

CLINICAL STUDY PROTOCOL CORT125134-556

Title	A Phase 3 Study of Relacorilant in Combination with Nab-Paclitaxel versus Nab-Paclitaxel Monotherapy in Advanced, Platinum-Resistant, High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian-Tube Cancer (ROSELLA)
EudraCT Number	2022-000662-18
EU CT Number	2024-514080-25-00
Study Treatment	Relacorilant and Nab-paclitaxel
Medical Monitor	██████████ Telephone (mobile): ██████████ Email: ██████████
Sponsor	Corcept Therapeutics Incorporated 101 Redwood Shores Pkwy Redwood City, California 94065 USA +1 (650) 327-3270
Version	Amendment 4
Date	15 February 2025

Good Clinical Practice Statement

This study will be conducted in compliance with the protocol, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, and with the ethical principles contained in the Declaration of Helsinki, 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

This document contains information that is the confidential and proprietary property of Corcept Therapeutics Incorporated. Any use, distribution, or disclosure without the prior written consent of Corcept Therapeutics Incorporated is strictly prohibited except to the extent required under applicable laws or regulations.

SPONSOR SIGNATURE PAGE

Protocol Title	A Phase 3 Study of Relacorilant in Combination with Nab-Paclitaxel versus Nab-Paclitaxel Monotherapy in Advanced, Platinum-Resistant, High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian-Tube Cancer (ROSELLA)
Protocol Number	CORT125134-556
Version	Amendment 4
Date	15 February 2025

APPROVAL STATEMENT

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

[REDACTED]

[REDACTED]

[REDACTED]

HISTORY OF AMENDMENTS

Document	Version	Sponsor Approval Date
CORT125134-556 Protocol Amd 4 (Global)	4	15 February 2025
CORT125134-556 Protocol Amd 3 (Consolidated: Global and South Korea)	3	14 November 2024
CORT125134-556 Protocol Amd 2 (Consolidated: Global and France)	2	30 October 2023
CORT125134-556 Protocol Amd (South Korea)	1.2	07 July 2023
CORT125134-556 Protocol Amd (France)	1.1	22 February 2023
CORT125134-556 Protocol Amd (Global)	1	29 June 2022
CORT125134-556 Original Protocol	Original	29 March 2022

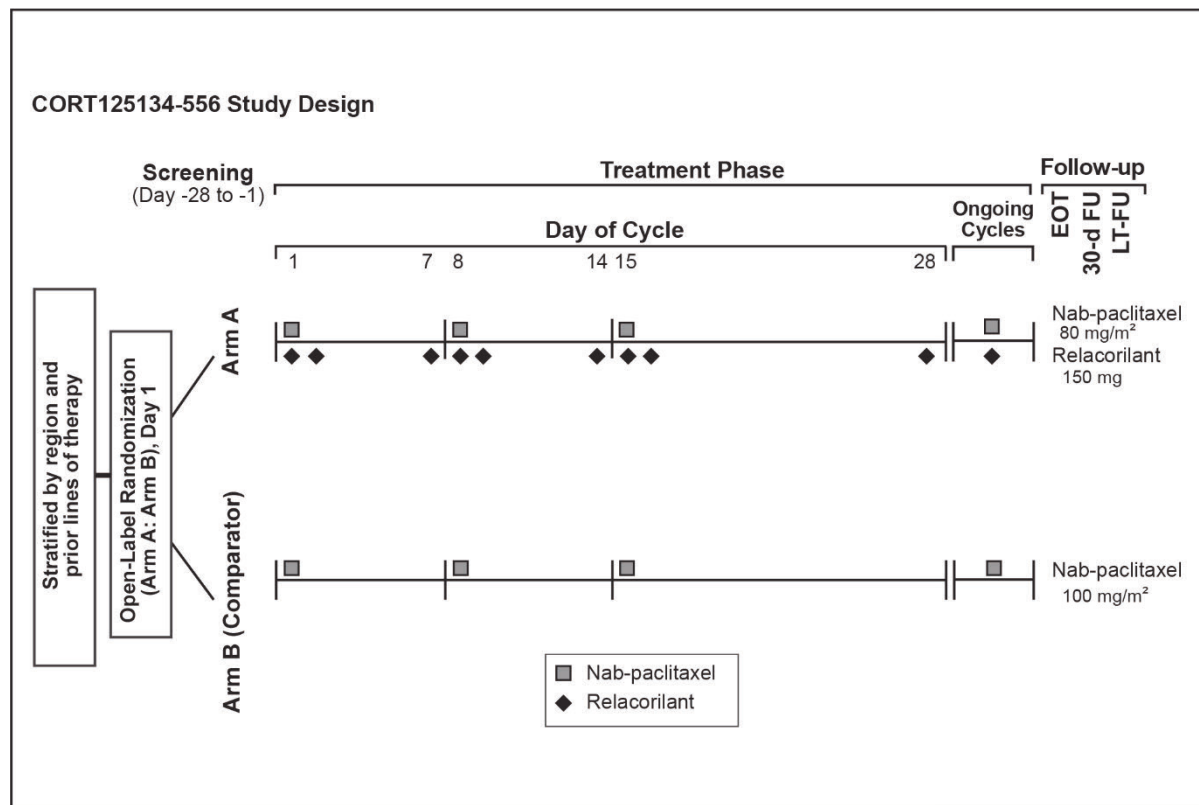
PROTOCOL SYNOPSIS

Name of Sponsor Corcept Therapeutics Incorporated	Name of Active Ingredient Relacorilant	Study Number CORT125134-556
Title of Study A Phase 3 Study of Relacorilant in Combination with Nab-Paclitaxel versus Nab-Paclitaxel Monotherapy in Advanced, Platinum-Resistant, High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian-Tube Cancer (ROSELLA)		
Study Centers Approximately 125 sites globally		
Phase of Development Phase 3		
Study Objectives For all efficacy objectives listed below, assessment for response and disease progression are according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer 2009) as assessed by blinded independent central review (BICR), unless otherwise noted. Primary Objectives: The primary efficacy objectives of this study are to evaluate progression-free survival (PFS) by BICR and overall survival (OS) in patients treated with an intermittent regimen of relacorilant in combination with nab-paclitaxel compared with patients treated with nab-paclitaxel monotherapy. Secondary Objectives: <u>Secondary Efficacy Objectives</u> The secondary efficacy objectives are to evaluate patients treated with an intermittent regimen of relacorilant in combination with nab-paclitaxel compared with nab-paclitaxel monotherapy: ▪ To evaluate PFS as assessed by the Investigator or local radiologist ▪ To evaluate objective response rate (ORR) ▪ To evaluate best overall response (BoR) ▪ To evaluate duration of response (DoR) ▪ To evaluate clinical benefit rate (CBR) at 24 weeks ▪ To evaluate response according to cancer antigen 125 (CA-125) using Gynecologic Cancer InterGroup (GCIg) criteria. A combined-response endpoint based on RECIST v1.1 and GCIg criteria will also be reported. <u>Safety Objective</u> ▪ To assess the safety of relacorilant treatment in combination with nab-paclitaxel compared with nab-paclitaxel monotherapy. Exploratory Objectives: <u>Pharmacodynamics/Biomarkers</u> ▪ To assess the relationship between Baseline and pharmacodynamic markers (eg, glucocorticoid receptor [GR] and expression of other genes) and the patient's response to relacorilant in combination with nab-paclitaxel. ▪ To assess pharmacodynamic effects of the intermittent regimen of relacorilant in combination with nab-paclitaxel. ▪ To explore mechanisms of resistance to relacorilant in combination with nab-paclitaxel.		

Name of Sponsor Corcept Therapeutics Incorporated	Name of Active Ingredient Relacorilant	Study Number CORT125134-556
<u><i>Patient-Reported Outcomes and Quality of Life</i></u> ▪ To describe changes from Baseline of Patient-Reported Outcomes (PRO) and Quality of Life (QoL) scores in the study population and to describe differences between treatment arms. <u><i>Pharmacokinetic Objective</i></u> ▪ To assess the pharmacokinetics (PK) of relacorilant.		
Population Women with recurrent platinum-resistant high-grade epithelial, non-mucinous and non-clear cell ovarian, primary peritoneal, or fallopian-tube cancer following at least one treatment, but less than 4 lines of therapy with the following specific histological subtypes: • High-grade (Grade 3) serous epithelial ovarian, primary peritoneal, or fallopian-tube carcinoma. • High-grade (Grade 3) endometrioid epithelial carcinoma. • Carcinosarcoma with a $\geq 30\%$ epithelial component.		
Number of Patients Planned A total of approximately 360 patients will be randomized in a 1:1 ratio to one of the 2 treatment arms (approximately 180 patients per arm).		
Methodology This is a Phase 3, randomized, 2-arm, open-label study to evaluate efficacy, safety, PK, pharmacodynamics, PRO and QoL of intermittent dosing of relacorilant in combination with nab-paclitaxel (Arm A) versus nab-paclitaxel monotherapy (Arm B). As shown in the Figure 1, patients will be randomized in a 1:1 ratio to one of the 2 treatment arms, Arm A or Arm B. Randomization will be stratified by the following stratification factors: region (North America versus Europe versus the rest of the world) and line of therapy (1 versus more than 1). In Arm A, study treatment will comprise of relacorilant + nab-paclitaxel. Patients will take relacorilant with approximately 8 oz (240 mL) of water and with food. On days when protocol-specified assessments require fasting, patients will bring their relacorilant to the clinic and take it with food and water after the fasting blood draws have been completed. In Arm B, study treatment will comprise of nab-paclitaxel monotherapy. Study treatment will begin on Cycle 1 Day 1. In Arm A (experimental arm; relacorilant + nab-paclitaxel), the patient will receive relacorilant 150 mg administered orally under fed conditions, once daily for 3 consecutive days on the day before (excluding Cycle 1 Day -1), the day of, and the day after nab-paclitaxel infusion, in combination with nab-paclitaxel (80 mg/m² IV) administered on Days 1, 8, and 15 of each 28-day cycle. Relacorilant will not be administered on Cycle 1 Day -1. On days in which both relacorilant and nab-paclitaxel are administered, it is preferable to administer relacorilant before nab-paclitaxel. In Arm B (comparator arm; nab-paclitaxel), the patient will receive nab-paclitaxel (100 mg/m² IV) administered on Days 1, 8, 15 of each 28-day cycle.		

Name of Sponsor Corcept Therapeutics Incorporated	Name of Active Ingredient Relacorilant	Study Number CORT125134-556
--	---	--

Figure 1: CORT125134-556 Study Design



Abbreviations: 30-d FU, 30-day follow-up visit (phone); EOT, end of treatment visit; LT-FU, long-term follow-up visit (phone).

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 OS. Patients are considered to have completed the study if they have completed all phases of the study including the long-term follow-up assessments.

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. Confirmed histologic diagnosis of high-grade (Grade 3) serous, epithelial ovarian, primary peritoneal, or fallopian-tube carcinoma (high-grade endometrioid epithelial or carcinosarcoma with $\geq 30\%$ epithelial component are eligible).
4. Patients must have platinum-resistant disease (defined as progression < 6 months (± 7 days) from completion of a platinum-containing therapy).

Name of Sponsor Corcept Therapeutics Incorporated	Name of Active Ingredient Relacorilant	Study Number CORT125134-556
Note: This is calculated from the date of the last administered dose of platinum therapy to the date of progression. Patients who have platinum-refractory disease during front-line treatment are excluded (primary platinum-refractory disease). 5. Must consent to provide archival tumor-tissue block or slides, if available. Patients may consent to an optional tumor biopsy if archival tumor-tissue is unavailable. 6. Has a life expectancy of ≥ 3 months. 7. At least one lesion that meets the definition of measurable disease by RECIST v1.1 (previously irradiated lesions not allowed as measurable disease unless there is documented evidence of progression in the lesions). 8. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. 9. Able to comply with protocol requirements. 10. Able to swallow and retain oral medication and does not have uncontrolled emesis. 11. Received at least 1 but ≤ 3 lines of prior systemic anticancer therapy (See Appendix G for the guidance in counting the number of prior lines of therapy) with documented progressive disease or intolerance to the most recent therapy. At least 1 prior line of platinum therapy is required and prior treatment with bevacizumab is required. 12. Has adequate organ function meeting the following laboratory test criteria: ▪ Absolute neutrophil count (ANC) ≥ 1500 cells/mm³ without granulocyte-colony-stimulating factor (G-CSF) support within 2 weeks before Screening laboratory sample collection. ▪ Platelet count $\geq 100,000$/mm³ without transfusion within 2 weeks before Screening laboratory sample collection. ▪ Hemoglobin ≥ 9 g/dL without transfusion within 2 weeks before Screening laboratory sample collection. ▪ Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\leq 2.5 \times$ upper limit of normal (ULN), or $\leq 5 \times$ ULN in context of liver metastases. ▪ Total bilirubin $\leq 1.5 \times$ ULN (patients with Gilbert's are eligible if total bilirubin $\leq 3 \times$ ULN). ▪ Albumin ≥ 2.5 g/dL. ▪ Serum creatinine ≤ 1.5 ULN or calculated creatinine clearance ≥ 35 mL/min (Cockcroft and Gault formula if serum creatinine is > 1.5 ULN). 13. Negative pregnancy test for patients of childbearing potential. Patients of childbearing potential must agree to use highly effective contraceptive method(s) (Section 4.7.4); hormonal contraceptives are not allowed. 14. COVID-19 approved vaccines (or vaccines with regulatory health authority's emergency use authorization/conditional marketing authorization) are accepted concomitant medications when recommended by the Investigator. Exceptions may apply should the Investigator and the Medical Monitor determine that the vaccine will interfere with the objectives of the study.		
Exclusion Criteria 1. Has clinically relevant and reversible toxicity from prior systemic anticancer therapies or radiotherapy that has not resolved to $\leq$ Grade 1 prior to randomization.		

Name of Sponsor Corcept Therapeutics Incorporated	Name of Active Ingredient Relacorilant	Study Number CORT125134-556
2. Has had any major surgery within 4 weeks prior to randomization. If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting the study treatment. 3. Has low-grade serous or endometrioid histology other than epithelial, or clear cell, or mucinous, or sarcomatous with less than 30% epithelial histology component, or mixed tumors containing any of these histologies, or borderline ovarian tumor. 4. Has primary platinum-refractory disease, defined as disease that did not respond to, or has progressed during or within ≤ 1 month from completion of a platinum-containing chemotherapy in first-line treatment (measured from the date of the last dose of platinum). 5. Has not received prior bevacizumab treatment. 6. Has been treated with the following prior to randomization: ▪ Chemotherapy, immunotherapy, investigational agent etc. treatments for disease under study within 5 times of half-life of the prior therapy, or 28 days if 5 times the half-life of the prior therapy is longer than 28 days, before the first dose of study drug. ▪ Radiotherapy not completed at least 2 weeks prior to first dose of study drug. ▪ Hormonal anticancer therapies within 7 days of first dose of study drug. ▪ Systemic, inhaled, or prescription strength topical corticosteroids within a period equivalent to 5 times the half-life of the corticosteroid used prior to first dose of study drug. 7. Has received wide-field radiation to more than 25% of marrow-bearing areas. 8. Has toxicities of prior therapies that are reversible and have not resolved to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, $\leq$ Grade 1. 9. Requires treatment with chronic or frequently used oral corticosteroids for medical conditions or illnesses (eg, rheumatoid arthritis, immunosuppression after organ transplantation). 10. Has a history of severe hypersensitivity or severe reaction to any of the study drugs. 11. Is receiving concurrent treatment with mifepristone or other GR modulators. 12. Has peripheral neuropathy from any cause $>$ Grade 1. 13. 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 6 months after the last dose of study treatment. 14. Has clinically significant uncontrolled condition(s) which, in the opinion of the Investigator, may confound the results of the trial or interfere with the patient's safety or participation. Examples of such conditions include but are not limited to the following: ▪ Unstable angina. ▪ Myocardial infarction (MI) within 6 months prior to the first dose of study treatment. ▪ Uncontrolled and/or severe concomitant diseases (uncontrolled hypertension, $\geq$ Grade 3 (per CTCAE v5.0) arrhythmia, heart failure, cirrhosis). ▪ Active infectious disease requiring intravenous (IV) therapy (bacteria, viruses) within 2 weeks prior to the first dose of study treatment. ▪ Gastric-outlet obstruction.		

Name of Sponsor Corcept Therapeutics Incorporated	Name of Active Ingredient Relacorilant	Study Number CORT125134-556
▪ Small bowel obstruction (SBO) $\leq$ 12 weeks of study entry, significant ascites/effusions requiring frequent therapeutic paracentesis or thoracentesis or $\leq$ 30 days of study entry. ▪ Known psychiatric disorder that would interfere with trial compliance. 15. Has current active (chronic/acute) infection with Human immunodeficiency virus, hepatitis C virus or hepatitis B virus. 16. Has any untreated or symptomatic central nervous system (CNS) metastases. 17. Patients with a history of other malignancy within 3 years prior to randomization Note: Does not include tumors with a negligible risk for metastases or death (eg, adequately controlled basal cell carcinoma or squamous-cell carcinoma of the skin, or carcinoma in situ of the cervix or breast). 18. Is taking a prohibited concomitant medication listed in Section 5.4.2 (some of the prohibited concomitant medications listed may require a washout period prior to the first dose of study drug). 19. Concurrent treatment on other investigational treatment studies for ovarian, fallopian-tube, or primary peritoneal cancer. 20. Has received a live vaccine within 30 days prior to the study start date. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (eg, Flu-Mist) are live attenuated vaccines, and are not allowed.		
Investigational Treatment, Dose, and Mode of Administration Arm A Study treatment: Relacorilant and nab-paclitaxel will be administered according to the assigned treatment arm, starting on Cycle 1 Day 1. Relacorilant (Arm A) • Description: 100 mg yellow, softgel capsules and 25 mg pinkish orange or brown, softgel capsules • Dose and mode of administration: Relacorilant dosing: 150 mg, administered orally, once daily for 3 consecutive days on the day before (excluding Cycle 1 Day -1), the day of, and the day after each nab-paclitaxel infusion. On days in which both relacorilant and nab-paclitaxel are administered, it is preferable to administer relacorilant before nab-paclitaxel. Patients should take their relacorilant dose with food and water. Nab-paclitaxel (Arm A) Description: commercially available and supplied in single-dose vials, each containing 100 mg paclitaxel and approximately 900 mg of human albumin as solubilizer. • Dose and mode of administration: Nab-paclitaxel will be administered according to the treatment arm as follows: – In combination with relacorilant: 80 mg/m² IV infusion over 30–40 minutes on Days 1, 8, and 15 of each 28-day cycle.		

Name of Sponsor Corcept Therapeutics Incorporated	Name of Active Ingredient Relacorilant	Study Number CORT125134-556
Arm B Study treatment: Nab-paclitaxel Monotherapy Comparator (Arm B) Description and packaging are described above in Arm A. Single-agent comparator 100 mg/m² IV infusion over 30–40 minutes on Days 1, 8, and 15 of each 28-day cycle.		
Criteria for Evaluation For all efficacy endpoints listed below, assessment for response and disease progression are according to RECIST v1.1 as assessed by BICR, unless otherwise noted. Primary Efficacy Endpoints The dual primary efficacy endpoints include the following: - PFS: Time from randomization until first documented progressive disease (PD) by RECIST v1.1 (as determined by BICR), or death due to any cause, whichever occurs first. - OS: Time from randomization to death by any cause. Secondary Endpoints <u>Efficacy</u> - PFS (Investigators): Time from randomization until PD or death whichever occurred first as assessed by Investigator by RECIST v1.1. - ORR: Proportion of patients with measurable disease at Baseline who attain complete response (CR) or partial response (PR) by RECIST v1.1. - BoR: Recorded from the date of randomization until PD/recurrence (or death). - DoR: Time from the first objective response (CR or PR) to first objectively documented PD or death (whichever occurs first). - CBR at 24 weeks: proportion of patients who attain CR, PR, or stable disease (SD) for 24 weeks as per RECIST v1.1. - CA-125 response will be assessed per GCIG criteria (Rustin 2011) defined as $\geq 50\%$ reduction in CA-125 from a pretreatment 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. Responses will be reported separately and combined for RECIST v1.1 and CA-125/GCIG criteria. <u>Safety</u> The safety of each treatment group will be assessed by evaluating the nature, frequency, and severity of adverse events (AE)s, including: - Incidence of AEs, serious AEs (SAEs), treatment-related AEs, AEs by severity, death due to AEs, all deaths, and changes in laboratory determinations, and vital sign parameters. - Discontinuation of treatment and study withdrawal due to AEs. Exploratory Endpoints <u>Pharmacodynamics/Biomarkers Endpoints</u> Baseline assessment of: - Tumor GR expression. - Expression of GR-regulated genes in whole blood.		

Name of Sponsor Corcept Therapeutics Incorporated	Name of Active Ingredient Relacorilant	Study Number CORT125134-556
- Salivary cortisol. Change from Baseline of: - Expression of GR-regulated genes in whole blood. <i>Patient-Reported Outcomes and Quality of Life</i> Changes from Baseline of PRO and QoL assessments scores using European Organization for Research and Treatment of Cancer (EORTC) ovarian cancer specific quality of life questionnaire (QLQ-OV28), European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) questionnaires, and the EuroQol-5 Dimension 5-level (EQ-5D-5L) questionnaires. A higher score represents a better quality of life. - The primary PRO will be the number of patients achieving at least 15-point absolute improvement at Week 8 or Week 9 in the abdominal/gastrointestinal (GI) scale of the European Organization for Research and Treatment of Cancer (EORTC) ovarian cancer specific QoL questionnaire (QLQ-OV28). A higher score represents a better quality of life. <i>Pharmacokinetic Endpoint</i> - Sparse PK sampling for relacorilant population PK.		
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 endpoints and all secondary efficacy endpoints. - Safety Analysis Population: All randomized patients who received at least 1 dose of study treatment, analyzed according to the treatment received. This population will be used in all analyses of safety endpoints. - PK Analysis Population: Subset of the Safety population with PK data collected and available for analysis. Statistical Analyses To maintain experiment-wise 2-sided type I error at 0.05, a group sequential weighted Holm procedure will be used for the dual primary endpoints PFS and OS. The study will be considered to have a positive outcome if either of the 2 primary endpoints reaches statistical significance. For the primary efficacy endpoint of PFS by BICR, the null hypothesis of no difference in PFS among the 2 study groups will be tested at a 2-sided $\alpha = 0.04$ level of significance using a stratified log-rank test. The alternative hypothesis is that there is a difference between groups. The primary endpoint of OS will be allocated a 2-sided $\alpha = 0.01$ level of significance for the stratified log-rank test. If PFS by BICR is rejected, then, per the Holm procedure, OS will be tested at $\alpha = 0.05$, using a stratified log-rank test. If PFS by BICR is not significant, then OS will be tested at $\alpha = 0.01$. An interim analysis of OS will be performed at the time of the primary analysis of PFS. At the interim analysis, OS data will be summarized to detect a trend in OS and the alpha spending function will be detailed in the Statistical Analysis Plan. The formal final analysis of OS will be conducted when approximately 292 deaths have been observed and will be performed using the ITT population. All other secondary endpoints will be tested at a nominal 2-sided $\alpha = 0.05$ level of significance, with no additional adjustment for multiplicity. P-values from tests of hypothesis associated with secondary and exploratory endpoints will be considered descriptive, and not inferential.		

Name of Sponsor Corcept Therapeutics Incorporated	Name of Active Ingredient Relacorilant	Study Number CORT125134-556
Sample Size For PFS, based on 1:1 randomization allocation ratio, a total of 230 events ensures the study has 86.4% power for a 2-sided log-rank test with a $\alpha = 0.04$ level of significance, to detect a 50% increase in PFS (HR = 0.66). Assuming an exponential distribution of PFS, this corresponds to an increase in median PFS from 3.8 months to 5.8 months. Up to 360 patients will be randomized (1:1) and followed until the required number of events are observed. This sample size allows for a 10% dropout rate in the first 12 months of follow-up. For OS, approximately 292 events will provide the study with 80% power for a 2-sided log-rank test with an overall $\alpha = 0.01$ level of significance to detect a 50% increase in OS (HR = 0.67). Assuming an exponential distribution of OS, this corresponds to an increase in median OS from 13 months to 19.4 months. Independent Data Monitoring Committee To ensure patient safety, an Independent Data Monitoring Committee (IDMC) will evaluate safety data in all dosed patients after approximately 40 patients have been dosed 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 upon by the IDMC members.		

TABLE OF CONTENTS

CLINICAL STUDY PROTOCOL CORT125134-556	1
SPONSOR SIGNATURE PAGE	2
HISTORY OF AMENDMENTS	3
PROTOCOL SYNOPSIS.....	4
TABLE OF CONTENTS.....	13
LIST OF TABLES	20
LIST OF FIGURES	20
LIST OF ABBREVIATIONS AND DEFINITIONS	21
1. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE	24
1.1. Therapeutic Area	24
1.2. Therapeutic Hypothesis	25
1.3. Relacorilant.....	25
1.3.1. Nonclinical and Clinical Experience with Relacorilant.....	25
1.3.2. Nonclinical Summary	25
1.3.3. Clinical Summary	26
1.4. Nab-paclitaxel.....	28
1.4.1. Nab-paclitaxel (Paclitaxel Protein-Bound Particles for Injectable Suspension - Albumin-Bound)	28
1.5. Rationale for Study Design and Dosage.....	29
1.5.1. Design Considerations	29
1.5.2. Rationale for Dose Selection	29
1.5.3. Rationale for Drug Regimen.....	30
1.6. Risk/Benefit Assessment	31
1.7. COVID-19 Related Risks and Risk Mitigation Measures	32
1.7.1. Relacorilant Risk	32
1.7.2. General COVID-19 Related Risk Mitigation Measures	32
1.7.3. COVID-19 Vaccine-Related Risk	33
2. STUDY OBJECTIVES	34
2.1. Primary Objectives	34
2.2. Secondary Objectives	34
2.2.1. Secondary Efficacy Objectives.....	34
2.2.2. Safety Objective.....	34

2.3.	Exploratory Objectives	34
2.3.1.	Pharmacodynamics/Biomarkers	34
2.3.2.	Patient-Reported Outcomes and Quality of Life	35
2.3.3.	Pharmacokinetic Objective	35
3.	STUDY DESIGN	36
3.1.	Overall Design	36
3.2.	Study Endpoints	37
3.2.1.	Primary Efficacy Endpoints	37
3.2.2.	Secondary Endpoints	37
3.2.2.1.	Efficacy	37
3.2.2.2.	Safety	38
3.2.3.	Exploratory Endpoints	38
3.2.3.1.	Pharmacodynamic/Biomarkers Endpoints	38
3.2.3.2.	Patient-Reported Outcomes and Quality of Life	38
3.2.3.3.	Pharmacokinetic Endpoint	39
3.3.	Number of Patients and Duration of Study Participation	39
3.3.1.	Number of Patients	39
3.3.2.	Duration of Patient Participation	39
3.3.3.	Discontinuation of Study Sites	39
3.3.4.	Study Termination by Sponsor	39
3.4.	Enrollment, Screen Failures, Randomization, Study Completion, End of Treatment, and End of Study	40
3.4.1.	Enrollment	40
3.4.2.	Screen Failures	40
3.4.3.	Randomization	40
3.4.4.	Study Completion	40
3.4.5.	End of Treatment	40
3.4.6.	End of Study	40
4.	STUDY POPULATION	41
4.1.	Number of Patients and Study Sites	41
4.2.	Inclusion Criteria	41
4.3.	Exclusion Criteria	42
4.4.	Screen Failures	44

4.4.1.	Rescreening.....	44
4.5.	Patient Discontinuation or Withdrawal	44
4.5.1.	Patient Discontinuation of Study Treatment.....	45
4.5.2.	Patient Withdrawal from Study/Study Completion	46
4.6.	Replacement of Patients	46
4.7.	Restrictions/Requirements/Recommendations During Study	46
4.7.1.	Dietary Restrictions	46
4.7.2.	Alcohol Restrictions	46
4.7.3.	Surgery or Radiation During the Study	46
4.7.4.	Contraception.....	47
4.8.	Gamete Donation	48
5.	STUDY TREATMENTS AND MANAGEMENT	49
5.1.	Description of Study Treatments, Doses, and Administration	49
5.1.1.	Description of Investigational Drug (Relacorilant)	49
5.1.2.	Other Medicinal Agent	50
5.1.3.	Administration of Study Treatment	51
5.2.	Dose-Escalation Process	52
5.3.	Dose Reductions or Delays.....	52
5.3.1.	Dose Reductions or Delays for Nab-paclitaxel	54
5.3.2.	Dose Reductions or Delays for Relacorilant	55
5.3.3.	Management of Signs of Excessive Glucocorticoid Receptor Antagonism	56
5.4.	Concomitant Medications	56
5.4.1.	Permitted Concomitant Medications	57
5.4.2.	Prohibited Concomitant Medications	57
5.5.	Method of Study Treatment Assignment and Randomization	58
5.6.	Blinding/Unblinding.....	58
5.7.	Dosing Diary (Arm A only).....	58
5.8.	Study-Drug Accountability and Treatment Adherence	58
5.9.	Continued Access to Study Treatment	59
5.10.	External Data Review Committee(s)	59
5.10.1.	Independent Data Monitoring Committee to Monitor Patient Safety	59
6.	DESCRIPTION OF STUDY ASSESSMENTS AND PROCEDURES	60
6.1.	Informed Consent and Screening.....	60

6.2.	Demographics and Baseline Disease Characteristics	60
6.3.	Medical and Oncologic History	60
6.4.	Safety Assessments.....	61
6.4.1.	Physical Examination and Vital Signs.....	61
6.4.2.	12-Lead Electrocardiogram	61
6.4.3.	ECOG Performance Status	62
6.4.4.	Adverse Events	62
6.4.5.	Clinical Laboratory Assessments	62
6.4.5.1.	Laboratory Parameters.....	62
6.4.5.2.	Sample Collection, Preparation, and Shipping	63
6.4.5.3.	Blood-Volume Summary	63
6.5.	Efficacy Assessments	63
6.5.1.	Measures of Anticancer Activity	64
6.6.	Pharmacokinetics Assessments	64
6.7.	Exploratory Pharmacodynamics/Biomarker Assessments	64
6.7.1.	Blood Collection for Glucocorticoid-Related Pathways and Exploratory Biomarkers.....	65
6.7.2.	Blood Collection for Longitudinal Resistance Evaluation	65
6.7.3.	Tumor-Tissue Collection for Immunohistochemistry for Glucocorticoid Receptor	65
6.7.4.	<i>BRCA1/2</i> Mutation and Homologous Recombination Deficiency Assessment	66
6.7.5.	Saliva Collection for Cortisol Diurnal Rhythm	66
6.8.	Other Assessments.....	66
6.8.1.	Patient-Reported Outcomes and QoL	66
6.8.2.	Clinician-Reported Outcomes	67
6.8.3.	Appropriateness of the Measures.....	67
7.	STUDY ASSESSMENTS AND PROCEDURES BY STUDY VISIT	68
7.1.	Screening (Day –28 to Day –1)	68
7.2.	Baseline (Cycle 1 Day 1).....	69
7.3.	Cycle 1 Day 8	71
7.4.	Cycle 1 Day 15	71
7.5.	Cycle 1 Day 17	71
7.6.	Cycle 2 (and Subsequent Cycles) Day 1.....	72
7.7.	Cycle 2 (and Subsequent Cycles) Day 8.....	73

7.8.	Cycle 2 (and Subsequent Cycles) Day 15.....	73
7.9.	Visit Following Observation of CR or PR.....	73
7.10.	End of Treatment Visit	74
7.11.	30-Day Post-Treatment Follow-Up Visit (Phone).....	74
7.12.	Long-Term Follow-Up Visit (Phone).....	74
7.13.	Unscheduled Visits	75
8.	SAFETY EVENT DOCUMENTATION AND REPORTING	76
8.1.	Investigator's Responsibilities.....	76
8.2.	Monitoring Safety Data During the Study.....	76
8.3.	Definition of an Adverse Event	76
8.4.	Definition of a Serious Adverse Event	76
8.5.	Expectedness.....	77
8.6.	Reporting Suspected Unexpected Serious Adverse Reaction	77
8.7.	Clinical Significance.....	77
8.8.	Clinical Laboratory Adverse Events.....	78
8.9.	Documentation of Adverse Events	78
8.10.	Adverse Event Classification.....	79
8.10.1.	Intensity Grades of Adverse Events	79
8.10.2.	Assessment of Causality: Relationship of Adverse Event to Study Drug or Study Procedure	79
8.11.	Procedures for Reporting a Serious Adverse Event	80
8.12.	Recording Disease Progression and Deaths	80
8.13.	Adverse Event Follow-Up and Recording.....	81
8.14.	Pregnancy	81
8.14.1.	Maternal Exposure.....	81
8.14.2.	Paternal Exposure	82
8.15.	Treatment of Overdose	82
8.16.	Special Situations, Definitions and Reporting.....	82
8.17.	Emergency Sponsor Contact.....	82
8.18.	SARS-CoV-2 Tests (If Required).....	83
9.	STATISTICAL METHODS.....	84
9.1.	Analysis Populations	84
9.2.	General Statistical Considerations	84

9.3.	Hypothesis Testing	84
9.4.	Sample-Size Calculation.....	85
9.5.	Analysis Plan	85
9.5.1.	Patient Disposition.....	85
9.5.2.	Demographic and Baseline Characteristics Data.....	85
9.5.3.	Prior and Concomitant Medications	86
9.5.4.	Analysis of Dual Primary Efficacy Endpoints.....	86
9.5.5.	Approach to Missing Data Analysis	87
9.5.6.	Secondary Efficacy Endpoint Analysis	87
9.5.7.	Exploratory Endpoint Analysis.....	88
9.5.8.	Safety Analyses	88
9.5.9.	Pharmacokinetics Analysis.....	89
9.5.10.	Pharmacodynamic Analysis.....	89
9.5.11.	Biomarker/Pharmacogenetic Analysis.....	89
9.5.12.	Interim Analysis.....	89
9.5.13.	Patient-Reported Outcomes/Quality of Life	89
10.	ETHICAL AND LEGAL CONSIDERATIONS	90
10.1.	Compliance with IRB/IEC Regulations.....	90
10.2.	Ethical Conduct of the Study	90
10.3.	Protection of Patients	90
10.3.1.	Compliance with Informed Consent Regulations.....	90
10.3.2.	Patient Confidentiality	91
10.3.3.	Patient Privacy	91
10.3.4.	Data Protection	91
11.	ADMINISTRATIVE CONSIDERATIONS	94
11.1.	Quality Management	94
11.2.	Study Monitoring.....	94
11.3.	Documentation.....	95
11.3.1.	Source Documentation.....	95
11.3.2.	Case Report Forms	95
11.3.3.	Retention of Study Essential Documents	95
11.3.4.	Sample Collection, Preparation, and Shipping	96
11.4.	Long-Term Retention of Biological Samples.....	96

11.5.	Clinical Supplies	97
11.5.1.	Inventory, Reconciliation, Return, and Disposition of Clinical Supplies.....	97
11.5.2.	Clinical Supply Inventory	97
11.5.3.	Return or Destruction of Study Drug and/or Supplies.....	97
11.5.4.	Study Drug Destroyed by the Site	97
11.5.5.	Study Drug Returned to Sponsor for Destruction.....	97
11.5.6.	Drug Accountability	98
11.6.	Post-Trial Care	98
11.7.	Protocol Noncompliance	98
11.8.	Financial Disclosure	98
11.9.	Publication and Disclosure Policy	98
11.10.	Electronic Systems.....	99
12.	REFERENCES	100
13.	APPENDICES	104
APPENDIX A.	SCHEDULE(S) OF ACTIVITIES	105
APPENDIX B.	GUIDANCE FOR IDENTIFYING HIGH-GRADE SEROUS CARCINOMA	113
APPENDIX C.	RESPONSE CRITERIA: RECIST VERSION 1.1 FOR DISEASE ASSESSMENT	114
APPENDIX D.	GENERAL CHEMOTHERAPY GUIDELINES.....	118
APPENDIX E.	EXAMPLES OF MEDICATIONS THAT ARE PROHIBITED	119
APPENDIX F.	GYNECOLOGICAL CANCER INTERGROUP DEFINITIONS FOR RESPONSE AND PROGRESSION IN OVARIAN CANCER CLINICAL TRIALS	120
APPENDIX G.	GUIDANCE FOR COUNTING PRIOR LINES OF THERAPY	124
APPENDIX H.	COUNTRY-SPECIFIC REQUIREMENTS	125
APPENDIX I.	SUMMARY OF CHANGES.....	127

LIST OF TABLES

Table 1:	Abbreviations and Definitions	21
Table 2:	Investigational Drug: Description, Packaging, and Storage	50
Table 3:	Description, Packaging, and Storage (Nab-paclitaxel)	51
Table 4:	Guidance on Dose Reductions or Delays Due to Treatment-Related Adverse Events	53
Table 5:	Nab-paclitaxel Dose Reductions	55
Table 6:	Relacorilant Dose Level Summary	56
Table 7:	ECOG Performance Status	62
Table 8:	Clinical Laboratory Variables Evaluated During the Study	63
Table 9:	Grades for Adverse Events Based on the Common Terminology Criteria for Adverse Events	79
Table 10:	Causal Attribution Guidance for Adverse Events	80
Table 11:	Definitions of Analysis Populations	84
Table 12:	Schedule of Activities for 28-day Treatment Cycle Patients in Arm A and Arm B	105
Table 13:	Sparse Pharmacokinetic Schedule of Assessments (ARM A Only)	110
Table 14:	Pharmacodynamic Schedule of Assessments	110
Table 15:	Best Overall Response in Patients with Measurable Disease and Who are also Evaluable by CA-125 (GCIG Criteria)	121
Table 16:	Example of Reporting Response According to RECIST v1.1, CA-125 (GCIG Criteria), and Combined-Response	122
Table 17:	Definition of Progression After First-Line Therapy in Ovarian Cancer as Proposed by the Gynecological Cancer Intergroup (GCIG)	123
Table 18:	Protocol Amendment 4 and Country-specific requirement(s)	125
Table 19:	Summary of Changes in Protocol CORT125134-556 Amendment 4:	128

LIST OF FIGURES

Figure 1:	CORT125134-556 Study Design	6
Figure 2:	CORT125134-556 Study Design	37

LIST OF ABBREVIATIONS AND DEFINITIONS

Table 1: Abbreviations and Definitions

Abbreviation	Definition
30-d FU	30-day follow-up
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin clotting time
AST	aspartate aminotransferase
BICR	blinded independent central review
BP	blood pressure
CA-125	cancer antigen 125
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CR	complete response
CT	computed tomography
CYP	cytochrome P450
DDI	Drug-drug interactions
DoR	duration of response
DUSP1	dual specificity phosphatase 1 gene
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Treatment
FDA	(United States) Food and Drug Administration
FFPE	formalin and embedded in paraffin
FU	follow-up
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
GI	gastrointestinal
G-CSF	granulocyte-colony–stimulating factor

Abbreviation	Definition
GR	glucocorticoid receptor
HIV	human immunodeficiency virus
HR	hazard ratio
HRD	homologous recombination deficiency
HRU	healthcare resource utilization
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	immunohistochemistry
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous, intravenously
IXRS	interactive voice and web-response system
Ki	inhibition constant
LT-FU	long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified intent-to-treat
<i>MKPI</i>	mitogen-activated protein kinase phosphatase gene
MRI	magnetic-resonance imaging
NCI-CTCAE	National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events
NE	not evaluable
ORR	objective response rate
OS	overall survival
PARPi	poly (ADP-ribose) polymerase (PARP) inhibitors
PCR	polymerase chain reaction
PD	pharmacodynamic

Abbreviation	Definition
PD	progressive disease
PDAC	pancreatic ductal adenocarcinoma
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	prothrombin time
QoL	quality of life
QC	quality control
RECIST	Response Evaluation Criteria in Solid Tumors
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBO	small bowel obstruction
SD	stable disease (clinical)
SD	standard deviation (statistical)
SGK1	serum glucocorticoid regulated kinase 1 gene
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOD	sum of the diameters
SOP	Standard operating procedures
SSRs	Special situation reports
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
US	United States
WBC	white blood cell
WT1	Wilms' Tumor 1

1. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

For detailed information on relacorilant and the nonclinical and clinical studies conducted to date, refer to the current Relacorilant Investigator's Brochure (IB) Solid Tumors, which supersedes information provided here in the event of a discrepancy.

1.1. Therapeutic Area

Ovarian cancer is the second most common gynecologic malignancy and the most common cause of gynecologic cancer death in the United States ([American Cancer Society 2021](#)). Ovarian cancer, including fallopian-tube, and primary peritoneal cancers, accounts for 3% of cancers in women and is responsible for 6.7 cancer deaths per 100,000 women annually ([Surveillance, Epidemiology, and End Results \[SEER\] 2018](#)). Most patients are asymptomatic until advanced stages of the disease, and for women with distant invasive epithelial ovarian cancer, the 5-year survival rate is approximately 30% ([SEER 2018](#)). The lifetime risk of developing ovarian cancer is 1.2% ([SEER 2018](#)). An estimated 235,281 women were living with ovarian cancer in the United States in 2018 ([SEER 2018](#)).

Despite initial therapy, the majority of women will relapse and require retreatment. Recurrence rates are high: approximately 20% in patients with early-stage disease and over 70% in patients with advanced disease ([Ushijima 2010](#)). Patients who develop a recurrence within 6 months of platinum based therapy (< 6 months) are deemed platinum-resistant, while patients who progress during platinum-based therapy are deemed platinum-refractory ([Raja 2012](#), [Ganghadaran 2016](#)). The most widely used clinical surrogate for predicting response to chemotherapy, prognosis, and stratification in clinical trials has been the platinum-free interval defined as the time point from end of primary platinum-based chemotherapy to disease recurrence or progression ([Friedlander 2011](#)). However, there are several limits depending on how patients are followed, especially, how recurrence is detected and defined. The Gynecologic Cancer InterGroup (GCIg) agreed that each trial should specify how progression was determined (eg, cancer antigen 125 [CA-125] alone, radiologic or symptomatic recurrence) for patients enrolling in clinical trials ([Friedlander 2011](#)). The electronic case report forms (eCRFs) should capture if patients had measurable disease, volume of disease (including the largest tumor diameter), number of sites, and treatment-free interval ([Friedlander 2011](#)).

The treatment options for advanced ovarian cancer include surgery, chemotherapy, molecularly targeted agents (antiangiogenic agents and poly (ADP-ribose) polymerase [PARP] inhibitors), and radiation. For recurrent platinum-sensitive ovarian cancer, one or a combination of these modalities may be of benefit for selected patients. With regards to systemic therapy, histology, BRCA status, the platinum-free interval, and any previous treatment with bevacizumab may influence the selection and the outcome of the next treatment regimen.

For patients receiving initial therapy for recurrent platinum-resistant ovarian cancer, single-agent chemotherapy with a non-platinum drug is considered standard therapy. The most common therapies used in this setting are paclitaxel, liposomal doxorubicin, topotecan, and gemcitabine. Bevacizumab as a single-agent or combined with single-agent chemotherapy is also an option for select patients ([Luvero 2014](#), [Pujade-Lauraine 2019](#)). Chemotherapy plus bevacizumab has shown the best results in patients who received less than 2 prior regimens, did not have refractory disease, and had no history of a bowel obstruction within 6 months of treatment

([Pujade-Lauraine 2014](#)). Sequential use of chemotherapy not previously administered and the incorporation of molecularly targeted agents has only modest response ([Luvero 2014](#)).

Patients ultimately succumb to their disease due to the emergence of chemotherapy resistance. Given the heterogeneity and adaptability of the tumors in patients with platinum-resistant or refractory recurrent disease, there is a clear unmet medical need for FDA-approved treatments to overcoming resistance to therapy in this population.

1.2. Therapeutic Hypothesis

Endogenous cortisol activates the glucocorticoid receptor (GR) and induces the expression of genes that inhibit chemotherapy-induced tumor apoptosis. These genes, including serum glucocorticoid regulated kinase 1 (*SGK1*) gene and mitogen-activated protein kinase phosphatase/dual specificity phosphatase 1 (*DUSP1/MKPI*) gene, directly interfere with the apoptotic pathways that paclitaxel and other cytotoxic agents utilize in tumor cells. GR antagonism via relacorilant may reverse these effects of endogenous cortisol and restore the ability of cytotoxic agents to induce tumor cell apoptosis.

1.3. Relacorilant

Relacorilant is an orally active, high-affinity, potent modulator of GR that is selective for GR over other steroid receptors. GR binding of relacorilant was observed with an inhibition constant (K_i) of 0.15 nM, while no measurable binding was detected with the progesterone, estrogen, or androgen receptors ([Hunt 2017](#)).

1.3.1. Nonclinical and Clinical Experience with Relacorilant

Detailed information about all studies with relacorilant is provided in the current Relacorilant IB Solid Tumors.

1.3.2. Nonclinical Summary

High rates of GR expression have been shown in several solid tumor types including ovarian cancer, triple-negative breast cancer, and pancreatic cancer ([Block 2017](#)). Cortisol is a ubiquitous and essential hormone that activates the GR. Elevated cortisol activity has been implicated in the pathophysiology of multiple cancer types, but even normal physiological levels achieve GR agonism ([Wang 2015](#)). Normal serum-cortisol concentrations range from 276–552 nM. GR agonism could contribute to tumor cell biology even in patients with normal cortisol levels.

Existing cytotoxic therapies, such as paclitaxel, induce apoptosis by interfering with key components of tumor cell growth ([Yamamoto 1999](#)). GR activation suppresses tumor cell apoptosis in the presence of cytotoxic therapies, via induction of genes such as *SGK1* and *DUSP1* ([Skor 2013](#)). Anti-apoptotic effects of GR agonism were demonstrated in pancreatic, bone, brain, breast, cervix, melanoma, and neuroblastoma cancer cells when combined with a fixed concentration of paclitaxel, cisplatin, or 5-FU ([Zhang 2006](#), [Pang 2006](#)). Building on this, pro-apoptotic effects of GR antagonism were demonstrated with cisplatin and gemcitabine in pancreatic cancer cells ([Zhang 2006](#)), paclitaxel in breast cancer cells ([Skor 2013](#), [West 2018](#)), carboplatin in ovarian cancer cells ([Stringer-Reasor 2015](#)), and docetaxel in prostate cancer cells ([Kroon 2016](#)). This mechanism has been demonstrated empirically with relacorilant in paclitaxel-treated ovarian cancer cells as well ([Greenstein and Hunt 2021](#)). In vitro and in

xenograft models, cortisol reduces and relacorilant restores paclitaxel-induced tumor cell apoptosis ([Greenstein and Hunt 2021](#)). Additional information is provided in the current Relacorilant Solid Tumors IB.

1.3.3. Clinical Summary

Updated information for all clinical studies is provided in the current Relacorilant Solid Tumors IB.

Study CORT125134-550

Study CORT125134-550 (NCT02762981) was a Phase 1/2 study to determine the preliminary efficacy and safety of relacorilant (in both intermittent and continuous schedules) in combination with nab-paclitaxel intravenously (IV) in patients with solid tumors ([Munster 2019](#) and Corcept data on file). Of the 73 patients who received at least one dose of relacorilant, 14 (19.2%) had ovarian cancer (which included fallopian-tube or primary peritoneal cancer), 37 (50.7%) had pancreatic adenocarcinoma, and the remaining 22 (30.1%) patients had other solid tumors. The response-evaluable population included 57 patients with at least one post-baseline tumor assessment. Most patients in this study had no standard of care treatment options. Thirteen of the 14 patients with ovarian cancer were response-evaluable. Across all cohorts, one patient (1.8%) experienced a best overall response (BoR) of complete response (CR), 8 patients experienced a partial response (PR, 14.0%), and 28 patients had stable disease (SD, 49.1%). For patients with ovarian cancers, there were 1 CR, 2 PRs and 7 SDs. Durable disease control ≥ 16 weeks was observed in 38.5% of the patients with ovarian cancer (the response-evaluable population); this compares to historical response rates of $< 15\%$ in third line-ovarian cancer ([Macarulla 2017](#), [Bruchim 2013](#)).

In this heavily pretreated study population, where 73.7% had prior taxane therapy, 33.3% (19/57) of the response-evaluable patients achieved durable disease control greater than 16 weeks and 28.6% (12/42) of the patients experienced longer duration of benefit than on prior taxane – up to 6.4x) (Corcept data on file). The clinical activity demonstrated by relacorilant in combination with nab-paclitaxel may be the result of modulation of GR-regulated genes that promote paclitaxel-induced apoptosis.

Study CORT125134-553

Study CORT125134-553 (NCT04329949) was a Phase 3, open-label, single-arm, multicenter study to assess the safety and effectiveness of relacorilant in combination with nab-paclitaxel IV in patients with metastatic pancreatic ductal adenocarcinoma (PDAC). A total of 43 patients with metastatic PDAC were treated with relacorilant (starting dose, 100 mg, titrated in increments of 25 mg per cycle to a potential maximum dose of 150 mg) in combination with 80 mg/m² nab-paclitaxel.

Study CORT125134-551

Study CORT125134-551 (NCT04373265) is a Phase 1b, open-label, single-arm study designed to evaluate the safety, efficacy, PD, and PK of relacorilant in combination with pembrolizumab IV in patients with advanced adrenocorticoid cancer with glucocorticoid excess. The study is currently enrolling.

Study CORT125134-552

Study CORT125134-552 (NCT03776812) is a Phase 2, open-label, 3-arm, multicenter study designed to evaluate the efficacy, safety, pharmacokinetics, pharmacodynamics, PRO, and QoL of the combination of relacorilant and nab-paclitaxel in 2 dose regimens in patients with recurrent platinum-resistant ovarian, fallopian-tube, or primary peritoneal cancer ([Colombo 2023](#)). This study is ongoing and has completed enrollment and end of study analysis. Clinical sites are in the United States, Canada, Belgium, Italy, and Spain.

In this study, women (n = 178) with platinum-resistant, high-grade serous, or endometrioid epithelial ovarian, primary peritoneal, or fallopian-tube cancer or ovarian carcinosarcoma with measurable or non-measurable disease, who were heavily pretreated with up to 4 prior chemotherapeutic regimens, were randomized in a 1:1:1 ratio to one of 3 treatment arms. In treatment Arm A (continuous relacorilant), patients received relacorilant 100 mg once daily (with titration up to 150 mg per Investigator decision) for 28 days in combination with nab-paclitaxel 80 mg/m² IV on Days 1, 8, and 15 of each 28-day cycle. In Arm B (intermittent relacorilant), patients received relacorilant 150 mg once daily, the day before (excluding Cycle 1 Day -1), the day of, and the day after nab-paclitaxel, in combination with nab-paclitaxel 80 mg/m² IV on Days 1, 8, and 15 of each 28-day cycle. In comparator nab-paclitaxel treatment Arm C, patients received nab-paclitaxel only, 100 mg/m² IV on Days 1, 8, and 15 of each 28-day cycle.

The primary endpoint of Study CORT125134-552 was progression-free survival (PFS) as determined by the Investigator per RECIST version 1.1. ([Eisenhauer 2009](#)). Key secondary endpoints included ORR, DoR, and OS. The primary analysis was conducted as of 22 March 2021 (data cutoff date). In this heavily pretreated study population (median number of prior therapies 3, range 1–5), at median follow-up of 11.07 months across all 3 arms, the intermittent regimen significantly improved median PFS compared with nab-paclitaxel alone (median PFS: 5.55 months versus 3.76 months; hazard ratio [HR], 0.66; 95% confidence interval [CI]: 0.44–0.98, log-rank test p = 0.038). In the continuous relacorilant dosing arm, the median PFS was 5.29 months (HR, 0.83; 95% CI: 0.56–1.23).

Although ORR was similar across all arms (35% in the relacorilant treatment arm, 36% in intermittent and nab-paclitaxel alone treatment arms), DoR was significantly improved in the intermittent regimen versus nab-paclitaxel alone (DoR: 5.55 months versus 3.65 months; HR, 0.36; 95% CI: 0.16–0.77; p = 0.006). DoR in the continuous treatment arm was 3.79 months. Safety and tolerability of relacorilant plus nab-paclitaxel were comparable to nab-paclitaxel monotherapy. The most common Grade ≥ 3 AEs from all 3 treatment arms were neutropenia, anemia, peripheral neuropathy, and fatigue or asthenia. All relacorilant-treated patients received prophylactic granulocyte-colony-stimulating factor (G-CSF) per protocol and 46.7% of patients in the comparator arm (nab-paclitaxel only) received G-CSF per the Investigator's standard practice. No additional toxicity was observed with the addition of intermittent relacorilant compared to nab-paclitaxel alone.

OS was evaluated on 7 March 2022, in a pre-planned analysis after 128 OS events had occurred across the 3 treatment arms: 37 of 60 (61.7%, intermittent), 42 of 58 (72.4%, continuous), and 49 of 60 (81.7%, nab-paclitaxel monotherapy). The median follow-up was 22.5 months. A trend toward improved OS was observed in the intermittent arm (HR, 0.67; 95% CI, 0.43-1.03; p = 0.066). An important post-hoc subgroup analysis for the patient population with 1 to 3 prior

anticancer therapies who had received bevacizumab prior to enrolling in the study (excluding those with primary platinum-refractory disease) is described herein, as this will be the population evaluated in the Phase 3 study. The intermittent relacorilant regimen had an improved OS compared with nab-paclitaxel monotherapy, with a median OS of 17.90 months (95% CI: 12.78, NR) versus 12.6 months (95% CI: 6.37, 15.28), respectively (HR 0.38, 95% CI: 0.17, 0.82, $p = 0.0106$).

After the study database was locked on 25 August 2023, the end of study OS analysis was conducted, with a median follow-up of 38 months. With an additional ~16 months of follow-up, the findings from the earlier ad-hoc OS analysis were confirmed: in the subgroup of patients being evaluated in the Phase 3 study, median OS in the intermittent relacorilant dosing arm versus the control nab-paclitaxel monotherapy arm was 17.91 months (95% CI: 11.89, 23.13) versus 12.55 months (95% CI: 6.37, 15.28), respectively (HR: 0.49, 95% CI: 0.25, 0.92).

Retrospective analysis of PFS, ORR and DoR from the primary analysis data cutoff date (22 March 2021) in this same subgroup of patients demonstrated improved PFS (HR 0.40, 95% CI: 0.21, 0.77, $p = 0.0052$), higher ORR (45.5% vs 36% in the intermittent and control arms, respectively), and improved DoR (HR 0.29, 95% CI: 0.09, 0.99, $p = 0.0162$).

1.4. Nab-paclitaxel

In this study nab-paclitaxel will be used for both the experimental arm (A) and the comparator arm (B). The dose of nab-paclitaxel is different between arms with 80 mg/m² IV administered in Arm A and 100 mg/m² IV administered in Arm B. The elimination of nab-paclitaxel is mediated in part by the drug metabolizing enzyme CYP3A4 for which relacorilant is a strong inhibitor, resulting in higher nab-paclitaxel exposures when administered in combination with relacorilant relative to nab-paclitaxel monotherapy, indicating that a lower dose of nab-paclitaxel can be used in combination with relacorilant as compared with nab-paclitaxel monotherapy. Accordingly, the dose of nab-paclitaxel 80 mg/m² IV in combination with relacorilant approximates the range of exposures achieved following 100–125 mg/m² IV nab-paclitaxel monotherapy.

1.4.1. Nab-paclitaxel (Paclitaxel Protein-Bound Particles for Injectable Suspension - Albumin-Bound)

Nab-paclitaxel is paclitaxel formulated as albumin-bound nanoparticles. Paclitaxel is a microtubule inhibitor that stabilizes microtubules by preventing depolymerization, which results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. As a result, cells become blocked in the G2/M phase of the cell cycle, which disrupts the mitotic spindles and causes cell death due to prolonged mitotic blockage ([Horwitz 1994](#)).

Nab-paclitaxel is indicated for the treatment of the following ([Abraxane SmPC 2021](#), [Abraxane USPI 2020](#), [Abraxane Product Monograph 2018](#)): metastatic breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, with prior therapy including an anthracycline unless clinically contraindicated; locally advanced or metastatic non-small cell lung cancer as first-line treatment in combination with carboplatin in patients who are not candidates for curative surgery or radiation therapy; and metastatic adenocarcinoma of the pancreas as first-line treatment in combination with gemcitabine.

In a Phase 2 study of patients with platinum-resistant ovarian cancer, 47 patients received 100 mg/m² nab-paclitaxel on Days 1, 8, and 15 of a 28-day cycle. The most commonly reported Grade 3 AEs occurring in these > 2 patients were neutropenia, 6 (12%), gastrointestinal, 2 (4.3%); metabolic (4.3%); and pain 2 (4.3%). Grade 2 fatigue was reported in 15 (32%) patients, Grade 2 neurotoxicity was reported in 5 (11%) patients, and 1 (2%) patient had Grade 3 neurotoxicity. There were no AEs > Grade 3 reported. Five patients had a dose reduced to 80 mg/m², and one of these was further reduced to 60 mg/m² ([Coleman 2011](#)).

The most common adverse reactions occurring ≥ 20% of patients with single-agent use of nab-paclitaxel in metastatic breast cancer (at a dose of 260 mg/m² IV every 3 weeks) are alopecia, neutropenia, sensory neuropathy, abnormal electrocardiogram (ECG), fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea ([Abraxane USPI 2020](#)).

Neutropenia is a dose-dependent and dose-limiting toxicity of nab-paclitaxel. In clinical studies of nab-paclitaxel in metastatic breast cancer, Grade 3–4 neutropenia occurred in 34% of patients. The frequency and severity of sensory neuropathy also increased with cumulative dose. Sensory neuropathy led to nab-paclitaxel discontinuation in 3% of patients. Twenty-four (10%) patients treated with nab-paclitaxel developed Grade 3 peripheral neuropathy, of whom 14 patients had documented improvement after a median of 22 days ([Abraxane USPI 2020](#)).

Warnings and precautions include bone marrow suppression (primarily neutropenia), sensory neuropathy, sepsis, pneumonitis, hypersensitivity, use in patients with hepatic impairment, and use in pregnancy ([Abraxane SmPC 2021](#), [Abraxane USPI 2020](#), [Abraxane Product Monograph 2018](#)), and in the European Union (EU) and Canada use in patients ≥ 75 years of age. Additional warnings and precautions in the EU include cardiotoxicity, gastrointestinal symptoms, and use in patients with central nervous system (CNS) metastases. The prescribing information indicates that nab-paclitaxel should only be administered when baseline neutrophil counts are > 1,500 cells/mm³ and patients who experience a severe hypersensitivity reaction to nab-paclitaxel should not be rechallenged with the drug. The metabolism of paclitaxel is catalyzed by cytochrome P450 CYP2C8 and CYP3A4. Caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to inhibit or induce CYP2C8 or CYP3A4.

1.5. Rationale for Study Design and Dosage

The current study aims to evaluate the combination of relacorilant and nab-paclitaxel compared with nab-paclitaxel monotherapy.

1.5.1. Design Considerations

This Phase 3 study is designed to further evaluate the combination of intermittent relacorilant and nab-paclitaxel in patients with recurrent platinum-resistant ovarian cancer versus nab-paclitaxel monotherapy.

1.5.2. Rationale for Dose Selection

Primary analysis results from the ongoing Phase 2 study (CORT125134-552) support the use of intermittent relacorilant 150 mg and nab-paclitaxel at 80 mg/m².

Relacorilant

The Phase 1/2 Study CORT125134-550 in patients with solid tumors evaluated relacorilant 100–150 mg once daily in continuous regimens and 150–200 mg in intermittent regimens (day before, day of and day after nab-paclitaxel infusion administered weekly $\times$ 3 of 28-day cycles). Subsequently, based on safety and efficacy, relacorilant regimens of 100 mg, once daily (continuous dosing) and 150 mg (intermittent dosing) were selected for further clinical evaluation in combination with nab-paclitaxel in the Phase 2 Study CORT125134-552 in patients with platinum-resistant ovarian cancer. Overall, across both Studies CORT125134-550 and CORT125134-552, a wide range of overlapping relacorilant exposures were observed in responders and non-responders or in the presence or absence of a given safety endpoint criterion and there was no detectable difference in the response profile of patients with the highest or lowest relacorilant exposures. Based on the Phase 2 results, the recommended dose of relacorilant in combination with nab-paclitaxel for the Phase 3 Study CORT125134-556 in patients with platinum-resistant ovarian cancer is 150 mg, once daily on the day before, the day of, and the day after nab-paclitaxel infusion.

Nab-paclitaxel

Nab-paclitaxel dosing for the control arm uses the standard dosing for weekly administration in other solid tumors (eg, breast, pancreatic) at 100 mg/m² for 3 weeks of 28-day cycles. However, in the experimental arm where nab-paclitaxel is combined with relacorilant, the dose is decreased as the elimination of nab-paclitaxel is mediated in part by the drug metabolizing enzyme CYP3A for which relacorilant is a strong inhibitor. Accordingly, a drug-drug interaction (DDI) occurs between relacorilant and nab-paclitaxel, resulting in higher nab-paclitaxel exposures when administered in combination with relacorilant relative to nab-paclitaxel alone. This observed DDI allows for a lower dose of nab-paclitaxel to be used in combination with relacorilant (Arm A: nab-paclitaxel 80 mg/m² with relacorilant 150 mg, once daily on the day before, the day of, and the day after nab-paclitaxel) as compared with nab-paclitaxel monotherapy (Arm B: nab-paclitaxel 100 mg/m² IV alone).

1.5.3. Rationale for Drug Regimen

The current study will evaluate the combination of relacorilant with nab-paclitaxel, to assess the added potential benefits associated with selective GR antagonism in ovarian cancer.

There are several lines of evidence suggesting that activation of GR in cancer cells leads to an activation of tumor survival signals and consequent reduction in the effect of chemotherapy. This is important because increased glucocorticoid production and up-regulation of its receptor (GR) during acute or chronic stressors, including the diagnosis of cancer and related medical treatment, has the theoretical ability to promote tumor growth ([Conzen 2008](#)). The concept of GR-mediated tumor survival in solid tumors, including ovarian cancer, is supported by the following:

- High levels of GR expression are associated with poor prognosis in multiple tumor types including, but not limited to, ovarian cancer ([Pan 2011](#), [Tangen 2017](#), [Veneris 2017](#)).
- Activation of GR induces the expression of a number of genes including those involved in anti-apoptosis such as the *SGK1* gene and *MKPI/DUSP1* gene ([Zhang 2006](#), [Pan 2011](#), [Skor 2013](#)).

- Apoptosis is inhibited when GR is activated in vitro in ovarian cancer cell lines ([Stringer-Reasor 2015](#)) or in vivo in xenografts treated with cytotoxic drugs such as paclitaxel ([Hou 2013](#)).
- GR antagonism directly promotes apoptosis of cancer cell lines in vitro and in xenograft models ([Greenstein and Hunt 2021](#)).
- GR antagonism may also relieve immune suppression mediated by endogenous cortisol ([Greenstein 2021](#), [Deng 2021](#)).
- Results from the Phase 1/2 Study CORT125134-550 indicate GR antagonism with relacorilant may overcome resistance to nab-paclitaxel in patients with ovarian cancer (Corcept Data on File, current Relacorilant Solid Tumors IB).

In in vitro and in vivo xenograft models under normal physiological glucocorticoid levels, cortisol reduces and relacorilant restores paclitaxel-induced cell apoptosis ([Greenstein and Hunt 2021](#)).

For clinical treatment applications, nab-paclitaxel is better suited for combination with relacorilant than other taxanes because it does not require pretreatment with steroids ([Skor 2013](#)).

Moreover, positive results from a Phase 2 study of nab-paclitaxel in the treatment of platinum-refractory or platinum-resistant ovarian, fallopian-tube, or primary peritoneal cancer, defined by progressive disease (PD) following primary chemotherapy or recurrence within 6 months of treatment completion, were reported ([Coleman 2011](#)). In this study, nab-paclitaxel had noteworthy single-agent activity and was tolerable in a cohort of patients with platinum and taxane-resistant ovarian cancer ([Coleman 2011](#)).

1.6. Risk/Benefit Assessment

In the Phase 2 Study CORT125134-552 ([Section 1.3.3](#)), the intermittent relacorilant and nab-paclitaxel regimen significantly improved PFS and DoR compared to nab-paclitaxel alone. Patients receiving intermittent relacorilant combined with nab-paclitaxel experienced significantly improved PFS compared to nab-paclitaxel alone, with a HR of 0.66 (95% CI: 0.44; 0.98). Their median PFS was 5.6 months (95% CI: 3.68; 7.20), 1.8 months longer than the nab-paclitaxel monotherapy group, where it was 3.8 months. These results were achieved despite a substantial overrepresentation of primary platinum-refractory patients in the intermittent arm. There was a similar ORR across the three study arms (35–36%). However, the median DoR was 5.55 months in the intermittent relacorilant arm compared to 3.65 months in the nab-paclitaxel monotherapy arm. In comparing DoR between the intermittent relacorilant combined with nab-paclitaxel arm to the nab-paclitaxel alone arm, the HR was 0.36 (95% CI: 0.16; 0.77) with an associated p-value of 0.006, based on 2-sided log-rank test.

While the continuous dosing regimen demonstrated an improvement in PFS compared to nab-paclitaxel monotherapy, the PFS improvement for the intermittent dosing regimen reached statistical significance when compared to nab-paclitaxel monotherapy. Patients who received intermittent relacorilant and nab-paclitaxel also experienced a more favorable safety profile compared to patients who received the continuous dosing regimen or nab-paclitaxel monotherapy (ie, a lower proportion of patients reported experiencing any SAEs).

In the Phase 2 Study CORT125134-552, the most frequently occurring treatment-emergent AEs (TEAEs) for patients who received intermittent relacorilant dosed at 150 mg around the time of

chemotherapy + 80 mg/m² nab-paclitaxel were nausea, 31 (51.7%); anemia, 29 (48.3%); alopecia, 22 (36.7%); peripheral sensory neuropathy, 19 (31.7%); fatigue, 19 (31.7%); constipation, 18 (30.0%); abdominal pain, 16 (26.7%); asthenia, 15 (25.0%); diarrhea, 15 (25.0%); vomiting, 15 (25.0%); decreased appetite, 13 (21.7%); and neutropenia, 11 (18.3%). The most common TEAEs leading to a relacorilant dose reduction that occurred in $\geq 2\%$ of patients in intermittent was fatigue, 2 (3.3%); and the most common TEAEs leading to a relacorilant dose interruption that occurred in $\geq 2\%$ of patients in intermittent treatment arm were neutropenia, 4 (6.7%); pyrexia, 4 (6.7%); abdominal pain, 3 (5.0%); anemia 3 (5.0%); nausea 2 (3.3%); palmar-plantar erythrodysesthesia syndrome 2 (3.3%); peripheral sensory neuropathy, 2 (3.3%); and pneumonia, 2 (3.3%). A total of 11 (18.3%) patients in intermittent treatment arm discontinued relacorilant as a result of an adverse event (AE) and none of these AEs occurred in more than 1 patients each.

Among the intermittent relacorilant treatment Arm, the primary reason patients discontinued relacorilant was disease progression, 40 (66.7%); AEs 7 (11.7%); patient withdrawal of consent for treatment, 1 (1.7%); and death, 1 (1.7%). The most common $\geq$ Grade 3 TEAEs were anemia, 8 (13.3%); abdominal pain 4 (6.7%); fatigue 4 (6.7%); and ascites, asthenia, hypertension, and intestinal obstruction in 2 patients each (3.3%). Across all dosing arms, a total of 65 (36.7%) patients reported at least 1 treatment-emergent serious adverse event (TESAE). Among the intermittent treatment arm patients, 15 (25%) had at least 1 TESAE. The most common TESAEs ≥ 2 patients in the intermittent treatment arm were intestinal obstruction, and malignant ascites (2; 3.3%, each).

The current Relacorilant Solid Tumors IB includes the most current information regarding the benefits and risks of relacorilant.

1.7. COVID-19 Related Risks and Risk Mitigation Measures

The following risks and risk mitigating measures apply to all parts of this study conducted during the coronavirus disease 2019 (COVID-19) pandemic.

1.7.1. Relacorilant Risk

Against the background of the COVID-19 pandemic, the potential risk of a patient developing COVID-19 has been considered in terms of the risk-benefit evaluation. The mode of action of relacorilant, as a GR modulator, has been considered alongside available pre-clinical and clinical data, and it is considered that a patient would not be at increased risk of either becoming infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes COVID-19) or experiencing a more severe illness. That is, relacorilant has no known immunomodulatory effect that would confer an increased risk to oncology patients enrolled in the study.

1.7.2. General COVID-19 Related Risk Mitigation Measures

General risk mitigation against COVID-19 will be implemented in accordance with the site's monitoring and prevention control measures.

COVID-19 testing may be performed based on current infection rates and availability of tests. If required by the site, testing will comprise an antigen polymerase chain reaction (PCR) test or

other antigen test. The risk mitigation measures, where applicable, will be amended based on emerging government guidance.

1.7.3. COVID-19 Vaccine-Related Risk

Approved (including health authority conditional marketing authorization) COVID-19 vaccines (eg, killed, inactivated, peptide, DNA and RNA vaccines are permitted) according to the Investigator's discretion and as per local guidance and will be recorded as prior or concomitant medication as appropriate.

Based on the mechanism of action of relacorilant as a GR modulator, there is no perceived impact on the safety of the study patients or on the study objectives for patients who may receive these vaccines. It is also very unlikely that administration of relacorilant would interfere with COVID-19 vaccination response; however, no specific pre-clinical or clinical investigations have been conducted at this point with relacorilant.

The emerging safety and efficacy data from millions of vaccinated people, many of whom are elderly and with underlying health conditions and taking multiple concomitant medications, indicate that these vaccines have an excellent safety and efficacy record. In the broader interests of society and to limit the extent of the global pandemic, it is important that patients receive a vaccine when it is offered to them.

2. STUDY OBJECTIVES

For all efficacy objectives listed below, assessment for response and disease progression are according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 ([Eisenhauer 2009](#)) as assessed by blinded independent central review (BICR), unless otherwise noted.

2.1. Primary Objectives

- The primary efficacy objectives of this study are to evaluate PFS by BICR and overall survival (OS) in patients treated with an intermittent regimen of relacorilant in combination with nab-paclitaxel compared with patients treated with nab-paclitaxel monotherapy.

2.2. Secondary Objectives

2.2.1. Secondary Efficacy Objectives

The secondary efficacy objectives are to evaluate patients treated with an intermittent regimen of relacorilant in combination with nab-paclitaxel compared with nab-paclitaxel monotherapy:

- To evaluate PFS as assessed by the Investigator or local radiologist.
- To evaluate ORR
- To evaluate BoR
- To evaluate DoR
- To evaluate CBR at 24 weeks
- To evaluate response according to CA-125 using GCIG criteria. A combined-response endpoint based on RECIST v1.1 and GCIG criteria will also be reported.

2.2.2. Safety Objective

- To assess the safety of relacorilant treatment in combination with nab-paclitaxel compared with nab-paclitaxel monotherapy.

2.3. Exploratory Objectives

2.3.1. Pharmacodynamics/Biomarkers

- To assess the relationship between Baseline and pharmacodynamic markers (eg, GR and expression of other genes) and the patient's response to relacorilant in combination with nab-paclitaxel.
- To assess pharmacodynamic effects of the intermittent regimen of relacorilant in combination with nab-paclitaxel.
- To explore mechanisms of resistance to relacorilant in combination with nab-paclitaxel.

2.3.2. 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 between treatment arms.

2.3.3. Pharmacokinetic Objective

- To assess the PK of relacorilant.

3. STUDY DESIGN

3.1. Overall Design

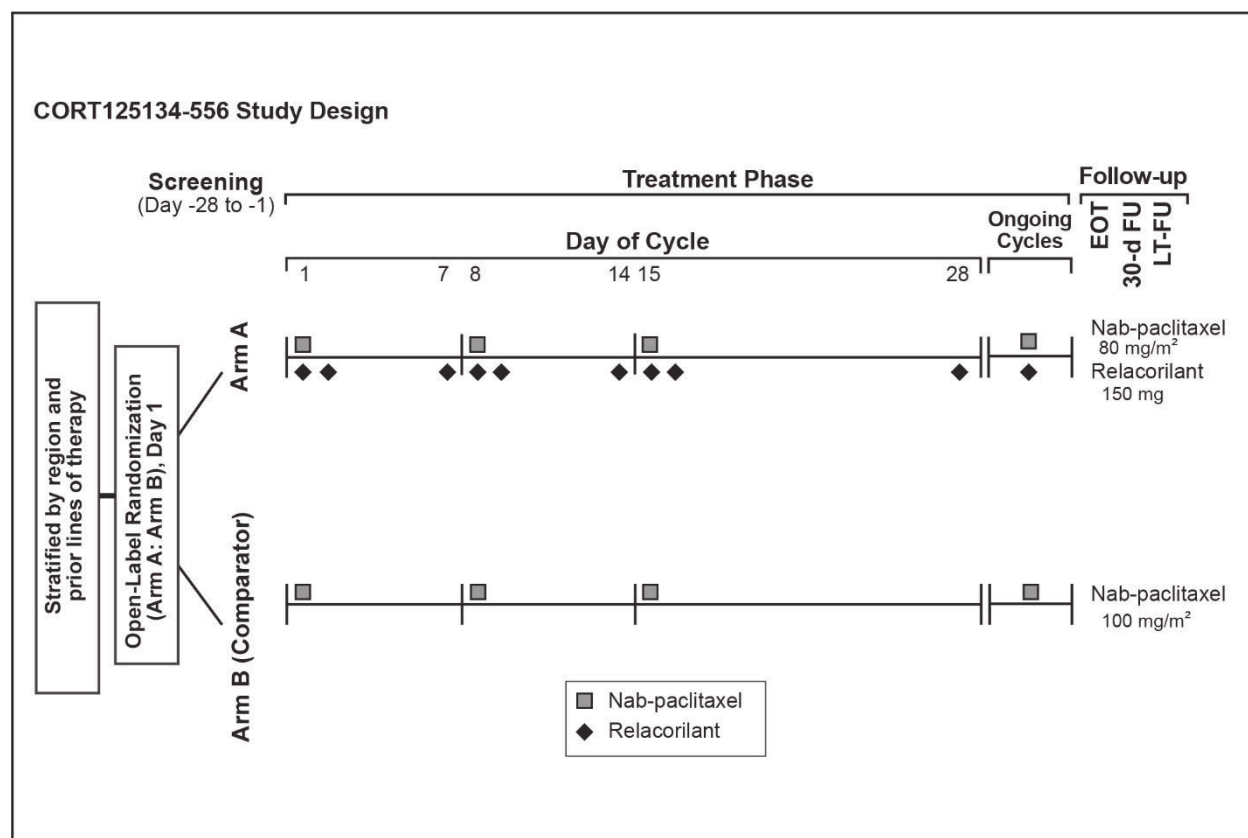
This is a Phase 3, randomized, 2-arm, open-label study to evaluate efficacy, safety, PK, pharmacodynamics, PRO and QoL of intermittent dosing of relacorilant in combination with nab-paclitaxel (Arm A) versus nab-paclitaxel monotherapy (Arm B).

As shown in the [Figure 2](#), patients will be randomized in a 1:1 ratio to one of the 2 treatment arms, Arm A or Arm B. Randomization will be stratified by the following stratification factors: region (North America versus Europe versus the rest of the world) and line of therapy (1 versus more than 1). In Arm A, study treatment will comprise of relacorilant + nab-paclitaxel. Patients will take relacorilant with approximately 8 oz (240 mL) of water and with food. On days when protocol-specified assessments require fasting, patients will bring their relacorilant to the clinic and take it with food and water after the fasting blood draws have been completed. In Arm B, study treatment will comprise of nab-paclitaxel monotherapy. Study treatment will begin on Cycle 1 Day 1.

In Arm A (experimental; relacorilant + nab-paclitaxel), the patient will receive relacorilant 150 mg, administered orally under fed conditions, once daily for 3 consecutive days on the day before (excluding Cycle 1 Day -1), the day of, and the day after nab-paclitaxel infusion, in combination with nab-paclitaxel (80 mg/m² IV) administered on Days 1, 8, and 15 of each 28-day cycle. Relacorilant will not be administered on Cycle 1 Day -1. On days in which both relacorilant and nab-paclitaxel are administered, it is preferable to administer relacorilant before nab-paclitaxel. The elimination of nab-paclitaxel is mediated in part by the drug metabolizing enzyme CYP3A4 for which relacorilant is a strong inhibitor, resulting in higher nab-paclitaxel exposures when administered in combination with relacorilant relative to nab-paclitaxel monotherapy, indicating that a lower dose of nab-paclitaxel can be used in combination with relacorilant as compared with nab-paclitaxel monotherapy.

In Arm B (comparator; nab-paclitaxel), the patient will receive nab-paclitaxel (100 mg/m² IV) administered on Days 1, 8, and 15 of each 28-day cycle.

Figure 2: CORT125134-556 Study Design



Abbreviations: 30-d FU, 30-day follow-up visit (phone); EOT, end of treatment visit; LT-FU, long-term follow-up visit (phone).

3.2. Study Endpoints

For all efficacy endpoints listed below, assessment for response and disease progression are according to RECIST version 1.1 ([Eisenhauer 2009](#)) as assessed by BICR, unless otherwise noted.

3.2.1. Primary Efficacy Endpoints

The dual primary efficacy study endpoints include the following:

- PFS: Time from randomization until first documented PD by RECIST v1.1 per BICR, or death due to any cause, whichever occurs first.
- OS: Time from randomization to death by any cause.

3.2.2. Secondary Endpoints

3.2.2.1. Efficacy

- PFS (Investigators): Time from randomization until PD or death whichever occurred first as assessed by Investigator using RECIST v1.1.

- ORR: Proportion of patients with measurable disease at Baseline who attain CR or PR by RECIST v1.1.
- BoR: Recorded from the date of randomization until PD/recurrence (or death).
- DoR: Time from the first objective response (CR or PR) to first objectively documented PD or death (whichever occurs first).
- CBR at 24 weeks: proportion of patients who attain CR, PR, or SD for 24 weeks as per RECIST v1.1.
- CA-125 response will be assessed per GCIG criteria ([Rustin 2011](#)) defined as $\geq 50\%$ reduction in CA-125 from a pretreatment 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. Responses will be reported separately and combined for RECIST v1.1 and CA-125/GCIG criteria.

3.2.2.2. Safety

The safety of each treatment group will be assessed by evaluating the nature, frequency, and severity of AEs, including:

- Incidence of AEs, SAEs, treatment-related AEs, AEs by severity, and deaths due to AEs, all deaths, and changes in laboratory determinations, and vital sign parameters.
- Discontinuation of treatment and study withdrawal due to AEs.

3.2.3. Exploratory Endpoints

3.2.3.1. Pharmacodynamic/Biomarkers Endpoints

Baseline assessment of:

- Tumor GR expression.
- Expression of GR-regulated genes in whole blood.
- Salivary cortisol.

Change from Baseline of:

- Expression of GR-regulated genes in whole blood

3.2.3.2. Patient-Reported Outcomes and Quality of Life

Changes from Baseline of PRO and QoL assessments scores using European Organization for Research and Treatment of Cancer (EORTC) ovarian cancer specific quality of life questionnaire (QLQ-OV28), European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) questionnaires, and the EuroQol-5 Dimension 5-level (EQ-5D-5L) questionnaires. A higher score represents a better quality of life.

- The primary patient-reported outcome will be the number of patients achieving at least 15-point absolute improvement at Week 8 or Week 9 in the abdominal/gastrointestinal (GI) scale of the EORTC ovarian cancer specific quality of life questionnaire (QLQ-OV28). A higher score represents a better quality of life.

3.2.3.3. Pharmacokinetic Endpoint

- Sparse PK sampling for relacorilant population PK.

3.3. Number of Patients and Duration of Study Participation

3.3.1. Number of Patients

A total of approximately 360 patients will be randomized in a 1:1 ratio to one of the 2 treatment arms (approximately 180 patients per arm).

3.3.2. Duration of Patient Participation

The assumed median PFS is approximately 5.8 months in the experimental arm (Arm A) and 3.8 months in the comparator arm (Arm B). Patients will receive treatment until reaching a protocol-defined event of PD, experiencing unmanageable toxicity, or meeting another treatment discontinuation criterion.

The duration of patient participation will vary depending on individual patient outcome.

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

3.3.3. Discontinuation of Study Sites

Participation of a study site may be discontinued if the Sponsor, its designee, the Investigator, or the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) determines it is necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and guidelines.

3.3.4. Study Termination by Sponsor

If the Sponsor/CRO, Investigator, Medical 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 in the study.
- Decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

Study suspension and/or termination (if required) and follow-up will be performed in compliance with applicable regulations and guidelines.

3.4. Enrollment, Screen Failures, Randomization, Study Completion, End of Treatment, and End of Study

3.4.1. Enrollment

Patients are considered enrolled in the study once the informed consent form (ICF) has been signed and the patient is entered in the IRT (interactive response technology) system.

3.4.2. Screen Failures

Patients are considered screen failures when they consent to participate in the clinical study, but do not meet eligibility criteria, and are not randomized to the study treatment.

3.4.3. Randomization

Patients are considered randomized once their eligibility has been verified and they are randomized to a treatment arm in IRT.

3.4.4. Study Completion

Patients are considered to have completed the study if they have completed the study including the long-term follow-up assessments.

3.4.5. End of Treatment

The end of treatment (EOT) is defined as the date on which the patient received her last treatment dose of relacorilant or nab-paclitaxel, whichever is last (Arm A); or the last day of nab-paclitaxel treatment (Arm B).

3.4.6. End of Study

The end of study is defined as the date of last contact (ie, visit, telephone, email) with the last patient in the study. The Sponsor will ensure that the IRB/ 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.

The end of study corresponds to "Study Completion Date" which is reported on ClinicalTrials.gov, a registry of clinical trials run by the United States National Library of Medicine at the National Institutes of Health.

4. STUDY POPULATION

4.1. Number of Patients and Study Sites

Approximately 360 patients will be randomized 1:1 to the experimental arm or the comparator arm (approximately 180 patients per arm). There will be approximately 125 sites globally, including North America, Europe (EU), and the rest of the world.

4.2. Inclusion Criteria

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

1. Signed and dated Institutional Review Board/Independent Ethics Committee-approved ICF prior to study-specific Screening procedures.
2. Female patients aged ≥ 18 years old at time of consent.
3. Confirmed histologic diagnosis of high-grade (Grade 3) serous, epithelial ovarian, primary peritoneal, or fallopian-tube carcinoma (high-grade endometrioid epithelial or carcinosarcoma with $\geq 30\%$ epithelial component are eligible).
4. Patients must have platinum-resistant disease (defined as progression < 6 months (+7 days) from completion of a platinum-containing therapy).
Note: This is calculated from the date of the last administered dose of platinum therapy to the date of progression. Patients who have platinum-refractory disease during front-line treatment are excluded (primary platinum-refractory disease).
5. Must consent to provide archival tumor-tissue block or slides, if available. Patients may consent to an optional tumor biopsy if archival tumor-tissue is unavailable.
6. Has a life expectancy of ≥ 3 months.
7. At least one lesion that meets the definition of measurable disease by RECIST v.1.1 (previously irradiated lesions not allowed as measurable disease unless there is documented evidence of progression in the lesions).
8. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
9. Able to comply with protocol requirements.
10. Able to swallow and retain oral medication and does not have uncontrolled emesis.
11. Received at least 1 but ≤ 3 lines of prior systemic anticancer therapy (See [Appendix G](#) for the guidance in counting the number of prior lines of therapy) with documented PD or intolerance to the most recent therapy. At least 1 prior line of platinum therapy is required and prior treatment with bevacizumab is required.
12. Has adequate organ function meeting the following laboratory test criteria:
 - Absolute neutrophil count (ANC) ≥ 1500 cells/mm³ without G-CSF support within 2 weeks before Screening laboratory sample collection.
 - Platelet count $\geq 100,000$ /mm³ without transfusion within 2 weeks before Screening laboratory sample collection.

- Hemoglobin ≥ 9 g/dL without transfusion within 2 weeks before Screening laboratory sample collection.
 - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\leq 2.5 \times$ upper limit of normal (ULN), or $\leq 5 \times$ ULN in context of liver metastases.
 - Total bilirubin $\leq 1.5 \times$ ULN (patients with Gilbert's are eligible if total bilirubin $\leq 3 \times$ ULN).
 - Albumin ≥ 2.5 g/dL.
 - Serum creatinine ≤ 1.5 ULN or calculated creatinine clearance ≥ 35 mL/min (Cockcroft and Gault formula if serum creatinine is > 1.5 ULN).
13. Negative pregnancy test for patients of childbearing potential. Patients of childbearing potential must agree to use highly effective contraceptive method(s) ([Section 4.7.4](#)); hormonal contraceptives are not allowed.
14. COVID-19 approved vaccines (or vaccines with regulatory health authority's emergency use authorization/conditional marketing authorization) are accepted concomitant medications when recommended by the Investigator. Exceptions may apply should the Investigator and the Medical Monitor determine that the vaccine will interfere with the objectives of the study.

4.3. Exclusion Criteria

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

1. Has clinically relevant and reversible toxicity from prior systemic anticancer therapies or radiotherapy that has not resolved to $\leq$ Grade 1 prior to randomization.
2. Has had any major surgery within 4 weeks prior to randomization. If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting the study treatment.
3. Has low-grade serous or endometrioid histology other than epithelial, or clear cell, or mucinous, or sarcomatous with less than 30% epithelial histology component, or mixed tumors containing any of these histologies, or borderline ovarian tumor.
4. Has primary platinum-refractory disease, defined as disease that did not respond to, or has progressed during or within ≤ 1 month from completion of a platinum-containing chemotherapy in first-line treatment (measured from the date of the last dose of platinum).
5. Has not received prior bevacizumab treatment.
6. Has been treated with the following prior to randomization:
 - Chemotherapy, immunotherapy, investigational agent etc. treatments for disease under study within 5 times of half-life of the prior therapy, or 28 days if 5 times the half-life of the prior therapy is longer than 28 days, before the first dose of study drug.
 - Radiotherapy not completed at least 2 weeks prior to first dose of study drug.

- Hormonal anticancer therapies within 7 days of first dose of study drug.
 - Systemic, inhaled, or prescription strength topical corticosteroids within a period equivalent to 5 times the half-life of the corticosteroid used prior to first dose of study drug.
7. Has received wide-field radiation to more than 25% of marrow-bearing areas.
 8. Has toxicities of prior therapies that are reversible and have not resolved the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, $\leq$ Grade 1.
 9. Requires treatment with chronic or frequently used oral corticosteroids for medical conditions or illnesses (eg, rheumatoid arthritis, immunosuppression after organ transplantation).
 10. Has a history of severe hypersensitivity or severe reaction to any of the study drugs.
 11. Is receiving concurrent treatment with mifepristone or other GR modulators.
 12. Has peripheral neuropathy from any cause $>$ Grade 1.
 13. 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 6 months after the last dose of study treatment.
 14. Has clinically significant uncontrolled condition(s) which, in the opinion of the Investigator, may confound the results of the trial or interfere with the patient's safety or participation.
Examples of such conditions include but are not limited to the following:
 - Unstable angina.
 - Myocardial infarction (MI) within 6 months prior to the first dose of study treatment.
 - Uncontrolled and/or severe concomitant diseases (uncontrolled hypertension, $\geq$ Grade 3 (per CTCAE v5.0) arrhythmia, heart failure, cirrhosis).
 - Active infectious disease requiring IV therapy (bacteria, viruses) within 2 weeks prior to the first dose of study treatment.
 - Gastric-outlet obstruction.
 - Small bowel obstruction (SBO) $\leq$ 12 weeks of study entry, significant ascites/effusions requiring frequent therapeutic paracentesis or thoracentesis or $\leq$ 30 days of study entry.
 - Known psychiatric disorder that would interfere with trial compliance.
 15. Has current active (chronic/acute) infection with Human immunodeficiency virus, hepatitis C virus or hepatitis B virus.
 16. Has any untreated or symptomatic CNS metastases.
 17. Patients with a history of other malignancy within 3 years prior to randomization
Note: Does not include tumors with a negligible risk for metastases or death (eg,

adequately controlled basal cell carcinoma or squamous-cell carcinoma of the skin, or carcinoma in situ of the cervix or breast).

18. Is taking a prohibited concomitant medication listed in [Section 5.4.2](#) (some of the prohibited concomitant medications listed may require a washout period prior to the first dose of study drug).
19. Concurrent treatment on other investigational treatment studies for ovarian, fallopian-tube, or primary peritoneal cancer.
20. Has received a live vaccine within 30 days prior to the study start date.
Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (eg, Flu-Mist) are live attenuated vaccines, and are not allowed.

4.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but did not meet eligibility criteria for the study and were not randomized to the study treatment.

Patients who have an exclusionary laboratory, ECG, or vital sign result on initial Screening tests may have that assessment repeated in consultation with the Corcept Medical Monitor once within the 28-day Screening period if the Investigator believes the result was spurious or otherwise confounded.

4.4.1. Rescreening

Patients who have failed meeting eligibility criteria (screen failures) can be rescreened at the discretion of the Investigator with the approval of the Corcept Medical Monitor. The same Screening number will be used for rescreening patients. Patients must meet all eligibility criteria prior to randomization.

4.5. Patient Discontinuation or Withdrawal

In this study, patient “discontinuation” refers to early discontinuation of study treatment while remaining on-study; that is, the patient may wish to stop treatment early, but may agree to continue with study visits and/or assessments for long-term follow-up (survival assessments).

If a patient wishes to withdraw consent to both treatment and study assessments, the patient should be asked if she is willing to continue with survival assessments (which can be conducted by telephone).

Early patient “withdrawal” refers either to patient withdrawal of consent to any further study participation or to an Investigator/Sponsor decision to permanently withdraw the patient and cessation of all study treatments, procedures, and assessments without further follow-up.

If a patient wishes to withdraw consent to further participation in the study entirely including the long-term follow-up, this should be clearly documented in, 1) the patient’s medical record and signed by the Investigator, and 2) the clinical study database/eCRF.

4.5.1. Patient Discontinuation of Study Treatment

Patients may discontinue treatment at any time at their own request, or patients 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 activities (SoA).

Study treatment may be discontinued in the event of any of the following occurrences:

- Disease progression.
- Unacceptable toxicity/AE.
- 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, but are not limited to, the following:
 - The patient requires prohibited medications.
 - The patient is not compliant with protocol requirements.
 - Global deterioration of health status requiring treatment discontinuation.
- Patient becomes pregnant.
- Any of the criteria listed in [Section 4.5.2](#) (patients who withdraw/complete the study will also discontinue treatment).

Patients who discontinue study treatment before unequivocal PD will complete an EOT visit which should occur prior to 21 days after last dose of study treatment. A follow-up phone visit will take place at 30 days (± 3 days) after last dose of study treatment to assess AEs. Investigators should encourage these patients to continue with all study visits and/or assessments per the patient's original study schedule.

If a patient is unable to continue with all the study-specified visits, they will be encouraged to complete the EOT visit at the very least. The date when the patient discontinues treatment, the reason for discontinuation, and any AEs must be recorded on the CRF.

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 radiographic PD per RECIST v1.1. For these patients, subsequent treatment information will be collected, every 8 weeks (± 7 days) for all patients for 40 weeks followed by every 12 weeks (± 7 days) for all patients (Arm A and Arm B) ([Section 6.5.1](#)).

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). Long-term follow-up (survival assessments) will continue until the end point of death, the patient is lost to follow-up, or other study exit criteria are met ([Section 4.5.2](#)).

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](#).

4.5.2. 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
- AE
- Death
- Early termination of the study by the Sponsor
- Lost to follow-up
 - All efforts to reach the patient, including at least three documented contact attempts, must be exhausted before a patient is deemed 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 of learning of patient withdrawal from the study.

4.6. Replacement of Patients

Not applicable.

4.7. Restrictions/Requirements/Recommendations During Study

The following restrictions apply to patients in this study (prohibited or limited-use medications are described in [Section 5.4.2](#) and [Appendix E](#)).

4.7.1. Dietary Restrictions

Not applicable.

4.7.2. Alcohol Restrictions

Not applicable.

4.7.3. Surgery or Radiation During the Study

Patients should not undergo surgery and/or radiation for the treatment of the disease under study from Screening through the follow-up visit. Palliative radiation to the bone without soft tissue involvement for pain management is allowed as long as area is not included as target lesions.

The Medical Monitor should be consulted for patients who require surgery and/or radiation for the disease under study.

4.7.4. Contraception

Women of childbearing potential will take pregnancy tests at scheduled visits (SoA [Table 12](#)).

A female patient is considered of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

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 prior to the first dose of study treatment and confirmed as negative prior to randomization. Subsequent pregnancy tests will be repeated at the frequency specified in the SoA ([Table 12](#)). Patients considered not of childbearing potential must be documented as being surgically sterile or postmenopausal.

If pregnancy test results are equivocal (eg, 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.

Patients are required to use a non-hormonal highly effective method of contraception from 28 days prior to Day 1 until 6 months after the last dose of nab-paclitaxel.

Highly effective forms of contraception include:

- Surgical sterilization (eg, bilateral salpingectomy and/or bilateral oophorectomy).
- Intrauterine device (IUD), provided that the patient has tolerated its use for at least 3 months before the first dose of study treatment and undertakes not to have it removed for 6 months after the last dose of nab-paclitaxel.
- Vasectomized male partner (only when the partner is the sole sexual partner of the study participant, and there has been a medical assessment confirming surgical success).
- Sterile male partner: one for whom azoospermia, in a semen sample, has been demonstrated as definitive evidence of infertility.
- True abstinence, without exception (in line with the preferred and usual lifestyle of the patient). Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception.

4.8. Gamete Donation

Patients of childbearing potential should not donate eggs from the date of their Screening visit until 6 months after the last dose of nab-paclitaxel.

5. STUDY TREATMENTS AND MANAGEMENT

5.1. Description of Study Treatments, Doses, and Administration

Study drugs are defined as relacorilant and nab-paclitaxel. In Arm A, study treatment will comprise of relacorilant + nab-paclitaxel. Patients will take relacorilant with approximately 8 oz (240 mL) of water and with food. On days when protocol-specified assessments require fasting, patients will bring their relacorilant to the clinic and take it with food and water after the fasting blood draws have been completed. In Arm B, study treatment will comprise of nab-paclitaxel monotherapy. Study treatment will begin on Cycle 1 Day 1:

- Arm A (experimental; relacorilant + nab-paclitaxel): the patient will receive relacorilant 150 mg, administered orally under fed conditions, once daily for 3 consecutive days on the day before (excluding Cycle 1 Day -1), the day of, and the day after nab-paclitaxel infusion, in combination with nab-paclitaxel (80 mg/m² IV) administered on Days 1, 8, and 15 of each 28-day cycle. On days in which both relacorilant and nab-paclitaxel are administered, it is preferable to administer relacorilant before nab-paclitaxel.

(For patients in Arm A, in the event of vomiting within 2 hours after taking relacorilant, the patient should be directed to retake relacorilant. If vomiting recurs, the patient should not take additional dose of relacorilant until the Investigator consults Medical Monitor to determine appropriate management for the patient.)
- Arm B (comparator; nab-paclitaxel): the patient will receive nab-paclitaxel (100 mg/m² IV) administered on Days 1, 8, and 15 of each 28-day cycle.

5.1.1. Description of Investigational Drug (Relacorilant)

Study drug includes the investigational drug, relacorilant.

A description of the investigational drug including packing and storage is in [Table 2](#).

Table 2: Investigational Drug: Description, Packaging, and Storage

Specifications	Relacorilant (CORT125134)
Description	Relacorilant (CORT125134) is prepared as a [REDACTED] [REDACTED] Softgel capsules containing 100 mg and 25 mg relacorilant are manufactured using this formulation.
Unit dose strength(s)	100 mg yellow, softgel capsules and 25 mg pinkish orange or brown, softgel capsules.
Missed doses	If the patient realizes they missed a dose within 6 hours of their normally scheduled dosing time, they should take their daily dose of study drug at that timepoint and then resume their normal schedule the following day. If a patient realizes they missed a dose > 6 hours after their scheduled time, they should skip that dose and resume their normal schedule the following day. Taking a double dose on a given day is prohibited.
Dispensing study drug	Dispense 1 bottle (30 capsules) of 100 mg relacorilant and 2 bottles (30 capsules each) of 25 mg relacorilant to patients every 2 cycles during the treatment period.
Packaging and labeling	Softgel capsules will be provided in a white bottle, containing 30 capsules each, with induction seal and child-resistant closure and labeled per country requirement.
Storage	In a secure location. Store at 20–25°C (68–77°F), temperature excursions permitted 15–30°C (59–86°F). Out of reach and sight of children.

Note: Non-investigational products are described in [Section 5.1.2](#). Procedures for inventory, reconciliation, and destruction or return of study drug are provided in [Section 11.5.3](#).

5.1.2. Other Medicinal Agent

In Arm A, nab-paclitaxel is combined with relacorilant ([Table 3](#)).

In Arm B, the comparator treatment is nab-paclitaxel ([Table 3](#)). Additional information on nab-paclitaxel is provided in [Section 1.4.1](#).

Table 3: Description, Packaging, and Storage (Nab-paclitaxel)

Specifications	Nab-paclitaxel ^a
Description	Paclitaxel protein-bound particles for injectable suspension (albumin-bound) is paclitaxel formulated as albumin-bound nanoparticles with a mean particle size of approximately 130 nanometers. Paclitaxel exists in particles in a non-crystalline, amorphous state. The chemical name for paclitaxel is 5 β ,20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -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 l (bound to human albumin) and approximately 900 mg of human albumin containing sodium caprylate and sodium acetyltryptophanate.
Appearance	White to yellow, sterile, lyophilized powder for reconstitution before use.
Missed doses	Refer to Appendix D and Section 5.3 .
Dispensing study treatment	Nab-paclitaxel will be administered in the clinic. Dose and mode of administration: Nab-paclitaxel will be administered according to the treatment arm as follows: in combination with relacorilant, 80 mg/m ² IV infusion over 30–40 minutes on Days 1, 8, and 15 of each 28-day cycle (Arm A) and 100 mg/m ² IV on days 1, 8, and 15 of a 28-day cycle as a single-agent comparator (Arm B).
Packaging and labeling	Refer to current prescribing information or Summary of Product Characteristics (eg, Abraxane USPI 2020 ; Abraxane SmPC). Nab-paclitaxel will be labeled per country requirement.
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 original carton to protect from bright light and store at 2–8°C (36–46°F) for a maximum of 24 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.

a. Commercially available; details available in current prescribing information (PI) and Summary of Product Characteristics (SmPC).

5.1.3. Administration of Study Treatment

Patients will be randomized in a 1:1 ratio to receive either:

- Arm A (experimental; relacorilant + nab-paclitaxel): the patient will receive relacorilant 150 mg, administered orally under fed conditions, once daily for 3 consecutive days on the day before (excluding Cycle 1 Day -1), the day of, and the day after nab-paclitaxel infusion, in combination with nab-paclitaxel (80 mg/m² IV) on Days 1, 8, and 15 of each

28-day cycle. Relacorilant will not be administered on Cycle 1 Day -1. On days in which both relacorilant and nab-paclitaxel are administered, it is preferable to administer relacorilant before nab-paclitaxel.

- Arm B (comparator; nab-paclitaxel): the patients will receive nab-paclitaxel (100 mg/m² IV) administered on Days 1, 8, and 15 of each 28-day cycle.

Patients should take relacorilant with approximately 8 oz (240 mL) of water. Patients should take their relacorilant dose with food. On days when protocol-specified assessments require fasting, patients will bring their relacorilant to the clinic and take it with food and water after the fasting blood draws have been completed.

General chemotherapy dosing guidelines are provided in [Appendix D](#).

Refer to [Section 5.4.2](#) for prohibited concomitant medications.

5.2. Dose-Escalation Process

If a relacorilant dose reduction is required per [Table 6](#), the relacorilant dose may be re-escalated after a discussion with the Medical Monitor.

5.3. Dose Reductions or Delays

Every effort should be made to administer study treatment on the planned dose and schedule.

However, dosing may be delayed, modified, temporarily interrupted, or permanently discontinued as a result of treatment-related AEs or abnormal laboratory values.

For patients in Arm A, if nab-paclitaxel is interrupted due to treatment-related AEs, relacorilant dosing will also be held following clinical decision to hold nab-paclitaxel. The patient may take relacorilant the day before and on the day of, before coming into the clinic, for the planned nab-paclitaxel infusion, however they should not take relacorilant if the decision is made to hold nab-paclitaxel. Please refer to [Table 4](#) for guidance on dose reductions or delays for treatment-related AEs. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed.

For patients in Arm A, if relacorilant dose needs to be held, nab-paclitaxel treatment should be also held.

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 4](#)), the patient will complete the planned response assessments (eg, radiographic, CA-125, etc.) per the SoA ([Table 12](#)) until resuming treatment. If the initiation of a cycle is delayed, the day when the first nab-paclitaxel infusion is re-initiated is considered Day 1 of a cycle for the purpose of counting 28-day cycle schedule.

If study treatment is interrupted for > 28 days with the approval of the Medical Monitor, clinical laboratory assessments may also be interrupted if no clinically significant laboratory abnormalities need to be followed at the Investigator's discretion. However, Tumor assessments (CT or magnetic-resonance imaging [MRI] and CA-125) and PRO/QoL assessments should continue at the frequency starting from Cycle 1 Day 1 per the SoA ([Table 12](#)).

Table 4: Guidance on Dose Reductions or Delays Due to Treatment-Related Adverse Events

Adverse Event	Nab-paclitaxel Dose Modification	Relacorilant Dose Modification for Arm A
Neutropenia: (ANC 1,000-1,499)	<u>Cycle Day 1:</u> Delay Day 1 nab-paclitaxel until ANC is 1,500 or higher. <u>Cycle Day 8 or 15:</u> No change	<u>Cycle Day 1:</u> Relacorilant would be held if nab-paclitaxel is held; Reinitiate relacorilant at same dose level once nab-paclitaxel is resumed. <u>Cycle Day 8 or 15:</u> No change
Neutropenia: (ANC < 1,000)	<u>Cycle Day 1:</u> Delay Day 1 nab-paclitaxel until ANC is 1,500 or higher. Reduce 1 dose level. <u>Cycle Day 8 or 15:</u> Omit dose and then reduce 1 dose level or continue the same dose level with prophylactic short acting G-CSF administered 24 hours after nab-paclitaxel for 2 days at Investigator's discretion.	<u>Cycle Day 1, 8, or 15:</u> Relacorilant would be held or omitted if nab-paclitaxel is held or omitted. Reinitiate relacorilant at same dose level once nab-paclitaxel is resumed.
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 nab-paclitaxel is resumed. Reinitiate at same dose level.
Thrombocytopenia: (Platelets < 100,000)	<u>Cycle Day 1:</u> Delay Day 1 nab-paclitaxel until platelet is 100,000 or higher. <u>Cycle Day 8 or 15:</u> Platelets 50,000 to 99,000: No change. Platelets < 50,000 omit dose and then reduce nab-paclitaxel by 1 dose level.	<u>Cycle Day 1, 8, or 15:</u> Relacorilant would be held or omitted if nab-paclitaxel is held or omitted. Reinitiate relacorilant at same dose level once nab-paclitaxel is resumed.
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.	Relacorilant would be held if nab-paclitaxel is held. Reinitiate relacorilant at same dose level once nab-paclitaxel is resumed.
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 for Arm A
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 if nab-paclitaxel is held. 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 if nab-paclitaxel is held. Reinitiate at same dose level when nab-paclitaxel is re-initiated.
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 AE: Grade 3 or 4 (Excluding non-clinically relevant laboratory abnormality) Other non-hematologic AE: Grade 3 (Excluding non-clinically relevant laboratory abnormality)	Withhold dose until severity of AE improves to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry. Reduce 1 dose level.	For AEs attributable only to nab-paclitaxel, continue relacorilant if nab-paclitaxel is re-initiated. For AEs attributable to relacorilant, withhold dose until severity of AE 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. Nab-paclitaxel treatment should be held if relacorilant dose is held.
Other non-hematologic AE: Grade 4 (Excluding non-clinically relevant laboratory abnormality)	Consider discontinuation of nab-paclitaxel in consultation with the Medical Monitor.	Consider discontinuation of relacorilant in consultation with the Medical Monitor.

Abbreviations: AE, adverse event; ANC, absolute neutrophil count.

5.3.1. Dose Reductions or Delays for Nab-paclitaxel

After Cycle 1 Day 1 for patients in Arm A (relacorilant + nab-paclitaxel) and patients in Arm B (single-agent nab-paclitaxel), if there is a delay in nab-paclitaxel administration for any reason, the following applies:

- If treatment with nab-paclitaxel is delayed for > 4 weeks (omission of nab-paclitaxel for > 28 days), the Medical Monitor should be notified.
- If the initiation of a cycle is delayed, the day when the first nab-paclitaxel infusion is re-initiated is considered Day 1 of a cycle for the purpose of counting 28-day cycle schedule.
- If the delay of the initiation of a cycle (eg, Cycle 3) is close to the next scheduled Cycle (eg, Cycle 4), the schedule of assessment for the next scheduled Cycle (eg, Cycle 4) should be followed.
- After the initiation of a cycle (Day 1), if there is a delay in nab-paclitaxel administration for any reason, the following applies:
 - If an infusion of nab-paclitaxel on Day 8 or Day 15 is delayed with a new date that is too close to the next scheduled infusion, that dose may be skipped, and the patient may resume treatment with the next scheduled infusion if appropriate in the judgment of the Investigator.
 - Two consecutive nab-paclitaxel infusions should not be given less than 7 days apart.

Nab-paclitaxel dose reductions (Table 5) should be made based on observed toxicities secondary to treatment, as indicated in (Table 4). 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 for Arm A patients, then relacorilant will also be discontinued.

Table 5: Nab-paclitaxel Dose Reductions

	Arm A	Arm B, Nab-paclitaxel
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.

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 doses (once daily) of relacorilant when the next nab-paclitaxel infusion is planned (eg, the patient takes her dose of relacorilant day before and day of before/on coming into the clinic for her scheduled nab-paclitaxel, even if labs may not permit nab-paclitaxel infusion. After her delay, she should again take her day before and day of doses of relacorilant before coming to the clinic for her planned nab-paclitaxel infusion).

5.3.2. Dose Reductions or Delays for Relacorilant

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 $\leq$ Grade 1 or baseline toxicity, relacorilant will be resumed at 1 dose level lower than the current level. (Table 6).

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

A maximum of 2 dose reductions of relacorilant will be allowed. The minimum dose of relacorilant to be administered is 100 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 6: Relacorilant Dose Level Summary

Relacorilant Dosing Regimen	
Dose Level -2	100 mg
Dose Level -1	125 mg
Starting Dose	150 mg

After a dose reduction, relacorilant dose re-escalation may be considered after a discussion with the Medical Monitor (from 100 mg to 125 mg and from 125 mg to 150 mg).

5.3.3. Management of Signs of Excessive Glucocorticoid Receptor Antagonism

For patients treated with relacorilant, signs or symptoms related to excessive GR antagonism may develop. Based on the mechanism of action of relacorilant, there is the possibility that patients could experience signs or symptoms related to excessive GR antagonism. At each study visit starting with the Baseline visit, patients will be evaluated for signs and symptoms of excessive GR antagonism. 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 (in the absence of antidiabetic medications) are present, particularly if coexistent, treatment with relacorilant should be interrupted then the Medical Monitor should be consulted to assist in evaluating whether study 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 dexamethasone should be considered (eg, dexamethasone 4 mg daily for 3 days and then tapered by 1 mg per day, or as indicated based on clinical response). In the event of significant trauma or surgery through 30 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.

5.4. Concomitant Medications

Administration of concomitant medications are at the discretion of the Principal Investigator and/or the Corcept Medical Monitor. Prohibited concomitant medications are outlined in Section 5.4.2 and Appendix E.

5.4.1. Permitted Concomitant Medications

The best supportive care and treatment should be prescribed, as appropriate, to each patient to manage disease-related symptoms (eg, 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 for prophylactic anti-emetic medications.

Permitted treatments also include standard therapies for concurrent medical conditions.

The metabolism of paclitaxel is catalyzed in part by CYP2C8 and caution should be exercised when administering nab-paclitaxel concomitantly with inhibitors or inducers of CYP2C8 (see [Section 5.4.2 Prohibited Medications](#) regarding moderate and strong inhibitors of CYP2C8), consistent with the prescribing information for nab-paclitaxel ([Abraxane USPI 2020](#); [Abraxane SmPC](#)). COVID-19 vaccines or other non-live vaccines are accepted concomitant medications. It is preferable for patients not to receive the vaccine within 72 hours prior to administration of relacorilant, where possible, so that by the time of dosing any effects of the vaccine (eg, pyrexia, fatigue, pain/stiffness at the site of injection) are likely to have abated; patients will not be excluded if they have had a vaccine within this window but, as with any patients medication, they should not be dosed if they have continuing symptoms that would place them at increased risk or may confound assessment of relacorilant safety (Inclusion Criteria [14](#)).

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.

Medications required to treat AEs, manage concurrent diseases, and supportive care agents, such as pain medications, growth factor support, anti-emetics, and antidiarrheal agents, are allowed at the discretion of the Investigator and/or the Corcept Medical Monitor.

Nab-paclitaxel has a documented incidence of neutropenia that meets ESMO/NCCN Practice Guideline criteria for the use of prophylactic growth factor. Thus, G-CSF treatment may be used to provide support for a patient with clinically relevant neutropenia or to maintain dose intensity as consistent with the institutional guidelines and standard practice. Preferably, two days of short acting G-CSF (eg, filgrastim) administered 24 hours after receipt of nab-paclitaxel will reduce the rate of severe neutropenia may improve retention of dose intensity for nab-paclitaxel.

5.4.2. Prohibited Concomitant Medications

The following medications are prohibited in Arm A during treatment with relacorilant in this study:

- Medications that are substrates of CYP3A that are prohibited for use with strong CYP3A inhibitors.

The following medications are prohibited in Arm B during treatment in this study:

- Strong inhibitors of CYP3A

The following medications are prohibited in both Arm A and B during treatment in this study:

- Strong inducers of CYP3A.
- Moderate and strong inhibitors of CYP2C8.
- Systemic use of corticosteroids eg, parenteral, oral, and rectal, etc, and use of potent dermatologic preparation corticosteroids (Class I to III).
- Concurrent anticancer therapy with agents other than study treatments is not allowed.

Relacorilant and nab-paclitaxel administration should be held and should not be re-initiated until prohibited concomitant corticosteroids have been adequately cleared from the blood stream (5 times of the half-life of the corticosteroids).

Additional information is included in [Appendix E](#). The Sponsor Medical Monitor should be contacted in case of any clarifications needed regarding concomitant therapy.

5.5. Method of Study Treatment Assignment and Randomization

Randomization will be centrally assigned using Interactive Response System (IRT). The log-in information and directions for the IRT will be provided to each site.

Patient randomization will be stratified by region (North America versus Europe versus the rest of the world) and prior line of therapy (1 line of therapy versus more than 1).

Statisticians involved in generation of randomization codes, or who have access to the randomization code will not be involved in the analyses of the study.

5.6. Blinding/Unblinding

Not applicable.

5.7. Dosing Diary (Arm A only)

A dosing diary will be provided, and patients will be instructed to return all unused relacorilant (including an empty bottle) and the dosing diary at their visits. Patients should complete an entry in the diary for each self-administered dose of relacorilant. Entries will include the number of capsules as well as the date and time of study drug administration. Time and dose administered should be documented in the clinic charts.

5.8. Study-Drug Accountability and Treatment Adherence

Study treatment adherence will be determined by review of the patient diary and counting capsules returned at each study visit. A patient who is assigned a study treatment will be considered nonadherent if she misses > 15% of the prescribed doses during the study unless the patient's study treatment was withheld by the Investigator for safety reasons. Similarly, a patient will be considered nonadherent if she is judged by the Investigator to have intentionally or repeatedly taken more than the prescribed amount of study treatment.

Patients found to be nonadherent with their assigned treatment regimen should be assessed to determine the reason for nonadherence and educated and/or managed as deemed appropriate by the Investigator to improve adherence. Sites should document compliance during visits and any training performed with patients to improve adherence.

Detailed information on clinical supply management is outlined in [Section 11.5](#) and details on drug accountability are outlined in [Section 11.5.6](#).

5.9. Continued Access to Study Treatment

There is no provision for continued access to study drug.

5.10. External Data Review Committee(s)

5.10.1. Independent Data Monitoring Committee to Monitor Patient Safety

An Independent Data Monitoring Committee (IDMC) will be established to conduct periodic reviews of data to ensure the safety of patients. The IDMC will be composed of at least 3 voting members: two physicians and one statistician.

The IDMC will meet to evaluate safety data in all dosed patients after approximately 40 patients have been dosed 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 upon by the IDMC members. Further details, including the description of the IDMC composition, contents of data reports, responsibilities, decision rules, etc., will be described in the IDMC charter.

6. DESCRIPTION OF STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 12). Protocol waivers or exemptions are not allowed.

The Investigator and Sponsor will conduct the study in accordance with ICH Good Clinical Practice (GCP) and local regulations. Adherence to the study design requirements, including those specified in the SoA (Table 12) is essential and required for study conduct, and the Investigator must ensure trial procedures are performed as described in the protocol. During the study, procedures and observations will be monitored to confirm study requirements as outlined in the SoA (Table 12).

In the event a patient is unable to attend study visits at the study clinic, Sponsor-approved alternative options to complete study procedures will be provided, based on the needs and safety of patients.

6.1. Informed Consent and Screening

Written informed consent, which has been approved by the appropriate IRB/IEC, must be obtained before initiating any study-mandated procedures.

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.

All Screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria.

Procedures conducted as part of the patient's routine clinical management (eg, physical exam) and obtained before signing of the ICF may be used for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 12).

6.2. Demographics and Baseline Disease Characteristics

Patient demographic data, including age, sex, and race (as allowed by local law), and baseline disease characteristics, will be documented at Screening.

6.3. Medical and Oncologic 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.
- 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 for tumor (somatic) or germline DNA mutations.

6.4. Safety Assessments

Safety will be determined by evaluating study-drug exposure (including dose delays, dose interruptions, and discontinuations), AEs, SAEs, all deaths, changes in laboratory determinations, and vital sign parameters. Vital signs, laboratory tests, and performance status assessments will be performed according to the SoA ([Table 12](#)).

6.4.1. Physical Examination and Vital Signs

Physical examinations will be performed according to the SoA ([Table 12](#)). A full physical examination will be performed at Screening, within 3 days prior to Day 1 of each cycle and at the End of Treatment Visit. A symptom-directed physical examination will be performed on Days 8 and Day 15 of each cycle. The performance of the physical examination will be recorded in the appropriate eCRF by the Investigator or designee.

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 recorded at Screening, EOT, and on each Day 1 of each patients' chemotherapy infusion cycle day. Height will be recorded at the Screening visit or on Cycle 1 Day 1. 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 SoA ([Table 12](#)) and include resting heart rate, blood pressure, respiratory rate, and body temperature.

6.4.2. 12-Lead Electrocardiogram

Twelve-lead resting ECG tracings will be obtained from all patients at the times indicated in the SoA ([Table 12](#)) in triplicate and when clinically indicated.

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.

6.4.3. ECOG Performance Status

ECOG performance status will be assessed according to [Table 7](#) and follow the visit schedule as per the SoA ([Table 12](#)).

Table 7: 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 1982](#).

6.4.4. Adverse Events

Details on definitions and reporting of AEs are provided in [Section 8](#).

6.4.5. Clinical Laboratory Assessments

6.4.5.1. Laboratory Parameters

Blood samples will be collected to monitor safety in all patients at the times indicated in the SoA ([Table 12](#)) and the laboratory tests to be performed are listed in [Table 8](#). Laboratory samples will be collected as noted in [Section 7](#). CA-125 data will also be used to derive CA-125 response via GCIG criteria. A complete blood count and differential and blood chemistry will be obtained within 3 days prior and the results will be reviewed prior to chemotherapy infusions on chemotherapy infusion days during each cycle while the patient is on therapy (Arm A and Arm B) with other laboratory blood testing obtained prior to each 28-day cycle.

The Investigator will review all laboratory reports and document evaluation of clinical significance. Laboratory data will be used for immediate treatment decisions and for safety assessment. Laboratory values for an analyte that are outside of the normal range for that analyte, per the applicable laboratory, will be identified and can be repeated at the Investigator's discretion. The Investigator will determine if any out-of-range laboratory values that emerge during the study are clinically significant and needs to be reported as an AE ([Section 8](#)). Patients with a clinically significant out-of-range laboratory value will be followed until the laboratory value returns to normal or becomes medically stable. The Investigator will treat the patient, as medically required, at appropriate intervals until this occurs.

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

Table 8: Clinical Laboratory Variables Evaluated During the Study

Hematology Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell count (WBC) WBC with 5-part differential: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Serum Chemistry Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Bilirubin (total and direct) Blood urea nitrogen (BUN) Calcium Chloride Creatinine Magnesium Phosphorus Potassium Sodium Total protein Uric acid	Urinalysis
		Pregnancy Serum/urine pregnancy test ^a
		Tumor Markers Cancer antigen CA-125
		Pharmacokinetics (Table 13) For Arm A patients only
		Pharmacodynamics (Table 14)
Coagulation Activated partial thromboplastin time International normalized ratio Prothrombin time		Serology HIV immunoassay ^b Hepatitis B/C serology ^c

a. For Women of childbearing potential, must be confirmed as negative prior to randomization within 72-hour of first dose of study drug, and prior to Day 1 of subsequent cycles while on treatment.

b. 4th generation immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen.

c. 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. Additional hepatitis B or C PCR test may be performed as clinically indicated to assess the presence of hepatitis virus RNA.

6.4.5.2. Sample Collection, Preparation, and Shipping

Instructions for collection, preparation, and shipping of all laboratory samples will be provided in the study laboratory manual. Shipping instructions for samples collected for PK analysis and biomarkers will also be provided in the laboratory manual. Long-term retention of biological samples is described in [Section 11.4](#).

6.4.5.3. Blood-Volume Summary

Blood samples will be used for analysis of safety laboratory, efficacy, PK, PD, and biomarker parameters. The total volume of blood to be collected from each patient will be specified in the ICF.

6.5. Efficacy Assessments

All efficacy assessments will be performed at the time points specified in the SoA ([Table 12](#)).

6.5.1. Measures of Anticancer Activity

Tumors will be assessed radiologically and response to treatment will be determined by using RECIST (version 1.1) ([Eisenhauer 2009](#); [Appendix B](#)).

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 45 days prior to the first dose of study treatment and subsequent scans are required every 8 weeks (± 7 days) from Cycle 1 Day 1 for 40 weeks followed by every 12 weeks (± 7 days) for all patients (Arm A and Arm B) 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 has been 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, submitted, and stored centrally.

CA-125 response will be assessed per GCIG criteria ([Rustin 2011](#); [Appendix F](#)). CA-125 will be assessed within 14 days prior to the first dose of study treatment and then every 8 weeks from Cycle 1 Day 1 (± 7 days) for the first 40 weeks of the study followed by every 12 weeks (± 7 days) irrespective of any treatment delay until progression. Once the best CA-125 response (at least 50% decrease from a pretreatment sample, which is defined as the most recent sample drawn before the first dose) is determined, a confirmatory CA-125 is required ≥ 28 days. The 28-day confirmatory sample must be less than or equal to the previous sample (within an assay variability of 10%) to calculate CA-125 responses accurately ([Rustin 2011](#)).

Patients who discontinue treatment at any time ([Section 4.5.1](#)) will continue to be followed for study endpoints ([Section 7.12](#)) 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 4.5.2](#)).

To ensure comparability, the Baseline radiographs/scan, and subsequent radiographs/scans to assess response, should be performed using consistent methods and identical techniques, and assessed by the same individual on each occasion when possible.

6.6. Pharmacokinetics Assessments

Sparse PK sampling will be conducted on Cycle 1, Day 15. A total of 2 blood samples will be collected for assessment of plasma concentrations of relacorilant ([Table 13](#)).

6.7. Exploratory Pharmacodynamics/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 ([Section 10.3.1](#)), biological samples (eg, blood, plasma, saliva, and tumor tissue) will be obtained, some for analysis during the study and others for 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.

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 14](#).

6.7.1. Blood Collection for Glucocorticoid-Related Pathways and Exploratory Biomarkers

Blood will be collected by venipuncture. The samples are to be obtained pre-dose, fasting, and preferably between 7–9 am at the time points outlined ([Table 14](#)). The collection, processing and storage should be performed as described in the study-specific manual.

Sampling is required from a minimum of 40 Arm A patients for plasma and RNA analysis at 1 additional time point: Cycle 1 Day 17. This is necessary because it follows three consecutive days of dosing (14, 15, and 16) with relacorilant. Thus, it will provide the maximum possible pharmacodynamic effect. Cycle 1 Day 17 samples will be collected for patients in Arm A only.

Ideally, the first 40 patients randomized in Arm A will be included in this subset for Day 17 biomarker collection. 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. Exceptions will be considered on a case-by-case basis for patients.

6.7.2. Blood Collection for Longitudinal Resistance Evaluation

To assess hallmarks of resistance to relacorilant + nab-paclitaxel, plasma and RNA collections will take place at Cycle 1 Day 1 (Baseline), Cycle 1 Day 15, Cycle 3 Day 1, at response, and at progression. Refer to the study laboratory manual for complete instructions and Schedule of Pharmacodynamic Assessments ([Table 14](#)).

6.7.3. Tumor-Tissue Collection for Immunohistochemistry for Glucocorticoid Receptor

If archival tissue is available, patients must provide consent for acquiring the archival tumor-tissue block or slides. This tumor tissue will be used for immunohistochemistry evaluation of GR. Archival tumor biopsies or resections collected within 12 months of Screening are preferred. If multiple archival tumor specimens are available, specimens obtained closest to the time of study enrollment are preferred, but not required. If archival tumor tissue, as defined above, is not available then the patient is still eligible provided they meet other eligibility criteria. An optional procedure to obtain an on-study tumor biopsy during the Screening period may be performed if/when medically feasible and considered of low risk to the patient. The biopsy can be from the primary tumor site or from a metastatic site, however, which should be noted on the sample. 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. The optional on-study tumor biopsy should be collected before the start of Cycle 1 Day 1 (C1D1) of the study.

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. FFPE blocks are preferred. If blocks are not

available, 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. Refer to the study laboratory manual for complete instructions.

6.7.4. *BRCA1/2* Mutation and Homologous Recombination Deficiency Assessment

Tumor mutations in *BRCA1/2* and genes related to HRD are important predictors of response to other therapies in patients with ovarian cancer. The results for germline or somatic *BRCA1/2* mutations and HRD testing will be recorded, unless prohibited by local regulations, for patients who have completed a relevant test any time prior to the study initiation. Results will be provided via the eCRFs. Prospective sequencing of germline or somatic DNA mutations is not planned for this study.

6.7.5. Saliva Collection for Cortisol Diurnal Rhythm

Salivary cortisol will be collected at home between the Screening and at Cycle 1 Day 1 visits. Patients will be provided with saliva collection kits and instructions at their Screening visit. Patients will submit the salivary cortisol at the Cycle 1 Day 1 visit. Refer to the study laboratory manual for complete instructions.

6.8. Other Assessments

6.8.1. Patient-Reported Outcomes and QoL

PRO and QoL assessments will be performed according to the SoA ([Table 12](#)). QoL will be assessed using EORTC ovarian cancer specific quality of life questionnaire (QLQ-OV28), European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) questionnaires, and the EuroQol-5 Dimension 5-level (EQ-5D-5L) questionnaires. A healthcare resource utilization (HRU) questionnaire will also be administered at these visits. All questionnaires will be provided in paper format.

The EORTC QLQ-C30 version 3, is an extensively validated and widely used measure of HRQOL, contains 30 items that assess five domains of functioning (physical, role, emotional, social, cognitive) global HRQOL, and 9 symptoms that commonly occur in cancer (pain, fatigue, nausea, vomiting, constipation, diarrhea, dyspnea, problems with sleep, appetite). It is complemented by the ovarian cancer module, EORTC QLQ-OV28. ([Friedlander and King 2013](#)).

The EORTC QLQ-OV28 assesses abdominal/gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side-effects, hormonal/menopausal symptoms, body image, attitude to disease/treatment and sexual functioning. ([Greimel 2003](#)).

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 EQ5D-5L also contains a visual analog score (VAS) to assess the patient's overall health ([EuroQoL 1990](#)).

Initial PRO, QoL, and HRU assessments will be performed at any time from the Screening visit up to prior to the first dose of study treatment. Post-baseline assessments will be completed at

Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1. After Cycle 4 Day 1, assessments will be performed every other cycle (starting with Cycle 6 Day 1) through the End of Treatment Visit.

PRO, QoL, and HRU 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 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. Any training performed by site to the patient should be documented in source to demonstrate efforts for adherence. 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.

6.8.2. Clinician-Reported Outcomes

Not applicable.

6.8.3. Appropriateness of the Measures

All efficacy and safety measurements are well-validated and the standard measurements in this patient population are appropriate for this study.

7. STUDY ASSESSMENTS AND PROCEDURES BY STUDY VISIT

An SoA is provided in [Table 12](#) (Arm A and Arm B). All assessments are for all patients except where indicated. Any deviation from protocol procedures will be noted in the patient's clinical chart and eCRF. In addition, the Sponsor will be promptly notified of any protocol deviations.

Tumor assessments (CT/MRI) will be performed every 8 weeks (± 7 days) for the first 40 weeks of the study followed by every 12 weeks (± 7 days) for all patients in Arms A and B until progression of disease.

CA-125 blood samples will be drawn within 14 days prior to the first dose of study treatment and then every 8 weeks (± 7 days) from Cycle 1 Day 1 for the first 40 weeks of the study followed by every 12 weeks (± 7 days) irrespective of any treatment delay until PD. Once the best response (CR or PR) is determined (at least 50% decrease from a pretreatment sample, which is defined as the most recent sample drawn before the first dose), a confirmatory CA-125 is required ≥ 28 days of the best response. The 28-day confirmatory sample must be less than or equal to the previous sample (within an assay variability of 10%) to calculate CA-125 responses accurately. ([Rustin 2011](#)).

7.1. Screening (Day -28 to Day -1)

Screening will occur within 28 days before the first dose. The patient should be instructed to fast (no food or drink other than water) for at least 8 hours before the Screening visit.

At the start of Screening, the study will be discussed with the patient, and a patient wishing to participate must give written 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 informed consent is obtained, prospective patients will be evaluated for entry into the study according to inclusion and exclusion criteria ([Section 4.2](#) and [Section 4.3](#)). The Sponsor will verify patient eligibility and approve study enrollment prior to patient randomization. Each patient who is randomized to receive study treatment will be assigned a patient number that will be used on patient documentation throughout the study.

Clinical assessments conducted as part of the patient's routine clinical management and obtained prior to signing of the ICF may be used for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The following Screening procedures and assessments will also be performed:

- Obtain informed consent.
- Review of eligibility criteria.
- Record demographics, medical history, baseline disease characteristics, and oncology history.
- Record prior and concomitant medications.
- Pregnancy testing for women of childbearing potential ([Section 4.7.4](#)): A serum or urine pregnancy test for female patients of childbearing potential will be performed prior to

randomization, prior to the first dose of study treatment (72-hour window prior to the first dose of study treatment).

- Pregnancy testing will be performed monthly for patients in Arm A and Arm B.
- Tumor Tissue: Archival tumor biopsies or resections collected within 12 months of Screening are preferred. If multiple archival tumor specimens are available, specimens obtained closest to the time of study enrollment are preferred, but not required. If archival tumor-tissue, as defined above, is not available then the patient is still eligible provided they meet other eligibility criteria. An optional procedure to obtain an on-study tumor biopsy during the Screening period may be performed if/ when medically feasible and considered of low risk to the patient (Section 6.7.3). The biopsy can be from the primary tumor site or from a metastatic site, however, which should be noted on the sample. The optional on-study tumor biopsy should be collected before the start of Cycle 1 Day 1 (C1D1) of the study.
- Record results of prior *BRCA1/2* mutation and homologous recombination deficiency assessment.
- Complete tumor assessment (CT/MRI): A CT or MRI scan of the chest, abdomen, and pelvis will be performed within 45 days prior to the first dose of study treatment.
- Record ECOG performance status.
- Perform full physical examination.
- Record vital signs, height, and weight.
- Draw blood samples for laboratory tests (CA-125, hematology, chemistry, prothrombin time [PT], activated partial thromboplastin time [aPTT], and INR).
 - CA-125 will be collected within 14 days prior to the first dose of study treatment.
- Collect urine sample for analysis.
- Hepatitis B and C serologies and HIV immunoassay.
- Perform 12-lead resting ECG (in triplicate).
- Pharmacodynamic sampling (Table 14).
 - Patients must be fasting, and samples to be collected pre-dose, preferably between 7:00 am and 9:00 am.
 - Cortisol diurnal rhythm assessment (Table 14).
- Initial PRO, QoL, and HRU must be collected prior to the first dose of study treatment.
- AEs are to be recorded from the time written informed consent is obtained.

7.2. Baseline (Cycle 1 Day 1)

Patients that continue to meet Inclusion and Exclusion Criteria will be randomized 1:1 to one of the following 2 treatment arms:

- **Arm A (Experimental; relacorilant + nab-paclitaxel):** the patient will receive relacorilant 150 mg, administered orally under fed conditions, once daily for 3

consecutive days 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/m² IV) on Days 1, 8, and 15 of each 28-day cycle. Relacorilant will not be administered on Cycle 1 Day -1. On days in which both relacorilant and nab-paclitaxel are administered, it is preferable to administer relacorilant before nab-paclitaxel.

- **Arm B (Comparator; nab-paclitaxel):** the patient will receive nab-paclitaxel (100 mg/m² IV) administered on Days 1, 8, and 15 of each 28-day cycle.

Study treatment will start on Cycle 1 Day 1 for all treatment arms. Note: All patients in Arm A and Arm B will follow the SoA in [Table 12](#).

Patients should receive their first dose of study treatment in the clinic in a fed state after all assessments have been completed on the same day as randomization wherever possible, and with no more than 7 days delay in administering the first dose of study treatment from the randomization.

If ECG, PRO, QoL, and HRU assessments were not completed at the Screening visit, these assessments must be completed prior to administration of study treatment.

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

- Review concomitant medications.
- A serum or urine pregnancy test for female patients of childbearing potential will be performed and reviewed prior to randomization, prior to the first dose of study treatment (72-hour window from the first dose of study treatment).
 - Pregnancy testing will be performed monthly for patients in Arm A and Arm B.
- Confirm a CT or MRI scan of the chest, abdomen, and pelvis was performed within 45 days prior to the first dose of study drug.
- Record ECOG performance status.
- Treatment randomization.
- Perform full physical exam within 3 days before administering the first dose of treatment.
- Record vital signs, height (if not recorded at Screening), and weight.
- Draw blood samples for laboratory tests within 3 days before administering the first dose of study treatment: hematology, chemistry and PT/aPTT/INR. Results of hematology and chemistry should be reviewed prior to the first dose. CA-125 samples to be collected if not obtained within 14 days prior to administering the first dose of treatment.
- Patients in Arm A will receive their first dose of relacorilant and be dispensed adequate supply of relacorilant to self-administer during the treatment cycle.
- Provide a dose diary card to all patients receiving relacorilant.
- Pharmacodynamic sampling require fasting to be collected pre-dose, preferably between 7:00 am and 9:00 am ([Table 14](#)).
- Record AEs (any since the last visit).

Screening laboratory results can be used for the Cycle 1 Day 1 visit if taken within 3 days of the first dose of study treatment.

7.3. Cycle 1 Day 8

Patients in Arm A will receive an infusion of 80 mg/m² nab-paclitaxel and continue with their intermittent relacorilant dosing. On days in which both relacorilant and nab-paclitaxel are administered, it is preferable to administer relacorilant before nab-paclitaxel. Patients in Arm B will receive an infusion of 100 mg/m² nab-paclitaxel.

The following assessments will be performed:

- Review concomitant medications.
- Perform symptom-directed physical exam as needed.
- Record vital signs.
- Draw blood samples for laboratory tests: hematology, and chemistry.
- Assess treatment compliance and review dosing diary (Arm A only).
- Record AEs.

7.4. Cycle 1 Day 15

Patients in Arm A will receive an infusion of 80 mg/m² nab-paclitaxel and continue with their intermittent relacorilant dosing. On days in which both relacorilant and nab-paclitaxel are administered, it is preferable to administer relacorilant before nab-paclitaxel.

Patients in Arm B will receive an infusion of 100 mg/m² nab-paclitaxel.

The following assessments will be performed:

- Record concomitant medications.
- Perform symptom-directed physical exam as needed.
- Record vital signs.
- Draw blood samples for patients receiving treatment: hematology, and chemistry.
- Sparse PK sampling (Arm A only) ([Table 13](#)).
- Pharmacodynamic sampling require fasting and to be collected pre-dose, preferably between 7:00 am and 9:00 am ([Table 14](#)).
- Assess treatment compliance and review dosing diary for patients in Arm A.
- Record AEs.

7.5. Cycle 1 Day 17

The following assessments will be performed for a minimum subset of 40 patients in Arm A:

- Pharmacodynamic sampling require fasting and to be collected pre-dose, preferably between 7:00 am and 9:00 am ([Table 14](#)).

7.6. Cycle 2 (and Subsequent Cycles) Day 1

For Cycle 2 and all subsequent treatment cycles, patients in Arm A will receive an infusion of 80 mg/m² nab-paclitaxel and continue with their intermittent relacorilant dosing. On days in which both relacorilant and nab-paclitaxel are administered, it is preferable to administer relacorilant before nab-paclitaxel.

Patients in Arm B will receive an infusion of 100 mg/m² nab-paclitaxel. Refer to study design schema ([Figure 2](#)).

The following assessments will be performed:

- Record concomitant medications.
- Perform pregnancy testing for women of childbearing potential.
 - Pregnancy testing for patients in Arm A and Arm B will be done monthly.
- Record ECOG performance status.
- Perform full physical exam within 3 days prior to the dosing.
- Record vital signs and weight.
- Draw blood samples for laboratory tests within 3 days before administering the first dose of study treatment: hematology, and chemistry.
- Assess treatment compliance, provide dose diary card and dispensed adequate supply of relacorilant to self-administer during the treatment cycle (Arm A only).
- Pharmacodynamic sampling (Cycle 3 Day 1) and/or the visit following response (Complete or PR on tumor assessment) ([Table 14](#)).
 - Patients must be fasting, and samples to be collected pre-dose, preferably between 7:00 am and 9:00 am
- Perform PRO, QoL, and HRU assessments at Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1. After Cycle 4 Day 1, assessments will be performed every other cycle (starting with Cycle 6 Day 1) through the End of Treatment Visit.
- Record AEs.

Note: Tumor assessments with CT or MRI are required every 8 weeks (± 7 days) from Cycle 1 Day 1 for 40 weeks followed by every 12 weeks (± 7 days) for all patients (Arm A and Arm B) irrespective of treatment delays until unequivocal PD is documented, including in patients who discontinue treatment prematurely.

CA-125 blood samples will be drawn every 8 weeks (± 7 d) from Cycle 1 Day 1 for the first 40 weeks; then every 12 weeks (± 7 d) irrespective of any treatment delay until PD. Once the best response (CR or PR) is determined (at least 50% decrease from a pretreatment sample, which is defined as the most recent sample drawn before the first dose), a confirmatory CA-125 is required ≥ 28 days of the best response. The 28-day confirmatory sample must be less than or equal to the previous sample (within an assay variability of 10%) to calculate CA-125 responses accurately. ([Rustin 2011](#)).

7.7. Cycle 2 (and Subsequent Cycles) Day 8

For Cycle 2 Day 8 and all subsequent treatment cycles:

Patients in Arm A will receive an infusion of 80 mg/m² nab-paclitaxel infusion and continue with their intermittent relacorilant dosing. On days in which both relacorilant and nab-paclitaxel are administered, it is preferable to administer relacorilant before nab-paclitaxel.

Patients in Arm B will receive a 100 mg/m² nab-paclitaxel infusion.

The following assessments will be performed:

- Review concomitant medications.
- Perform symptom-directed physical exam for patients receiving study treatment.
- Record vital signs for patients receiving study treatment.
- Draw blood samples for laboratory tests within 3 days before administering the first dose of study treatment: hematology, and chemistry.
- Assess treatment compliance and review dosing diary (Arm A only).
- Record AEs.

7.8. Cycle 2 (and Subsequent Cycles) Day 15

For Cycle 2 Day 15 and all subsequent treatment cycles:

Patients in Arm A will receive an infusion of 80 mg/m² nab-paclitaxel infusion and continue with their intermittent relacorilant dosing. On days in which both relacorilant and nab-paclitaxel are administered, it is preferable to administer relacorilant before nab-paclitaxel.

Patients in Arm B will receive an infusion of 100 mg/m² nab-paclitaxel.

The following assessments will be performed:

- Record concomitant medications.
- Perform symptom-directed physical exam for patients receiving study treatment.
- Record vital signs for patients receiving study treatment.
- Draw blood samples for laboratory tests within 3 days before administering the first dose of study treatment: hematology, and chemistry.
- Assess treatment compliance and review dosing diary (Arm A only).
- Record AEs.

7.9. Visit Following Observation of CR or PR

Pharmacodynamic sampling require fasting and to be collected pre-dose, preferably between 7:00 am and 9:00 am for all patients who achieve a CR or PR ([Table 14](#)).

7.10. End of Treatment Visit

The following assessments will be performed (visit window provided in the SoA, [Table 12](#)):

- Record concomitant medications.
- Perform pregnancy testing for women of childbearing potential.
- Complete tumor assessment (CT/MRI) (if ≥ 4 weeks have elapsed since the last radiographic tumor assessment, unless there has been documented PD).
- Record ECOG performance status.
- Perform full physical exam.
- Record vital signs and weight.
- Draw blood samples for laboratory tests: CA-125, hematology, chemistry and PT/aPTT/INR.
- Collect urine sample for analysis.
- Perform 12-lead resting ECG (in triplicate).
- Assess treatment compliance and review and collect dosing diary (Arm A only).
- Pharmacodynamic sampling require fasting and to be collected pre-dose, preferably between 7:00 am and 9:00 am ([Table 14](#)).
- Perform PRO, QoL, and HRU assessments.
- Record AEs.

7.11. 30-Day Post-Treatment Follow-Up Visit (Phone)

The following assessments will be performed:

- Record AEs.
- Record concomitant medications.
- Laboratory tests to be performed at the Investigator's discretion.

7.12. Long-Term Follow-Up Visit (Phone)

During long-term follow-up, patients who discontinued treatment will continue to be followed for survival information (ie, the date and cause of death) and subsequent treatment information (ie, 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, any subsequent treatment information will be collected at the same time as radiographic tumor assessments (every 8 weeks [± 7 days]) for 40 weeks, then every 12 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, survival information and subsequent treatment

information will be collected every 3 months (± 7 days) after the last dose of study treatment.

- For women of childbearing potential, pregnancy tests will be repeated at the frequency specified in the SoA ([Table 12](#)).

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 4.5](#)). Study staff will consult, where permissible by local regulations, public records for survival status if the patient is lost to follow-up. All efforts to reach the patient, including at least three documented contact attempts, must be exhausted before a patient is deemed lost to follow-up. These contact attempts should be conducted a minimum of 1 week and not more than 2 weeks from previous attempt.

7.13. Unscheduled Visits

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

8. SAFETY EVENT DOCUMENTATION AND REPORTING

8.1. Investigator's Responsibilities

Investigators are responsible for monitoring the safety of patients who have entered this study and for providing appropriate medical care. By exercising appropriate healthcare options, the Investigator remains responsible for managing AEs. All SAEs must be reported to the Sponsor within 24 hours from awareness of the event.

The Investigator (or medically qualified designee) is responsible for determining whether an AE is clinically significant. All available information regarding the AE must be documented on the eCRF and in the patient's medical record.

8.2. Monitoring Safety Data During the Study

Safety results collected during the study (eg, AEs, laboratory results, physical findings) will be monitored on an ongoing basis by the Corcept Medical Monitor and the Investigator. All abnormal laboratory results, and ECG and exam findings will be assessed for clinical significance. The use of CTCAE v5.0 severity grading will be implemented systematically and consistently.

The Sponsor or its designee will promptly evaluate all reported safety information against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable regulatory authorities. Investigators, in turn, are responsible for notifying their IRB/IEC of new safety findings according to their local requirements.

In addition, an IDMC will be established to conduct periodic reviews of data to ensure the safety of patients ([Section 5.10.1](#)).

8.3. Definition of an Adverse Event

An AE is defined as any unfavorable or unintended sign (including clinically significant abnormal laboratory findings inconsistent with the patient's baseline findings), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to the study drug or not.

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 documented on the AE eCRF.

8.4. Definition of a Serious Adverse Event

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death.
- Is in the opinion of the Investigator immediately life-threatening (ie, the patient is at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization.

- Emergency room visits and hospital stays less than 24 hours do not qualify as inpatient hospitalizations.
- Pre-Planned or Elective Hospitalization: A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for convenience, social reasons, or solely for the administration of therapy are also not SAEs.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life-threatening, result in death, or require hospitalization, but based on appropriate medical judgment, it jeopardizes the patient, or 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 dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

AEs (including clinically significant lab abnormalities that constitute AEs) should be described using a unifying diagnosis whenever possible, rather than individual underlying signs and symptoms.

8.5. Expectedness

An SAE is considered unexpected for relacorilant if it was not identified in the RSI (Section 7.0) of the current Relacorilant IB Solid Tumors or if the event is of greater severity or frequency than described in this IB. An SAE is considered unexpected if it was not identified in the nab-paclitaxel (Abraxane) Section 4.8 of the European Medicine Agency SmPC, or if the event is of greater severity or frequency than described in the SmPC ([Abraxane SmPC](#)).

8.6. Reporting Suspected Unexpected Serious Adverse Reaction

The Sponsor/Sponsor representative will ensure any Suspected Unexpected Serious Adverse Reaction (SUSAR) for relacorilant and/or nab-paclitaxel is reported to regulatory authorities and governing bodies according to the local regulations. The Investigator (or Sponsor/Sponsor representative where required) must report these events to the appropriate IRB/EC that approved the protocol unless otherwise required and documented by the IRB/EC.

8.7. Clinical Significance

The Investigator (or medically qualified designee) is responsible for determining whether an AE is clinically significant for the patient. Clinical significance will be documented in the patient's medical records with the AE information.

8.8. 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 meets any of the following criteria will be recorded as an AE on the eCRF:

- Leads to dose modification or patient withdrawal from treatment or the study.
- Is accompanied by clinical symptoms.
- Requires a change in concomitant medications.

Other clinically significant laboratory values should be reported as AEs at the discretion of the Investigator.

Patients with a clinically significant out-of-range laboratory value will be followed until the laboratory value returns to normal, or the patient's baseline value, or the value becomes medically stable, or the patient is deemed by the Investigator to be lost to follow-up. The Investigator will treat the patient as medically required at appropriate intervals until this occurs.

8.9. Documentation of Adverse Events

Collection of AEs will start immediately following signing of the ICF and will continue throughout the study up to 30 days after the last dose of study drug(s) or until the date of initiation of a new anticancer therapy (whichever occurs first).

Any AEs reported more than 30 days after the last dose of study drug or after initiation of a new anticancer therapy do not need to be reported to Corcept, unless the AE meets the definition of serious (see [Section 8.4](#)) and the relationship to the study drug or study procedure is considered possibly or probably related by the Investigator (see [Section 8.10.2](#)). In such cases, these SAEs need to be reported per the process in [Section 8.11](#) and are not to be entered in eCRF.

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 on the appropriate eCRF(s).

If a patient is withdrawn from the study because of an AE, the event must be recorded on the Termination eCRF as the reason for discontinuation.

All AEs will be documented on the patient's medical record and AEs for all the randomized patients will be documented in the eCRF. The following attributes must be assigned: 1) description, 2) dates of onset and resolution, 3) severity ([Section 8.10](#)), 4) relationship to the study drug ([Section 8.10.2](#)), 5) seriousness criteria if applicable ([Section 8.4](#)), 6) action taken, and 7) outcome of event. 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.

8.10. Adverse Event Classification

8.10.1. Intensity Grades of Adverse Events

To describe the maximum severity of the AE on the AE eCRF, the Investigator will use NCI-CTCAE, v5.0 ([NCI CTCAE 2017](#)). (The seriousness and severity of an AE are different assessments. For information on seriousness assessment, see [Section 8.4](#)).

For events not listed in the NCI-CTCAE v5.0, use the definitions provided in [Table 9](#) to evaluate the Grade of severity for the AE.

Table 9: Grades for Adverse Events Based on the 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 (eg, 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 (eg, 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 AE

Source: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 ([NCI CTCAE 2017](#)).

8.10.2. Assessment of Causality: Relationship of Adverse Event to Study Drug or Study Procedure

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 10](#). The Investigator's assessment of causality must be provided for all AEs (serious and nonserious), as required for safety reporting to health authorities.

Alternative causes, such as the natural history of the underlying disease(s), concomitant therapy, other risk factors, biological plausibility, and the temporal relationship of the AE or SAE to the study drug should be considered and investigated.

There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is critical that the Investigator always assess causality for every SAE prior to the transmission of the SAE report to the Sponsor, since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator may change his/her opinion of causality in light of follow-up information received, amending the SAE report accordingly.

Several factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of the study treatment/study procedure.
- Whether an alternative etiology has been identified.
- Mechanism of action of the study drug.
- Biological plausibility.

Table 10: Causal Attribution Guidance for Adverse Events

Category	Description
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 drug (s), concurrent disease (s).
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 drug(s) or concurrent disease(s).

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

8.11. Procedures for Reporting a Serious Adverse Event

Any SAE occurring from the time of informed consent and for up to 30 days after the last dose of the study drug or until the date of initiation of a new anticancer therapy (whichever occurs first) must be reported within 24 hours a) to the Corcept Medical Monitor listed on the cover page and b) to the designated safety contact by completing and submitting the SAE form. All patients with an SAE must be followed and the outcomes reported. The Investigator must supply the Sponsor and the IRB with any additional requested information (eg, autopsy reports and terminal medical reports).

SAE reporting details are reported below:

Email: [REDACTED]

8.12. Recording Disease Progression and Deaths

Disease Progression:

Disease progression is expected in this study population, and the term “disease progression” should not be reported as an AE term. Disease progression also includes the development of new metastasis, or the progression of existing metastasis, to the primary cancer under study.

If the primary cause of death is disease progression, the cause of death should be clearly identified on the Death eCRF as progression of the cancer under study and not reported as an AE or SAE.

SAE Leading to Death:

All deaths not due to disease progression within 30 days of the last dose of study drug or until the date of initiation of a new anticancer therapy (whichever occurs first) must be reported as an SAE, regardless of causality, per [Section 8.11](#). All deaths not due to disease progression after 30 days of the last dose of study drug or until the date of initiation of a new anticancer therapy (whichever occurs first) will not be reported as SAE, unless the event is considered possibly or probably related to study drug or study procedure by the Investigator.

For SAEs leading to death, the outcome of this event will be recorded as fatal and death will not be recorded as a separate event. The eCRF should reflect that death was due to an AE with the corresponding reason documented. If the cause of death is unknown and cannot be ascertained at the time of the reporting, report it as an SAE and record as “unexplained death”. Every effort must be pursued to establish a cause of death. Update the SAE report when more specific information becomes available.

- The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.

8.13. Adverse Event Follow-Up and Recording

All AEs considered to be related to study drug ([Section 8.10.2](#)) and all SAEs will be followed until resolution, until deemed stable by the Investigator, or until the patient is deemed by the Principal Investigator to be lost to follow-up. Responses to follow-up queries about the reported event(s) should be recorded and reported to the Sponsor as soon as possible.

8.14. Pregnancy

All pregnancies that occur during the study and within 6 months of the last dose of the study drug should be immediately reported to the Sponsor. The outcome of any conception occurring from the date of the first dose of study treatment through 6 months of the last dose of study treatment will be followed and documented for up to 2 months after the completion of pregnancy.

8.14.1. Maternal Exposure

If a patient becomes pregnant during the study, study drug should be discontinued immediately. Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

If any pregnancy occurs during the study or within 6 months of the final dose of the study drug, the Investigator or designee should inform the appropriate Sponsor representatives by completing and submitting a Pregnancy Form immediately but no later than 24 hours of when he or she becomes aware of it.

Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and managed as SAEs. Elective abortions without complications should not be considered AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed and documented for up to 2 months after the completion of pregnancy, even if the patient discontinued the study.

The Investigator or designee should ensure that all relevant information is provided to the responsible Clinical Safety Group. All pregnancy outcomes must be reported by the Investigator within 24 hours after he or she becomes aware of it.

8.14.2. Paternal Exposure

Not applicable.

8.15. Treatment of Overdose

There is currently no experience with overdose of relacorilant. The Sponsor 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.
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor's Medical Monitor based on the clinical evaluation of the patient.

8.16. Special Situations, Definitions and Reporting

Special situation reports (SSRs) include reports of medication error and overdose involving study drug regardless of an associated AE. SSRs must be reported on the SAE form within 24 hours of the Investigator becoming aware of the situation.

All clinical sequelae in relation to these SSRs should also be reported as AEs or SAEs at the same time using the AE CRF/eCRF and/or the SAE report form.

Special Situation Definitions

Overdose: An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively that is above the maximum recommended dose as per protocol. In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the Investigator has reason to suspect that the subject has taken the additional dose(s).

Medication error: Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

8.17. Emergency Sponsor Contact

In a medical emergency (ie, an event requiring immediate attention regarding the treatment of a patient, operation of the clinical study, and/or the use of study drug), study site personnel will apply appropriate medical intervention according to current standards of care and contact the Sponsor's Medical Monitor listed on the cover page.

8.18. SARS-CoV-2 Tests (If Required)

COVID-19 testing may be performed based on current infection rates and availability of tests. If required by the site, testing will comprise an antigen PCR test, other antigen test, or other novel approved COVID-19 testing.

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

The analysis populations are defined in [Table 11](#).

Table 11: Definitions of Analysis Populations

Population	Description
Screened	All patients who sign the ICF.
Intent-to-Treat Population (ITT)	All patients randomized. All patients will be analyzed according to the treatment assigned at randomization. This analysis population will be used for analysis of the primary endpoints and all secondary efficacy endpoints.
Safety	All randomized patients who received at least 1 dose of study treatment will be analyzed according to the treatment received. This population will be used in all analyses of safety endpoints.
Pharmacokinetics (PK)	Subset of the Safety population with PK data collected and available for analysis.

9.2. General Statistical Considerations

All summaries will be presented by treatment group (as randomized), regardless of the actual treatment received 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 treatment group as randomized.

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

To maintain experiment-wise 2-sided type I error at 0.05, a group sequential weighted Holm procedure will be used for the dual primary endpoints PFS and OS. The study will be considered to have a positive outcome if either of the 2 primary endpoints reaches statistical significance.

For the primary efficacy endpoint of PFS by BICR, the null hypothesis of no difference in PFS among the 2 study groups will be tested at a 2-sided $\alpha = 0.04$ level of significance using a stratified log-rank test. The alternative hypothesis is that there is a difference between groups. The primary endpoint of OS will be allocated a 2-sided $\alpha = 0.01$ level of significance for the stratified log-rank test. If PFS by BICR is rejected, then, per the Holm procedure, OS will be tested at $\alpha = 0.05$, using a stratified log-rank test. If PFS by BICR is not significant, then OS will be tested at $\alpha = 0.01$.

An interim analysis of OS will be performed at the time of the primary analysis of PFS. At the interim analysis, OS data will be summarized to detect a trend in OS and the alpha spending function will be detailed in the Statistical Analysis Plan. The formal final analysis of OS will be conducted when approximately 292 deaths have been observed and will be performed using the ITT population.

All other secondary endpoints will be tested at a nominal 2-sided $\alpha = 0.05$ level of significance, with no additional adjustment for multiplicity. P-values from tests of hypothesis associated with secondary and exploratory endpoints will be considered descriptive, and not inferential.

9.4. Sample-Size Calculation

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 the Phase 2 study CORT125134-552, the observed median PFS was 3.8 months with nab-paclitaxel alone (95% CI: 3.5–5.4) versus 5.6 months with relacorilant plus nab-paclitaxel (95% CI: 3.7–7.2). The observed results are the basis for the assumptions for study CORT125134-556.

For PFS, based on 1:1 randomization allocation ratio, a total of 230 events ensures the study has 86.4% power for a 2-sided log-rank test with a $\alpha = 0.04$ level of significance, to detect a 50% increase in PFS (HR = 0.66). Assuming an exponential distribution of PFS, this corresponds to an increase in median PFS from 3.8 months to 5.8 months.

Up to 360 patients will be randomized (1:1) and followed until the required number of events are observed. This sample size allows for a 10% dropout rate in the first 12 months of follow-up.

For OS, approximately 292 events will provide the study with 80% power for a 2-sided log-rank test with an overall $\alpha = 0.01$ level of significance to detect a 50% increase in OS (HR = 0.67). Assuming an exponential distribution of OS, this corresponds with an increase in median OS from 13 months to 19.4 months.

9.5. Analysis Plan

9.5.1. Patient Disposition

Patient disposition summaries will include the number of enrolled patients, the number of patients in each analysis population, the number of patients who complete the study, and the number of patients who terminate the study early broken out by the primary reason for discontinuation.

9.5.2. Demographic and Baseline Characteristics Data

Categorical demographic and baseline data will be summarized by frequency while continuous variables will be summarized by mean, standard deviation, median, minimum, and maximum. Summaries will be presented by treatment group and for all patients combined.

9.5.3. Prior and Concomitant Medications

Verbatim terms will be mapped to Anatomical Therapeutic Chemical (ATC) class and Generic Drug Names using the most current version of the World Health Organization Drug Dictionary. The number and percentage of patients will be presented for each medication by treatment group and for all patients combined.

9.5.4. Analysis of Dual Primary Efficacy Endpoints

The dual primary endpoints PFS and OS are defined in [Section 3.2.1](#).

PFS

The first primary efficacy analysis is the comparison of PFS by BICR in patients treated with the combination of relacorilant and nab-paclitaxel compared with nab-paclitaxel monotherapy.

PFS is defined as time from randomization until the date of radiologic PD per RECIST v1.1 or death from any cause, whichever comes first, as determined by BICR. Clinical deterioration determined by Investigators will not be considered progression events for the primary analysis. The primary analysis of PFS will be conducted when at least 230 PFS events have been observed.

A stratified log-rank 2-sided test with a 0.04 level of significance will be used to compare treatment groups. The stratification factors will be the same used to stratify the randomization schedule as documented in the interactive voice and web-response system (IXRS): region (North America versus Europe versus the rest of the world) and line of therapy (1 versus more than 1).

The median PFS and the associated 95% confidence interval (CI) for each treatment arm will be estimated using the Kaplan-Meier method. The HR ($\lambda_{\text{active}}/\lambda_{\text{control}}$) and the associated 95% CI will be estimated using a Cox regression model with treatment group as the only main effect in the presence of stratification factors at randomization. An unstratified HR and the associated 95% CI will also be presented.

If the p-value for the stratified log-rank test is statistically significant (< 0.04 , 2-sided) and the observed HR ($\lambda_{\text{active}}/\lambda_{\text{control}}$) is < 1 , the null hypothesis of no difference in PFS will be rejected and it will be inferred that PFS is statistically prolonged in the group receiving relacorilant + nab-paclitaxel compared with the group receiving nab-paclitaxel monotherapy.

Overall Survival

The second primary efficacy analysis is the comparison of OS in patients treated with the combination of relacorilant and nab-paclitaxel compared with nab-paclitaxel monotherapy.

OS is defined as the time from randomization to death due to any cause. There will be an interim and final analysis for OS. The interim analysis of OS will be conducted at the time of the primary analysis of PFS. At the interim analysis, OS data will be summarized to detect a trend in OS. The formal analysis of OS will be conducted when approximately 292 deaths have been observed and will be performed using the ITT population.

The testing of OS will be conducted using a stratified log-rank 2-sided test. The stratification factors will be the same used to stratify the randomization schedule as documented in the IXRS.

The median OS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. The HR and the associated 95% CI will be estimated using a Cox regression model with treatment group as the main effect and stratification factors at randomization as covariates. An unstratified HR and the associated 95% CI will also be presented.

9.5.5. Approach to Missing Data Analysis

All available data will be used. No efficacy or PK data will be imputed; missing values will be treated as missing. All sensitivity analyses will be specified in the Statistical Analysis Plan (SAP).

9.5.6. Secondary Efficacy Endpoint Analysis

The secondary efficacy endpoints are defined in [Section 2.2.1](#).

Best Overall Response

BoR as determined by BICR is defined as the best response by RECIST v1.1 recorded from the date of randomization until PD or death. BoR will be summarized for the following types of responses: CR, PR, SD, PD and NE, categorically and graphically with a waterfall plot.

Objective Response Rate

The ORR will be determined by BICR and is defined as the proportion of patients with a partial or CR as defined by RECIST v1.1. The primary analysis of ORR will be performed among the patients with baseline measurable disease in the ITT population. In the analysis of ORR, patients who do not have any post-baseline adequate tumor assessments will be counted as non-responders. A stratified Cochran-Mantel-Haenszel (CMH) test will be used to test differences in ORR between treatment arms. The stratification factors will be the same used to stratify the randomization schedule as documented in the IXRS. The CR responders will be reported separately for the patients with non-measurable disease at Baseline.

Duration of Response

DoR is defined as the time from the date objective response (CR or PR) was documented (whichever came first) until first observation of PD or death due to any cause. DoR will be assessed only in patients with baseline measurable disease in the ITT population who have an objective response (CR or PR) 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 tumor assessment.

Clinical Benefit Rate

CBR by RECIST v1.1 is defined as proportion of patients who attain CR, PR, or SD by RECIST v1.1 at 24 weeks. In the analysis of CBR, patients who do not have any post-baseline adequate tumor assessments will be counted as non-responders. The CBR by RECIST v1.1 will be reported as rates and 95% CI using exact methods. A stratified CMH test will be used to test differences in CBR between treatment arms. The stratification factors will be the same used to stratify the randomization schedule as documented in the IXRS.

Combined-Response According to RECIST Version 1.1 + GCIG Criteria

CA-125 response will be assessed per GCIG criteria ([Rustin 2011, Appendix F](#)) defined as $\geq 50\%$ reduction in CA-125 from a pretreatment 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 fall to within the reference range will be classified as CA-125 complete responders. CA-125 response will be reported as percentage and 95% CI.

Response will be reported separately and combined for RECIST v1.1 and CA-125/GCIG criteria. Combined-response will be reported as percentage and 95% CI.

9.5.7. Exploratory Endpoint Analysis

The exploratory endpoints are defined in [Section 3.2.3](#).

Analysis of the exploratory endpoints will be performed on the ITT population and will be described in the SAP.

9.5.8. Safety Analyses

AEs will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) version 24 ([MedDRA Guidance 2021](#)). TEAEs will be summarized overall and displayed by system organ class and preferred term, as well as by severity, seriousness, and relationship to the study treatment. Serious AEs and AEs that lead to study treatment discontinuation or withdrawal from the study will be listed by individual patient.

Clinical laboratory test results, vital sign measurements, and ECG interval results will be summarized as changes from Baseline by parameter by treatment and visit using descriptive statistics. Categorical laboratory results may also be summarized using shift tables.

The safety analyses will include all patients who receive any study drug (relacorilant + nab-paclitaxel or nab-paclitaxel monotherapy) throughout the study duration.

All AEs will be coded using MedDRA v24. The Investigator will classify the severity of AEs using the CTCAE v5.0.

A TEAE is defined as any event with an onset date on or after date of first dose of study drug, or any event present before treatment that worsens after treatment. Only TEAEs with an onset date prior to date of last dose + 30 days or the date of initiation of a new anticancer therapy (whichever occurs first) will be tabulated in summary tables.

The number and percentage of patients with AEs will be summarized by system organ class, preferred term, relationship to study drug, and severity for each treatment group. A by-patient listing will be provided for those patients who experience an SAE, including death, or experience an AE associated with discontinuation of study drug. Clinical laboratory data will be summarized by the type of laboratory test. The number and percentage of patients who experience abnormal (ie, outside of reference ranges) and/or clinically significant abnormalities after study-drug administration will be presented for each clinical laboratory measurement. For each clinical laboratory measurement, descriptive statistics will be provided for Baseline and all subsequent post-treatment scheduled visits. Changes from Baseline to the post-treatment visits will also be provided.

Descriptive statistics of vital signs will also be provided in a similar manner. In addition, shift from Baseline in CTCAE grade (where applicable) and by high/low flags (where CTCAE grades are not defined) will be presented by treatment group.

9.5.9. Pharmacokinetics Analysis

Sparse PK sampling will be conducted for relacorilant on Cycle 1, Day 15 (Table 13). Relacorilant plasma exposures will be estimated using population PK methods, which will be described in a separate analysis plan finalized before database lock.

9.5.10. Pharmacodynamic Analysis

PD analyses will be described in a separate PD analysis plan finalized before database lock.

9.5.11. Biomarker/Pharmacogenetic Analysis

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

9.5.12. Interim Analysis

There will be an interim and final analysis for OS. An interim analysis of OS will be conducted at the time of the primary analysis of PFS. As the OS data are not expected to be mature at the time of interim analysis, OS data will be summarized to detect a trend and the alpha spending function will be specified in the SAP. The formal analysis of OS will be conducted when approximately 292 death events have been observed.

9.5.13. Patient-Reported Outcomes/Quality of Life

Analyses of PRO endpoints will be specified in the SAP finalized before database lock.

10. ETHICAL AND LEGAL CONSIDERATIONS

10.1. Compliance with IRB/IEC Regulations

This study is to be conducted in accordance with IRB/IEC, and applicable local regulations. The protocol, IB, ICF(s), recruitment materials, and all patient materials will be submitted to the IRB/IEC for review and approval. Approval of both the protocol and the ICF(s) 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 ensuring annual reviews by the IRB/IEC occur, and that they receive approval. The Investigator is also responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements before implementing any changes.

Any changes to the ICF must be approved by the IRB/IEC. A determination will be made as to whether previously consented patients need to be re-consented. Other documents related to the clinical trial may also need IRB/IEC approvals prior to implementing.

The Sponsor or their designee 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 retained and provided to the Sponsor or their designee.

Progress reports and notifications, including required safety information, 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 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 must be obtained from each patient before initiating any study-mandated Screening procedures. The ICF will contain all the elements required by ICH guidelines for GCP and any additional elements required by local regulations.

The Investigator(s) at each center will ensure 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 informed consent process discussion should be documented in patient's record.

Investigator(s) must maintain the original, signed ICF. A copy or an original of the signed ICF must be given to the patient depending on local regulatory requirements.

The ICF should include information about possible retention of biological samples at the conclusion of this study, the purpose of retaining the samples and the time period for which they will be retained. With the patient's permission, samples, including blood, plasma, serum, and tissue, may be retained for

- Future identification of biomarkers of disease or treatment with study drug.
- Future analysis of active metabolite concentrations and possible biomarkers related to drug response.

10.3.2. Patient Confidentiality

To maintain patient confidentiality, all source documents, study reports, and communications will identify the patient by the assigned patient number.

The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee, the IRB, and regulatory authority(ies) access to the patient's original source records for data verification 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

Before enrollment into the study, the Investigator or designee must explain to each patient their personal information will be shared with the Sponsor and companies working with the Sponsor, as well as shared with regulatory agencies and the IRB/IEC. Personal information is shared to ensure the study is being conducted properly, to evaluate the study results, and to develop and approve the study drug if it is shown to be safe and effective.

It is the Investigator's (or designee's) responsibility to obtain the patient's written acknowledgement or written permission to use their personal information per country-specific regulations. This must be obtained before initiating any study-mandated procedures.

If the patient withdraws permission to use their personal information, it is the Investigator's responsibility to, 1) document the patient's request to withdraw (ie, as a written request), 2) ensure no further data will be collected from the patient, and 3) ensure the patient will be removed from the study.

10.3.4. Data Protection

The Sponsor ensures that all processing activities involving personal data performed in the scope of this clinical study are compliant with, but not limited to, the requirements set by EU General Data Protection Regulation (GDPR 679/2016), its subsequent amendments and any additional national laws on data protection, recommendations, and guidelines as applicable.

The applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorized access, disclosure, dissemination, alteration or loss of information and processed personal data, the Sponsor has implemented and maintains the following measures:

- Restriction and monitoring of physical access to the offices and information processing facilities to employees, personnel, and approved visitors.

- Appropriate and restricted user access relevant to the function and type of activity performed in relation to the clinical trial.
- Effective pseudonymisation of personal data in compliance with European Data Protection Board (EDPB) recommendations (Version 2.0; 18 June 2021).
- Encryption of personal data where necessary for integrity, availability and resilience of processing systems and services.
- Network, application, and database security by means of firewalls and antivirus/anti-malware; ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures, and response to such attacks.
- Means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident.
- Logging of security events and/or incidents in information systems.
- Procedures covering reporting, analysis, monitoring and resolution of security incidents.
- Ensuring that information systems, computers and software involved in the performance of the services provided in this clinical study are backed up.
- A process for regularly testing, assessing, and evaluating the effectiveness of technical, and organizational measures for ensuring the security of the processing.
- Procedures to capture, mitigate, and respond to personal data breaches in a timely manner.
- Business continuity procedures ensuring that the Sponsor can continue to provide services through operational interruption.
- All locations, personnel and information systems used to perform services for this clinical study will be covered.
- The Sponsor will ensure technical and organizational security measures described above, are regularly reviewed, and updated to consider and evaluate any evolution on technological developments.
- The Sponsor may apply additional specific statutory requirements, where applicable in the national laws, and will implement the necessary security measures even if they are not expressly listed above.
- In addition to the already above-mentioned technical and organizational measures, The Sponsor, by means of internal measures and imposed contractual clauses to the selected vendors and partners (in their role of processors), ensures the confidentiality of records and personal data of subjects.

With exception of the activities in the scope of the on-site monitoring, inspections, or audits the patient's name will neither be asked for, nor recorded by the Sponsor. An identification number will be allocated to each patient registered in this clinical study. This number will identify the patient and will be included on all case report forms and corresponding material and data associated with the patient.

Monitors acting on behalf of the Sponsor will have access to fully identifiable information only in the scope of the on-site monitoring visits, and only for the source data verification mandatory under clinical trial framework, including the ICH-GCP obligations applicable to the conduct of this clinical study. Staff responsible for this task are bound by additional stricter confidentiality clauses imposed upon them, as compared to other staff members.

The Sponsor has put in place a functional process of reporting of any data breach occurring at their facility or its vendor's and partner's (in their role of processor) facilities and premises. In event of any data breach, the Sponsor will immediately apply relevant measures to mitigate the risks to data subjects as appropriate in relation to the specific context of the data breach, taking into account its source, underlying intentions, possibilities of recovery. Any data breach will be reported to the appropriate supervisory data protection authority within 72 hours of the Sponsor becoming aware of the data breach, unless the data breach is unlikely to result in a risk to the rights and freedoms of data subjects. If the personal data breach is likely to result in a high risk to the rights and freedoms of data subjects, the data subject will be informed by the Sponsor through the study site.

11. ADMINISTRATIVE CONSIDERATIONS

11.1. Quality Management

As part of quality management based on a risk-based approach per current ICH E6: risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to SOPs, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

Study sites, the study database, and study documentation will be monitored regularly and may be subject to a quality assurance (QA) audit during the study by the IRB/IEC and/or the Sponsor or its designee. In addition, inspections may be conducted by regulatory agencies and/or at their discretion.

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

Following written SOPs and the study-specific monitoring plan, the monitors will verify that the clinical study is conducted, data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (eg, Good Laboratory Practices, Good Manufacturing Practices).

Upon request, the investigational site will provide direct access and allow the Sponsor (or its representative including monitors and/or auditors), IRB/IEC and regulatory authorities to review and inspect all trial-related sites, drug storage area, study-drug stock, drug accountability records, patient charts, source documents, and other records related to study conduct.

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

11.2. Study Monitoring

The Sponsor, or designee, will be responsible for the monitoring of the study. Study monitors, or other authorized representatives of Sponsor will contact and visit the Investigators at regular intervals throughout the study to answer study questions, and to systematically and independently examine all study-related activities, verify adherence to the protocol, and assess the completeness, consistency, and accuracy of the data.

Monitoring may include, but is not limited to:

- Reviewing eCRFs for accuracy and completeness.
- Assessing compliance with the protocol and adherence to regulatory and GCP requirements.

- Verifying that the site maintains an adequate supply of study drugs, any necessary supplies, and that appropriate storage conditions are maintained.

Monitoring visits will be conducted according to the ICH Guideline for GCP and all applicable country and local regulations and guidance.

By agreeing to participate in this research study, the Investigators agree to co-operate with the study monitor to ensure that any problems detected during the monitoring visits are promptly resolved.

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

11.3. Documentation

11.3.1. Source Documentation

Source documents provide all original records of clinical findings, observations, or other information from a clinical trial necessary for the reconstruction and evaluation of the trial (eg, a patient's medical records, hospital charts, clinic charts, the Investigator's patient study files, results of diagnostic tests, including x-rays, laboratory tests and ECGs). All source data should be attributable, legible, contemporaneous, original, accurate, and completed. Changes to source data should be traceable (ie, dated and initialed), should not obscure the original entry, and should be explained, if necessary.

Investigators must retain all original source documents. The Sponsor or its designee will notify Investigators in writing when the trial-related records are no longer needed.

11.3.2. Case Report Forms

The Investigator must generate and maintain complete, adequate, accurate, reliable, and legible records in a timely manner to enable full documentation of study conduct. All data entered into CRFs (paper or electronic) must be substantiated by and consistent with a source document.

Discrepancies between eCRFs and their respective source documents should be explained. All changes in eCRF data entry at the study site will be performed by personnel delegated by the Principal Investigator and will be in the clinical database audit trail.

In the event paper CRFs are utilized, any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry.

All changes in CRF data entry at the study site, whether using an eCRF or paper CRF, will be performed by designated site personnel.

11.3.3. Retention of Study Essential Documents

The Investigator must retain adequate and accurate records so study conduct can be fully documented and the study data to be subsequently verified.

Study essential documents, which include the patient identification code list (ie, patient names and corresponding study numbers), 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 study drug. 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. If the Investigator can no longer maintain the records, it is the responsibility of the Investigator to contact the Sponsor. 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. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

11.3.4. Sample Collection, Preparation, and Shipping

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

11.4. Long-Term Retention of Biological Samples

All biological samples will be retained by the Sponsor or designee under the original informed consent of the patient and the IRB/IEC approval. Samples will be held for a period up to 15 years after completion of the clinical study report. The Sponsor or the designee may store the patient's sample(s) longer if required to address regulatory agency questions; in this event, the patient's sample(s) will be destroyed after all questions are adequately answered.

An individual patient can choose to withdraw consent to have her samples used for future research at any time without affecting their participation in the study, or their care by the health provider. After receipt of a request for sample destruction, that patient's sample(s) will then no longer be used for future research purposes beyond the current study, and their sample(s) will be destroyed. However, if there are ongoing regulatory questions, the patient's sample(s) will be destroyed after all questions are adequately answered.

The long-term retention samples will be coded to allow de-identification according to applicable regulatory guidelines. It is the responsibility of the trial site to ensure samples are appropriately labeled in accordance with trial procedures to comply with all applicable laws.

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.

Such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

Samples may be subject, but not limited to European Directives 2002/58/EC, the General Data Protection Regulation 2016/679, and any legislation and/or regulation implementing or made pursuant to them, or which amends, replaces, re-enacts, or consolidates any of them, and all other applicable laws relating to processing of personal data and privacy that may exist in any relevant jurisdiction.

11.5. Clinical Supplies

11.5.1. 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 2](#).

11.5.2. Clinical Supply Inventory

Each clinical site is required to complete and maintain a detailed inventory 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 designated and qualified person to patients in the study. The investigational drug will be dispensed every 2 cycles during the treatment period.

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-by-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 (on-site clinical research associate) has confirmed the accountability data and Sponsor has approved return or destruction.

11.5.3. Return or Destruction of Study Drug and/or Supplies

At the end of the study, after final drug-inventory reconciliation by the study monitor, the study site will either return study drug and/or supplies to the Sponsor or designee, or destroy all unused study drug and/or supplies, including empty containers, according to institutional policy.

11.5.4. Study Drug Destroyed by the Site

Unused/undispensed study drug and/or supplies 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.

Any destruction of study drug on-site must be documented. Documentation must be provided to the Sponsor and retained in the Investigator study files.

11.5.5. Study Drug Returned to Sponsor for Destruction

If a site is unable to destroy unused/undispensed study drug and/or supplies appropriately, the site can request return of study drug and/or supplies to the Sponsor or designee.

The return of study drug and/or supplies must be accounted for on a Study Drug Return Form provided by the Sponsor or designee.

11.5.6. Drug Accountability

It is the responsibility of the Investigator to maintain drug accountability at the study site and ensure a current record of study-drug disposition is maintained. It is the responsibility of the Investigator to ensure that the study 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, lost, or accidentally or deliberately destroyed study product.

Dispensing records will document quantities received from the Sponsor (or designee) and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, the initials of the person dispensing the drug, quantities of drug returned by the patients and disposal/return of returned study drug.

11.6. Post-Trial Care

There is no provision for continued access to study drug ([Section 5.9](#)).

11.7. Protocol Noncompliance

A protocol deviation is any noncompliance with requirements in the clinical trial protocol, GCP, or the manual of procedures (MOP) requirements. The noncompliance may be on the part of the patient, the Investigator, or the study-site staff. As a result of deviations, corrective actions consistent with current ICH E6 may be implemented.

Prospective approval of deviations from the inclusion and exclusion criteria, known as protocol waivers or exemptions, is not permitted. Changes to the conduct of the protocol may not be made, except to address an immediate risk to the patient, unless the change has been submitted to the regulatory authorities for review and the change has been approved by the IRB/IEC.

Sponsor, clinical study staff and contractors may acknowledge, but not approve, protocol deviations reported by a site that have happened or are planned to happen.

Any important protocol deviations affecting patient eligibility and/or safety or data integrity must be recorded in study source documents and submitted to the IRB/IEC and regulatory authorities, as applicable, prior to implementation.

After the protocol is approved by the Sponsor and by IRB/IEC, any change that might affect the approval of the IRB/IEC must be documented in the form of a protocol amendment. The amended protocol must be approved by the IRB/IEC and annually, as local regulations require.

11.8. 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.

11.9. 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 the Sponsor. The Investigator agrees to submit all manuscripts or abstracts to the Sponsor for review before submission to the publisher.

The Sponsor 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 (ICMJE) requirements.

11.10. Electronic Systems

All electronic systems, including clinical study sites, clinical operations, data management, biostatistics, safety, and CRO systems, etc., used to collect, manage, and storage study data should be validated and in compliance with 21 CFR Part 11 and EU Annex 11 guideline, and other applicable country regulations. The validation documentation should be made available at all times during inspection or Sponsor audits. Any modification to the validated system should be documented via a quality change control process and justified to their intend of use.

12. REFERENCES

- Abraxane Prescribing Information (USPI). September 2020. Accessed at <https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=24d10449-2936-4cd3-b7db-a7683db721e4>.
- 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. European Medicines Agency. 14 January 2013. Available from: https://www.ema.europa.eu/en/documents/product-information/abraxane-epar-product-information_en.pdf.
- American Cancer Society. Cancer Facts & Figures 2021. Atlanta, Ga: American Cancer Society; 2021.
- Block TS, Murphy TI, Munster PN, Nguyen DP, Lynch FJ. 2017. Glucocorticoid receptor expression in 20 solid tumor types using immunohistochemistry assay. *Cancer Manag Res.* 9:65–72.
- Bruchim I, Jarchowsky-Dolberg O, Fishman A. 2013. Advanced (>second) line chemotherapy in the treatment of patients with recurrent epithelial ovarian cancer. *Eur J Obstet Gynecol Reprod Biol.* 166(1):94–98.
- 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. 122(1):111–115.
- Colombo N, Van Gorp T, Matulonis UA, Oaknin A, Grisham RN, Fleming GF, Olawaiye AB, Nguyen DD, Greenstein AE, Custodio JM, Pashova HI, Tudor IC, Lorusso D. Relacorilant + Nab-Paclitaxel in Patients With Recurrent, Platinum-Resistant Ovarian Cancer: A Three-Arm, Randomized, Controlled, Open-Label Phase II Study. *J Clin Oncol.* 2023 Jun 26;;JCO2202624. doi: 10.1200/JCO.22.02624. [Epub ahead of print]
- Conzen SD. 2008. Minireview: nuclear receptors and breast cancer. *Mol Endocrinol.* 22(10):2215–2228.
- Deng Y, Xia X, Zhao Y, Zhao Z, Martinez C, Yin W, et al. 2021. Glucocorticoid receptor regulates PD-L1 and MHC-I in pancreatic cancer cells to promote immune evasion and immunotherapy resistance. *Nat Commun.* 6;12(1):7041.
- EuroQol Group. 1990. EuroQol: A new facility for the measurement of health-related quality of life. *Health Policy* 16(3):199–208.
- 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.
- Friedlander M L, King M T. 2013. Patient-reported outcomes in ovarian cancer clinical trials. *Ann Oncol.* 24 Suppl 10:x64–x68.

- Friedlander M, Trimble E, Tinker A, Alberts D, Avall-Lundqvist E, Brady M, et al. 2011. Gynecologic Cancer InterGroup. Clinical trials in recurrent ovarian cancer. *Int J Gynecol Cancer*. May;21(4):771-5.
- Ganghadaran, SGD. 2016. Management of Platinum Resistant – Refractory Ovarian Cancer: A Short Review. *Journal of Cancer Research and Treatment* 4(2), 32–36.
- Greenstein AE, Habra MA, Wadekar SA, Grauer A. 2021. Adrenal tumors provide insight into the role of cortisol in NK cell activity. *Endocr Relat Cancer*. 29;28(8):583–592.
- Greenstein AE, Hunt HJ. 2021. Glucocorticoid receptor antagonism promotes apoptosis in solid tumor cells. *Oncotarget* 12(13):1243–1255.
- Greimel E, Bottomley A, Cull A, Waldenstrom A-C, Arraras J, Chauvenet L, et al. 2003 EORTC Quality of Life Group and the Quality of Life Unit. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. *Eur J Cancer*. 39(10):1402–1408.
- Horwitz SB. Taxol (paclitaxel): mechanisms of action *Ann Oncol*. 1994;5 Suppl 6:S3–6.
- Hou WJ, Guan JH, Dong Q, Han YH, Zhang R. 2013. Dexamethasone inhibits the effect of paclitaxel on human ovarian carcinoma xenografts in nude mice. *Eur Rev Med Pharmacol Sci*. 17(21):2902–2908.
- Hunt HJ, Belanoff JK, Walters I, Gourdet B, Thomas J, Barton N, et al. 2017. Identification of the clinical candidate (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl) (4-(trifluoromethyl)pyridin-2-yl)methanone (CORT125134): a selective glucocorticoid (GR) antagonist. *J. Med. Chem*. 60:3405–3421.
- Kroon J, Puhf M, Buijs JT, van der Horst G, Hemmer DM, Marijt KA, et al. 2016. Glucocorticoid receptor antagonism reverts docetaxel resistance in human prostate cancer. *Endocr Relat Cancer*. 23:35–45.
- Luvero D, Milani A, Ledermann JA. 2014. Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. *Ther Adv Med Oncol*. 6(5):229–239.
- Macarulla TM, Siveke JT, Wang-Gillam A, Li C-P, Bodoky G, Dean AP, et al. 2017. Subgroup analysis by prior lines of metastatic therapy (mtx) in NAPOLI-1: a global, randomized phase 3 study of liposomal irinotecan (nal-IRI) ± 5-fluorouracil and leucovorin (5-FU/LV), vs. 5-FU/LV in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) who have progressed following gemcitabine-based therapy. *JCO*. 35 (15_suppl):4127.
- MedDRA® International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). MedDRA Term Selection, ICH-Endorsed Guide for MedDRA Users. Release 4.21 March 2021. Accessed February 18, 2022 at https://admin.meddra.org/sites/default/files/guidance/file/000571_termselptc_r4_21_mar2021.pdf
- Munster PN, Sachdev JC, Fleming GF, Borazanci EH, Grabowsky JA, Sharma M. 2019. Relacorilant (RELA) with nab-paclitaxel (NP): safety and activity in patients with pancreatic ductal adenocarcinoma (PDAC) and ovarian cancer (OvCA). *J Clin Oncol*. 37, no. 15_suppl (May 20, 2019) 4130–4130.

NCI (National Cancer Institute). 2017. Common Terminology Criteria for Adverse Events (CTCAE), 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, Horton J, Davis TE, McFadden ET, et al. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 5(6):649–55. PMID: 7165009.

Pan D, Kocherginsky M, Conzen SD. 2011 Activation of the glucocorticoid receptor is associated with poor prognosis in estrogen receptor-negative breast cancer. *Cancer Res*. 71(20):6360–6370.

Pang D, Kocherginsky M, Krausz T, Kim SY, Conzen SD. 2006. Dexamethasone decreases xenograft response to Paclitaxel through inhibition of tumor cell apoptosis. *Cancer Biol Ther*. 5:933–940.

Pujade-Lauraine E, Banerjee S, Pignata S. 2019. Management of Platinum-Resistant, Relapsed Epithelial Ovarian Cancer and New Drug Perspectives. *J Clin Oncol*. 20;37(27):2437-2448.

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*. 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.

Rustin GJ, Quinn M, Thigpen T, du Bois A, Pujade-Lauraine E, Jakobsen A, et al. 2004. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Natl Cancer Inst*. 96(6):487–488.

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.

Shimizu Y, Kamoi S, Amada S, Akiyama F, and Silverberg SG. 1998. Toward the development of a universal grading system for ovarian epithelial carcinoma: testing of a proposed system in a series of 461 patients with uniform treatment and follow-up. *Cancer*. 1998 Mar 1;82(5):893–901.

Skor MN, Wonder EL, Kocherginsky M, Goyal A, Hall BA, Cai Y, et al. 2013. Glucocorticoid receptor antagonism as a novel therapy for triple-negative breast cancer. *Clin Cancer Res*. 19:6163–6172.

Stringer-Reasor EM, Baker GM, Skor MN, Kocherginsky M, Lengyel E, Fleming GF, et al. 2015. Glucocorticoid receptor activation inhibits chemotherapy-induced cell death in high-grade serous ovarian carcinoma. *Gynecol Oncol*. 138:656–662.

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov). SEER*Stat Database: Incidence - SEER Research Data, 9 Registries, Nov 2020 Sub (1975-2018) - Linked To County Attributes - Time Dependent (1990-2018) Income/Rurality, 1969-2019 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2021, based on the November 2020 submission.

- Tangen IL, Veneris JT, Halle MK, Werner HM, Trovik J, Akslen LA, et al. 2017. Expression of glucocorticoid receptor is associated with aggressive primary endometrial cancer and increases from primary to metastatic lesions. *Gynecol Oncol.* 147(3):672–677.
- Taylor PT, Haverstick D. 2005. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Natl Cancer Inst.* 97(2):151; author reply 152.
- Ushijima K. 2010. Treatment for recurrent ovarian cancer-at first relapse. *J Oncol.* Volume 2010, Article ID 497429, 7 pages.
- Veneris JT, Darcy KM, Mhawech-Fauceglia P, Tian C, Lengyel E, Lastra RR, et al. 2017. High glucocorticoid receptor expression predicts short progression-free survival in ovarian cancer. *Gynecol Oncol.* 146(1):153–160.
- Wang JC, Harris CL. Glucocorticoid signaling. In: Wang JC and Harris C, eds. *Adv Exp Med Biol.* (New York, NY: Springer New York). 2015; 2895–2898.
- West DC, Kocherginsky M, Tonsing-Carter EY, Dolcen DN, Hosfield DJ, Lastra RR, et al. 2018. Discovery of a Glucocorticoid Receptor (GR) Activity Signature Using Selective GR Antagonism in ER-Negative Breast Cancer. *Clin Cancer Res.* 24:3433–3446.
- Yamamoto K, Ichijo H, Korsmeyer SJ. 1999. BCL-2 is phosphorylated and inactivated by an ASK1/Jun N-terminal protein kinase pathway normally activated at G(2)/M. *Mol Cell Biol.* 19:8469–8478.
- Zhang C, Beckermann B, Kallifatidis G, Liu Z, Rittgen W, Edler L, et al. 2006. Corticosteroids induce chemotherapy resistance in the majority of tumour cells from bone, brain, breast, cervix, melanoma and neuroblastoma. *Int J Oncol.* 29:1295–1301.

13. APPENDICES

APPENDIX A. SCHEDULE(S) OF ACTIVITIES

Table 12: Schedule of Activities for 28-day Treatment Cycle Patients in Arm A and Arm B

Study Procedure	Screening	Open-Label, Randomized-Treatment Phase							EOT ^b	30-Day FU ^c	Long- term FU ^d
		Cycle 1				Cycle 2 and Subsequent Cycles					
		Day 1	Day 8	Day 15	Day 17 ^a	Day 1	Day 8	Day 15			
Visit Name											
Informed consent	X	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X		-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-
Medical/oncologic history	X ^e	-	-	-	-	-	-	-	-	-	-
Concomitant medications	X	X	X	X	-	X	X	X	X	X	-
Serum/Urine Pregnancy test ^f	X	X	-	-	-	X	-	-	X	-	
Tumor biopsy ^g	X	-	-	-		-	-	-	-	-	-
Tumor assessment (CT/MRI) ^h	X	Every 8 weeks (±7 d) from C1D1 for the first 40 weeks; then every 12 weeks (±7 d)							X	-	-
ECOG performance status	X	X	-	-	-	X	-	-	X		-
Randomization ⁱ	-	X	-	-	-		-	-	-	-	-
Physical examination ^j	X	X	X	X	-	X	X	X	X		-
Vital signs ^k	X	X	X	X	-	X	X	X	X		-

Study Procedure	Screening	Open-Label, Randomized-Treatment Phase							EOT ^b	30-Day FU ^c	Long-term FU ^d
		Cycle 1				Cycle 2 and Subsequent Cycles					
		Day 1	Day 8	Day 15	Day 17 ^a	Day 1	Day 8	Day 15			
Height ^l	X	X	-	-	-	-	-	-	-	-	-
Weight ^l	X	X	-	-	-	X	-	-	X		-
CA-125 ^m	X	X	Every 8 weeks (±7 d) from C1D1 for the first 40 weeks; then every 12 weeks (±7 d) until PD. A confirmatory CA-125 is required ≥ 28 days of the best CA-125 response after the best CA-125 response is determined.						X	-	-
Chemistry ⁿ , Hematology ^o	X	X	X	X	-	X	X	X	X	X	-
Urinalysis ^p	X	-	-	-	-	-	-	-	X		-
PT/aPTT/INR ^q	X	X	-	-	-	-	-	-	X	-	-
Hepatitis B and C serologies and HIV	X	-	-	-	-	-	-	-	-	-	-
12-Lead ECG (in triplicate) ^r	X	X	At Cycle 3 (± 1 month) from C1D1						X		
Pharmacodynamic Sampling ^s	X	X	-	X	X	C3D1 and the visit following response			X	-	-
Cortisol diurnal rhythm assessment ^t	X	-	-	-	-	-	-	-	-	-	-
PRO, QoL, HRU assessments ^u	X		-	-	-	X	-	-	X		-
Record AEs	X	X	X	X	-	X	X	X	X	X	-

Study Procedure	Screening	Open-Label, Randomized-Treatment Phase							EOT ^b	30-Day FU ^c	Long-term FU ^d
		Cycle 1				Cycle 2 and Subsequent Cycles					
		Day 1	Day 8	Day 15	Day 17 ^a	Day 1	Day 8	Day 15			
Follow-up	-	-	-	-	-	-	-	-	-	-	X
Patients in Arm A: receiving relacorilant + nab-paclitaxel											
Provide dose diary card	-	X	-	-	-	X	-	-	-	-	-
Dispense relacorilant	-	X	-	-	-	X	-	-	-	-	-
Relacorilant dosing ^v	-	X	Refer to Section 5.1 for details of dose schedule						-	-	-
Assess treatment compliance and review Dosing Diary ^w	-	-	X	X	-	X	X	X	X	-	-
Nab-paclitaxel dosing (IV) ^x	-	X	X	X	-	X	X	X	-	-	-
Sparse PK sampling ^y	-	-	-	X	-	-	-	-	-	-	-
Patients in Comparator Arm B: receiving nab-paclitaxel											
Nab-paclitaxel dosing (IV) ^x	-	X	X	X	-	X	X	X	-	-	-

Abbreviations: AE, adverse event; aPTT, activated partial thromboplastin time; CA-125, cancer antigen 125; C1D1, Cycle 1 Day 1; C3D1, Cycle 3 Day 1; CR, complete response; CT, computerized tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End of Treatment; 30-d FU, 30-day follow-up; GR, glucocorticoid receptor; HIV, human immunodeficiency virus; HRU, health care resource utilization; INR, international normalized ratio; IV, intravenously; LT-FU, long-term follow-up; MRI, magnetic-resonance imaging; OS, overall survival; PD, progressive disease; 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 the patient's chemotherapy infusion days during the Treatment Phase. Refer to [Appendix D](#) for acceptable treatment windows for chemotherapy for scheduling conflicts. For dose delays of nab-paclitaxel due to toxicity, see [Section 5.3](#). For Arm B, study visits will align with infusion dates of nab-paclitaxel, or those visits required for tumor assessment or PD sampling collection.

Procedural Window Note Screening: laboratory tests can be used for the Cycle 1 Day 1 values if collected within 3 days prior to the first dose of study treatment.

- a. An additional pharmacodynamic assessment at C1D17 will be collected from 40 Arm A patients. Blood sample draws on Cycle 1 Day 15 and Cycle 1 Day 17 include RNA (GC-mediated gene expression) and plasma collections (longitudinal resistance evaluation) ([Table 14](#)).
- b. EOT Visit should occur prior to 21 days after last dose of study treatment. Patients who discontinue treatment prior to PD will continue radiographic tumor assessments every 8 weeks (± 7 days) from Cycle 1 Day 1 for the first 40 weeks; then every 12 weeks (± 7 days) until unequivocal radiographic disease progression per RECIST v1.1. The same method should be used for each assessment for a particular patient.
- c. Follow-up visit by phone should be performed 30 days (± 3 days) after the patient receives their final dose of study treatment.
- d. Long-term Follow-up: For patients who discontinue before PD, subsequent treatment information will be collected at the same time as radiographic tumor assessments (ie, every 8 weeks (± 7 days) for the first 40 weeks; then every 12 weeks (± 7 days) for the remainder of the study [footnote g]), 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.
- e. Results of prior *BRCA1/2* mutation and homologous recombination deficiency assessment are provided via the molecular profiling eCRFs.
- f. A serum or urine pregnancy test for female patients of childbearing potential will be performed prior to randomization, prior to the first dose of study treatment (72-hour window from the first dose of study treatment) and preferably monthly on D1 of each cycle for patients in Arm A and Arm B on 28-day treatment. (refer to [Appendix H](#), [Table 18](#) for France-specific requirements and for Argentina-specific requirements).
- g. Enrollment does not require submission of either archival tumor-tissue or an on-study tumor biopsy. If archival tissue is available, patients must provide consent for acquiring the archival tumor-tissue block or slides. Archival tumor biopsies or resections collected within 12 months of Screening are preferred. If multiple archival tumor specimens are available, specimens obtained closest to the time of study enrollment are preferred, but not required. If archival tumor-tissue, as defined above, is not available then the patient is still eligible provided they meet other eligibility criteria. An optional procedure to obtain an on-study tumor biopsy during the Screening period may be performed if/when medically feasible and considered of low risk to the patient. The biopsy can be from the primary tumor site or from a metastatic site, however, which should be noted on the sample.
- h. Tumor assessments (CT/MRI) will be performed within 45 days prior to the first dose of study treatment and then every 8 weeks (± 7 days) from Cycle 1 Day 1 for the first 40 weeks; then every 12 weeks (± 7 days). Tumor assessments will be performed irrespective of treatment delays until unequivocal disease progression is documented (determined according to RECIST v1.1), including in patients who prematurely discontinue therapy. The same method should be used for each assessment for each 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 has been documented PD.
- i. Randomization to be performed prior to administration of study treatment. Patients should receive their first dose of study treatment on the same day as randomization if possible, and with a minimum delay (≤ 7 days) where unavoidable and with no more than 7 days delay in administering the first dose of study treatment from the randomization.
- j. A full physical examination will be performed at Screening, within 3 days prior to Day 1 of each treatment cycle and at the End of Treatment Visit. Subsequently, a symptom-directed physical examination will be performed on Days 8 and 15 of chemotherapy infusion.
- k. Resting vital signs: BP, heart rate, respiratory rate, and body temperature will be recorded.
- l. Height is only measured at Screening or on Cycle 1 Day 1 and weight is recorded on Screening and Day 1 of each treatment cycle, EOT.
- m. CA-125 will be assessed within 14 days prior to the first dose of study treatment, and every 8 weeks from Cycle 1 Day 1 (± 7 days) for the first 40 weeks of the study followed by every 12 weeks (± 7 days) irrespective of any treatment delay until PD. Once the best CA-125 response (at least 50% decrease from a

pretreatment sample, which is defined as the most recent sample drawn before the first dose) is determined, a confirmatory CA-125 is required ≥ 28 days of the best CA-125 response. The 28-day confirmatory sample must be less than or equal to the previous sample (within an assay variability of 10%) to accurately calculate CA-125 responses. ([Rustin 2011](#)).

- n. Chemistry parameters: A full chemistry profile including albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, magnesium, phosphorus, potassium, sodium, total and direct bilirubin, total protein, uric acid ([Table 8](#)). Assessment of chemistry parameters will not be conducted on non-treatment days. Chemistry labs may be collected within 3 days prior to the administration of nab-paclitaxel.
- o. Hematology parameters: a complete blood count and differential ([Table 8](#)). Assessment of hematology parameters will not be conducted on non-treatment days. Hematology labs may be collected within 3 days prior to the administration of nab-paclitaxel.
- p. Urinalysis assessments will be done by dipstick. Microscopy is required only to follow-up clinically significant urine dipstick findings.
- q. If Screening PT/aPTT/INR is completed within 3 days of C1D1, then collection is not needed at C1D1.
- r. Triplicate resting ECG-measurements should be performed prior to the first dose of study treatment. If not completed at Screening, ECG can be completed at Cycle 1 Day 1. ECG will be performed one time during treatment at Cycle 3 (± 1 month) during treatment and when clinically indicated.
- s. [Table 14](#) details pharmacodynamic and biomarker sampling.
- t. Salivary cortisol for diurnal assessment samples are collected at home between Screening and Cycle 1 Day 1.
- u. Baseline PRO, QoL, and HRU assessments must be collected prior to the first dose of study treatment. If not performed at Screening, these assessments can be completed at Cycle 1 Day 1 prior to the administration of study treatment. Post-baseline assessments will be collected at Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1. After Cycle 4 Day 1, assessments will be performed every other cycle (starting with Cycle 6 Day 1) through End of Treatment. PRO, QoL, and HRU assessments should be completed prior to discussing the results of tumor assessments or disease-related clinical changes with the patient.
- v. For patients in Arm A, the first dose of relacorilant will be administered on Cycle 1 Day 1 and then administered the day prior, the day of, and the day following nab-paclitaxel infusion. On days in which both relacorilant and nab-paclitaxel are administered, it is preferable to administer relacorilant before nab-paclitaxel.
- w. Dosing diary only required for patients receiving relacorilant (Arm A). Review and collect the dosing diary at EOT.
- x. Refer to [Appendix D](#) for chemotherapy guidelines.
- y. [Table 13](#) details sparse PK sampling for Arm A patients only.

Table 13: Sparse Pharmacokinetic Schedule of Assessments (ARM A Only)

PK Sample	Day	Nominal Time	Window
Relacorilant	Cycle 1, Day 15	0 hr, pre-dose	Within 15 minutes BEFORE the relacorilant dose
		Anytime between 0.5 hr and 4 hr post-dose	+30 minutes

Table 14: Pharmacodynamic Schedule of Assessments

Procedure/Assay	Tissue Source	Visit Schedule Cycle Day	Methodology; Examples of Biomarkers
GC-Related Pathways and Exploratory Biomarkers	Blood (PAXgene)	Fasting, required pre-dose (preferably between 7–9 am for all patients, all visits) at: Screening Cycle 1 Day 1 Cycle 1 Day 15 Cycle 3 Day 1 Visit following observation of response (CR or PR) Disease progression/EOT ^a	mRNA expression by technologies such as NanoString
		For a subset of 40 patients in Arm A, a collection will be performed: Fasting required (preferably between 7–9 am) at Cycle 1 Day 17	
Immunohistochemistry for GR and/or Other Exploratory Markers	Pretreatment tumor-tissue (FFPE block) ^b	Screening ^b (for all patients with tissue samples)	CLIA-validated IHC assay for GR and/or other IHC or IF methods

Procedure/Assay	Tissue Source	Visit Schedule Cycle Day	Methodology; Examples of Biomarkers
Longitudinal Resistance Evaluation	Blood (plasma)	Fasting, required pre-dose (preferably between 7–9 am for all patients, all visits) at: Screening Cycle 1 Day 1 Cycle 1 Day 15 Cycle 3 Day 1 Visit following observation of response (CR or PR) Disease progression/EOT ^a	Analysis of protein, nucleic acid, or chemical markers of drug resistance evolution
		For a subset of 40 patients in Arm A, a collection will be performed: Fasting required (preferably between 7–9 am) at Cycle 1 Day 17	
Cortisol Diurnal Rhythm Assessment	Saliva	Screening ^c (for all patients)	HPLC and LC-MS/MS
<i>BRCA1/2</i> Mutation and Homologous Recombination Deficiency Assessment	N/A (collected via eCRF)	Screening (for all patients)	Submission of prior DNA testing (ie, BRCA Analysis [®] or TumorNext-HRD [®] or FoundationOne CDX [®]) results for <i>BRCA1/2</i> and other HRD related somatic or germline mutations

Abbreviations: *BRCA1/2*, breast cancer 1 and 2; CLIA, Clinical Laboratory Improvement Amendments; CR, complete response; eCRF, electronic case report form; DNA, deoxyribonucleic acid; EOT, end of treatment; GC, glucocorticoid; GR, glucocorticoid receptor; IF, immunofluorescence; IHC, immunohistochemistry; FFPE, formalin-fixed paraffin-embedded; LC-MS/MS, liquid chromatography with tandem mass spectrometry; N/A, not applicable; mRNA, messenger ribonucleic acid; PR partial response.

- a. After EOT, no pharmacodynamic samples should be collected (even if a disease progression visit is required).
- b. A pretreatment archival sample or recent tumor-tissue sample for tumor-biomarker assay collected within 12 months of Screening are preferred. If multiple archival tumor specimens are available, specimens obtained closest to the time of study enrollment are preferred, but not required. If archival tumor-tissue, as defined above, is not available then the patient is still eligible provided they meet other eligibility criteria. An optional procedure to obtain an on-study tumor biopsy during the Screening period may be performed if/when medically feasible and considered of low risk to the patient. The biopsy can be from the

primary tumor site or from a metastatic site, however, which should be noted on the sample. The optional on-study tumor biopsy should be collected before the start of Cycle 1 Day 1 (C1D1) of the study.

- c. A total of 6 salivary samples (3 pairs) for cortisol diurnal rhythm assessment will be collected at home between Screening and Cycle 1 Day 1. Patients will be provided with take-home collection kits for paired morning (7 am to 9 am) and late-night collections (9 pm to 11 pm) of salivary cortisol samples on 3 separate days.

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 ([Shimizu 1998](#)) 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 times).
- More than 10 mitotic figures per 10 high power fields.
- Typically disseminated at presentation of Wilms' Tumor 1 (WT1) Expression should be sought for Stage I tumors.
- WT1, p53, and/or p16 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. RESPONSE CRITERIA: RECIST VERSION 1.1 FOR DISEASE ASSESSMENT

Tumor response and assessment according to RECIST version 1.1 is described below. This appendix is not exhaustive, and the source should be referred to for further detail ([Eisenhauer 2009](#)).

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 will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, 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 ≤ 5 mm cuts 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. The 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 ≤ 5 mm).
- 15 mm on short axis for nodal disease by CT/MRI scan (slice thickness ≤ 5 mm).
- 10 mm caliper measurement by clinical exam and lesions that cannot be accurately measured with calipers should be recorded as non-measurable.

Non-measurable Tumors: Patients With Non-measurable Disease ONLY Are Not Eligible for Enrollment

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

measurable by reproducible imaging techniques. Additional lesions considered truly non-measurable are abdominal masses/abdominal organomegaly identified through physical exam but 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 based on their size (lesions with the longest diameter), be representative of all involved organs, and also have reproducible repeated measurements. If the

largest lesion does not have best reproducible measurement, then the next largest lesion with measurable reproducibly should be selected.

Response criteria as defined below should be used:

Evaluation of Target Lesions

CR: is the disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.

PR: At least a 30% decrease in the sum of the diameters (SOD) of target lesions, taking as reference the baseline SOD.

PD/Disease Progression: At least a 20% increase in the target lesions SOD, with the smallest sum recorded since the treatment started or the appearance of 1 or more new lesions taken as a reference. 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.

SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, with the smallest SOD since the treatment started taken as a reference.

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 < 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

CR: Disappearance of all nontarget lesions and normalization of tumor marker level.

Incomplete Response/SD (non-CR/non-PD): Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.

PD/Disease Progression: 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’ based on 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 PD, 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, ie, not attributable to differences in scanning technique, timing of scanning, phase of contrast administration, change in imaging 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 D. GENERAL CHEMOTHERAPY GUIDELINES

- If a delay of chemotherapy is inevitable:
 - If treatment with nab-paclitaxel is delayed for > 4 weeks (omission of nab-paclitaxel for > 28 days), the Medical Monitor should be notified.
 - If the initiation of a cycle is delayed, the day when the first nab-paclitaxel infusion is re-initiated is considered Day 1 of a cycle for the purpose of counting 28-day cycle schedule.
 - If the delay of the initiation of a cycle (eg, Cycle 3) is close to the next scheduled cycle (eg, Cycle 4), the schedule of assessment for the next scheduled cycle (eg, Cycle 4) should be followed.
 - After the initiation of a cycle (Day 1), if there is a delay in nab-paclitaxel administration for any reason, the following applies:
 - If an infusion of nab-paclitaxel on Day 8 or Day 15 is delayed with a new date that is too close to the next scheduled infusion, that dose may be skipped, and the patient may resume treatment with the next scheduled infusion if appropriate in the judgment of the Investigator.
 - Two consecutive nab-paclitaxel infusions should not be given less than 7 days apart.
- Chemotherapy doses can be “rounded” according to institutional standards without being considered a protocol deviation (most institutions use a rule of approximately $\pm 5\%$ 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.
- For scheduling purposes, Day 1 of subsequent cycle could be started up to 2 days earlier.

APPENDIX E. EXAMPLES OF MEDICATIONS THAT ARE PROHIBITED

The following are examples of medications prohibited during the study:

	Prohibited
CYP3A Inducers	Apalutamide, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenytoin, rifampin, rifapentine and St. John's wort
CYP3A Inhibitors	Boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole
CYP2C8 Inhibitors	Gemfibrozil, clopidogrel, deferasirox, teriflunomide, selpercatinib, pirtobrutinib, letemovir,
CYP3A Substrates	Alprazolam, amiodarone, eplerenone, ergotamine, flibanserin, lercanidipine, lovastatin, rupatadine, salmeterol, simvastatin, tamsulosin, ticagrelor
Corticosteroids or GR Modulators	Systemic use of corticosteroids such as parenteral, oral, and rectal, etc, and use of potent dermatologic preparation corticosteroids (Class I to III). Topical corticosteroids (Class I – III) 0.05% Clobetasol propionate; 0.05% halobetasol propionate, 0.1% amcinonide, 0.05% betamethasone dipropionate, 0.05% fluocinide Mifepristone or other GR modulators

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

Note: 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:

<https://www.fda.gov/drugs/development-resources/drug-interactions-labeling>

<https://drug-interactions.medicine.iu.edu/MainTable.aspx>

Gabros S, Nessel TA, Zito PM. Topical Corticosteroids. [Updated 2023 Jul 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK532940/>

APPENDIX F. GYNECOLOGICAL CANCER INTERGROUP DEFINITIONS FOR RESPONSE AND PROGRESSION IN OVARIAN CANCER CLINICAL TRIALS

Tumor response and assessment according to Gynecological Cancer Intergroup (GCIg) criteria is described below. This appendix is not exhaustive, and the reference resource should be referred to for further detail ([Rustin 2011](#)).

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 QC 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 anti-mouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (eg, paracentesis). If assessing therapy that includes 2 treatment modalities for relapse (eg, surgery and chemotherapy), any CA-125 response would be considered the result 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 GCIg 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. 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 15](#) and [Table 16](#) where CA-125 is normalized or normal, then the CA-125 is within the reference range.

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 criteria and who may have events at different time points. It should be determined according to [Table 15](#). 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 used. In the combined assessment of CA-125 and RECIST v1.1 response, the following algorithm applies when determining the BoR. If patients have 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 PR. Patients whose best response according to RECIST v1.1 is SD but who have a CA-125 response are classified as CA-125 responders.

Table 15: Best Overall Response in Patients with Measurable Disease and Who are also Evaluable by CA-125 (GCIG Criteria)

Target Lesion ^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.

- Target lesions include up to 5 measurable lesions (2 per organ) as defined by RECIST v1.1.
- Nontarget lesions include ascites and peritoneal thickening that are not measurable according to RECIST v1.1.
- CA-125 response must be confirmed and maintained for at least 28 days.
- 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 Version 1.1 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 16](#).

A combined-response endpoint based on both RECIST v1.1 and GCIG criteria will also be reported. Tumor response will be assessed by BICR and the Investigator or local radiologist using RECIST v1.1. CA-125 response and the combined-response will be derived based on CA-125 results.

Table 16: 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	<i>4</i>	<i>0</i>	<i>0</i>	<i>4</i>
PR	<i>3</i>	<i>1</i>	<i>1</i>	<i>5</i>
SD	<i>3</i>	<i>12</i>	<i>1</i>	<i>16</i>
PD	<i>0</i>	<i>8</i>	<i>2</i>	<i>10</i>
NE	<i>3</i>	<i>5</i>	<i>2</i>	<i>10</i>
Total CA-125	<i>13</i>	<i>26</i>	<i>6</i>	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 v1.1, 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 v1.1 or CA-125 response) is 15 (35%) of 43 total patient count.

a. RECIST v1.1 includes normalization of CA-125 to achieve CR (Table 15).

Definition of Progression on Therapy and Recurrence After Therapy According to CA-125

PD is conventionally defined according to RECIST v1.1 but can also be based on serum CA-125 (defined below). Assigning the date of progression, PD by objective change in tumor size should always take precedence over CA-125 should it occur first.

When categorizing patients according to time to progression, it is necessary to specify how the date of progression was defined by CA-125 alone, CA-125 and clinical symptoms, and RECIST v1.1.

Evaluation of Progression According To CA-125

Disease progression or recurrence based on serum CA-125 levels will be defined based on a progressive serial elevation of serum CA-125 according to Table 17 the following criteria:

- A. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart, or
- B. Patients with elevated CA-125 before treatment, which never normalizes, must show evidence of CA-125 greater than, or equal to, 2 times the nadir value on 2 occasions at least 1 week apart or,
- C. Patients with CA-125 in the reference range before treatment must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart. CA-125 progression will be assigned the date of the

first measurement that meets the criteria as noted. Patients are not evaluable by CA-125 if they have received mouse antibodies unless the CA-125 assay used was not influenced by human anti-mouse antibody ([Taylor 2005](#), [Rustin 2004](#)) or if there has been medical and/or surgical interference with their peritoneum or pleura (eg, paracentesis) during the previous 28 days.

A patient may be declared to have PD based on either the objective RECIST v1.1 criteria or the CA-125 criteria. The date of progression will be the date of the earlier of the 2 events if both are documented.

Table 17: Definition of Progression After First-Line Therapy in Ovarian Cancer as Proposed by the Gynecological Cancer Intergroup (GCIG)

A	Compared to baseline (or lowest sum while on study if less than baseline), a 20% increase in sum of diameters (RECIST 1.1 definition) or Any new lesions (measurable or nonmeasurable) or Unequivocal increase in nontarget disease Date of PD: date of documentation of increase or new lesions	A	CA 125 $\geq 2 \times$ ULRR documented on 2 occasions*
		N	
		D	Date of PD: first date of the CA 125 elevation to $\geq 2 \times$ ULRR
		/	
B	As for A	O	CA 125 $\geq 2 \times$ nadir value on 2 occasions*
		R	
			Date of PD: first date of the CA 125 elevation to $\geq 2 \times$ nadir value
C	As for A		As for A
GCIG groups A, B, and C defined above. CA 125 levels sampled after patients received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody ^{4,5}) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days should not be taken into account. *Repeat CA 125 any time but normally not less than 1 week after the first elevated CA 125 level. ULRR, upper limit of response range.			

Modified from Table 5 in [Rustin 2011](#).

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 for recurrent disease).
- If a treatment was initiated after disease progression or the 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.
 - Maintenance hormonal therapies are not counted as separate therapies.

APPENDIX H. COUNTRY-SPECIFIC REQUIREMENTS

Table 18: Protocol Amendment 4 and Country-specific requirement(s)

Applicable Section(s)	Global Protocol Amendment 4 Text	Argentina-specific language	France-specific language
SoA: Footnote 'f'.	A serum or urine pregnancy test for female patients of childbearing potential will be performed prior to randomization, prior to the first dose of study treatment (72-hour window from the first dose of study treatment) and preferably monthly on D1 of each cycle for patients in Arm A and Arm B on 28-day treatment. (refer to Appendix H, Table 18 for France-specific and Argentina-specific requirements).	A serum or urine pregnancy test for female patients of childbearing potential will be performed prior to randomization, prior to the first dose of study treatment (72-hour window from the first dose of study treatment) and then preferably monthly on D1 of each cycle for patients in Arm A and Arm B on 28-day treatment until 6 months after treatment discontinuation.	A serum or urine pregnancy test for female patients of childbearing potential will be performed prior to randomization, prior to the first dose of study treatment (72-hour window from the first dose of study treatment) and then preferably monthly on D1 of each cycle for patients in Arm A and Arm B on 28-day treatment until 6 months after treatment discontinuation.
Applicable Section(s)	Global Protocol Amendment 4 Text	South Korea-Specific language	
Sec 4.2: Inclusion Criteria 11	Received at least 1 but $\leq$ 3 lines of prior systemic anticancer therapy (See Appendix G for the guidance in counting the number of prior lines of therapy) with documented progressive disease or intolerance to the most recent therapy. At least 1 prior line of platinum therapy is required and prior treatment with bevacizumab is required.	Received at least 1 but $\leq$ 3 lines of prior systemic anticancer therapy (See Appendix G for the guidance in counting the number of prior lines of therapy) with documented progressive disease or intolerance to the most recent therapy. At least 1 prior line of platinum therapy is required and prior treatment with bevacizumab is required. • Patients who have documented <i>BRCA</i> mutations (somatic and/or germline) must have received prior treatment with a PARP inhibitor.	
Sec 4.3: Exclusion Criteria 6	N/A	Patients who have documented <i>BRCA</i> mutations (somatic and/or germline) and have NOT received prior treatment with a PARP inhibitor.	

Applicable Section(s)	Global Protocol Amendment 4 Text	South Korea-Specific language
Sec 5.2 Dose-Escalation Process	If a relacorilant dose reduction is required per Table 6, the relacorilant dose may be re-escalated after a discussion with the Medical Monitor.	If a relacorilant dose reduction is required per Table 6, the relacorilant dose may be re-escalated after a discussion with the Medical Monitor. This scenario would be rare. All requests for re-escalation must initiate from the Investigator. Although the circumstances in possible re-escalation cases will vary, overarching guidelines for agreement for re-escalation would include: • The AE(s) for which the dose reduction(s) were made have resolved, not recurred and are not believed to be “possibly related” or “probably related” to relacorilant. • Nab-paclitaxel dosing is currently at no less than Dose -1 (60 mg/m² IV). • Overall disease status has not reached either clinical or RECIST v1.1 definition for progressive disease.

Abbreviations: AE, adverse events; *BRCA*, BReast CAncer gene; D, Day; IV, intravenous; N/A, not applicable; PARPi, poly (ADP-ribose) polymerase (PARP) inhibitors; RECIST, Response Evaluation Criteria in Solid Tumors; SoA, Schedule of Activities.

a. New exclusion criteria specific to only South Korea.

APPENDIX I. SUMMARY OF CHANGES

Significant changes in Protocol Amendment 4 dated 15 February 2025 compared with the Amendment 3 dated 14 November 2024 are summarized below with additional details in [Table 19](#); deleted text is shown as a strikethrough and new text is shown in bold.

Minor editorial or stylistic changes made for consistency are not summarized and may not be shown in the redline version of the amendment (eg, punctuation, spelling, abbreviations). Throughout the document, sections, tables, and figures were renumbered as appropriate. Table of Contents and lists of tables or figures are updated without redline.

Significant revisions to the protocol include the following:

- Due to recent health authority feedback, the following changes were made to the primary and secondary objectives/endpoints:
 - Addition of OS to primary objectives, and removal from secondary objectives
 - Addition of OS as a dual primary endpoint, and removal as a key secondary endpoint
- Changes to include a dual primary endpoint led to updates to the statistical methods specifically to the following sections:
 - Hypothesis testing to include OS in addition to PFS
 - Sample size calculations
 - Analyses of primary endpoints

Table 19: Summary of Changes in Protocol CORT125134-556 Amendment 4:

Section	Summary of Change	Revisions
Synopsis/ Section 2.1 Primary Objectives Section 2.2 Secondary Objectives	Addition of overall survival (OS) as a primary objective and deletion as secondary objective.	Primary Objectives: The primary efficacy objectives of this study is are to evaluate progression-free survival (PFS) by BICR and overall survival (OS) in patients treated with an intermittent regimen of relacorilant in combination with nab-paclitaxel compared with patients treated with nab-paclitaxel monotherapy. Secondary Objectives: <u>Secondary Efficacy Objectives</u> The secondary efficacy objectives are to evaluate patients treated with an intermittent regimen of relacorilant in combination with nab-paclitaxel compared with nab-paclitaxel monotherapy: • To evaluate the overall survival (OS)
Synopsis/ Section 3.2.1 Primary Efficacy Endpoints Section 3.2.2.1 Efficacy	Addition of overall survival (OS) as a dual primary endpoint and deletion as secondary endpoint.	<u>Synopsis</u> Primary Efficacy Endpoints The co-dual primary efficacy study endpoints include the following: will be • PFS: defined as the tTime from randomization until first documented PD by RECIST v1.1 per BICR, or death due to any cause, whichever occurs first • OS: Time from randomization to death by any cause. Secondary Endpoints <u>Efficacy</u> • OS: Time from randomization to death by any cause. <u>Body</u> 3.2.1. Primary Efficacy Endpoints The co-dual primary efficacy study endpoints include the following: will be • PFS: defined as the tTime from randomization until first documented PD by RECIST v1.1 per BICR, or death due to any cause, whichever occurs first • OS: Time from randomization to death by any cause. 3.2.2. Secondary Endpoints 3.2.2.1 Efficacy • OS: Time from randomization to death by any cause.

Section	Summary of Change	Revisions
Synopsis/ Section 9.3 Hypothesis Testing	Updates to the hypothesis testing parameters due to OS being a dual primary endpoint.	<u>Synopsis</u> Statistical Analyses To maintain experiment-wise 2-sided type I error at 0.05, a group sequential weighted Holm procedure will be used for the dual primary endpoints PFS and OS. The study will be considered to have a positive outcome if either of the 2 primary endpoints reaches statistical significance. For the dual primary efficacy endpoint PFS by BICR, the null hypothesis of no difference in PFS among the 2 study groups will be tested at a 2-sided $\alpha = 0.04$ level of significance using a stratified log-rank test. The alternative hypothesis is that there is a difference between groups. The primary endpoint of OS will be allocated a 2-sided $\alpha = 0.01$ level of significance for the stratified log-rank test. If PFS by BICR is rejected, then per the Holm procedure OS will be tested at $\alpha = 0.05$, using a stratified log-rank test. If PFS by BICR is not significant, then OS will be tested at $\alpha = 0.01$. An interim analysis of OS will be performed at the time of the primary analysis of PFS. At the interim analysis, OS data will be summarized to detect a trend in OS and the alpha spending function will be detailed in the Statistical Analysis Plan. The formal final analysis of OS will be conducted when approximately 292 deaths have been observed and will be performed using the ITT population. The primary efficacy endpoint (PFS by BICR) will be summarized using Kaplan-Meier methods. The log-rank test, stratified by stratification factors used at randomization, will be used to compare the 2 treatment groups. Estimates of the treatment differences will be obtained using the hazard ratio (HR) and 2-sided 95% confidence intervals obtained from a stratified Cox regression model that includes treatment as a covariate and is stratified by the stratification factors used at randomization. The null hypothesis of no difference in PFS among the 2 study groups will be tested at a 2-sided $\alpha = 0.05$ level of significance. Using a hierarchical (gate-keeping) procedure, the testing of the key secondary endpoint, OS, will proceed only if there is a statistically significant difference between treatment groups in terms of the primary endpoint (PFS). An interim analysis of OS will be performed at the time of the primary analysis of PFS. At the interim analysis, OS data will be summarized to detect a statistical trend in OS. The formal final analysis of OS will be conducted when approximately 247 deaths have been observed and will be performed using the ITT population.

Section	Summary of Change	Revisions
		All other secondary endpoints will be tested at a nominal 2-sided $\alpha = 0.05$ level of significance, with no additional adjustment for multiplicity. P-values from tests of hypothesis associated with from secondary and exploratory tests endpoints will be considered descriptive, and not inferential. <u>Section 9.3 Hypothesis Testing</u> To maintain experiment-wise 2-sided type I error at 0.05, a group sequential weighted Holm procedure will be used for the dual primary endpoints PFS and OS. The study will be considered to have a positive outcome if either of the 2 primary endpoints reaches statistical significance. For the primary efficacy endpoint of (PFS by BICR), the null hypothesis of no difference in PFS among the 2 study groups will be tested at a 2-sided $\alpha = 0.045$ level of significance using a stratified log-rank test. The alternative hypothesis is that there is a difference between groups. To maintain experiment wise 2 sided type I error at 0.05, a hierarchical testing procedure for the primary endpoint (PFS) and key secondary endpoint (OS) will be used. Hence, hypothesis testing for the key secondary The primary endpoint of (OS) will be allocated a 2-sided $\alpha = 0.01$ level of significance for the stratified log-rank test. proceed only if there is a statistically significant difference between treatment groups in terms of the primary endpoint (PFS). If PFS by BICR is rejected, $\alpha = 0.04$ will be passed on to OS and then per the Holm procedure OS will be tested at $\alpha = 0.05$, using a stratified log-rank test. If PFS by BICR is not significant, then OS will be tested at $\alpha = 0.01$. An interim analysis of OS will be performed at the time of the primary analysis of PFS. At the interim analysis, OS data will be summarized to detect a statistical trend in OS and the alpha spending function will be detailed in the Statistical Analysis Plan. The formal final analysis of OS will be conducted when approximately 29247 deaths have been observed and will be performed using the ITT population.

Section	Summary of Change	Revisions
Synopsis/ Section 9.4 Sample-Size Calculation	Updates to the hypothesis testing parameters due to OS being a dual primary endpoint.	<u>Synopsis/Body</u> For PFS, based on 1:1 randomization allocation ratio, a total of 244230 events ensures the study has 86.490% power for a 2-sided log-rank test with a $\alpha = 0.045$ level of significance, to detect a 50% increase in PFS (HR = 0.66). Assuming an exponential distribution of PFS, this corresponds to an increase in median PFS from 3.8 months to 5.8 months. For OS, approximately 29247 events will provide the study with 80% power for a 2-sided log-rank test with an overall $\alpha = 0.015$ level of significance to detect a 5030% increase in OS (HR = 0.67570). Assuming an exponential distribution of OS, this corresponds with to an increase in median OS from 13 months to 19.4 18.6 months.
Section 9.5.4 Analysis of Ce -Dual Primary Efficacy Endpoints	Updates to PFS and addition of OS to primary endpoint section.	The ce-dual primary endpoints PFS and OS are defined in Section 3.2.1. PFS The first primary efficacy analysis is the comparison of PFS by BICR in patients treated with the combination of relacorilant and nab-paclitaxel versus compared with nab-paclitaxel monotherapy. The primary endpoint is PFS, which PFS is defined as time from randomization until the date of radiologic PD per RECIST v1.1 or death from any cause, whichever comes first, as determined by BICR. The primary analysis of PFS will be conducted when at least 23044 PFS events have been observed. A stratified log-rank 2-sided test with a 0.045 level of significance will be used to compare treatment groups. The stratification factors will be the same used to stratify the randomization schedule as documented in the interactive voice and web-response system (IXRS): region (North America versus Europe versus the rest of the world) and line of therapy (1 versus more than 1). If the p-value for the stratified log-rank test is statistically significant (< 0.045, two2-sided) and the observed HR ($\lambda_{\text{active}}/\lambda_{\text{control}}$) is < 1, the null hypothesis of no difference in PFS will be rejected and it will be inferred that PFS is statistically prolonged in the group receiving relacorilant + nab paclitaxel compared with the group receiving nab-paclitaxel monotherapy.

Section	Summary of Change	Revisions
		Overall Survival The second primary efficacy analysis is the comparison of OS in patients treated with the combination of relacorilant and nab-paclitaxel compared with nab-paclitaxel monotherapy. OS is defined as the time from randomization to death due to any cause. There will be an interim and final analysis for OS. The interim analysis of OS will be conducted at the time of the primary analysis of PFS. At the interim analysis, OS data will be summarized to detect a trend in OS. The formal analysis of OS will be conducted when approximately 292 deaths have been observed and will be performed using the ITT population. The testing of OS will be conducted using a stratified log-rank 2-sided test. The stratification factors will be the same used to stratify the randomization schedule as documented in the IXRS. The median OS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. The HR and the associated 95% CI will be estimated using a Cox regression model with treatment group as the main effect and stratification factors at randomization as covariates. An unstratified HR and the associated 95% CI will also be presented.

Section	Summary of Change	Revisions
Section 9.5.6 Secondary Efficacy Endpoint Analysis	Removal of OS from secondary endpoint section.	The key secondary efficacy endpoint is OS. To maintain experiment wise 2-sided type I error at 0.05, a hierarchical testing procedure (gate keeping) procedure for PFS and OS endpoints will be used and will be provided in the SAP. Overall Survival OS is defined as the time from randomization to death due to any cause. There will be an interim and final analysis for OS. The interim analysis of OS will be conducted at the time of the primary analysis of PFS. At the interim analysis, OS data will be summarized to detect a statistical trend in OS. The formal analysis of OS will be conducted when approximately 247 deaths have been observed and will be performed using the ITT population. The testing of OS will be conducted using a stratified log-rank 2-sided test. The stratification factors will be the same used to stratify the randomization schedule as documented in the IXRS. The median of OS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. The HR and the associated 95% CI will be estimated using a Cox regression model with treatment group as the main effect and stratification factors at randomization as covariates. An unstratified HR and the associated 95% CI will also be presented.
Section 9.5.12 Interim Analysis	Updates to interim analysis parameters.	As the OS data are not expected to be mature at the time of interim analysis, OS data will be summarized to detect a statistical trend and the alpha spending function will be specified in the SAP. The formal analysis of OS will be conducted when approximately 247 death events have been observed.