrollment. Tissue acquisition, with or without anesthesia, must be considered of low risk to the patient. Biopsy of lesions that pose an undue risk to the patient, such as mediastinal lymph nodes, will not be performed as part of this study. In the case where biopsy samples are unable to be obtained for a given patient, the patient will remain on study, receive study medication and all study procedures will be performed. Please contact the Medical Monitor if any of the specimens are not feasible to collect.

Samples collected during screening should be fixed in formalin and embedded in paraffin (FFPE) according to standard institutional procedures. Tumor samples should be stored according to institutional procedures until shipment to the central laboratory. Overfixation in formalin for >24 hours should be avoided where possible. While sending FFPE blocks is preferred, slides prepared by the local pathology laboratory are acceptable and should be prepared as described in the study-specific laboratory manual. A minimum of 15 FFPE slides will be required for each tumor tissue collection (tissue block preferred). Refer to the study laboratory manual for complete instructions.

6.7 Patient-Reported Outcomes and Quality of Life

PRO and QoL assessments will be performed according to the schedule of assessments (Table 10). QoL will be assessed using FACT NFOSI-18 (Jensen et al. 2011), EQ-5D-5L/VASc scales (EuroQoL 1990), and PROMIS Physical Function-Short Form score (Cella et al. 2007, Rose et al. 2008, Rose et al. 2014). A healthcare utilization questionnaire will also be administered at these visits.

The FACT NFOSI-18 consists of 18 items and separates disease-related symptoms from treatment-related side effects, in 4 subscales: 1) disease-related symptoms (DRS) (9 items), 2) emotional well-being (1 item), 3) treatment side-effects (5 items), and 4) functional well-being (3 items). The EQ-5D-5L is a generic preference instrument that has been validated in numerous populations. The 5 dimensions of the EQ-5D-5L (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) will be measured on a 5-level scale. The EQ-5D-5L also contains a visual analog score (VAS) to assess the patient's overall health.

Baseline PRO and QoL assessments will be performed prior to the first dose of study treatment (relacorilant or nab-paclitaxel, whichever is earliest), at the Screening Visit. At this visit, patients will also be asked to answer the following 2 questions to assess for patient bias that could influence the PRO/QoL assessments in this open-label study:

1. Do you expect to have side effects? (Yes/No)
2. Do you expect to have benefit? (Yes/No)

Post-baseline assessments will be performed every other cycle starting with Cycle 2 Day 1, at the End-of-Treatment Visit, and at the 30-Day Follow-up Visit.

Patients will be asked to complete the FACT NFOSI-18 first, followed by the EQ-5D-5L. PRO and QoL assessments will be completed prior to discussing the results of tumor assessments or disease-related clinical changes with the patient. Patients should be encouraged to respond to all of the questions. While the patient is still at the site, the Investigator or designee will need to check the forms for completeness. If a patient is not able to complete the forms for any reason, this should be documented in the source. If the patient cannot self-administer the forms, the forms can also be administered by interview format (person-to-person and over the telephone). If a patient is not able to come to the site, the questionnaires may be sent with a request to complete them and return to the site as instructed by the site staff, or by telephone interview.

6.8 Appropriateness of the Measures

Standard clinical, PK, statistical, and laboratory procedures will be utilized in this study. The efficacy measurements in this study are standard.

7 STUDY ASSESSMENTS AND PROCEDURES BY STUDY VISIT

A schedule of assessments with scheduled visit dates and acceptable visit windows is provided in Table 10. A schedule of PK assessments is provided in Table 11. A schedule of pharmacodynamic assessments is provided in Table 12.

Patients should come to the clinic in a fasted state (no eating or drinking [other than water] for ≥8 hours beforehand) for pre-dose pharmacodynamic assessments as follows:

- All patients: Screening, Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 Day 1, Cycle 6 Day 1, End of Treatment
- The first 20 patients in Arm A (subset for intensive pharmacodynamic sampling [Section 6.6.1]): Screening, Cycle 1 Day 1, Cycle 1 Day 2, Cycle 1 Day 3, Cycle 1 Day 5, Cycle 1 Day 10, Cycle 1 Day 15, Cycle 3 Day 1, Cycle 6 Day 1, End of Treatment

7.1 Screening

Screening will be within 28 days before the first dose of study treatment (relacorilant or nab-paclitaxel, whichever is earliest) and may take place on more than 1 day within the 4-week Screening Period. If a patient was screened more than 4 weeks before the date of their first administration of study treatment (e.g., if the study is delayed or the patient was initially screened as a standby patient for an earlier cohort), that patient must be re-screened. A patient who has failed screening due to a reason that is temporary and expected to resolve (e.g., mild intercurrent infection) may be re-screened.

At the start of screening, the study will be discussed with the patient, and a patient wishing to participate must give written informed consent prior to any study-related procedures or change in treatment. The patient must also give written authorization regarding privacy requirements prior to any study-related procedures or change in treatment.

After written informed consent is obtained, prospective patients will be evaluated for entry into the study according to the Inclusion and Exclusion Criteria (Sections 4.1 and 4.2). Each patient who receives study treatment will be assigned a patient number that will be used on patient documentation throughout the study.

A CT or MRI scan of the chest, abdomen, and pelvis will be performed within 28 days prior to the first dose of study treatment to evaluate disease status per RECIST v1.1. CA-125 will be assessed within 14 days prior to the first dose of study treatment.

The following screening procedures will also be performed:

- Record baseline demographics
- Record medical/oncologic history
- Record prior and concomitant medications
- A serum or urine pregnancy test for female patients of childbearing potential will be performed prior to the first dose of study treatment (48-hour window from the first dose of study treatment, and then every 12 weeks ±7 days)
- Tumor biopsy prior to initiating study treatment (availability and consent to provide an archival or recent tumor biopsy for biomarkers is required for patient inclusion in the study)

- ECOG PS
- Complete physical examination
- Measure height
- Measure body weight
- Record vital signs
- 12-lead ECGs (performed in triplicate)
- Local laboratory tests (CA-125, hematology, chemistry, urinalysis, prothrombin time (PT), activated partial thromboplastin time (aPTT), INR; see Table 7 for details)
- Hepatitis B and C serologies and HIV immunoassay
- Baseline PRO and QoL must be collected prior to the first dose of study treatment
- Pharmacodynamic sampling (see Table 12 for details)
- AEs are to be recorded from the time written informed consent is obtained

7.2 Cycle 1 Day 1

Following confirmation that the patients continue to meet Inclusion and Exclusion Criteria, the patients will be randomized (Section 4). Eligible patients will be randomized 1:1:1 to one of the following 3 treatment arms:

- **Arm A (continuous):** relacorilant 100 mg, administered orally, once daily every day, in combination with nab-paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle.
- **Arm B (intermittent):** relacorilant 150 mg, administered orally, once daily on the day before (excluding Cycle 1 Day -1), the day of, and the day after nab-paclitaxel, in combination with nab-paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle.
- **Arm C (comparator):** nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle.

Study treatment will start on Cycle 1 Day 1 for all treatment arms.

Patients should receive their first dose of study treatment on the same day as randomization wherever possible, and with a minimum of delay where unavoidable.

The following procedures will also be performed at the Cycle 1 Day 1 Visit:

- A serum or urine pregnancy test for female patients of childbearing potential will be performed and reviewed prior to the first dose of study treatment (48-hour window from the first dose of study treatment) and then every 12 weeks ±7 days
- Record concomitant medications
- Patients in Arm A, Arm B, or the Crossover should receive their first dose of relacorilant and be dispensed adequate relacorilant according to their dose regimen
- Provide a dose diary card to all patients receiving relacorilant
- Pharmacodynamic sampling (see Table 12 for details)
- Record AEs (any since the last visit)

Screening laboratory samples can be used for the Cycle 1 Day 1 Visit if taken within 48 hours of the first dose of study treatment.

7.3 Treatment Phase

Visits will be conducted on Day 1, 8, and 15 of each cycle, starting with Cycle 1 and continuing until the End-of-Treatment Visit is complete. The acceptable visit window for scheduling conflicts during the Treatment Phase is +1 day for all visits unless the window spans a weekend, in which case the acceptable window extends to the following Monday (Day 3 past due). This acceptable visit window also applies to pharmacodynamic sampling. Visit windows are relative to the most recent infusion of nab-paclitaxel (Appendix C). Refer to Section 5.4 for delays that may occur due to toxicity.

Study procedures at each visit will be performed according to the schedule of assessments (Table 10).

A serum or urine pregnancy test for female patients of childbearing potential will be performed and reviewed prior to the first dose of study treatment (48-hour window from the first dose of study treatment) and then every 12 weeks ±7 days while on study treatment.

All patients will receive their first dose of nab-paclitaxel on Cycle 1 Day 1.

All patients will receive dosing with nab-paclitaxel on Days 1, 8, and 15 of each cycle. Patients receiving relacorilant will also receive their relacorilant dose in the clinic at visits when pre-dose samples for PK (Table 11) or pharmacodynamics (Table 12) are scheduled to be collected.

Radiographic tumor assessments will be performed every 8 weeks (±7 days) from Cycle 1 Day 1 irrespective of treatment delays until unequivocal PD is documented. The same method should be used for each assessment for a particular patient.

Availability and consent to provide an archival or recent tumor biopsy (pre-treatment tumor biopsy) is required for patient inclusion in the study. For patients who consent to provide optional paired (pre-treatment and post-treatment) tumor biopsies, biopsies will be obtained within 6 weeks prior to treatment initiation (this can be the same pre-treatment biopsy used to meet eligibility criteria) and at Cycle 2 Day 1 (±7 days).

Pharmacodynamic sampling will occur as described in the schedule provided in Table 12. Pharmacodynamic markers will include mRNA gene panel (blood and tumor expression profiles), cytokines, cancer antigens, tumor biomarker assays (tumor tissue), and other exploratory biomarkers. Additionally, the neutrophil-to-lymphocyte ratio will be evaluated as a pharmacodynamic marker from the hematology results.

CA-125 will be assessed within 14 days prior to the first dose of study treatment, and every 4 weeks from Cycle 1 Day 1 for the first 12 months of study treatment.

PK sampling will occur as described in Table 11.

The following procedures should be performed **on only Day 1 of each cycle** according to Table 10:

- ECOG PS
- Measure weight
- Provide new dose diary card to all patients receiving relacorilant
- Patients in Arm A, Arm B, or the Crossover should be dispensed adequate relacorilant, according to their dose regimen, to self-administer until their next visit

- PRO and QoL assessments will be collected every other cycle (-7-day window) starting with Cycle 2 Day 1, prior to discussing the results of tumor assessments or disease-related clinical changes with the patient

The following procedures should be performed **at all study visits** during the Treatment Phase according to Table 10.

- Record concomitant medications
- Assess treatment compliance. Patients receiving relacorilant will be instructed to return all unused study drug and their dose diary card at each study visit.
- Physical examinations (full examination on Day 1 of each cycle, targeted examinations on Days 8 and 15 [or the day before] of each cycle)
- Vital signs
- Record AEs
- Local laboratory tests (hematology and chemistry. See Table 7 for details

7.4 End of Treatment (In-clinic Visit)

The following assessments should be performed during the End-of-Treatment Visit according to the schedule of assessments (Table 10):

- Tumor assessments by RECIST v1.1: a final radiographic tumor assessment will be done if ≥4 weeks have elapsed since the last radiographic tumor assessment, unless there is documented PD. *Note: Patients who discontinue before PD will continue radiographic tumor assessments every 8 weeks (±7 days) until equivocal disease progression.*
- ECOG PS
- Record concomitant medications
- Complete physical examination
- Record vital signs
- Measure body weight
- 12-lead ECGs (performed in triplicate)
- Local laboratory tests (hematology, chemistry and urinalysis; see Table 7 for details)
- Assess treatment compliance per dose diary card and returned unused study drug (for patients receiving relacorilant)
- PRO and QoL assessments
- Record AEs
- Pharmacodynamic sampling (Table 12)

If treatment discontinuation occurs during a regularly scheduled study visit, that visit may serve as the End-of-Treatment Visit. All required assessments will be combined for the regularly scheduled study visit and the End-of-Treatment Visit. Assessments that overlap between these 2 visits do not have to be repeated if the visits are combined; however, all assessments unique to each visit must be performed.

7.5 30-Day Follow-up

The following assessments should be performed 30 days (±3 days) after the patient's final dose of study treatment according to the schedule of assessments (Table 10):

- ECOG PS
- Record concomitant medications
- Complete physical examination
- Record vital signs
- Measure body weight
- Local laboratory tests (hematology, chemistry, urinalysis, PT, aPTT, and INR; see Table 7 for details)
- PRO and QoL assessments
- Record AEs

7.6 Long-Term Follow-up Assessment of Survival

During the Long-Term Follow-up, patients who discontinue treatment at any time will continue to be followed for survival information (i.e., the date and cause of death) and subsequent treatment information (i.e., name[s] of subsequent therapy regimen[s], dates of initiation and completion, PD on subsequent therapy, and response to subsequent therapy).

- For patients who discontinue treatment before PD, subsequent treatment information will be collected at the same time as radiographic tumor assessments (i.e., every 8 weeks [±7 days]) until unequivocal PD. After PD, they will be followed every 3 months (±7 days) for the remainder of the Long-Term Follow-up.
- For patients who discontinue treatment at the time of PD, or for patients who decline further radiographic tumor assessments, long-term follow-up information will be collected every 3 months (±7 days) after the last dose of study treatment.

Long-term follow-up for survival and subsequent therapies will continue per this schedule (or as requested by the Sponsor to support data analysis), until the endpoint of death, the patient is lost to follow-up, or other study exit criteria are met (Section 4.4). Study staff will consult public records for survival status if the patient is lost to follow-up.

7.7 Unscheduled Visits

As appropriate, assessments deemed clinically necessary by the Investigator may be performed at unscheduled visits.

8 SAFETY EVENT DOCUMENTATION AND REPORTING

8.1 Adverse Event

8.1.1 Definition

An AE is any untoward medical occurrence in a study patient administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically relevant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product that emerges or worsens relative to the patient's pretreatment baseline, whether or not it is considered to be related to the investigational product.

Illnesses present before the patient signs the ICF are considered pre-existing conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF.

8.1.2 Performing Adverse Events Assessments

Investigators are responsible for monitoring the safety of patients who have entered this study and for providing appropriate medical care. The Investigator remains responsible for managing AEs that are serious or that cause a patient to withdraw before completing the study. Frequency of follow-up of any particular AE is left to the discretion of the Investigator. Duration of follow-up and requirements for immediate SAE reporting (within 24 hours of the event) are described below.

Safety results collected during the study (e.g., AEs, laboratory test results and physical findings) will be monitored on an ongoing basis by the Medical Monitor and Investigator.

Collection of AEs will start immediately following signing of the ICF and will continue until 30 days after the last dose of relacorilant or nab-paclitaxel, whichever is latest. Any worsening AEs or any SAEs that occur more than 30 days after the last dose of study treatment, which are attributed to study treatment, will also be recorded on the corresponding AE eCRF. Events of death that are considered related to study treatment, which occur more than 30 days after the last dose of study treatment, should also be recorded on the AE eCRF.

New signs or symptoms or worsening in severity of a cancer symptom that occur in association with PD should be recorded as AEs. AEs that occur after the first dose of study treatment and up to and including 30 days after administration of the last dose of study treatment will be considered TEAEs. Adverse events reported more than 30 days after the last dose of study treatment will be considered post-treatment AEs.

All AEs will be documented on the AE eCRF and in the patient's medical record. The following attributes must be assigned:

1. Description
2. Dates of onset and resolution
3. Severity (see Section 8.1.3)
4. Relationship to study treatment (see Section 8.1.4)
5. Seriousness criteria if applicable (see Section 8.2.1)
6. Action taken

The Investigator will actively solicit this information and assess the AEs in terms of severity and relationship to each study drug. AEs (including lab abnormalities that constitute AEs) should be described using a unifying diagnosis whenever possible, rather than individual underlying signs and symptoms. The Investigator will treat the patient as medically required until the AE either resolves or becomes medically stable. This treatment may extend beyond the duration of the study. The Investigator will record treatment and medications required for treatment of the AE on the appropriate pages of the eCRF.

If an AE leads to treatment discontinuation, the corresponding event must be recorded on the End-of-Treatment eCRF as the reason for treatment discontinuation. In the event that a patient is withdrawn from the study because of an AE, the corresponding event must be recorded on the End-of-Study eCRF as the reason for discontinuation.

All AEs considered to be related (see Section 8.1.4) to study treatment and all SAEs will be followed until resolved or until a stable status has been achieved (see Section 8.2.2 for details on SAE reporting).

All SAEs that are related to study treatment and unexpected (not reported in the RSI in the IB or if the event is of greater severity or frequency than that described in the RSI) must be reported to the governing IRB/IEC as required by the IRB/IEC, local regulations, and the governing health authorities (see Section 8.2.2.2).

8.1.2.1 Adverse Event Follow-up and Recording

All AEs will be followed until resolution, until deemed stable by the Investigator, or until the patient is deemed by the Investigator to be lost to follow-up.

8.1.3 Severity

The seriousness of an AE should not be confused with its severity. To describe the maximum severity of the AE on the AE eCRF, the Investigator will use the NCI-CTCAE criteria v5.0 (NCI-CTCAE 2017). For events not listed in the NCI-CTCAE, the definitions from the NCI-CTCAE provided in Table 8 should be used to evaluate the grade of severity for the AEs.

Table 8 Adverse Event Grades Based on the National Cancer Institute Common Terminology Criteria for Adverse Events

Grade	Description
1	**Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	**Moderate:** minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, and managing money)
3	**Severe**: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
4	**Life-threatening:** Life-threatening consequences; urgent intervention indicated
5	**Death:** Death related to adverse event

Source: National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE 2017).

8.1.4 Relationship to Study Treatment

The Investigator responsible for the patient's care or qualified designee will assess causality of AEs and SAEs based on the causal attribution guidance in Table 9. The Investigator's assessment of causality must be provided for all AEs (serious and non-serious).

Table 9 Causal Attribution Guidance for Adverse Events

Not related to study drug	An AE that is judged to be clearly due only to extraneous causes such as diseases, environment, and the like or for which it is temporally implausible to be related to use of the study drug. The cause must be noted on the AE eCRF
Possibly related to study drug	An AE that might be due to the use of the drug. The relationship in time is reasonable; therefore, a causal relationship cannot be excluded. An alternative explanation is inconclusive (e.g., concomitant drugs, concurrent diseases)
Probably related to study drug	An AE that might be due to the use of the drug. The relationship in time is suggestive. An alternative explanation is less likely (e.g., concomitant drugs or concurrent diseases)

Abbreviations: AE, adverse event; eCRF, electronic case report form.

8.1.5 Expectedness

An AE, regardless of seriousness, is considered unexpected if not reported in the RSI in the IB or if the event is of greater severity or frequency than described in the RSI.

8.1.6 Clinical Significance

The Investigator is responsible for determining whether an AE is clinically significant for the patient or the study overall. Clinical significance will be documented in the patient's medical records with the AE information.

8.1.7 Clinical Laboratory Adverse Events

All out-of-range laboratory values will be determined to be clinically significant or not clinically significant by the Investigator. An abnormal laboratory value that leads to a dose modification/interruption, treatment discontinuation, or patient withdrawal from the study will be recorded as an AE on the eCRF. Other clinically significant laboratory values may be reported as AEs at the discretion of the Investigator.

8.2 Serious Adverse Events

8.2.1 Definition

An SAE is any AE that meets any of the following criteria:

- Results in death (i.e., the AE caused or led to the fatality).
- Is life-threatening (i.e., the AE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires hospitalization or prolongation of existing hospitalization (i.e., hospitalizations for scheduled treatments and elective medical/surgical procedures are not SAEs by this criterion).
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial reduction of the patient's ability to perform activities of daily living).
- Results in a congenital anomaly or birth defect (i.e., an adverse finding in a child or fetus of a patient exposed to the study treatment before conception or during pregnancy).
- Involves other medically important conditions (i.e., the AE does not meet any of the above serious criteria but based on appropriate medical judgment, may jeopardize the patient or require medical or surgical intervention to prevent one of the serious outcomes listed in these criteria).

Important medical events that might not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasia or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.2 Reporting Serious Adverse Events

Any SAE occurring during the study period (beginning with informed consent) and for at least 30 days after the last dose of study treatment must be reported within 24 hours to the designated safety contact (Section 8.2.2.1) and recorded on the SAE Form. All patients with an SAE must be followed and the outcomes reported. The Investigator must supply the Sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

If an SAE results in death, the death should be considered an outcome, not an event. The event or condition leading to death should be recorded and reported as a single medical concept on the AE eCRF. Generally, only 1 such event should be reported. "Fatal" will be recorded as the outcome of this respective event; death will not be recorded as a separate event. The eCRF should reflect that death was due to an AE with the corresponding reason (e.g., sepsis) documented.

If the primary cause of death is PD, the cause of death should be clearly identified on the Death eCRF as progression of the cancer under study.

All SAEs occurring from the time of informed consent until 30 days following the last administration of study treatment (relacorilant or nab-paclitaxel, whichever is latest) must be reported to the designated safety contact (Section 8.2.2.1) within 24 hours of the knowledge of the occurrence. After this period, Investigators should continue to report all deaths and SAEs that are considered to be related to prior treatment with study drug. Any death occurring greater than 30 days after the last dose of study treatment requires expedited reporting within 24 hours only if it is considered possibly or probably related to study treatment.

The Investigator or designee will complete the SAE reporting form, including whether the event was or was not related to the investigational drug and send to the designated safety contact. The clinical staff will obtain and maintain all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient within the patient files.

The Investigator or designee will promptly inform the governing IRB/IEC of all serious, unexpected, drug-related events that occur at his or her site or per the IRB/IEC regulations. It is the responsibility of each site to submit Investigational New Drug (IND) Safety Reports, as applicable, provided to them by the Sponsor to their IRB/IEC as required by the IRB/IEC, local regulations, and the governing health authorities.

The Investigator or designee will fax or email additional follow-up information, if required and available, to the contact provided within 24 hours of receipt. This information should be included on a follow-up SAE Form, placed with the original SAE Form, and kept with the appropriate section of the eCRF and/or study patient file.

8.2.2.1 Safety Reporting Contact

[redacted] is the vendor for this study to report SAEs to and can be contacted via the following:

- [redacted]
- [redacted]

8.2.2.2 Suspected Unexpected Serious Adverse Reactions

The Sponsor will ensure that the regulatory authority is informed promptly of any Suspected Unexpected Serious Adverse Reaction (SUSAR) for the Investigational Medicinal Product in accordance with US Regulations and EU Directive 2001/20/EC. The reference document used for SUSAR reporting will be the most current version of the IB for relacorilant and the current US package insert or Summary of Product Characteristics for nab-paclitaxel.

8.2.3 Emergency Sponsor Contact

In a medical emergency (i.e., an event that requires immediate attention regarding the treatment of a patient, operation of the clinical study, and/or the use of investigational product), study site personnel will apply appropriate medical intervention according to current standards of care and contact the Medical Monitor.

8.3 Pregnancy

All pregnancies occurring during the study and within 30 days of the last dose of study treatment should be immediately reported to Corcept. The outcome of any conception occurring from the date of the first dose of study treatment through within 30 days of the last dose of study treatment will be followed and documented for up to 2 months after the completion of pregnancy.

8.4 Treatment of Overdose

There is currently no experience with overdose of relacorilant. Corcept does not recommend specific treatment for an overdose; however, the Investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities until any symptoms resolve.
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

9 STATISTICAL METHODS

This section outlines the statistical design consideration, analyses and descriptive summaries to be performed on the collected data. Further details of the statistical analyses and methods will be provided in a Statistical Analysis Plan, to be completed prior to the study database lock.

9.1 Analysis Populations

Analysis populations for this study are:

- Intent-to-Treat (ITT): All randomized patients, analyzed according to the randomized treatment arm. This population will be used for analysis of the primary endpoint and all secondary efficacy endpoints.
- Safety Analysis Population (SAF): All randomized patients who received at least 1 dose of study treatment, analyzed according to the treatment actually received. This population will be used in all analyses of safety endpoints.
- Pharmacokinetics Analysis Population (PKA): All patients in the SAF who have PK data collected and available for analysis.

9.2 General Statistical Considerations

The statistical analysis will be conducted by the Sponsor and/or their designee. Detailed descriptions of all analyses and statistical methods will be prespecified and documented in a Statistical Analysis Plan (SAP), to be finalized before database lock.

All summaries will be presented by starting dose group (as randomized), regardless of the actual dose level at the time point associated with the data collection. In addition, data will be tabulated for all patients combined. All relevant data collected on the eCRF will be presented in by-patient data listings, to include the site identifier, patient number, and starting dose group. Listings presenting study data over time will include the dose level the patient received at the time of data collection.

In general, continuous variables will be summarized by the number of patients with non-missing data, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by the number and percentage of patients in each category.

The baseline value will be defined as the most recent value prior to the first dose of study treatment (relacorilant or nab-paclitaxel, whichever occurs earliest).

9.3 Hypothesis Testing

The primary efficacy endpoint will each be tested at a 1-sided 0.05 level of significance to test the null hypothesis of no difference in PFS between 2 study treatment groups. Hochberg step-up procedure will be applied in order to control for multiplicity of testing when comparing the 2 relacorilant-containing arms (Arms A and B) vs the nab-paclitaxel-only control (Arm C).

Secondary endpoints will be tested at a 1-sided 0.05 level of significance, with no additional adjustment for multiplicity of testing. P-values from secondary and exploratory tests will be considered descriptive.

9.4 Sample Size Calculation

In order to estimate the total sample size and the number of events needed in this study, estimates of median PFS were considered from previous studies for the treatment of recurrent or persistent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer. In a single arm study of nab-paclitaxel alone (Coleman et al. 2011), where a majority of 47 evaluable patients had a recurrence within 6 months of treatment completion, the observed median PFS was 4.5 months (95% confidence interval [CI]: 2.2–6.7). In a Phase 3 study of bevacizumab in combination with chemotherapy for platinum-resistant recurrent ovarian cancer (Pujade-Lauraine et al. 2014), the observed median PFS was 3.4 months with chemotherapy alone (95% CI: 2.2–3.7) vs 6.7 months with bevacizumab-containing therapy (95% CI: 5.7–7.9).

Based on these data, the assumed median PFS in the current study is 3.8 months in the nab-paclitaxel alone arm (Arm C) and 5.4 and 6.8 months, respectively, in Arm B and Arm A. For the comparison between Arm C and Arm A, 91 PFS events will provide approximately 79% power for a 1-sided log-rank test at a 0.05 significance level to detect a hazard ratio [HR]=0.56. Assuming an exponential distribution of PFS, this corresponds to an increase in median PFS from 3.8 months in Arm C to 6.8 months in Arm A. For the comparison between Arm C and Arm B, 92 PFS events will provide approximately 39% power for a 1-sided log-rank test at a 0.05 significance level to detect a HR=0.7. Assuming an exponential distribution of PFS, this corresponds to an increase in median PFS from 3.8 months in Arm C to 5.4 months in Arm B. A total of approximately 177 patients will need to be randomized (1:1:1 ratio), assuming approximately 10% drop-out in each study arm.

The total accrual duration is expected to be 24 months, with expected study duration of 43 months.

Assuming a median survival of 13.3 months in the control group, and 16.6 and 17.4 months in Arms B and A, respectively, approximately 120 OS events can be expected to be observed during the 43 months of study duration. This will provide 33% global power for the comparison of time to OS among the 3 treatment arms.

9.5 Analysis Plan

9.5.1 Patient Disposition

Patient disposition summaries will include the number of enrolled patients, the number of enrolled patients in each analysis population, the number of patients completing the study per protocol, and the number of patients terminating the study early by the primary reason for discontinuation.

9.5.2 Demographic and Baseline Data

Demographics baseline data will include frequency and percentages for categorical variables, and mean, standard deviation, median, minimum, and maximum for continuous variables. Demographic and baseline characteristics will be summarized by treatment regimen dose group, and overall.

9.5.3 Concomitant Medications

Verbatim terms on the eCRFs will be mapped to Anatomical/Therapeutic Chemical class and Generic Drug Names using the most current version of the World Health Organization Drug Dictionary. Concomitant medications will be summarized for all treatment patients by treatment regimen dose group and overall.

9.5.4 Efficacy Analyses

Time-to-event variables will be summarized using Kaplan-Meier estimates and plots. Event probabilities at 6-month and 12-month time points and the median time-to-event (if estimable) will be presented. The log-rank test, stratified by stratification variable(s) used at randomization, will be used to compare the treatment groups with respect to time-to-event variables.

Primary estimates of the treatment differences will be obtained using the hazard ratios and 1-sided 95% CIs from stratified Cox regression model that includes treatment as a covariate and are stratified by stratification variables used at randomization.

Response rate endpoints will be summarized by providing the point and interval estimates.

9.5.4.1 Primary Efficacy Analysis

The primary endpoint is defined in Section 3.2.1.

The primary efficacy analysis will be performed on the ITT population as described in Section 9.1. Additional sensitivity analyses will be performed to evaluate the robustness of the primary efficacy analysis.

PFS is defined as the time from the date of randomization to the date of first documented PD by RECIST v1.1 (Appendix E), or death due to any cause. All events of disease progression (as determined by the Investigator) or death will be included, regardless of whether the event occurred while the patient was still taking study drug or had previously discontinued study drug. However, if a disease progression event occurs after a patient misses 2 or more consecutive tumor assessments, this patient will be censored at the last tumor assessment prior to the missing assessments. If a patient has not progressed or died before the analysis cutoff date, PFS will be censored at the date of last adequate tumor assessment.

Additional sensitivity analyses will be completed where patients receiving other anticancer therapies are censored at the time other anticancer treatment is initiated.

Hochberg's step-up procedure will be used for the control of multiplicity of testing in the primary efficacy analysis.

9.5.4.2 Secondary Efficacy Analyses

The secondary efficacy endpoints are defined in Section 3.2.2.

Analysis of the secondary efficacy endpoints will be performed on the ITT population as described in Section 9.1. Time-to-event type secondary endpoints will be analyzed in the same manner as the primary efficacy endpoint, unless otherwise pre-specified in the SAP. Each secondary endpoint will be evaluated at the 0.05 level of significance without the additional adjustment for multiplicity of testing across secondary analyses.

ORR is defined as the proportion of patients with measurable disease at baseline who attain CR or PR by RECIST v1.1. Confirmation is not required to be counted toward ORR.

DoR is defined as the time from the date response was documented (whichever came first) until first observation of PD or death due to any cause. DoR will be assessed only in patients who have a response at any time on study. If a patient does not have documented PD or death before the analysis cutoff date, DoR will be censored at the date of last study visit.

BoR is defined as the best response recorded from the date of randomization until PD/recurrence (or death). BoR will be summarized for the following types of responses: CR, PR, SD, and PD, categorically and graphically with a waterfall plot.

OS is defined as the time from the date of randomization to the date of death due to any cause. If a patient has not died before the analysis cutoff date, OS will be censored at the date of last contact.

An evaluation of OS will be performed at the time of the primary analysis after 135 PFS events have occurred. An additional OS analysis will be performed when at least 120 OS events have occurred, which will be used for the purposes of final OS reporting.

DoR, PFS, and OS will be analyzed and presented using the Kaplan-Meier method (for PFS and OS), along with the estimated median (in months) with 95% CIs, 25th and 75th percentiles.

PFS, ORR, and BoR will also be evaluated among patients who were in Arm C and Crossover to continuous relacorilant + nab-paclitaxel (Section 3.1.1) following unequivocal PD. Additional sensitivity analyses will be performed to evaluate the impact of various assumptions on the evaluation of efficacy when considering this treatment switch following PD.

9.5.4.3 Exploratory Efficacy Analyses

Exploratory efficacy endpoints are defined in Section 3.2.3.

Analysis of the exploratory efficacy endpoints will be performed on the ITT population as described in Section 9.1.

9.5.4.4 Interim Analysis

No interim efficacy analysis will be performed.

9.5.5 Safety Analyses

Safety analyses will be conducted on the SAF as described in Section 9.1.

The incidence of TEAEs, defined as AEs occurring after the first dose of study treatment through 30 days after the last dose of study treatment, will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred term. TEAEs will be further summarized by severity and relationship to study treatment. For each patient, if multiple incidences of the same AEs occur, the maximum severity reported will be used in summaries.

All AEs (whether TEAEs or not) will be listed by individual patient, including information regarding onset, duration, severity, and relationship to study drug. SAEs and AEs that lead to withdrawal from the study will be listed by individual patient.

The following AEs will be summarized separately: AEs leading to discontinuation of study treatment (relacorilant or nab-paclitaxel), dose reduction or interruption, Grade ≥3 AEs and SAEs.

All deaths and causes of deaths will be summarized and listed.

Clinical laboratory test results, vital sign measurements, and abnormal ECG values will be summarized overall and for each treatment regimen dose group by parameter, visit, and time point using descriptive statistics.

By-patient safety listings will be provided.

9.5.6 Pharmacokinetic Analysis

Intensive PK sampling for relacorilant and nab-paclitaxel will take place on Cycle 1 Day 15 and will consist of a total of 5 samples collected at the following time points: pre-dose (0 hour) and at 1, 2, 4, and 6 hours post-dose.

Standard PK parameters will be included. Further details of the PK analyses will be described in the SAP finalized before database lock.

Pharmacokinetic analyses will be performed on the PKA population as described in Section 9.1.

9.5.7 Pharmacodynamic Analysis

Biomarker and pharmacogenomic exploratory analyses will be described in the SAP finalized before database lock.

9.5.8 Patient-Reported Outcomes/Quality of Life

For the FACT NFOSI-18, 4 subscale scores will be constructed and analyzed: 1) disease-related symptoms (DRS) scores, 2) emotional well-being (DRS-E) score, 3) treatment side effect (TSE) score, and 4) a functional well-being (FWB) score. For the primary PRO and QoL analysis, the overall mean change from baseline for the DRS scores between groups will be assessed, using a longitudinal repeated measures model that takes into account the DRS measured at each assessment point up to 6 months or PD, whichever is later. Additional analyses based upon PRO endpoints will be specified in the SAP.

10 ETHICAL AND LEGAL CONSIDERATIONS

10.1 Compliance with Institutional Review Board/Independent Ethics Committee Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103), IEC regulations, or applicable local regulations. The protocol, ICFs, recruitment materials, and all patient materials will be submitted to the IRB/IEC for review and approval. Approval of both the protocol and the consent form must be obtained before any patient is enrolled, and the Investigator must submit written approval to the Sponsor, before enrolling any patient. The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB/IEC on receipt of amendments and annually, as local regulations require.

All changes to the consent form must be approved by the IRB/IEC; a determination will be made regarding whether previously consented patients need to be re-consented

Corcept is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the Investigator should be provided to Corcept.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines.

10.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP and applicable regulatory requirements.

The Principal Investigator will ensure that the study procedures outlined in this protocol will be conducted in accordance with applicable country and local regulations.

10.3 Protection of Patients

10.3.1 Compliance with Informed Consent Regulations

Written informed consent is to be obtained from each patient before enrollment into the study, and/or from the patient's legally authorized representative.

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

- The ICF will contain all of the elements required by ICH GCP and any additional elements required by local regulations.
- The ICF must include information about the possible retention of biological samples at the conclusion of this study; with the patient's permission, samples may be retained for

future determination of active metabolite concentrations and possible biomarkers related to drug response.

- The patient's signed and dated ICF must be obtained before conducting any study procedures.
- The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.
- The ICF must include information about the possible retention of biological samples at the conclusion of this study; with the patient's permission, blood, plasma, serum and tissue samples may be obtained for future analysis to help identify biomarkers of disease or relacorilant treatment.
- The informed consent process should be documented in the patient's record.

10.3.2 Patient Confidentiality

To maintain patient privacy, all source documents, study reports, and communications will identify the patient by initials and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or their designee and regulatory authority access to the patient's original study records for verification of data gathered on source documents and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by applicable laws and regulations.

10.3.3 Patient Privacy

The Investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with the Sponsor, regulatory agencies, and IRB/IEC/Research Ethics Board. It is the Investigator's or designee's responsibility to obtain written permission to use protected health information per country-specific regulations from each patient or, if appropriate, the patient's legally authorized representative. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the patient, and the patient will be removed from the study.

Written authorization is to be obtained from each patient before enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Study Monitoring

Monitoring of the study site (including, but not limited to, reviewing eCRFs for accuracy and completeness, and assessing compliance with the protocol and adherence to regulatory and GCP requirements) will be performed by the Sponsor's Clinical Monitor or designee.

- Monitoring will be performed in accordance with applicable federal regulations and guidance.
- Monitoring will include regular site visits and communication with the Investigator and site staff as appropriate to discuss and answer study questions; ensure compliance with the protocol; and ensure quality and integrity of the data.
- Monitors will ensure the site maintains an adequate supply of investigational products; any necessary supplies and ensure that appropriate storage conditions are maintained.
- Monitoring visits will be conducted according to the US CFR Title 21 parts 50, 56, and 312; and ICH GCP.

Monitoring methods, responsibilities, and requirements will be outlined in a monitoring plan.

11.2 Quality Management

Study sites, the study database, and study documentation will be monitored regularly and may be subject to a quality assurance audit during the study by the Sponsor or its designee on behalf of the Sponsor. In addition, inspections may be conducted by regulatory agencies at their discretion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices, Good Manufacturing Practices).

The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

11.3 Documentation

11.3.1 Electronic Case Report Forms and Study Records

The Investigator must generate and maintain complete, adequate, accurate, reliable, and consistent records to enable full documentation of study conduct. Study data will be captured on eCRFs. Investigators must retain all original source documents, and Corcept or its designee will notify Investigators in writing when the trial-related records are no longer needed.

11.3.2 Access to Source Documentation

The Sponsor or its representative will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and original source documents, and other records relative to study conduct.

By signing the protocol, the Principal Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the Sponsor, a regulatory authority, and/or an IRB/IEC may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, patient charts and source documents, and other records relative to study conduct. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents (e.g., laboratory reports, x-rays, workbooks, and patients' medical records) to determine whether these activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, ICH GCP, and any applicable regulatory requirements.

The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

11.3.3 Source Documents

Source documents are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, a patient's medical records, hospital charts, clinic charts, the Investigator's patient study files, as well as the results of diagnostic tests such as x-rays, laboratory tests, and ECGs. All data entered into the eCRFs must be substantiated by a source document.

11.3.4 Study Files and Retention of Study Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

Patient identification codes (patient names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator or designee must contact the Sponsor before disposing of any study records.

11.4 Sample Collection, Preparation, and Shipping

Instructions for collection, preparation, and shipping of all laboratory samples will be provided in the study laboratory manual.

11.5 Long-Term Retention of Biological Samples

No samples will be retained long-term (i.e., beyond end of study and database closure) without prior written consent of the patient and IRB/IEC approval.

All long-term, retention samples will be retained by Corcept or designee. The long-term retention samples will be coded to allow de-identification according to applicable regulatory guidelines.

After conclusion of this study, the long-term samples will be held for a period up to 10 years, after which they will be destroyed. If a study patient does not provide consent for future use, that patient's samples will be destroyed.

During the conduct of the study, an individual patient can choose to withdraw consent to have her samples stored for future research. However, withdrawal of consent with regard to biological sample storage will not be possible after the study is completed.

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with all applicable laws, which may include but are not limited to European Directives 95/46/EC and 2002/58/EC and any legislation and/or regulation implementing or made pursuant to them, or which amends, replaces, re-enacts, or consolidates any of them (including the General Data Protection Regulation [EU] 2016/679), and all other applicable laws relating to processing of personal data and privacy that may exist in any relevant jurisdiction. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with all applicable laws relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

11.6 Clinical Supplies

11.6.1 Inventory, Reconciliation, Return, and Disposition of Clinical Supplies

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations/government health authorities and study procedures. Storage of study drug is described in Table 1.

11.6.2 Clinical Supply Inventory

A detailed inventory must be completed for all study drug. The study drug is to be used in accordance with the protocol by patients who are under the direct supervision of an Investigator. The study drug must be dispensed only by an appropriately qualified person to patients in the study.

Unused study drug must be kept in a secure location for accountability and reconciliation by the study monitor. The Investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of study drug(s) received, patients to whom study drug is dispensed (patient dose specific accounting), and study drug lost or accidentally or deliberately destroyed. The Investigator or designee must retain all unused or expired study supplies until the study monitor (onsite clinical research associate) has confirmed the accountability data and Sponsor has approved return or destruction.

11.6.3 Return or Disposal of Study Drug and/or Supplies

All clinical study drug and/or supplies will either be destroyed by the site per institutional policy or returned to Corcept or Corcept designee for destruction.

Unused study drug may be destroyed on site, per the site's SOPs, but only after Sponsor has granted approval for drug destruction. The study monitor must account for all study drug in a formal reconciliation process, before study drug destruction. All study drug destroyed on site must be documented.

Documentation must be provided to the Sponsor and retained in the Investigator study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to the Sponsor upon request. The return of study drug or study drug materials must be accounted for on a Study Drug Return Form provided by the Sponsor.

11.7 Drug Accountability

It is the responsibility of the Investigator to maintain drug accountability at the study site and ensure that a current record of investigational product disposition is maintained. It is the responsibility of the Investigator to ensure that the investigational product is used only in accordance with the approved protocol. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from Corcept or designee and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the drug. At the end of the study, after final drug inventory reconciliation by the study monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to SOPs.

11.8 Post-Trial Care

There is no provision for continuation of the investigational drug beyond the end of study treatment. The Sponsor will work with the Investigator to ensure that patients continue to receive appropriate care, which may include referral to an ongoing clinical trial with this or another investigational treatment or may involve transition to medical management outside the research context.

11.9 Noncompliance with the Protocol

Prospective approval of deviations from the Inclusion and Exclusion Criteria, also known as protocol waivers or exemptions, is not permitted.

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or manual of procedures requirements. The noncompliance may be either on the part of the patient, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6.

The Investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor in writing and in accordance with the IEC/IRB and local regulations, except when necessary to eliminate an immediate hazard to study patients. When a deviation from the protocol is deemed necessary for an individual patient, the Investigator must obtain approval in writing from the Sponsor.

Such contact must be made as soon as possible to permit a review by the Sponsor to determine the impact of the deviation on the patient and/or the study.

Any significant protocol deviations affecting patient eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

11.10 Financial Disclosure

Investigators will be required to disclose any financial equity interests in the Sponsor and any conflicts of interest, as defined by the Sponsor.

11.11 Publication and Disclosure Policy

Corcept, as the Sponsor, has a proprietary interest in this study.

No individual publications will be allowed before publication of the multicenter results except as agreed with Corcept. The Investigator agrees to submit all manuscripts or abstracts to Corcept for review before submission to the publisher.

Corcept will comply with the requirements for publication of study results and determination of authorship in accordance with standard editorial and ethical practice and with the International Committee of Medical Journal Editors requirements.

11.12 Study Termination by Sponsor

If the Sponsor, Investigator, study monitor, or regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study site's participation should be terminated, this action may be taken after appropriate consultation between the Sponsor and Investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- Discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study
- Decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product

Study termination and follow-up will be performed in compliance with applicable regulations.

12 REFERENCES

American Cancer Society. Cancer Facts & Figures 2018. Atlanta, Ga: American Cancer Society; 2018.

Abraxane® Product Monograph. 31 August 2018. Accessed at https://media.celgene.com/content/uploads/sites/23/Abraxane_Product_Monograph_English_Version.pdf

Abraxane® Summary of Product Characteristics (SPC). 03 April 2019. Accessed at https://www.medicines.org.uk/emc/product/6438/smpc/print

Abraxane® Prescribing Information (USPI). August 2018. Accessed at https://media.celgene.com/content/uploads/abraxane-pi.pdf

Block TS, Murphy TI, Munster, PNM, et al. 2017. Glucocorticoid receptor expression in 20 solid tumor types using immunohistochemistry assay. Cancer Manag Res. 9:965–972.

Bogaerts J, Ford R, Sargent D, Schwartz LH, Rubinstein L, Lacombe D, et al. 2009. Individual patient data analysis to assess modifications to the RECIST criteria. Eur J Cancer. 45:248–60

Cella D, Yount S, Rothrock N, Gershon R, Cook K, Reeve B, et al. 2007. The Patient-Reported Outcomes Measurement Information System (PROMIS): Progress of an NIH roadmap cooperative group during its first two years. Medical Care. 45(5 Suppl 1):S3–S11.

Coleman RL, Brady WE, McMeekin DS, Rose PG, Soper JT, Lentz SS, et al. 2011. A phase II evaluation of nanoparticle, albumin-bound (nab) paclitaxel in the treatment of recurrent or persistent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer: a Gynecologic Oncology Group study. Gynecol Oncol. Jul;122(1):111–115.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. 2009. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 45:228–247.

EuroQol Group. 1990. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 16(3):199–208.

Ganghadaran SGD. 2016. Management of platinum resistant – refractory ovarian cancer: a short review. J Cancer Res Treat. 2016;4(2):32–36.

Horwitz SB. 1994. Taxol (paclitaxel): mechanisms of action. Ann Oncol. 5 (Suppl 6):S3–S6.

Isikbay M, Otto K, Kregel S, et al. 2014. Glucocorticoid receptor activity contributes to resistance to androgen-targeted therapy in prostate cancer. Horm Cancer. 5(2):72–89.

Jensen SE, Rosenbloom SK, Beaumont JL, Abernethy A, Jacobsen PB, Syrjala K, Cella D. 2011. A new index of priority symptoms in advanced ovarian cancer. Gynecol Oncol. 120(2):214–219.

Melhem A, Yamada SD, Fleming GF, et al. 2009. Administration of glucocorticoids to ovarian cancer patients is associated with expression of the anti-apoptotic genes SGK1 and MKP1/DUSP1 in ovarian tissues. Clin Cancer Res. 15(9):3196–3204.

Munster PN, Gray S, Sachdev JC, Fleming GF et al. 2018. A phase 1/2 study of relacorilant + Nab-paclitaxel in patients with solid tumors: The dose-finding phase, poster presentation. American Society of Clinical Oncology Annual Meeting, 1–5 June 2018, Chicago, IL.

NCI (National Cancer Institute). 2017. Common Terminology Criteria for Adverse Events, version 5.0 published: November 27, 2017. US Department of Health and Human Services, National Institutes of Health, Accessed at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Oken MM, Creech RH, Tormey DC et al. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 5:649–655.

Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. 2014. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol. May 1;32(13):1302–1308.

Raja FA, Chopra N, Ledermann JA. 2012. Optimal first-line treatment in ovarian cancer. Ann Oncol. 23 Suppl 10:x118-x127.

Rose M, Bjorner JB, Becker J, Fries JF, Ware JE. 2008. Evaluation of a preliminary physical function item bank supports the expected advantages of the Patient-Reported Outcomes Measurement Information System (PROMIS). J Clin Epidemiol. 61:17–33.

Rose M, Bjorner JB, Gandek B, Bruce B, Fries JF, Ware Jr JE. 2014. The PROMIS Physical Function Item Bank Was Calibrated to a Standardized Metric and Shown to Improve Measurement Efficiency. J Clin Epidemiol. 67(5):516–526.

Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. 2011. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA-125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 21(2):419–423. doi: 10.1097/IGC.0b013e3182070f17.

Skor MN, Wonder E, Kocherginsky M, et al. 2013. Glucocorticoid receptor antagonism as a novel therapy for triple negative breast cancer. Clin Cancer Res. 19(22):6163–6172.

Stringer EM, Saha P, Swoboda A, Kocherginsky M, Baker G, Olberkyte S, et al. 2017. A phase I trial of mifepristone (M), carboplatin (C), and gemcitabine (G) in advanced breast and ovarian cancer. J Clin Oncol. 35:15_suppl, 1083–1083.

Stringer-Reasor EM, Baker GM, Skor MN, et al. 2015. Glucocorticoid receptor activation inhibits chemotherapy-induced cell death in high-grade serous ovarian carcinoma. Gynecolog Oncol. 138(3):656–662.

Appendix A: Schedules of Assessments and Procedures

Table 10 Schedule of Assessments and Procedures

Study Period/ Visit	Screening	Treatment Phase						EOT [a]	30-Day Follow-up [b]	Long-Term Follow-up [c]
		Cycle 1			Cycle 2 and Subsequent Cycles					
Day (See Note below table for windows)	Within 28 days prior to first dose of study treatment	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15		30 days after final treatment	
Informed Consent	X									
Inclusion and Exclusion Criteria	X	X								
Demographics	X									
Medical/Oncologic History	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	
Serum/Urine Pregnancy Test [d]	X	X			X [d]					
Tumor Biopsy [e]	X				X					
Tumor Assessment (CT/MRI) [f]	X	Every 8 weeks (±7 days) from Cycle 1 Day 1 [f]						X [f]		
CA-125 [g]	X	X			X			X [g]		
ECOG PS	X	X			X			X	X	
Randomization [h]		X								
Physical Examination [i]	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	
Height	X									
Weight	X	X			X			X	X	
Hematology [j]	X	X	X	X	X	X	X	X	X	

Study Period/ Visit	**Screening**	**Treatment Phase**						**EOT [a]**	**30-Day Follow-up [b]**	**Long-Term Follow-up [c]**
		Cycle 1			**Cycle 2 and Subsequent Cycles**					
Day (See Note below table for windows)	**Within 28 days prior to first dose of study treatment**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**		**30 days after final treatment**	
PT/aPTT/INR	X								X	
Biochemistry [k]	X	X	X	X	X	X	X	X	X	
Urinalysis [l]	X							X	X	
Hepatitis B and C Serologies & HIV	X									
12-lead ECG (in triplicate)	X [m]							X		
Patients in Arm A or B, or Crossover:										
Provide dose diary card		X			X					
Dispense relacorilant		X			X					
Relacorilant dosing (oral) [n]		Refer to Section 5 for details of continuous and intermittent dose schedules								
Assess treatment compliance			X	X	X	X	X	X		
Nab-Paclitaxel Dosing (IV)		X	X	X	X	X	X			
Intensive PK Blood Sampling [o]				X						
Pharmacodynamic Sampling [p]	X	X		X	X [p]		X	X		
PRO and QoL Assessments [q]	X				X [q]			X	X	
Record AEs	X	X	X	X	X	X	X	X	X	
Follow-up										X

Abbreviations: AE, Adverse event; aPTT, activated partial thromboplastin time; CA-125, cancer antigen 125; CEA, carcinoembryonic antigen; CR, complete response; CT, computerized tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End of Treatment; GR, glucocorticoid

receptor; HIV, human immunodeficiency virus; INR, international normalized ratio; IV, intravenously; MRI, magnetic resonance imaging; OS, overall survival; PD, disease progression (progressive disease per RECIST v1.1); PK, pharmacokinetic; PRO=patient-reported outcomes; PS, performance status; PT, prothrombin time; QoL=quality of life; SAE, serious adverse event.

Visit Window Note: Study visits will align with nab-paclitaxel infusion days during the Treatment Phase. Refer to Appendix C for acceptable treatment windows for nab-paclitaxel for scheduling conflicts. For dose delays of nab-paclitaxel due to toxicity see Section 5.4.

Procedural Window Note: Screening hematology and chemistry laboratory tests can be used for the Cycle 1 Day 1 values if collected within 48 hours of the first dose of study treatment. For all other visits, hematology and chemistry assessments can be conducted up to 72 hours prior to the study visit/nab-paclitaxel infusion. Post-baseline PRO and QoL assessments can be performed up to 7 days early.

[a.] Patients who discontinue treatment prior to disease progression will continue radiographic tumor assessments every 8 weeks (±7 days) until unequivocal disease progression.

[b.] Follow-up Visit should be performed 30 days (±3 days) after the patient receives their final dose of study treatment (relacorilant or nab-paclitaxel, whichever is latest).

[c.] Long-Term Follow-up: For patients who discontinue before PD, subsequent treatment information will be collected at the same time as radiographic tumor assessments (i.e., every 8 weeks [±7 days]), until unequivocal PD, after which they will be followed every 3 months (±7 days). For patients who discontinue treatment at the time of PD, or for those who decline further radiographic tumor assessments, survival and subsequent treatment information will be collected every 3 months (±7 days) from the last dose of study treatment (Section 7.6).

[d.] A serum or urine pregnancy test for female patients of childbearing potential will be performed prior to the first dose of study treatment (48-hour window from the first dose of study treatment) and then every 12 weeks ±7 days.

[e.] Availability and consent to provide an archival or recent (pre-treatment) tumor biopsy for biomarkers are required for patient inclusion in the study. Optional paired tumor biopsies will be obtained within 6 weeks prior to treatment initiation (this can be the same pre-treatment biopsy used to meet eligibility criteria) and at Cycle 2 Day 1. In order to assess the study endpoints, paired biopsies from a minimum of 6 patients per treatment arm are needed. If additional patients are enrolled to achieve this target, consent to provide biopsies will become mandatory for enrollment in the study. Refer to Table 12 for further details of pharmacodynamic assessments.

[f.] Tumor assessments will be performed within 28 days prior to the first dose of study treatment and then every 8 weeks (±7 days) from Cycle 1 Day 1 irrespective of treatment delays until unequivocal disease progression is documented, including in patients who prematurely discontinue therapy. The same method should be used for each assessment for a particular patient. At the EOT visit, a final radiographic tumor assessment will be done if ≥4 weeks have elapsed since the last radiographic tumor assessment, unless there is documented PD.

[g.] CA-125 will be assessed by the local laboratory within 14 days prior to the first dose of study treatment and every 4 weeks from Cycle 1 Day 1 for the first 12 months of treatment. If Investigators collect CA-125 beyond 12 months as per their standard of care, this information will be documented in the eCRF.

[h.] Randomization to be performed prior to administration of study medication. Patients should receive their first dose of study treatment on the same day as randomization wherever possible, and with a minimum of delay where unavoidable.

[i.] A full physical examination will be performed at Screening, Cycle 1 Day 1 of each cycle, and at the End-of-Treatment Visit. A targeted physical examination will be performed at Days 8 and 15 of each cycle (or the day before).

[j.] Hematology assessments are listed in Table 7. On Cycle 1 Day 1, hematology samples should be collected pre-dose and 4 hours post-dose. For Arms A and B, and Crossover, the nominal time for this sample collection is relative to the dose of relacorilant. For Arm C, the nominal time for this sample collection is relative to the start of the nab-paclitaxel infusion.

[k.] Biochemistry assessments are listed in Table 7.

[l.] Urinalysis assessments are listed in Table 7. Microscopy is required only to follow-up clinically significant urine dipstick findings.

[m.] Triplicate ECG-measurements should be performed prior to the first dose of study treatment. If not performed at Screening, ECGs can be done at Cycle 1 Day 1.

[n.] For patients in Arm A (continuous) or the Crossover, the first dose of relacorilant will be Cycle 1 Day 1 and will then continue to be administered once daily through the Treatment Phase. For patients in Arm B (intermittent), the first dose of relacorilant is to be administered on Cycle 1 Day 1 and then will continue to be administered on the day prior, the day of, and the day following nab-paclitaxel. Nab-paclitaxel will be administered on Day 1, 8, and 15 for all arms. See Section 5 for full details of dosing for both relacorilant and nab-paclitaxel.

[o.] Intensive PK sampling for relacorilant and nab-paclitaxel to take place on Cycle 1 Day 15 and will consist of a total of 5 samples collected at the following time points: pre-dose (0 hour) and at 1, 2, 4, and 6 hours post-dose (Table 11).

[p.] A schedule of pharmacodynamic assessments is provided in Table 12, this includes timing of blood samples and timing of paired tumor biopsies.

[q.] Baseline PRO and QoL assessments must be collected prior to the first dose of study treatment (relacorilant or nab-paclitaxel, whichever occurs earlier). Post-baseline assessments will be collected every other cycle (-7-day window) starting with Cycle 2 Day 1, at the End-of-Treatment Visit, and at the 30-Day Follow-up Visit. PRO and QoL assessments should be completed prior to discussing the results of tumor assessments or disease-related clinical changes with the patient.

Table 11 Pharmacokinetic Schedule of Assessments

PK Sample	Day	Nominal Time [a]	Window
Relacorilant & nab-paclitaxel	Cycle 1 Day 15	0 hr, pre-dose	Within 15 minutes before the relacorilant dose
		1 hr	±10 minutes
		2 hr	
		4 hr	
		6 hr	

Abbreviation: PK, pharmacokinetic

[a] For Arms A and B, and Crossover, the nominal time of PK sample collection is relative to the dose of relacorilant. For Arm C, the nominal time for the PK sample collection is relative to the start of the nab-paclitaxel infusion.

Table 12 Pharmacodynamic Schedule of Assessments

Procedure/Assay	Tissue Source	Visit Schedule Cycle Day	Methodology; Examples of Biomarkers
Immune, tumor, and GC-related gene panel including [redacted]	Blood	Fasting, pre-dose (between 7-9 am) at: Screening Cycle 1 Day 1 Cycle 1 Day 15 Cycle 3 Day 1 Cycle 6 Day 1 EOT [a] Disease progression [a]	mRNA expression by technologies such as NanoString
		For a subset of 20 patients enrolled into Arm A, an intensive collection schedule will be followed: Fasting, pre-dose (between 7-9 am) at: Screening Cycle 1 Day 1 **Cycle 1 Day 2** **Cycle 1 Day 3** **Cycle 1 Day 5** **Cycle 1 Day 10** Cycle 1 Day 15 Cycle 3 Day 1 Cycle 6 Day 1 EOT [a] Disease progression [a] Post-dose (between 11 am-1 pm), fasting not required (please note whether fasting or not fasting): Cycle 1 Day 1	

Procedure/Assay	Tissue Source	Visit Schedule Cycle Day	Methodology; Examples of Biomarkers
Exploratory cytokines	Blood	Fasting, pre-dose (between 7-9 am) at: Screening Cycle 1 Day 1 Cycle 1 Day 15	Immunoassay panel for cytokines related to immune and GC function
Cancer antigens	Blood	Pre-dose (between 7-9 am): Screening, Every 6-8 weeks to coincide with radiographic assessments.	Analytes measured by technologies such as immunoassay; Antigens such as CA15-3, CA19-9, or carcinoembryonic antigen (CEA)
Immune, tumor, and GC-related gene panel including [redacted]	Pre-treatment and post-treatment (when available) tumor biopsies	Screening Cycle 2 Day 1 [b]	Formalin fixed, paraffin embedded tissue sample; microdissection and assessment of mRNA expression of genes involved in tumor GR-signaling, chemotherapy resistance, tumor immune response, apoptosis, and metabolism
Immunohistochemistry for GR and/or other exploratory markers	Pre-treatment and post-treatment (when available) tumor biopsies	Screening Cycle 2 Day 1 [b]	Formalin fixed, paraffin embedded tissue sample; CLIA-validated IHC assay for GR and/or other IHC or IF methods
Mutation and homologous recombination deficiency assessment	Pre-treatment tumor biopsy	Screening	Formalin fixed, paraffin embedded tissue sample; DNA sequencing analysis, such as [redacted]

Footnotes for Table 12

Abbreviations: CA-125, cancer antigen 125; CA15-3, cancer antigen 15-3; CA19-9, cancer antigen 19-9; CLIA, Clinical Laboratory Improvement Amendments; DNA, deoxyribonucleic acid; EOT, End of Treatment; [redacted] GC, glucocorticoid; GR, glucocorticoid receptor; IF, immunofluorescence; IHC, immunohistochemistry; mRNA, messenger RNA; PD, disease progression.

[a] If a patient discontinues treatment for reasons other than PD, a sample will be collected upon PD.

[b] Availability and consent to provide an archival or recent tumor biopsy (pre-treatment tumor biopsy) for tumor biomarker assays are required for patient inclusion in the study. Optional paired (pre-treatment and post-treatment) tumor biopsies will be obtained within 6 weeks prior to treatment initiation (this can be the same pre-treatment biopsy used to meet eligibility criteria) and at Cycle 2 Day 1 (±7 days). Patients will also have the option to provide an additional on-study biopsy (1) obtained during procedure conducted as standard of care; or (2) at the time of PD.

Appendix B: Guidance for Identifying High Grade Serous Carcinoma

The following should be considered when determining a diagnosis of high grade serous carcinoma:

- Diagnosed as Grade 2 or Grade 3 serous carcinoma using Shimizu-Silverberg grading scheme.
- Wide spectrum of architectural patterns, including solid, glandular, and cribriform patterns, and patterns resembling transitional cell carcinoma. At least focal papillae and micropapillae with gaping and slit-like architectural features are present.
- Histologic variants such as transitional cell carcinoma or serous carcinoma with microcystic features.
- High nuclear grade, with extreme nuclear size variability (>5×).
- More than 10 mitotic figures per 10 high power fields.
- Typically disseminated at presentation. WT1 expression should be sought for Stage I tumors.
- WT1, p53, and/or pl6 overexpression may be sought if the differential diagnosis includes low grade serous carcinoma, endometrioid carcinoma, or clear cell carcinoma.
- Can be distinguished from serous borderline tumor by the presence of high nuclear grade if obvious stromal invasion is not identified after examination of multiple sections.

Appendix C: General Chemotherapy Guidelines

- A patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol deviation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.
- It will be acceptable for nab-paclitaxel doses to be delivered within a 1-day window after the scheduled date of treatment, except if the treatment due date is a Friday. In that case, if the patient cannot be treated on the Friday, then the acceptable window for treatment would include the following Monday (Day 3 past due).
  For example:
  - "Day 8 chemotherapy" can be delivered on Day 8 or Day 9, unless Day 9 is a Saturday and then Day 8 chemotherapy can be delivered on Day 11
  - "Day 15 chemotherapy" can be given on Day 15 or Day 16, unless Day 16 is a Saturday and then Day 15 chemotherapy can be delivered on Day 18
- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol deviation (most institutions use a rule of approximately ±5% of the calculated dose).
- Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for <10% weight changes.

Appendix D: Examples of Medications and Foods that are Prohibited or to be Used with Caution

The following medications and foods are examples of prohibited medications/foods or medications/foods to be used with caution during the study:

	Prohibited	Not Recommended	Use with Caution
CYP3A Inducers	St. John's wort, rifampin	Bosentan, efavirenz, etravirine, modafinil, nafcillin Carbamazepine, phenytoin	
CYP3A Inhibitors	Grapefruit and Seville oranges (including marmalade and juices made from these fruits) Boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	--	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil
CYP3A Substrates	Alfentanil, aprepitant, astemizole, budesonide, buspirone, cisapride, conivaptan, cyclosporine, darifenacin, darunavir, dasatinib, dihydroergotamine, dronedarone, eletriptan, eplerenone, ergotamine, everolimus, felodipine, fentanyl, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, pimozide, quetiapine, quinidine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, tolvaptan, tipranavir, triazolam, ticagrelor, vardenafil	--	--
CYP2C8 Inhibitors	Gemfibrozil	--	Glimepiride, tolbutamide [a]
Corticosteroids or GR Modulators	Mifepristone or other GR antagonists		Topical or oral corticosteroids
QT-prolonging Medications	--	--	Substitute or eliminate QT-prolonging medications, when possible (https://www.crediblemeds.org/)

Abbreviations: CYP, cytochrome P450; GR, glucocorticoid receptor.

[a.] For patients receiving sulfonylureas, conduct close glucose monitoring to assess for diabetic control.

The table of examples above is not comprehensive. For additional information or to review specific medications, see the prescribing information of the respective medications and the following websites for information on drug interactions:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

http://medicine.iupui.edu/clinpharm/ddis/main-table/

Appendix E: RECIST v1.1 for Disease Assessment

Tumor response and assessment according to RECIST v1.1 is described below. This appendix is not exhaustive and the source (Eisenhauer 2009) should be referred to for further detail.

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

CT is the best currently available and reproducible method to measure lesions selected for response assessment. CT (with IV and oral contrast) should be performed with cuts of 5 mm or less in slice thickness contiguously. MRI can be performed if required but should have sponsor approval.

For accurate objective response evaluation, ultrasound should not be used to measure tumor lesions.

Measurable Tumors

Tumor lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm on long axis for non-nodal lesions by CT/MRI scan (slice thickness no greater than 5 mm).
- 15 mm on short axis for nodal disease by CT/MRI scan (slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

Non-measurable Tumors

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone Lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

Patients with measurable or non-measurable disease are eligible. Measurable disease is defined as above, by the presence of at least 1 measurable lesion.

Baseline Documentation of 'Target' and 'Nontarget' Lesions

When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Response criteria as defined below should be used:

- Evaluation of Target Lesions
  - Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
  - Partial Response (PR): At least a 30% decrease in the sum of the diameters (SOD) of target lesions, taking as reference the baseline SOD.
  - Progressive Disease / Disease Progression (PD): At least a 20% increase in the SOD of target lesions, taking as reference the smallest sum recorded since the treatment started or the appearance of 1 or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The development of unequivocal new lesions (not attributed to differences in scanning technique, imaging modality, or flare/healing of pre-existing lesions) will also be considered PD.
  - Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest SOD since the treatment started.
- Special Notes on the Assessment of Target Lesions
  - Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.
  - All lesions at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (<5 mm). If the lesion is believed to be present, but too small to measure, a default value of 5 mm should be assigned (as derived from the 5 mm CT slice thickness). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- Evaluation of Nontarget Lesions
  - Complete Response (CR): Disappearance of all nontarget lesions and normalization of tumor marker level.
  - Incomplete Response/Stable Disease (non-CR/non-PD): Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
  - Progressive Disease / Disease Progression (PD): Appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget lesions.
- Special Notes on Assessment of Progression of Nontarget Disease

  To achieve 'unequivocal progression' on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. **A modest increase in the size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal disease progression. In the**

absence of radiographic or clinical evidence of progressive disease, a rise in CA-125 alone is not sufficient to declare progression.

New lesions

- The appearance of new lesions denotes disease progression. The findings of a new lesion should be unequivocal; i.e., not attributable to differences in scanning technique, timing of scanning, phase of contrast administration, change in imagining modality, or finding thought to represent something other than tumor. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.
- If a new lesion is equivocal, continue therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm there is a new lesion, then progression should be declared using the date of the initial scan.

Appendix F: Gynecological Cancer Intergroup Definitions for Response and Progression in Ovarian Cancer Clinical Trials

Tumor response and assessment according to GCIG criteria is described below. This appendix is not exhaustive and the source (Rustin 2011) should be referred to for further detail.

Definition of Response

A CA-125 response is defined as at least a 50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

To calculate CA-125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the reference range of CA-125 levels will not interfere with the response definition.
- For each patient, the same assay method must be used, and the assay must be tested in a quality control scheme.
- Patients are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (e.g., paracentesis). If assessing therapy that includes 2 treatment modalities for relapse (e.g., surgery and chemotherapy), any CA-125 response results from both treatment modalities. CA-125 cannot distinguish between the effects of the 2 treatments.

The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response. To calculate response per GCIC criteria, an intent-to-treat analysis will be used that includes all patients with an initial CA-125 level of at least twice the upper limit of the reference range as eligible and evaluable. In addition, as a separate analysis, those patients who have a CA-125 response and whose CA-125 level falls to within the reference range can be classified as CA-125 complete responders. In Table 13 and Table 14 where CA-125 is stated as normalized or normal, means within the reference range.

Evaluation of Best Overall Response in Patients without Initial Measurable Disease and Evaluable by CA-125 (GCIG Criteria)

CA-125 may be used to evaluate response in patients without initial measurable disease either because no measurable disease is evident on radiological imaging or because appropriate imaging has not been performed as demonstrated in Table 13.

Table 13 Evaluation of Best Overall Response in Patients Without Initial Measurable Disease and Who are Evaluable by CA-125 (GCIG Criteria)

CA-125	Nontarget Lesions [a]	New Lesions	Overall Response	Best Response for This Category Also Requires
Response and Normalized	CR	No	CR	Confirmed and maintained for at least 28 days
Response	Non-PD	No	PR	
Normalized but no response	Non-CR/Non-PD	No	SD	
Non-PR/non-PD	Non-PD	No	SD	
PD	Any	Yes or No	PD	
Any	PD [b]	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CA-125, cancer antigen 125; CR, Complete response; PD, progressive disease; PR, partial response; SD, stable disease.

[a] Nontarget lesions include ascites and peritoneal thickening, which are not measurable according to RECIST.

[b] Unequivocal progression in nontarget lesions may be accepted as disease progression.

Evaluation of Best Overall Response in Patients with Initial Measurable Disease and Who are Also Evaluable by CA-125 (GCIG Criteria)

A report that combines both CA-125 and RECIST v1.1 is likely to include patients who are measurable by one or both of the criteria and who may have events at different time points. It should be determined according to Table 14. In patients who have measurable disease by both criteria, the date of response will be the date of the earlier of the 2 events if this approach to combined response reporting is to be used. In the combined assessment of CA-125 and RECIST v1.1 response, the following algorithm applies when determining the best overall response. If patients have progressive disease (PD) according to RECIST v1.1 within 28 days of CA-125 response, they are classified as having PD. If the PD according to RECIST v1.1 is longer than 28 days before or after the CA-125 response, they are classified as having partial response. Patients whose best response according to RECIST v1.1 is stable disease but who have a CA-125 response are classified as CA-125 responders.

Table 14 Best Overall Response in Patients with Measurable Disease and Who are also Evaluable by CA-125 (GCIG Criteria)

Target Legion [a]	Nontarget [b]	New Lesion	CA-125 [c]	Best Overall Response
CR	CR	No	Normal	CR
CR	Non-CR Non-PD	No	Not PD	PR
CR	CR	No	PR but not normal	PR
CR	NE	No	PR	PR
PR	Non-PD or NAE	No	Not PD	PR
NAE	Non-PD	No	PR	PR
PD or New >28 days from CA-125 PR [d]			PR	PR
SD	Non-PD	No	PR	PR
SD	Non-PD or NAE	No	Not PR and not PD	SD
PD or New ≤28 days from CA-125 PR [d]			PR	PD
PD	Any	Yes or No	Any	PD
Any	PD	Yes or No	Any	PD
Any	Any	Yes	Any	PD
Any	Any	Yes or No	PD	PD

Abbreviations: CA-125, cancer antigen 125; CR, Complete response; NE, not evaluated; NAE, not all evaluated; PD, progressive disease; PR, partial response; SD, stable disease.

[a] Target lesions include up to 5 measurable lesions (2 per organ) as defined by RECIST v1.1.

[b] Nontarget lesions include ascites and peritoneal thickening which are not measurable according to RECIST v1.1.

[c] CA-125 response must be confirmed and maintained for at least 28 days.

[d] Patients who have a CA-125 response that occurs more than 28 days from PD according to RECIST v1.1 are considered a PR, according to best response, but PD if the RECIST v1.1 PD is within 28 days of CA-125 response.

Reporting of Response According to both RECIST v1.1 and CA-125 (GCIG Criteria)

In this study, responses will be reported separately for both tumor response per RECIST v1.1 and CA-125 response per GCIG criteria as shown in the hypothetical example in Table 15. A combined response endpoint based on both RECIST v1.1 and GCIG criteria will also be reported. Tumor response will be assessed by the Investigator or local radiologist using RECIST v1.1. CA-125 response and the combined response will be derived based upon local CA-125 results.

Table 15 Example of Reporting Response According to RECIST v1.1, CA-125 (GCIG Criteria), and Combined Response

Bolded numbers, CA-125 responders; ***bolded and italicized numbers***, both RECIST and CA-125 responders; *italicized numbers*, RECIST responders.

RECIST	CA-125 Response			
	Yes	**No or PD**	**NE**	**Total RECIST**
CR [a]	***4***	0	0	*4*
PR	***3***	*1*	*1*	*5*
SD	**3**	12	1	16
PD	**0**	8	2	10
NE	**3**	5	2	10
Total CA-125	**13**	26	6	Total entered = 45

Abbreviations: CA-125, cancer antigen 125; CR, complete response; GCIG, Gynecologic Cancer Intergroup; NE, not evaluated; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

Note: In the above example, the RECIST v1.1 response rate is 9 (25.7%) of 35 patients evaluable by RECIST v1.1, the CA-125 response rate is 13 (33%) of 39 patients evaluable by CA-125, and the combined overall response rate (either RECIST or CA-125 response) is 15 (35%) of 43 patients total.

[a] RECIST v1.1 includes normalization of CA-125 to achieve CR (Table 14).

Appendix G: Guidance for Counting Prior Lines of Therapy

The following guidance applies with respect to counting the number of prior lines of anticancer therapy for each patient:

- Line of therapy includes therapy that was given in any setting (adjuvant or neoadjuvant treatment or for recurrent disease).
- If a treatment was initiated after disease progression or discontinuation of a previous regimen due to toxicity, then the treatment should be considered a separate line of therapy, with exception of the following:
  - If 1 component of a regimen/planned treatment duration was transitioned to a similar class/regimen due to toxicity, then the continuation of doublet therapy should be considered as 1 line of therapy. For example, adjuvant treatment with carboplatin and paclitaxel, with a change from paclitaxel to docetaxel after 3 cycles due to toxicity, to complete the planned 6 cycles of treatment, would be considered 1 line of therapy. Similarly, if the same patient received maintenance treatment with bevacizumab following completion of carboplatin and paclitaxel/docetaxel, all therapies would be considered as 1 line of therapy.
- If a patient completed a planned course of treatment, subsequent treatments should be considered as a new line of therapy.
- Maintenance therapy is not considered a separate regimen and should be counted as part of the line of therapy most recently completed.

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted] tumor assessments or disease-related clinical changes [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]