Title: Phase 1/2 Study of CORT125134 in Combination with Nab-paclitaxel in Patients with Solid Tumors

NCT Number: NCT02762981

Date: 13 January 2020

CLINICAL STUDY PROTOCOL CORT125134-550

Protocol Title	**Phase 1/2 Study of CORT125134 in Combination with Nab-paclitaxel in Patients with Solid Tumors**
Study Phase	1/2
IND Number	128631
Investigational Product	CORT125134
International Nonproprietary Name	Relacorilant
Medical Monitor	[redacted]
Sponsor	Corcept Therapeutics Incorporated 149 Commonwealth Drive Menlo Park, California 94025 USA (650) 327-3270
Version	Amendment 6
Date	13 January 2020

Good Clinical Practice Statement

This study will be conducted in accordance with good clinical practice (GCP) as defined in International Conference on Harmonisation (ICH) guidelines and US Code of Federal Regulations Title 21, Parts 11, 50, 54, 56, and 312 and Title 45, Parts 46, 160, and 164; the ICH document "ICH Harmonized Tripartite Guideline, Guideline for Good Clinical Practice E6(R1)"; the Declaration of Helsinki (1989); IRB Guidelines; and applicable local legal and regulatory requirements.

Confidentiality Statement

SPONSOR SIGNATURE PAGE

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APPROVAL STATEMENT

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

Signed:

[redacted]

1-16-2020

Date

INVESTIGATOR SIGNATURE PAGE

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INVESTIGATOR AGREEMENT

By my signature below, I attest to the following:

1. I have read the attached protocol.
2. I agree to conduct the study as outlined in the protocol and in accordance with all applicable regulations and guidelines, including the Declaration of Helsinki (version as currently endorsed by the European Medicines Evaluation Agency and the United States Food and Drug Administration [FDA]); the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 21 CFR parts 50, 54, 56, and 312 and the ICH document "E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)," dated 9 Nov 2016. Further, I will conduct the study in keeping with local legal and regulatory requirements.
3. I will initiate this study only with written and dated approval from the appropriate Institutional Review Board (IRB). I understand that any changes in the protocol must be approved in writing by the Sponsor, the IRB, and, in certain cases the FDA or other applicable regulatory agencies, before they can be implemented.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signed:

Signature	Date
Name	Institution

SYNOPSIS

Name of Sponsor Corcept Therapeutics	**Name of Active Ingredient** CORT125134	**Study number:** CORT125134-550
Title of Study Phase 1/2 Study of CORT125134 in Combination with Nab-paclitaxel in Patients with Solid Tumors		
Rationale Some solid tumors develop chemotherapy resistance in part via stimulation or upregulation of the glucocorticoid receptor (GR) with subsequent expression of cell survival gene products. GR antagonists enhance the efficacy of taxanes in GR-positive solid tumor mouse xenograft studies. Nab-paclitaxel is an effective form of paclitaxel that does not require pretreating patients with intravenous (IV) steroids. This study will evaluate the combination of CORT125134, a novel GR antagonist, and nab-paclitaxel in patients with solid tumors with the goal of developing a treatment regimen that bypasses the GR-mediated chemotherapy resistance pathway.		
Study Centers: Approximately 12 centers in the United States		
Study Period: Approximately 36 months	**Phase of Development:** Phase 1/2	

Objectives

These objectives will apply to all regimens evaluated during the study.

Primary Objective

- To determine the maximum tolerated dose (MTD) and the development regimen of the combination of CORT125134 and nab-paclitaxel in patients with solid tumors.

Secondary Objectives

- To characterize the safety profile of the combination of CORT125134 and nab-paclitaxel.
- To characterize the preliminary anticancer activity (objective response rate [ORR], progression-free survival [PFS], and overall survival [OS]) of the combination of CORT125134 and nab-paclitaxel in patients with solid tumors in a dose-finding phase and in patients with specific tumor types.
- To characterize the preliminary anticancer activity (ORR, PFS, and OS) of the combination of CORT125134 and nab-paclitaxel in patients with GR-positive or GR-negative solid tumors enrolled in any part of the study.
- To characterize the pharmacokinetics (PK) and exposure-response of the combination of CORT125134 and nab-paclitaxel in patients with solid tumors in a dose-finding phase and in patients with specific tumor types.
- To characterize the pharmacodynamics (PD) of the combination of CORT125134 and nab-paclitaxel indicative of modulation of GR function, including hormonal changes and FKBP5.

Exploratory Objectives

- To evaluate molecular, cellular, and soluble markers in peripheral blood and/or tumor tissue that may be relevant to the mechanism of action of or response/resistance to CORT125134.
- To evaluate pharmacogenomic (PG) markers to assess genetic factors affecting drug metabolism and transporters.

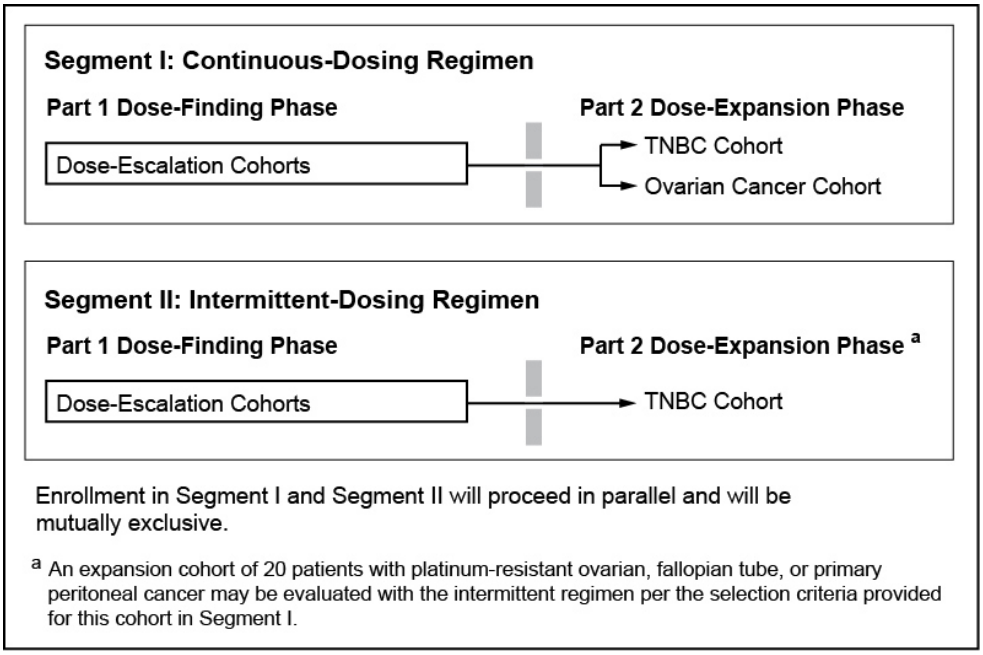
Overview of Study Design

This is a Phase 1/2 single-arm, open-label, multicenter study to determine the MTD and to assess safety, PK, PD, and preliminary anticancer activity of the combination of CORT125134 and nab-paclitaxel in patients with solid tumors.

The study will consist of two segments to evaluate alternative dosing schedules of CORT125134: Segment I will evaluate a continuous-dosing regimen and Segment II will evaluate an intermittent-dosing regimen. As shown in Figure S1, in Segment I, dose-escalation cohorts will be enrolled to determine the maximum tolerated dose (MTD) and the development regimen for the continuous-dosing regimen; thereafter, expansion cohorts will be enrolled and treated with the continuous-dosing development regimen to better characterize the antitumor activity in patients with specific tumor types and to better define the safety profile. In Segment II, dose-escalation cohorts will be enrolled to determine the MTD and the development regimen for the intermittent-dosing regimen; thereafter, expansion cohort(s) will be enrolled and treated with the intermittent-dosing development regimen to better characterize the antitumor activity of that regimen in patients with specific tumor types and to better define the safety profile for that regimen.

Enrollment in Segment I and Segment II will be mutually exclusive, and the two segments will enroll patients concurrently.

Figure S1 Overview of Study Design Showing Segment I and Segment II Regimens



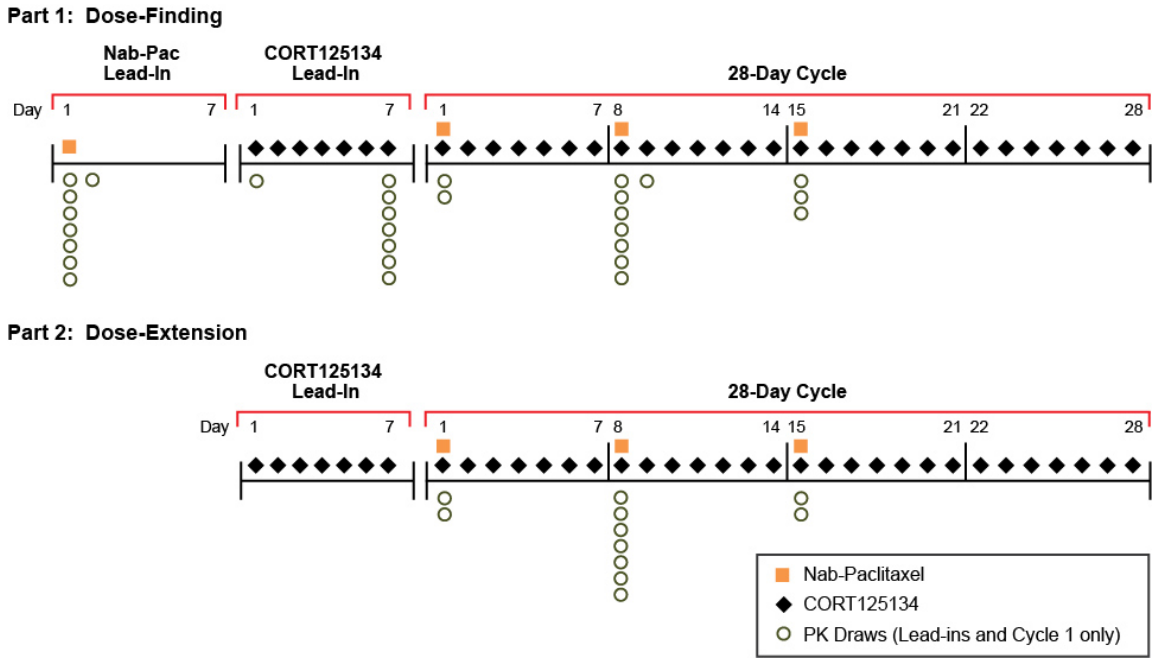
Design of Segment I and Segment II

The treatment cycle in each segment will consist of 28 days, and PK, PD, and safety evaluations will be performed throughout the study along with preliminary evaluations of antitumor activity as shown in the Schedule of Visits and Procedures (Table 9 for Segment I and Table 11 for Segment II).

Segment I Continuous-Dosing Regimen

The dosing and PK sampling schedule for the Segment I Continuous-Dosing Regimen is shown schematically in Figure S2.

Figure S2 Segment I Continuous-Dosing Regimen: Schematic of Study Drug Dosing and PK Sampling Schedule



Abbreviations: Nab-Pac, nab-paclitaxel; PK, pharmacokinetic.

Segment I, Part 1: Dose-Finding Phase

- Patients with any solid tumor, for whom nab-paclitaxel is an appropriate therapy in the opinion of the Investigator, will be enrolled according to a standard 3+3 cohort design.
- The starting dose level will be 100 mg CORT125134, administered once daily (QD), in combination with 80 mg/m^2 nab-paclitaxel, administered on Days 1, 8, and 15 of a 28-day cycle.
- In Part 1 there will be a 1-week nab-paclitaxel lead-in (1 dose of nab-paclitaxel on Day 1) and a 1-week CORT125134 lead-in (CORT125134 daily for 7 days) before the start of Cycle 1, and then 28 day cycles consisting of CORT125134 daily for 28 days plus nab-paclitaxel weekly for 3 weeks (Figure S2).
- PK will be characterized after dosing with nab-paclitaxel alone, after 7 days of dosing with CORT125134 alone, and after dosing with the combination of nab-paclitaxel and CORT125134, in Cycle 1 only (Figure S2).
- After a minimum of two dose levels are observed in Part 1, the nab-paclitaxel lead-in may be discontinued per DRC recommendation. If the nab-paclitaxel lead-in is discontinued, the first dose of study drug will be the CORT125134 dose on Day 1 of the CORT125134 lead-in.
- The Data Review Committee (DRC) will review safety, laboratory, and any available PK data from each cohort before selecting the dose for the next cohort. Dosing will follow the dose-finding Table S1 (see Dose-Finding Procedures below). Dose-limiting toxicities (DLTs) will be identified at each dose level. The MTD and development regimen to be used in Part 2 will be determined.
- A given dose level may be expanded to further evaluate safety, tolerability, PK, or preliminary efficacy at that dose level or in a more restricted patient population.

- A dose of CORT125134 100 mg continuous dosing and nab-paclitaxel 60 mg/m^2 with prophylactic G-CSF support will be explored in patients with pancreatic cancer. Initially, approximately 6–8 patients will be enrolled in this cohort. The DRC will review the safety and tolerability after 6 DLT-evaluable patients complete 1 cycle of therapy. If the dose-limiting toxicity (DLT) rate exceeds 33%, the dose will be declared non-tolerable for this population (tumor type and similar line of therapy) and no additional patients will be enrolled to that cohort. Alternatively, a higher or lower dose level may be evaluated, per the recommendation of the DRC based on safety and PK data. Once the dose level is declared tolerable, the cohort will be expanded to include approximately 12–15 additional patients to further assess the safety and efficacy of this dose level. Safety and efficacy data from all pancreatic cancer patients receiving this dose level will be summarized. The DRC will take into consideration the overall tolerability and toxicities observed in this cohort(s) to inform dose escalation decisions and the recommended Phase 2 dose.

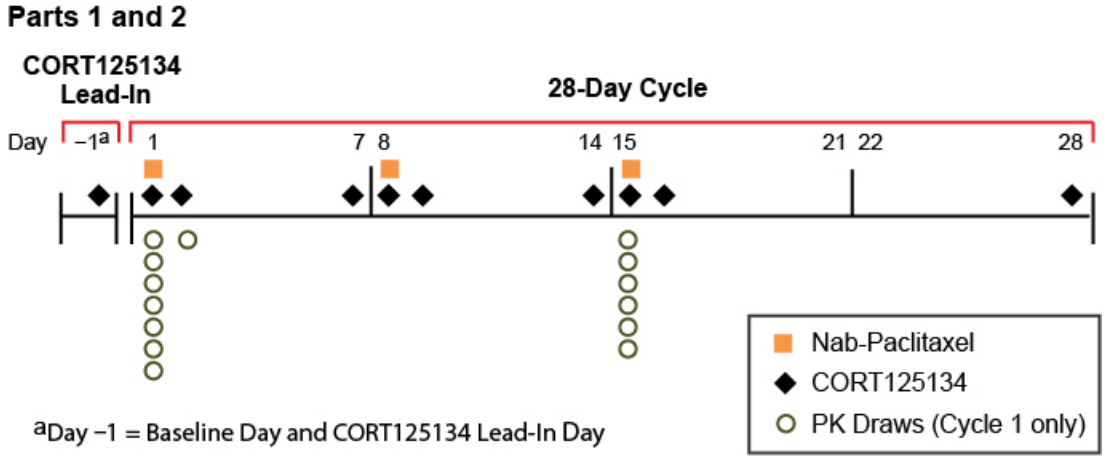
Segment I, Part 2: Dose-Expansion Phase

- Preliminary anticancer activity will be assessed in patients treated with the development regimen.
- Patients in Part 2 will have the same dose schedule as patients in Part 1, but without the nab-paclitaxel lead-in (Figure S2).
- Expansion cohorts will include approximately 20 patients in each, with a plan to evaluate the following tumor types: (1) platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer and, (2) triple-negative breast cancer (TNBC). Additional tumor types may be identified by data from Part 1, in which case additional expansion cohorts may be added by amendment.
- PK will be characterized in Part 2 Cycle 1 only during treatment with combination nab-paclitaxel and CORT125134.

Segment II, Intermittent-Dosing Regimen

The dosing and PK sampling schedule for the Segment II Intermittent-Dosing Regimen is shown schematically in Figure S3.

Figure S3 Segment II Intermittent-Dosing Regimen: Schematic of Study Drug Dosing and PK Sampling Schedule



Abbreviations: PK, pharmacokinetic.

Segment II, Part 1: Dose-Finding Phase

- Patients with any solid tumor, for whom nab-paclitaxel is an appropriate therapy in the opinion of the Investigator, will be enrolled according to a standard 3+3 cohort design.
- The starting dose level will be 200 mg CORT125134 in combination with 100 mg/m^2 nab-paclitaxel. CORT125134 will be administered once daily on the day before, the day of, and the day after the nab-paclitaxel infusions that will be administered on Days 1, 8, and 15 of the 28-day cycle.
- PK will be characterized in Cycle 1 only, during treatment with combination nab-paclitaxel and CORT125134 (Figure S3).
- The DRC will review safety, laboratory, and any available PK data from each cohort before selecting the dose for the next cohort. Dosing will follow the dose-finding Table S2 (see Dose-Finding Procedures below). DLTs will be identified at each dose level. The MTD and development regimen to be used in Part 2 will be determined.

Segment II, Part 2: Dose-Expansion Phase

- Preliminary anticancer activity will be assessed in patients treated with the development regimen.
- Patients in Part 2 will have the same dose schedule as patients in Part 1.
- Expansion cohort(s) will include approximately 20 patients in each, with a plan to evaluate triple-negative breast cancer (TNBC). Expansion cohorts of 20 patients with platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer may be evaluated with the intermittent regimen, per the same selection criteria as provided for Segment I. Additional tumor types may be identified by data from Part 1, in which case additional expansion cohorts may be added by amendment.
- PK will be characterized in Cycle 1 only, during treatment with combination nab-paclitaxel and CORT125134

Dose-Finding Procedures

Enrollment in the Part 1 Dose-Finding Phases of Segment I and Segment II will proceed in parallel and independently.

Dose Levels

Segment I Continuous-Dosing Regimen—Example target dose levels for evaluation in Part 1 are shown in Table S1.

- CORT125134 dose escalation will proceed by a maximum of 50 mg per dose level, per DRC recommendation. The starting dose of 100 mg CORT125134 is at the low end of the anticipated range of doses, yet retains the potential for PD effect.
- Nab-paclitaxel will start at the low end of the standard dose range (80 mg/m^2) since CORT125134 inhibits both cytochrome P450(CYP) 3A4 and CYP2C8 (the primary routes of metabolism of nab-paclitaxel) in nonclinical studies. With the starting dose level set in a conservative manner, the plan is to escalate the investigational product, CORT125134, sequentially through the dose-finding phase of the study as outlined in Table S1. However, taking PK and safety data into account, the DRC could recommend modifying the nab-paclitaxel dose with an increase to 100 mg/m^2 or a decrease to 60 mg/m^2.

Table S1 Segment I Continuous-Dosing Regimen: Example Dose-Finding Table of CORT125134 / Nab-paclitaxel Dose Levels for Part 1

Dose Level	CORT125134 Dose (mg)	Nab-paclitaxel Dose [a] (mg/m^2)
−1	50	80
1 – Starting dose	100	80
2	150	80
3	200	80
4	250 [b]	80

[a] Taking the nab-paclitaxel exposure and safety data into account, the nab-paclitaxel dose may be increased to 100 mg/m^2 or decreased to 60 mg/m^2. Nab-paclitaxel and CORT125134 will not be escalated simultaneously; therefore, a change in dose for nab-paclitaxel would constitute a separate dose level.

[b] Doses may exceed 250 mg CORT125134 based on safety and PK data and DRC recommendation.

Segment II Intermittent-Dosing Regimen—Example target dose levels for evaluation in Part 1 are shown in Table S2.

The starting dose in Part 1 is 200 mg CORT125134 in combination with 100 mg/m^2 nab-paclitaxel. CORT125134 dose escalation is expected to proceed by 100 mg per dose level. The DRC may recommend modifying the nab-paclitaxel dose to 80 mg/m^2 based on the nab-paclitaxel exposure and safety data.

Table S2 Segment II Intermittent-Dosing Regimen: Example Dose-Finding Table of CORT125134 / Nab-paclitaxel Dose Levels for Part 1

Dose Level	CORT125134 Dose (mg)	Nab-paclitaxel Dose (mg/m^2)
−1	150	100
1 – Starting dose	200	100
2	300	100
3	400 [a]	100

[a] Doses may exceed 400 mg CORT125134 based on safety and PK data and DRC recommendation.

Dose-finding Process

Dose-finding decisions, including selection of dose levels for cohorts, determination of the MTD and development regimen, and stopping enrollment, as applicable, will be performed by the DRC. The key principles guiding DRC recommendations for dose levels in dose-finding are to ensure that patients receive nab-paclitaxel at therapeutic exposures and to sequentially increase the dose of CORT125134 as tolerated. Dose escalation will be guided by safety and PK profiles.

The DRC will recommend dose escalation or de-escalation after review of data from the current cohort. For dose escalation, either CORT125134 or nab-paclitaxel, but not both, will be changed in the next dose level, based on recommendations by the DRC. If a lower dose level is explored and is well tolerated, the DRC may recommend re-escalating either CORT125134 or nab-paclitaxel.

All patients in the Part 1 cohorts will be treated with the CORT125134/nab-paclitaxel combination and assessed for 1 cycle. Approximately 5 patients may be initially enrolled to a cohort, and non-DLT evaluable patients may be replaced to allow for a minimum of 3 evaluable patients for each cohort. Depending on the number of patients with DLTs, additional patients will be enrolled in the same cohort or additional cohorts will be enrolled following the criteria described in Table S3.

Table S3 Rules for Dose-Finding to Define Maximum Tolerated Dose in Part 1 Dose-Finding Phase of Segments I and II

No. of Evaluable Patients with DLT at a Dose Level (cohort of <6 evaluable patients)	Dose-Finding Decision Rule for Dosing in Subsequent Cohort
0	• Enroll cohort at next higher dose level.
1	• Expand current dose level to 6 patients. [a] • If 1 of 6 patients (<33%) experiences DLT, enroll cohort at next higher dose level. • If ≥2 of 6 patients (≥33%) experience DLT: – Enroll cohort at next lower dose level, if available. OR – Declare next lower dose level as the MTD.
≥2	• If ≥2 patients experience DLT: – Enroll cohort at next lower dose level, if available. OR – Declare next lower dose level as the MTD.

[a] The DRC may make the recommendation to adjust the size of a cohort to more than 6 patients to further the evaluation of a given dose level, such as further evaluation of PK data or tolerability. If cohorts are >6 patients, the decision rule will be based on the percentage of patients experiencing DLT within that cohort.

The MTD is defined as the highest dose at which <33% (eg, 0 of 3 or 1 of 6 patients, with a minimum of 6 patients if 1 DLT is observed) experiences a DLT during Cycle 1. Alternatively, a different (lower) dose level may be declared the MTD depending on the nature, severity, and frequency of toxicities to date. Safety data that become available for patients remaining on-study after Cycle 1 will be taken into consideration when making decisions about dose escalation.

The dose level selected for the development regimen may be equal to or lower than the MTD and its selection will take into account other issues such as safety data occurring after the first cycle.

A sufficient number of DLT-evaluable patients will be enrolled in each cohort to ensure that there are DLT-evaluable patients available for determination of the MTD and identification of the development regimen. The number of DLT-evaluable patients may be inclusive of all cohorts at that dose level and schedule (such as advanced solid tumor and pancreatic cancer cohorts in Segment I) for determination of the MTD or dose-finding decisions, per DRC recommendation. If two distinct DLTs, such as events occurring in different MedDRA system organ classes, are observed within a dose level, the DRC may recommend expanding the cohort to >6 patients to further evaluate the tolerability of that dose level.

- DLT-evaluable patients will include those who complete one cycle of treatment or those who withdraw from the study due to toxicity during Cycle 1.

Non-evaluable patients will include patients who withdraw from the study prior to completion of Cycle 1 for reasons other than toxicity (eg, lost to follow-up, withdrawal of consent, or disease

progression, or received ≤80% of CORT125134 dosing due to reasons other than toxicity). These patients may be replaced.

PK for patients with a history of GI resection or gastric bypass surgery will be considered separately from the remainder of the cohort. The safety data for these patients will be taken into consideration in the assessment of the overall tolerability of a given cohort. A minimum number of patients evaluable for DLT will be enrolled to a cohort to consider the tolerability at this dose level who don't have a history of GI resection/gastric bypass surgery.

For non-hematological events, a DLT is defined as any TEAE not attributable to disease or disease-related processes that occurs during the observation period (Cycle 1) and that:

- Is Grade 3 or higher according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03, excluding the exceptions listed below.
  or
- Results in a dose omission or > 1-week delay of nab-paclitaxel.
  Note: if a >1-week delay of nab-paclitaxel occurs for logistical reasons, it will not be considered a DLT.

Exceptions include the following non-hematological AEs that are *not* considered DLTs:

- Grade 3 fatigue lasting <7 days
- Rigors lasting <24 hours
- Grade ≥3 nausea or vomiting that has resolved to Grade ≤2 within 48 hours after standard antiemetic therapies
- Grade 3 diarrhea that has resolved to Grade ≤2 within 48 hours after standard antidiarrheal therapies
  and/or
- Isolated laboratory findings not associated with signs or symptoms, including Grade 3/4 alkaline phosphatase, uric acid, amylase, and lipase elevations, and Grade 3 hyponatremia lasting <72 hours.

The following non-hematological AEs *are* considered DLTs:

- Any elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥10 × upper limit of normal (ULN) lasting more than 3 days with discontinuation of therapy
- Any elevation of AST or ALT >20 × ULN
- Any elevation of AST and ALT >3 × ULN associated with serum bilirubin >2 × ULN without evidence of another cause for the hyperbilirubinemia is a DLT requiring immediate discontinuation of all study therapy.

For hematologic events: a DLT is defined as follows:

- Grade 4 neutropenia lasting >7 days.
- Grade ≥3 febrile neutropenia (ANC <1000 cells/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour).
- Grade 4 thrombocytopenia or Grade ≥3 thrombocytopenia lasting >7 days or associated with Grade ≥2 bleeding.
- Dose delay >7 days of scheduled chemotherapy secondary to myelosuppression.

Data Review Committee

A DRC consisting of at least one Investigator from each site experienced in evaluating oncology treatments, a clinical pharmacologist, and the Medical Monitor will perform safety monitoring of the study drugs in accordance with procedures detailed in a DRC Charter.

The DRC will convene prior to each planned dose escalation during the dose-finding phase (Part 1), at least every 6 months during the dose-expansion phase of the study (Part 2), and on an ad hoc basis as necessary throughout study conduct. The DRC will perform the following tasks:

- Evaluate suspected DLTs, using criteria defined above for adjudication of treatment-related AEs.
- Determine the appropriateness of dose escalation or dose de-escalation and cohort expansion based on all available data, leading to a specific recommendation for the next dose to be evaluated during the dose-finding phase.
- Make recommendations to hold dosing or enrollment, or to adjust the size of any cohort as needed to further evaluate safety, tolerability, PK, or preliminary efficacy at a given dose level or in a more restricted patient population.
- Make recommendations to adjust the size of any cohort as needed to obtain more PK data (eg, at the development regimen).
- Make recommendations to end dosing or enrollment.
- Make recommendations to enroll specific cohort(s) in dose-finding to investigate the use of G-CSF at a dose level associated with high rates of neutropenia. Once a cohort is defined as a G-CSF cohort, the rules for G-CSF usage may be carried forward to additional cohorts at the recommendation of the DRC.
- Monitor emerging PD, PK, and clinical activity data throughout the course of dose-finding (Part 1) to form basis of recommendation for subsequent dose according to Table S2, and make recommendations regarding the dose and schedule of CORT125134 and nab-paclitaxel (ie, the development regimen) to be evaluated in the dose-expansion phase of the study (Part 2).
- If supported by data, the DRC may recommend changes to schedule of dosing with nab-paclitaxel (ie, every other week schedule or two out of three week schedule) in a subsequent cohort.
- The DRC may recommend dose titration of either CORT125134 or nab-paclitaxel to optimize exposure and tolerability. If dose titration is instituted, feasibility of that dose level will be assessed over the number of cycles during which titration occurs.

In the event that a decision is made by the Sponsor to reject a safety recommendation by the DRC, the decision and rationale will be communicated to the Food and Drug Administration (FDA) and site Institutional Review Boards (IRBs) before enrolling additional patients.

Number of Patients

- Segment I Continuous-Dosing Regimen—Part 1, approximately 62 patients; Part 2, approximately 20 patients in each expansion cohort
- Segment II Intermittent-Dosing Regimen—Part 1, approximately 24 patients; Part 2, approximately 20 patients in each expansion cohort

Inclusion and Exclusion Criteria

The following study entry criteria apply to both Segment I and Segment II.

Inclusion Criteria

For all patients

1. Signed and dated IRB-approved informed consent form (ICF) prior to study-specific screening procedures. Note: standard-of-care assessments completed before the ICF is signed can be used for eligibility if done within the 28-day screening period.
2. Consent to provide archived tumor tissue (primary or metastatic) or pretreatment tumor biopsy if available for the purpose of staining for GR status. Note: Neither tissue sample nor immunohistochemistry (IHC) results are required prior to starting study treatment due to potential delays in obtaining tumor block or results from GR assay. Tumor biopsy sample proximal to study entry in addition to archived tumor tissue is preferred.
3. Age ≥18 years old.
4. Patients with advanced or metastatic solid tumors who have disease progression after treatment with available therapies that are known to confer clinical benefit, or who are intolerant to treatment and for whom nab-paclitaxel treatment is appropriate.
5. Up to 3 prior cytotoxic chemotherapeutic regimens or myelosuppressive therapies in the advanced setting. (Hormonal or non-myelosuppressive biologic, targeted, or immune therapies will not be counted toward the maximum lines of prior therapy.)
6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
7. Organ and marrow function meeting the following criteria at the Screening Visit:
   - Absolute neutrophil count (ANC) ≥1,500 cells/mm^3
   - Platelet count ≥100,000/mm^3
   - Hemoglobin ≥9 g/dL
   - AST or ALT ≤2.5 × ULN (or ≤5 × ULN in the context of liver metastasis)
   - Total bilirubin ≤1.5 × ULN
   - Serum creatinine ≤1.5 × ULN

   or

   - Creatinine clearance >60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
8. For female patients of childbearing potential, a negative pregnancy test. Female study patients of childbearing potential and male study patients with female partners of childbearing potential must be willing to use two effective methods of contraception (one of which is a barrier method) during the treatment period and for at least 3 months after the last dose of the study drug. Hormonal contraceptives are not permitted (hormonal intrauterine device [IUD] is acceptable).
9. Ability to take oral medications.
10. Albumin ≥3.0 g/dL (≥30 g/L)
11. If patient has undergone gastric bypass surgery and/or surgery of GI or hepatobiliary tract, the patient must demonstrate adequate absorption as evidenced by: albumin ≥3.0 g/dL, controlled pancreatic insufficiency (if present), lack of evidence of malabsorption.

For patients in Dose-Finding Part 1

12. Measurable or evaluable disease.

For patients enrolled in a specific dose-finding cohort in Part 1 limited to diagnosis of pancreatic cancer.

13. Histologically confirmed diagnosis of pancreatic adenocarcinoma. Patients with pancreatic neuroendocrine tumors, lymphoma of the pancreas, or ampullary cancer are not eligible.
14. CA19-9 (or CEA, CA-125 in non-CA 19-9 elevated tumors) measured within 14 days prior to first dose of study drug
15. Metastatic (non-irradiated) lesion that is measurable by RECIST 1.1

For patients in Dose-Expansion Part 2

For all patients in Part 2

16. Platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer or TNBC that, in the opinion of the Investigator, is appropriate to treat with nab-paclitaxel.

For patients in Part 2 with ovarian, fallopian tube, or primary peritoneal cancer only

17. Must have a histologic diagnosis of epithelial ovarian, primary peritoneal, or fallopian tube cancer or ovarian carcinosarcoma. Note: Mucinous and borderline histologic subtypes are excluded.
18. Treatment-free interval after platinum-based therapy of less than 12 months, or disease progression during platinum-based therapy.
19. Measurable or nonmeasurable disease. Previously irradiated lesions are not allowed as measurable disease, unless there is documented evidence of progression in the lesions. To be eligible with nonmeasurable disease, patients must have evaluable disease with cancer antigen 125 (CA-125) levels of ≥100 U/mL along with radiographically evaluable disease by computed tomography (CT) or magnetic resonance imaging (MRI). A minimum of 10 patients with measurable disease will be enrolled.

For patients in Part 2 with TNBC only

20. Histologically confirmed diagnosis of TNBC: Triple-negative for ER and PR (<1% cells positive for ER/PR) and HER2 per the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) Guidelines (Wolff et al. 2013) (HER2 test results show [a] IHC 1+ negative or IHC 0 negative or [b] in situ hybridization [ISH]-negative using single-probe ISH or dual-probe ISH).
21. Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in at least one lesion. Previously irradiated lesions are not allowed as measurable disease, unless there is documented evidence of progression in the lesions.

Exclusion Criteria

1. Clinically relevant toxicity from prior systemic cytotoxic therapies or radiotherapy that in the opinion of the Investigator has not resolved to Grade 1 or less prior to the first dose of study drug (ie, Day 1 of the first scheduled 1-week lead-in).
2. Clinically significant uncontrolled condition(s) or any medical condition which in the opinion of the study investigator places the subject at an unacceptably high risk for toxicities, or puts the patient at high risk for not completing the DLT evaluation period of the study.
3. Any major surgery within 4 weeks prior to the first dose of study drug (ie, Day 1 of the first scheduled 1-week lead-in).

4. Treatment with the following prior to the first dose of study drug (ie, Day 1 of the first scheduled 1-week lead-in):
    - An investigational product within 21 days or 5 half-lives, whichever is longer.
    - Systemic, inhaled, or prescription strength topical corticosteroids for the purposes of treating a chronic non-oncologic indication within 21 days.
    - Systemic cytotoxic therapies within 21 days.
    - Monoclonal antibodies (eg, pembrolizumab, nivolumab) or anticancer vaccines within 60 days.
    - Hormonal anticancer therapies within 7 days.
5. Requirement for treatment with chronic or frequently used oral corticosteroids for medical conditions or illnesses (eg, rheumatoid arthritis, immunosuppression after organ transplantation).
6. History of significant cardiac disease defined as New York Heart Association (NYHA) class III or IV, myocardial infarction (MI) within 6 months of first dose of study drug, or unstable angina within 6 months of first dose of study drug.
7. Pregnancy or breast feeding.
8. History of hypersensitivity or severe reaction to either study drug or to similar classes of either study drug.
9. Any intercurrent medical condition that in the opinion of the Investigator would confound study analysis or impair study participation or cooperation.
10. Any patient requiring chronic maintenance of white blood cell counts or granulocyte counts through the use of growth factor support (eg, Neulasta, Neupogen) or transfusion required for red blood cell or platelet support.

Study Drug, Dose and Mode of Administration

Study treatments will be administered at the dose levels described above in the Dose-Finding Procedures (Dose Levels) section.

- **Investigational product (CORT125134):** Drug product contains CORT12534 drug substance, a synthetically prepared small molecule, [redacted]
  CORT125134 50-mg capsules are white, size 2, hard gelatin capsules. The hard gelatin capsules are provided in sealed, foil blister strips. CORT125134 100-mg softgel capsules are yellow, and the 25-mg softgel capsules are brown. The softgel capsules are provided in bottles containing 30 capsules each. In Segment I, CORT125134 is to be administered orally once daily in the morning, each day; in Segment II, CORT125134 is to be administered orally once daily in the morning the day before, the day of, and the day after the nab-paclitaxel infusion.
  On the days nab-paclitaxel is administered, CORT125134 should be taken within 15 minutes before the start of the nab-paclitaxel infusion.
- **Nab-paclitaxel (Abraxane):** Commercially available and supplied in single-dose vials. Each single-use 50 mL vial contains 100 mg paclitaxel and approximately 900 mg of human albumin as a stabilizer. Nab-paclitaxel is supplied as a white to off-white sterile lyophilized powder for reconstitution before use, with the reconstituted formulation to be administered as an IV infusion over 30 minutes (±5 minutes).

Duration of Treatment

Patients in any part of the study who tolerate treatment in the first cycle are eligible to continue to receive treatment until they experience unacceptable toxicity, disease progression, or any of the other withdrawal criteria, or until the study is terminated by the Sponsor.

Criteria for Evaluation

Safety

Safety will be assessed by AEs including DLTs, clinical laboratory tests, vital signs, ECOG performance status, physical examinations, and electrocardiograms (ECGs). Laboratory testing will include hematology, serum biochemistry, urinalysis, coagulation (international normalized ratio [INR]) for patients taking warfarin, pregnancy testing as applicable, hormone levels, and thyroid function testing. In the event of a serious adverse event (SAE) or DLT, ACTH and cortisol should be assessed as close to the time of the event as possible, and a PK sample may be drawn at the discretion of the Investigator. Additional safety assessments may be made at any time if clinically indicated.

Anticancer Activity

Tumor assessments: In both segments, assessments of the chest, abdomen, and pelvis (CAP) using computed tomography (CT) scans or magnetic resonance imaging (MRI) will be performed at Screening, at the end of Cycle 2 (Cycle 3 Day 1 ±7 days), and thereafter every 6 to 8 weeks (no more than 8 weeks between scans) and at time of clinical suspicion of disease progression. The same method (radiological or physical) should be employed and assessed by the same individual on each occasion, if possible. Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 will be used to determine response (Eisenhauer et al. 2009). Confirmation of objective responses is defined as responses that persist on repeat imaging for two assessments with a time period of at least 4 weeks between two assessments (if possible, 4–6 weeks). In the event of a confirmed response, the timing of subsequent tumor assessment will be reset at the 6–8 week interval from confirmatory scan. At the Posttreatment/Early Termination Visit, tumor assessment will be done if ≥4 weeks have elapsed since the last tumor assessment, unless there is documented progressive disease. If progressive disease is documented, an additional tumor assessment is not required as part of the final visit.

In patients with ovarian, fallopian tube, or primary peritoneal cancer, CA-125 will be assessed at the time of radiologic tumor assessments (baseline and every 6–8 weeks) and response reported per GCIG criteria (Rustin et al. 2011) in addition to RECIST v1.1.

Patients will be followed for survival quarterly for 1 year following the last dose of study drug in the final patient enrolled.

Pharmacokinetics

Blood samples will be collected for determination of plasma concentrations of CORT125134 and its metabolites and nab-paclitaxel. In Segment I, serial PK data for Part 1 and for Part 2 will be obtained as shown in Figure S2. In Segment II, serial PK data will be obtained during Cycle 1 as shown in Figure S3. Should a patient require a dose reduction on study, a PK profile at the new dose level may be obtained with patient consent.

Standard PK parameters will be included in the characterization and evaluation of the dose-exposure relationship and related analyses. An assessment of the correlation of anticancer activity, AEs, and plasma drug concentrations will be undertaken. An optional PG sample will be collected to assess genetic factors affecting drug metabolism, transporters, and other PK parameters.

Pharmacodynamics and Biomarkers

Consent for tumor biopsy specimens is mandatory in Parts 1 and 2, and the tissue will be used for analysis of GR expression by IHC, in addition to other exploratory correlative biomarkers. Tumor tissue most proximal to study entry is preferred; historical tumor tissue is acceptable as an alternative and may be submitted in addition to tissue most proximal to study entry to assess for changes in GR expression over time and line of therapy. Tumor biopsy specimens may be collected at disease progression or during procedures required for patient management and are optional; these will be assessed for GR expression along with other exploratory biomarkers.

Pharmacodynamics will be assessed by measuring blood levels of insulin, C-peptide, adrenocorticotropic hormone (ACTH), morning cortisol, tumor characterization, and mRNA expression tests, including FKBP5 and glucocorticoid-induced genes or biomarkers of GR activity. Cytokines and T-cell profiles will be assessed to explore the effect of CORT125134 when given alone and in combination with nab-paclitaxel. Additional exploratory correlative biomarkers may be evaluated to correlate with disease status, target engagement, or response.

General Statistical Methods

Statistical Analyses

The primary analyses will include determination of the MTD/development regimen and the incidence and duration of toxicities according to the NCI-CTCAE, version 4.03.

Secondary analyses will characterize anticancer activity for the following endpoints:

- Objective response rate consisting of the percentage of patients with measurable disease who achieve an objective tumor response.
- Response rate for ovarian, fallopian tube, and primary peritoneal cancer will include measures by GCIC and by RECIST v1.1.
- Best response defined as the best response recorded from the date of the first dose of CORT125134 or nab-paclitaxel, whichever is earliest, across all time points during study observation period.
- Clinical benefit rate (CBR) defined as the percentage of patients who have achieved CR or PR, or SD for 6 months or greater.
- Progression-free survival defined as the time from the date the patient receives the first dose of CORT125134 or nab-paclitaxel, whichever is earliest, to the date the patient experiences unequivocal disease progression per RECIST v1.1 or death (all causes of mortality).
- Duration of response as measured from the date that the criteria are met for complete response (CR) or partial response (PR) until the first date that progressive disease is objectively documented.
- Overall survival defined as the time from date of the first dose of CORT125134 or nab-paclitaxel, whichever is earliest, until the date of death from any cause.

Pharmacokinetic parameters of nab-paclitaxel and CORT125134 and its metabolites will be calculated and analyte concentration-versus-time plots will be provided. PD parameters and biomarker results will be listed and summarized as appropriate.

All analyses of safety and anticancer activity for this open-label Phase 1/2 study will be descriptive and presented by dose group, tumor type, GR status, and overall, as appropriate. Patient listings will also be provided. The incidence and duration of TEAEs, defined as AEs occurring after the first dose of study treatment through 28 days after the last dose of either CORT125134 or nab-paclitaxel, will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study drug.

Sample Size

An adequate number of DLT-evaluable patients will be enrolled in Part 1 of both segments to determine the MTD and development regimen.

Approximately 20 patients will be enrolled in each expansion cohort in Part 2 of the study, with two expansion cohorts planned in Segment I and one planned in Segment II to provide a preliminary estimate of activity.

CONTENTS

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List of Abbreviations and Definitions

Term/Abbreviation	Definition
ACTH	adrenocorticotropic hormone
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	androgen receptor
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0–24}$	AUC values from time 0 to 24 hours postdose
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of last measurable concentration
AUC_{inf}	area under the plasma concentration-time curve from time 0 to infinity
BCRP	breast cancer resistance protein
BRCA1	breast cancer 1 (gene)
BUN	blood urea nitrogen
CA 15-3	cancer antigen 15-3
CA 19-9	cancer antigen 19-9
CA-125	cancer antigen 125
CAP	chest, abdomen, and pelvis
CAP	College of American Pathologists
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CL	systemic plasma clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum plasma concentration
C_{min}	predose plasma concentration
CRA	clinical research associate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DHEA-S	dehydroepiandrosterone sulfate
DLT	dose-limiting toxicity
DRC	Data Review Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ER	estrogen receptor
FDA	Food and Drug Administration
FKBP5	mRNA expression test for FK506 binding protein 5

Term/Abbreviation	Definition
FSH	follicle-stimulating hormone
GCIG	Gynecological Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
GR	glucocorticoid receptor
HER2	human epithelial receptor-2
HIPAA	Health Insurance Portability and Accountability Act
HPA	hypothalamic-pituitary-adrenal
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
IL-2, 4, 10, 12, 13	interleukins 2, 4, 10, 12, 13
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous(ly)
Ki	binding affinity constant
LC/MS/MS	liquid chromatography-tandem mass spectrometry method
LDH	lactic dehydrogenase
LH	luteinizing hormone
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MKP1/DUSP1	mitogen-activated protein kinase phosphatase/dual-specificity phosphatase 1
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events (v4.03)
NOAEL	no-observed-adverse-effects level
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PFS	progression-free survival
P-gp	permeability glycoprotein
PK	pharmacokinetic(s)
PG	pharmacogenomic
PoPE	proof of pharmaceutical effect
PR	progesterone receptor
PSA	prostate-specific antigen

Term/Abbreviation	Definition
QTc	corrected QT (interval)
RBC	red blood cell
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SGK1	serum glucocorticoid regulated kinase 1
shRNA	short hairpin RNA
$t_{1/2}$	apparent terminal elimination half-life
TA	tumor assessment
TAT	tyrosine amino transferase
TEAE	treatment-emergent adverse event
Th1, Th2, Th17	type 1, 2, and 17 T helper (cells)
T_{max}	time to reach maximum plasma concentration
TNBC	triple-negative breast cancer
Treg	regulatory T (cells)
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
V_{ss}	volume of distribution at steady state
WBC	white blood cell
WNL	within normal limits

1 INTRODUCTION AND BACKGROUND

CORT125134 is a small molecule being developed by Corcept Therapeutics (Corcept) for indications that may benefit from the modulation and/or antagonism of the glucocorticoid receptor (GR). GR mediates many biological processes, including inflammation, gluconeogenesis, immunity, cardiovascular system processes, bone metabolism, brain function, and homeostasis/development, predominantly through transcriptional mechanisms. Binding of the hormone cortisol to GR is responsible for regulating many of these processes. In preclinical models, GR was shown to be involved in chemotherapy resistance developed in tumor cells, with stimulation of GR shown to reduce chemotherapy sensitivity and blockade of GR shown to enhance chemotherapy sensitivity (Skor et al. 2013, Isikbay et al. 2014).

As a selective and potent GR antagonist, CORT125134 has the potential to provide a clinical benefit in oncologic indications in combination with appropriate chemotherapeutic agents by reversing the GR-mediated chemotherapy resistance mechanism and potentially restoring tumor sensitivity to the chemotherapeutic agent. This study was designed to evaluate the combination of CORT125134 and the commercially available chemotherapeutic agent nab-paclitaxel (Abraxane) in patients with solid tumors for whom nab-paclitaxel is an appropriate therapy. The goals of the study are to identify the maximum tolerated dose (MTD) and development regimens of this combination in patients with solid tumors appropriate for treatment with nab-paclitaxel and to evaluate the preliminary activity of the combination using the development regimens in expansion cohorts of patients with specific solid tumors (eg, platinum-resistant ovarian, fallopian tube, and primary peritoneal cancer or triple-negative breast cancer [TNBC]). Two CORT125134 dosing schedules will be evaluated (continuous dosing in Segment I and intermittent dosing in Segment II). Additional goals include characterizing the safety, pharmacokinetic (PK), and pharmacodynamic (PD) profile of the development regimens selected for further evaluation in this and other studies.

1.1 CORT125134

1.1.1 Nonclinical Data

Details of all nonclinical studies are provided in the Investigator's Brochure (IB).

1.1.1.1 Pharmacology

CORT125134 is a selective GR antagonist with a high binding affinity (Ki) of 0.15 nM in the human GR binding assay. CORT125134 has high selectivity for the GR relative to the progesterone receptor (PR), estrogen receptor (ER), and androgen receptor (AR), showing 100%, 7%, −1%, and 6% inhibition, respectively, in radioligand binding assays at a 1 μM concentration. Functional GR antagonism was demonstrated *in vitro* by the ability of CORT125134 to block the effects of dexamethasone (a potent GR agonist) on tyrosine amino transferase (TAT) activity in a human liver carcinoma cell line (Ki of 7.2 nM) and a rat hepatoma cell line (Ki of 1.2 nM).

1.1.1.2 Safety

To characterize the nonclinical safety of CORT125134, preliminary ascending single-dose, repeat-dose, and Good Laboratory Practice (GLP) 14-day repeat-dose toxicology studies were

conducted in rats and cynomolgus monkeys. The results of the general toxicology studies indicated that CORT125134 produced many anticipated effects related to the antagonism of GR and compensatory perturbations of the hypothalamic-pituitary-adrenal (HPA) axis. In these studies, safety pharmacology assessments included cardiovascular effects in monkeys, respiratory function in rats, and neurobehavioral effects in rats. In general, there were no remarkable central nervous, respiratory, or cardiovascular system effects in rats or monkeys following single oral doses up to 200 mg/kg (highest dose tested). In cynomolgus monkeys, administration of 200 mg/kg, and to a lesser extent, 100 mg/kg was associated with slight increases in QT interval and corrected QT (QTc) interval (<10%) in only a single animal. Given the magnitude of change in these parameters seen in this animal, the alterations noted were not judged to be adverse in nature.

During a 14-day GLP toxicology study in rats, three rats administered the highest dose (200 mg/kg) either died or were euthanized prior to the end of the study. The macroscopic and microscopic findings in these animals were generally similar and included a generalized depletion in body fat, and microscopic observations in the liver (mild panlobular hypertrophy and mild periportal vacuolation), bone marrow of the femur (minimal decrease in cellularity), spleen (minimal generalized lymphoid depletion), thymus (mild generalized lymphoid depletion), mandibular and parotid salivary glands (mild secretory depletion and mild atrophy, respectively), lymph nodes and gut-associated lymphoid tissue (mild generalized lymphoid depletion), and/or larynx (mild subacute/chronic inflammation). These findings suggest that death was a combination of direct test article effects, some of which were related to a compensatory response to the GR antagonistic properties of the test article and/or GR agonism, inappetence, and generalized lymphoid depletion. The no-observed-adverse-effect-level (NOAEL) is this study was 80 mg/kg/day.

In a 90-day GLP toxicology study in rats, a dose of 10 mg/kg was well tolerated. Dose dependent effects associated with the intended pharmacological activity of the test article were observed. The only effect considered adverse was an effect on body weight/body weight gain in male and female rats at 40 mg/kg/day. The NOAEL was considered to be 10 mg/kg/day in male and female rats.

In a chronic toxicology study in rats, doses of 2.5, 10, and 30 mg/kg/day were administered daily for 6 months. The only effect considered adverse was a reduction in body weight or body weight gain at the highest dose. The NOAEL was considered to be 10 mg/kg/day in male and female rats.

During a 14-day GLP toxicology study in monkeys, 1 animal died unexpectedly and 5 animals were euthanized prior to completion of the study. Although a definitive cause of death could not be determined microscopically, changes in the adrenal gland (degeneration of the medulla) may have contributed to the moribundity/death of these monkeys. The high dose was reduced from 200 mg/kg to 80 mg/kg partway through the study, and the mid dose was reduced from 100 mg/kg to 40 mg/kg. Adverse clinical findings observed prior to the unexpected death/early euthanasias included decreased activity, ataxia, watery feces, inappetence, hunched posture, tremors/convulsions, swollen eyes, and vomiting. Of these, soft or water feces (which was also seen in vehicle control and other test article treatment groups), inactivity, and inappetence typically preceded more pronounced neurobehavioral observations and morbidity or death. The

clinical observations along with the morbidity/mortality were instrumental in the lowering of the mid and high dose levels midway through the study. The NOAEL in this study was 20 mg/kg/day.

In a 90-day GLP toxicology study in monkeys, once-daily oral gavage doses of CORT125134 at dose levels of 3, 10, and 30 mg/kg/day were well tolerated. Non-adverse CORT125134-related effects were noted in clinical observations, clinical pathology, and anatomic pathology parameters. The predominant effects seen in this study were reversible, expected, and consistent with the anticipated pharmacology of the test article. Therefore, the NOAEL was 30 mg/kg/day.

In a chronic toxicology study in monkeys, doses of 3, 10, and 30 mg/kg/day were administered daily for 9 months. No adverse effects were noted at any dose, and the NOAEL was 30 mg/kg/day.

Effects seen in rats and/or monkeys upon the adrenal gland, thymus, bone marrow, and pituitary were considered likely direct and/or secondary effects resulting from GR antagonism. The liver and kidney (rats) were also affected, though the noted changes were largely adaptive responses or, in the case of the kidney, an effect unlikely to be of clinical relevance.

Two pilot embryo-fetal-development (EFD), DRF studies–one in the rat and one in the rabbit– were undertaken to determine the dose levels for subsequent definitive developmental studies. The results of the definitive studies are described below:

- A definitive GLP embryo-fetal-development study was conducted in pregnant rabbits at doses of 1, 3, and 10 mg/kg/day. Doses of 3 and 10 mg/kg/day revealed evidence of developmental toxicity in the form of fetal malformations (eg, whole body edema, abnormal forepaw flexure, hind limb malrotation, microencephaly, cleft palate and exencephaly, skeletal malformations, and pathological visceral findings), and at a dose of 10 mg/kg/day, post-implantation loss and early and late resorptions were statistically increased, while statistically significant decreases were observed in litter size and viable fetuses. Maternal toxicity occurred in the 10 mg/kg/day group as evidenced by reduced body weight gain or body weight loss, and reduced food consumption. Based on these results in pregnant rabbits, the NOAEL for maternal toxicity was 3 mg/kg, and the NOAEL for developmental toxicity was 1 mg/kg.
- A definitive GLP embryo-fetal development study was also performed in pregnant rats, at doses of 1, 2.5, and 10 mg/kg/day. No CORT125134-related fetal malformations or total litter resorptions were observed at any of the dose levels evaluated in the study. Maternal toxicity occurred in the 10 mg/kg dose group as evidenced by reduced body weight gain or body weight loss, and reduced food consumption. Based on these results in pregnant rats, the NOAEL for maternal toxicity was 2.5 mg/kg, and the NOAEL for developmental toxicity was 10 mg/kg.
- A study of fertility and early embryonic development to implantation in rats showed that CORT125134 had no effect on male or female fertility up to doses of 40 mg/kg/day, the highest dose tested. There were the expected effects on body weight in both sexes

CORT125134 was not genotoxic in in vitro bacterial and mammalian cell assays or in vivo in the rat micronucleus assay.

1.1.1.3 Other In Vitro Studies

CORT125134 is not a substrate for permeability glycoprotein (P-gp) or breast cancer resistance protein (BCRP). It appears to be eliminated via multiple metabolic pathways including cytochrome P450 (CYP) 2C8, CYP3A4 and CYP3A5 and a non-CYP pathway but not via renal elimination. This is reassuring with respect to the risk of drug-drug interactions affecting exposure to CORT125134. Based on *in vitro* studies, CORT125134 appears to be a potent inhibitor of CYP3A4 and CYP2C8 and a modest inhibitor of CYP2C9, CYP2C19, CYP2D6, and CYP3A5. No significant induction of CYP1A2, CYP2B6, or CYP3A4 was noted in a study carried out in human hepatocytes. Limited data are available concerning the potential of CORT125134 to affect transporter function. Additional details are provided in Section 1.3.2.2.

1.1.2 Clinical Data on CORT125134 Monotherapy

Clinical experience with CORT125134 is derived from two studies conducted in healthy subjects: Study CORT125134-120, which evaluated single ascending and multiple ascending doses of the Phase 1 formulation in healthy subjects, and Study CORT125134-122, which evaluated a single dose of 150 mg of the Phase 2 formulation in healthy subjects.

Study CORT125134-120: The clinical phase of Part 1 and Part 2, in which the safety, tolerability, and PK of single and multiple-ascending-doses, respectively, in healthy volunteers were assessed, is complete; final unblinded data are available, data analysis is complete. In total across all single dose groups, 69 subjects received CORT125134 and 12 received placebo. By dose level, 8 subjects received each of 5, 15, and 50 mg fasted; 7 received 150 mg fasted; 6 received 300 mg fasted and 24 received 500 mg fasted, and a further 8 received 150 mg fed. Across all multiple-dose groups, 25 subjects received up to 14 days treatment with CORT125134 and 9 received placebo. By dose level, 9 subjects received each of 50 and 150 mg, and 7 subjects received 250 mg once daily after an overnight fast. Dosing in Part 3 of the study, in which the safety, tolerability and PK of a higher multiple dose (500 mg) daily in healthy volunteers were assessed, was terminated prematurely due to lack of tolerability (principally musculoskeletal complaints).

Study CORT125134-122: This study evaluated the safety, tolerability, and PK of a single 150 mg dose of the CORT125134 Phase 2 formulation in 8 healthy male volunteers. The PK data analysis is complete and the clinical study report is in preparation. All 8 subjects completed the study without important protocol deviations or tolerability issues. There were no serious adverse events (SAEs) reported.

More information is provided in the Investigator's Brochure.

1.1.2.1 Safety

Study CORT125134-120: Overall, CORT125134 appeared to be safe and well tolerated following single doses up to 500 mg or repeated doses up to 250 mg once daily in Study CORT125134-120.

In the single-ascending-dose portion (Part 1), the overall incidence of treatment-emergent adverse events (TEAEs) was low after administration of CORT125134, with no notable difference in the percentage of subjects reporting TEAEs after dosing with active drug compared

with placebo. In the multiple-ascending-dose study (Part 2), TEAEs in the musculoskeletal and connective tissue disorders system organ class were reported more frequently by subjects treated with CORT125134, and with increasing frequency with increasing dose. The proportions of subjects with reports of musculoskeletal and connective tissue disorder TEAEs by daily dose were Placebo: 0 subjects; 50 mg: 2 subjects (22.2%); 150 mg: 4 subjects (44.4%); and 250 mg: 4 subjects (57.1%). The events reported were coded as back pain, pain in extremity, myalgia, arthralgia, musculoskeletal pain, spinal osteoarthritis, and tendon discomfort. However, back pain (0% [0/9] placebo, 22.2% [2/9] 50 mg, 11.1% [1/9] 150 mg, and 28.6% [2/7] 250 mg), pain in extremity (0% [0/9] placebo, 0% [0/9] 50 mg, 11.1% [1/9] 150 mg, and 28.6% [2/7] 250 mg), and myalgia (0% [0/9] placebo, 0% [0/9] 50 mg, 22.2% [2/9] 150 mg, and 0% [0/7] 250 mg) were the only TEAEs reported for at least 2 subjects in any of the three multiple ascending dose cohorts. Two subjects in Part 2 withdrew from the study due to a TEAE (severe back pain in a subject in the 150 mg group and moderate constipation and upper abdominal pain in a subject in the 250 mg group).

There was also some evidence that gastrointestinal TEAEs such as abdominal pain upper, epigastric pain, nausea, vomiting and constipation were reported with increasing frequency with dose of CORT125134, with the majority assessed as treatment-related following both single and multiple doses. Most events were mild, but moderate abdominal pain and constipation in one subject treated with CORT125134, 250 mg daily, resulted in withdrawal of treatment.

Findings in Part 3, the multiple-ascending-dose extension cohort, show that CORT125134 500 mg once daily exceeds the maximum well-tolerated dose in healthy volunteers, with musculoskeletal symptoms and earache being the most frequently reported limiting symptoms.

One SAE has been reported in this Phase 1 study. A subject treated with CORT125134, 50 mg daily was admitted to hospital overnight due to a head injury during the follow-up period. The subject declared this was due to an accidental fall; however, the hospital record states that the subject was assaulted. The event was considered unrelated to study treatment and the subject made a full recovery.

There were no clinically significant findings in any laboratory assessments, vital signs, 12-lead electrocardiograms (ECGs), Holter ECGs, or body weight. Five CORT125134-treated subjects in the multiple-dose part of the study had substantial reductions in platelet count during the treatment period, with prompt recovery subsequently. The average of the absolute platelet counts decreased in the CORT125134 treated groups when compared with placebo. None of the individual values was considered clinically significant, and an independent review did not consider these findings a safety concern.

Based on the mechanism of action of CORT125134, there is a theoretical risk of excessive GR blockade, which could manifest with findings such as weakness, tiredness, dizziness, hypoglycemia, dehydration, weight loss, nausea, vomiting, diarrhea and muscle aches. Since CORT125134 does not block the mineralocorticoid receptor, it is unlikely that hypotension would be seen in the absence of anti-hypertensive medication.

1.1.2.2 Pharmacokinetics

In Study CORT125134-120, PK analysis demonstrated that plasma CORT125134 concentrations declined in a multiphasic manner. In Part 2 of Study 120, plasma concentrations appeared to

plateau by Day 7 with little accumulation from Day 7 to Day 14, indicating that concentrations were likely at or near steady state by Day 7. Concentrations declined to unmeasurable levels prior to or by the last sampling time point, indicating that the concentration-time profile was completely captured within the planned sampling time window. The half-life for CORT125134 in Part 2 after the last dose on Day 14 averaged 11.99, 19.09, and 14.71 hours at 50, 150, and 250 mg/day, respectively. Approximately 20% increase in exposure was observed in the fasted state relative to following a United States Food and Drug Administration (FDA) high-fat breakfast. This mild food effect was observed in the extreme case of fasted vs high-fat diet and, hence, is likely less pronounced with a normal diet. Nutrition is of utmost importance to patients with cancer, and for that reason this protocol puts no restrictions around timing of meals.

Dose proportionality analysis from Study CORT125134-120 showed that for both maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC), exposure increased in a greater than proportional manner with dose increment for both single and daily dosing.

In Part 1 there were no subjects with AUC values from time 0 to 24 hours postdose (AUC_{0-24}) values greater than the animal data stopping rule limit of 22,944 ng·h/mL. Based on AUC_{inf}, there were 5 subjects with values higher than the limit, all at a dose of 500 mg. In Part 2 there were 3 subjects with AUC_{0-24} values greater than this limit, all at a dose of 250 mg/day. Metabolite (CORT125201) exposure was small compared to parent drug. At presumed steady state, metabolite AUC_{0-24} was less than 5% that of parent drug.

In Study CORT125134-122, which evaluated single, 150-mg doses of the Phase 2 capsule formulation in 8 healthy volunteers, CORT125134 was absorbed rapidly (median time to reach maximum plasma concentration [T_{max}] 1 hour, range 1–2 hours) to a mean C_{max} of 200.5 ng/mL. Thereafter, elimination was rapid (median T_{last} 24 hours; mean t½ 7.7 hours), giving a mean AUC_{inf} of 801 ng•h/mL.

In comparison of the Phase 2 capsule formulation with historical data for the Phase 1 capsule formulation, exposure from the Phase 2 formulation was substantially lower, with C_{max} being approximately 30 to 52% and AUC_{inf} 22% to 36% that of the Phase 1 formulation.

1.1.2.3 Pharmacodynamics

In Study CORT125134-120, the PD effects of CORT125134 were assessed by evaluating the ability of CORT125134 to prevent selected effects of the GR agonist prednisone. This evaluation was conducted after the administration of a single dose of CORT125134 (500 mg) in Part 1 of the study, and 14 days repeat dosing of CORT125134 (250 mg/day) in Part 2 of the study. In Part 1, a single dose of mifepristone (600 mg) was used as a comparator.

Administration of a single dose of prednisone (25 mg) resulted in a rapid drop in eosinophils, lymphocytes, and osteocalcin, and an increase in neutrophils. After administration of 600 mg mifepristone with 25 mg prednisone, the effect of prednisone on these parameters was ameliorated to a large extent. Similarly, after administration of 500 mg CORT125134 the effect of prednisone was also ameliorated. The 24-hour AUC on time point deltas for proof of pharmaceutical effect (PoPE) parameters for both mifepristone and CORT125134 were significantly different from those for prednisone alone on Day −19 ($p < 0.05$) for eosinophils and neutrophils but not plasma osteocalcin. For lymphocyte 24 h AUC, CORT125134 with

prednisone (but not mifepristone with prednisone) was significantly different to prednisone alone.

In Part 2 of the study, the 24-hour AUC on time point deltas for PoPE parameters for CORT125134 on Day 14 were significantly different from those for prednisone alone on Day −5 ($p < 0.05$) for eosinophils, neutrophils, and osteocalcin but not lymphocytes. Because there were only 3 placebo-treated subjects, no statistical comparison was done between placebo- and CORT125134-treated subjects. However, it was evident from plotting the data that active treatment on Day 14 resulted in an amelioration of the prednisone effect whereas placebo treatment did not.

The administration of prednisone increased FK506 binding protein 5 (FKBP5) mRNA expression, and this increase was prevented by co-administration of either mifepristone (600 mg) or CORT125134 (500 mg) with the prednisone in Part 1 of the study. After dosing with CORT125134 (250 mg) for 14 days in Part 2 of the study, prednisone did not induce FKBP5 mRNA expression. Administration of placebo for 14 days did not prevent prednisone-induced FKBP5 mRNA expression.

Due to inhibition of the negative feedback mechanism, the administration of a GR antagonist causes an increase in morning serum plasma cortisol levels. After administration of CORT125134 for 14 days, there appeared to be a dose-related effect, with increased cortisol levels at the higher doses. A comparison between morning cortisol levels on Day 13 for CORT125134-treated subjects with placebo-treated subjects showed that 50 mg CORT125134 did not have a statistically significant effect ($p = 0.2634$), whereas 150 mg and 250 mg CORT125134 did have a statistically significant effect ($p = 0.0025$ and 0.0006, respectively).

1.1.2.4 Pharmacodynamic Interactions - QTc Effects

Analysis of ECG safety data from Study CORT125134-120, showed that CORT125134 at doses up to 500 mg, which resulted in plasma concentrations up to approximately 4 µg/mL, did not have a clinically relevant effect on ECG parameters (cardiac safety report, data on file). Based on the exposure-response analysis of the QT effect, the data demonstrated that CORT125134 does not have a clinically relevant effect on the QTc interval. An effect on ΔΔQTcF above 10 ms could clearly be excluded within the studied range of plasma concentrations up to approximately 4 µg/mL, which corresponded to single doses up to 500 mg or repeated doses up to 250 mg once daily.

1.2 Nab-paclitaxel

Nab-paclitaxel (Abraxane) 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 (Abraxane Prescribing Information 2015; Horwitz 1994).

Nab-paclitaxel is indicated for the treatment of the following: 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 the current study, nab-paclitaxel will be administered in a dose-finding part to patients with solid tumors for whom nab-paclitaxel is considered appropriate by the Investigator, and followed by expansion cohorts of patients with platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer or with TNBC.

The recommended dosage of nab-paclitaxel in the metastatic breast cancer setting is 260 mg/m^2 administered intravenously (IV) over 30 minutes every 3 weeks. The approval of nab-paclitaxel for use in metastatic breast cancer was based on results from two single-arm, open-label studies and one randomized comparative study. In the open-label studies, objective responses were observed in patients with metastatic breast cancer administered nab-paclitaxel as 30-minute infusions at a dose of 175 mg/m^2 (n = 43) or 300 mg/m^2 (n = 63) at 3-week intervals.

In the randomized comparative study, 460 patients with metastatic breast cancer were randomized to receive either nab-paclitaxel at 260 mg/m^2 as a 30-minute infusion or paclitaxel injection at 175 mg/m^2 as a 3-hour infusion. In the primary analysis, patients in the nab-paclitaxel treatment arm had a statistically significantly higher reconciled target lesion response rate of 21.5% compared to 11.1% for patients in the paclitaxel injection treatment arm. There was no statistically significant difference in overall survival (OS) between the two study arms.

In the randomized comparative study, the most common adverse reactions (in at least 20% of patients) associated with single-agent nab-paclitaxel in metastatic breast cancer were alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, aspartate aminotransferase (AST) elevation, alkaline phosphatase (ALP) elevation, anemia, nausea, infections, and diarrhea. Grade 3–4 neutropenia occurred in 34% of patients. The incidence of Grade 4 neutropenia was lower in patients treated with nab-paclitaxel (9%) than in patients treated with paclitaxel injection (22%). The frequency and severity of sensory neuropathy increased with cumulative dose. Sensory neuropathy led to nab-paclitaxel discontinuation in 3% of patients. Twenty-four patients (10%) treated with nab-paclitaxel developed Grade 3 peripheral neuropathy, of whom 14 had documented improvement after a median of 22 days. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy. No Grade 4 sensory neuropathies were reported.

Warnings and precautions include bone marrow suppression (primarily neutropenia), sensory neuropathy, sepsis, hypersensitivity, use in patients with hepatic impairment, and use in pregnancy. The prescribing information indicates that nab-paclitaxel should not be used in patients who have baseline neutrophil counts of <1,500 cells/mm^3 and that patients who experience a severe hypersensitivity reaction to nab-paclitaxel should not be rechallenged with the drug. The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. Caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4 (see Section 1.3.2.2 for data concerning CORT125134).

The nab-paclitaxel dose for Segment I selected for this study starts at 80 mg/m^2 (range from 60 mg/m^2 to 100 mg/m^2 dependent on tolerability) administered in 28-day cycles by IV infusion over 30 minutes weekly for 3 weeks followed by 1 week of no treatment. A weekly dose schedule was reported to improve tolerability and reduce side effects of the therapy and was

associated with greater efficacy (Gradishar et al. 2009). Because of the potential of CORT125134 to inhibit metabolism of nab-paclitaxel, a conservative starting dose of nab-paclitaxel 80 mg/m^2 is selected in combination with CORT125134 100 mg for Segment I. Segment II intermittent dosing will start with a nab-paclitaxel dose of 100 mg/m^2 based on the lower CORT125134 exposures expected with intermittent dosing (see rationale for dose regimens, Section 1.5, and starting doses, Section 1.6)

1.3 Rationale for Combination of CORT125134 and Nab-paclitaxel in Chemotherapy-Resistant Tumor Types

1.3.1 Rationale for Use of CORT125134 in Chemotherapy-Resistant Tumor Types

1.3.1.1 Nonclinical Data

Preclinical studies have demonstrated that stimulation with a GR agonist triggers tumor cells to promote the expression of cell survival (anti-apoptotic) genes, enhancing their ability to escape chemotherapy that would otherwise induce cell death via apoptosis. *In vitro* studies have shown that the mechanism of chemotherapy resistance induced by the GR agonist dexamethasone is reproducible across several tumor cell line models (Zhang et al. 2006, Stringer-Reasor et al. 2015). Several *in vitro* xenograft studies have demonstrated that the addition of GR antagonists to a tumor cell line treated with chemotherapeutic agents, including taxanes, enhances the effects of chemotherapy. The addition of a GR agonist such as dexamethasone reduced the efficacy of the chemotherapeutic agent. *In vivo* models of mouse xenografts have shown that across several human tumor cell line models including ovarian cancer, TNBC, and castration-resistant prostate cancer, GR antagonists enhance the efficacy of chemotherapeutic agents, including taxanes, in the presence of circulating endogenous glucocorticoids (Stringer-Reasor et al. 2015, Szmulewitz et al. 2012; Skor et al. 2013, data on file).

There are several lines of evidence suggesting that activation of GR in cancer cell leads to an activation of tumor survival signals and consequent reduction in the effect of chemotherapy. This is important because increase of adrenal glucocorticoid production and up-regulation of its receptor (GR) during acute or chronic stressors (including diagnosis of cancer and related medical treatment) has the theoretical ability to promote tumor growth (Conzen 2008). In addition, dexamethasone, a potent GR agonist, is given as routine prophylaxis for emesis and side effects associated with many cancer chemotherapies (Basch et al. 2011). Specifically, dexamethasone is a standard prophylactic pretreatment given prior to administration of paclitaxel, a widely used chemotherapeutic agent, in order to prevent allergic reactions to a key excipient in the formulation of paclitaxel known as cremophor. Nab-paclitaxel, an effective and well-tolerated form of paclitaxel, does not require pretreatment with dexamethasone and hence is an ideal candidate for this line of research inquiry.

The concept of GR-mediated tumor survival is supported by the following: (a) high levels of GR expression are associated with poor prognosis in ER-negative breast cancer patients (Pan et al. 2011); (b) apoptosis is reduced when dexamethasone is added to *in vitro* cancer cell lines or to mouse xenografts treated with cytotoxic drugs such as paclitaxel; (c) up-regulation of GR by dexamethasone induces expression of a number of genes including those involved in anti-apoptosis such as the serum glucocorticoid regulated kinase 1 gene (SGK1) and

MKP1/DUSP1 (mitogen-activated protein kinase phosphatase/dual-specificity phosphatase 1) gene (Pan et al. 2011); and (d) in prostate cancer potent inhibition of the AR pathway by agents such as enzalutamide leads to a compensatory increase in GR expression that facilitates tumor survival signals and leads to the development of resistance (Balbas et al. 2013).

The hypothesis that a GR antagonist such as CORT125134 would potentiate the effects of chemotherapy is supported by several lines of evidence. GR is highly expressed in TNBC tumors (>10% of tumor cells stain positive by immunohistochemistry [IHC]) and/or having significantly increased tumor NR3C1 (GR) mRNA levels compared with normal breast tissue (Skor et al. 2013). High expression of GR appears to correlate with adverse outcomes in patients with ER-negative breast cancer (Pan et al. 2011). However, this effect does not occur in patients with ER-positive disease, and in fact the presence of GR expression in ER-positive disease is a positive prognostic marker. In a meta-analysis of 1,378 early-stage breast cancer patients, those patients with ER-negative tumors and high levels of GR expression had a significantly increased risk of early relapse compared to tumors with low GR expression (ie, GR-negative). In contrast, in patients with ER-positive disease high GR expression was associated with a better outcome (Pan et al. 2011).

Withdrawal of glucocorticoid from defined media triggers apoptosis of the immortalized human mammary epithelial cell line MCF10A, despite the presence of epidermal growth factor and insulin (Moran et al. 2000), suggesting that glucocorticoids mediate a potent survival pathway in these cells. Subsequent experiments showed that dexamethasone decreases response to paclitaxel in xenografts of the ER/PR/human epithelial receptor-2 (HER2)/neu-negative human breast cancer MDA-MB-231 through an inhibition of apoptosis (Pang et al. 2006).

Glucocorticoids initiate anti-apoptotic signaling through GR, which in turn regulates the transcription of genes that initiate signaling cascades. Induction of SGK1 and MKP-1 is required for anti-apoptotic signaling following GR activation in epithelial cells and breast cancer cell lines such as MDA-MB-231 (Mikosz et al. 2001, Wu et al. 2004, Engelbrecht et al. 2003). Following induction, the serine/threonine kinase SGK-1 is phosphorylated and activated downstream of the phosphatidylinositol 3-kinase pathway by phosphoinositide-dependent kinases 1 and 2. In addition to SGK-1, GR-induced MKP-1 expression is also required for glucocorticoid mediated cell survival in breast cancer cell lines (Wu et al. 2005). Following GR activation, induction of MKP-1 activity is associated with the dephosphorylation and inactivation of extracellular regulated kinases 1,2 and c-Jun NH2-terminal kinases 1 (Amsterdam et al. 2002, Engelbrecht et al. 2003). Inhibition of either endogenous SGK-1 or MKP-1 expression by short hairpin RNA (shRNA) in dexamethasone-treated breast cancer cells reverses GR-induced protection from chemotherapy suggesting that induction of both genes is required for cell survival signaling downstream of GR activation (Wu et al. 2004).

In vitro studies in ER-negative human breast tumor cell lines have shown that GR activation by the glucocorticoid agonist dexamethasone initiated an anti-apoptotic effect that increased cell survival, and that a GR antagonist could reverse this effect (Mikosz et al. 2001). Similarly, Skor et al. (2013) demonstrated that when added to dexamethasone and paclitaxel treatment, the GR antagonist mifepristone significantly increased cytotoxicity *in vitro* and inhibited MDA-MB-231 xenograft tumor growth. These effects were accompanied by an antagonism of

GR-induced SGK1 and MKP1/DUSP1 gene expression. CORT125134 treatment alone had no significant effect on TNBC cell viability or clonogenicity in the absence of chemotherapy

Overall, these results suggest that co-administration of CORT125134 with a chemotherapeutic agent may help overcome the resistance resulting from increased activation of GR that occurs as a result of a stimulation of GR by either endogenous or exogenous glucocorticoids.

1.3.1.2 Clinical Data for Combination of a Glucocorticoid Receptor Antagonist and Nab-paclitaxel

A recent Phase 1 dose-ranging study evaluated the combination of nab-paclitaxel and mifepristone (Korlym®), a GR antagonist similar to CORT125134, in patients with metastatic breast cancer (Nanda et al. 2016). In Cycle 1, patients received nab-paclitaxel on Days 1, 8, and 15 and either oral mifepristone (300 mg once daily) or matching placebo on the day before and the day of nab-paclitaxel administration. In Cycle 2 and later, patients received the combination of mifepristone and nab-paclitaxel. In the first cohort (100 mg/m^2 nab-paclitaxel, n = 4), 2 patients received placebo and 2 received mifepristone; both mifepristone-treated patients had dose-limiting neutropenia in the first cycle. In the second cohort (80 mg/m^2 nab-paclitaxel, n = 5), 2 patients received placebo and 3 patients received mifepristone; 2 of the mifepristone-treated patients had dose-limiting neutropenia in the first cycle. Of the 9 treated patients, 2 had complete response, 3 had partial response, 1 had stable disease, and 3 had disease progression. The 6 patients with best responses of complete response, partial response, or stable disease received between 4 and 10 cycles of treatment. Five of these 6 patients were GR-positive and 1 patient who achieved partial response was GR-negative. Of the 3 patients with a best response of disease progression, 1 was weakly GR-positive and 2 were GR-negative. The study provided evidence of anticancer activity but was stopped early due to dose-limiting toxicity (DLT, neutropenia).

1.3.2 Rationale for Use of Nab-paclitaxel in Conjunction with CORT125134

The current study sets out to evaluate the combination of CORT125134 with nab-paclitaxel, to enable the added potential benefits associated with selective GR antagonism. Nab-paclitaxel was selected in the current study for the following reasons:

1. The mechanism of reversal of chemotherapy resistance with GR antagonists has been reproducibly demonstrated in several preclinical models across several tumor cells lines, with taxanes as the chemotherapy agent.
2. Taxanes are a widely used and efficacious chemotherapy, with applicability to many tumor types.
3. Data from a small study evaluating nab-paclitaxel in conjunction with the GR antagonist mifepristone in patients with metastatic breast cancer revealed data suggestive of durable response (Nanda et al. 2016; see Section 1.3.1.2).
4. Nab-paclitaxel has a similar safety and efficacy profile to paclitaxel; however, it does not require pretreatment with steroids to avoid allergic reaction and hence is an ideal candidate to evaluate further in the model of GR antagonism to reduce chemotherapy.

In selecting the combination of CORT125134 and nab-paclitaxel for evaluation in this study, the potential for drug-drug interactions has been considered. Data on absorption, distribution,

metabolism, and excretion (ADME) characteristics of nab-paclitaxel and interactions of nab-paclitaxel with other drugs is described below.

1.3.2.1 ADME Characteristics of Nab-paclitaxel

In vitro studies with human liver microsomes and tissue slices show that paclitaxel is metabolized primarily to 6α-hydroxypaclitaxel and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6α-3'-p-dihydroxypaclitaxel. The formation of these hydroxylated metabolites is catalyzed by CYP2C8, CYP3A4, and both CYP2C8 and CYP3A4 isoenzymes, respectively.

Paclitaxel exposure (AUC) increased from 2653 to 16736 ng·h/mL in a dose-proportional manner following doses in the clinical dose range, 80 to 300 mg/m^2. The mean plasma clearance of paclitaxel ranges from 13 to 30 L/h/m^2, and the mean apparent terminal half-life ranges from 13 to 27 hours. The mean cumulative urinary excretion of unchanged active substance accounted for 4% of the total administered dose, with less than 1% as the metabolites 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel, indicating extensive non-renal clearance. Paclitaxel is principally eliminated by hepatic metabolism and biliary excretion.

Based on population PK analysis, the total volume of distribution is approximately 1741 L, indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

Intrapatient variability in AUC was 19% (range = 3.21% to 27.70%). There was no evidence for accumulation of paclitaxel with multiple treatment courses.

Nab-paclitaxel comprises paclitaxel formulated as albumin-bound nanoparticles. The characteristics of paclitaxel administered as nab-paclitaxel have been compared with those following administration as a solvent-based paclitaxel formulation. The fraction of free paclitaxel (and, therefore, exposure to unbound paclitaxel) was significantly higher with Abraxane (nab-paclitaxel; 6.2%) than with solvent-based paclitaxel (2.3%), possibly due to paclitaxel not being trapped in Cremophor EL micelles as with solvent-based paclitaxel. The plasma clearance and volume of distribution of paclitaxel with nab-paclitaxel were larger (43% and 53%, respectively) than following a solvent-based paclitaxel injection. Terminal half-lives were comparable.

1.3.2.2 Drug-Drug Interactions with Paclitaxel and Nab-paclitaxel

Few if any formal PK drug-drug interaction studies have been performed with nab-paclitaxel; most of the label guidance appears to be from studies with paclitaxel.

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxy-paclitaxel *in vitro*.

The PK of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. Caution should be exercised when administering Abraxane (nab-paclitaxel) concomitantly with medicines known to inhibit (eg, ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil,

cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (eg, rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A4.

A PK interaction between CORT125134 and nab-paclitaxel following administration of nab-paclitaxel is likely. In *in vitro* testing, CORT125134 showed potent inhibition of CYP2C8 (IC_{50} <1 µM) and substantial inhibition of CYP3A4 (IC_{50} ~1 µM). Modest inhibition of CYP3A5, CYP2C19 and CYP2D6 (IC_{50} 4.9 µM, 8 µM and 9 µM, respectively) and partial inhibition of CYP2C9 were also noted. CORT125134 did not inhibit CYP1A2 or CYP2B6 (IC_{50} ≥10 µM). Pending further investigation as to the clinical relevance of these findings, concomitant administration of CORT125134 with drugs metabolized by CYP2C8, CYP3A4, CYP3A5, CYP2C9, CYP2C19 or CYP2D6, particularly drugs with a narrow therapeutic ratio, should be performed with caution.

In this study, patients will initially receive nab-paclitaxel in cycles of 3 doses at weekly intervals followed by 1 week off treatment, in combination with continuous CORT125134 dosing in Segment I and intermittent CORT125134 dosing in Segment II. The initial cohort of patients will be treated in Segment I with a unit dose of nab-paclitaxel of 80 mg/m^2. Exposure to nab-paclitaxel will be evaluated with PK sampling, and patients will be monitored closely for evidence of toxicity. If there is evidence of nab-paclitaxel toxicity, individual patients will receive appropriate supportive treatment and adjustment of subsequent nab-paclitaxel dose(s) in accordance with the prescribing information. The Data Review Committee (DRC; see Section 3.5) will review safety and PK data and, if appropriate, recommend dose-adjustment for nab-paclitaxel and/or CORT125134 for subsequent patients. The DRC may recommend that CORT125134 be administered intermittently (eg, if there is evidence of clinically significant enzyme induction associated with treatment with CORT125134). The rationale for the treatment regimens and starting doses is provided in Sections 1.5 and 1.6, respectively.

1.4 Rationale for Selection of Specific Tumor Types

The specific tumor types planned to be evaluated under this protocol are:

- Platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer
- TNBC
- Pancreatic Cancer

Additional expansion cohorts may be added by amendment. Expansion cohorts will include approximately 20 patients each.

The selection of additional tumor types for the expansion cohorts will be based on data from Part 1, as well as the current knowledge base and emerging data on GR-mediated chemotherapy resistance in tumor cells. The factors listed below will be used to select additional tumor types for evaluation in the dose-expansion phases of the study.

- Rate of GR expression in various tumor types (data on file).
  A recently completed evaluation of rates of GR expression by IHC across 20 solid tumor types showed that high rates of GR expression are present in several tumor types including melanoma, sarcoma, lung, and pancreatic cancer, as well as previously reported tumor types of TNBC and ovarian cancer.
- *In vitro* evidence of GR-mediated chemotherapy resistance (Zhang et al. 2006).

- *In vivo* (xenograft) evidence of GR-mediated chemotherapy resistance (Pang et al. 2006).
  Ongoing mouse xenograft studies with tumor cell lines from breast, ovarian, pancreatic, cervical, and other cancer types will continue to inform the development program and will likely contribute to choice in expansion cohorts.
- Clinical evidence of benefits of GR antagonism in GR-positive tumors.
  Ongoing Investigator-sponsored trials are evaluating the use of the GR antagonist mifepristone in castration-resistant prostate cancer, breast and ovarian cancer, and lung cancer. Corcept has an ongoing sponsored trial exploring the use of eribulin in combination with mifepristone in TNBC, which will inform the utility of that treatment regimen. Data from the dose-finding portion of Study CORT125134-550 may also provide clinical evidence of benefit.

Candidates for treatment in additional tumor-specific cohorts in either dose finding or dose expansion phases may include patients with pancreatic cancer, cervical cancer, lung cancer, and other solid tumors of epithelial origin that have high expression of GR or documented GR-mediated chemotherapy resistance. Details on the rationale for the initial selection of platinum-resistant ovarian, fallopian tube, and primary peritoneal cancer, TNBC, and pancreatic cancer are provided below.

1.4.1 Ovarian Cancer

Ovarian cancer, including fallopian tube, and primary peritoneal cancer, accounts for 3% of cancers in women and is the fifth most common cancer death in women. Women with early stage ovarian cancer have the best prognosis with cure rates of 70–90%. However, most patients are asymptomatic until advanced stages of the disease, and women with late stage ovarian cancer have a much worse prognosis with only a 15–30% cure rate. The limited treatment options for late stage ovarian cancer include tumor debulking and administration of a combination of nonplatinum- and platinum-based chemotherapy. Recurrence rates are high and most patients succumb to the disease. First line chemotherapeutic treatment of advanced ovarian cancer is combination therapy with carboplatin and paclitaxel. Patients who develop a recurrence within 6 months of the original platinum-based therapy are deemed platinum resistant. Standard of care for platinum-resistant ovarian cancer is treatment with single agent chemotherapy, often paclitaxel, with or without the addition of bevacizumab.

A research group at the University of Chicago has published data from a small proof-of-principle study with 10 ovarian cancer patients who received 20 mg of dexamethasone or placebo 30 minutes before surgery for ovarian cancer (Melhem et al. 2009). All human ovarian tumors from the enrolled patients expressed GR via IHC. The dexamethasone-treated patients experienced an average 6.1-fold increase in the GR target genes SGK1 and an average 8.2-fold increase in MKP1/DUSP1 tumor gene expression, while placebo-treated patients had no significant GR-mediated gene expression changes. Therefore, GR activation appears to result in increased anti-apoptotic gene expression in patients with ovarian tumors. Recently, the group has found that several high-grade serous ovarian cancer cell lines HeyA8, SKOV3, CAOV3, and Monty-1 expressed detectable amounts of the GR by Western analysis and quantitative reverse-transcription polymerase chain reaction. Seventy-nine percent of high-grade ovarian epithelial cancers (n = 52 total) had strong GR expression in most cells (Stringer et al. 2013).

Xenograft studies in ovarian cancer cell lines demonstrated that the addition of the GR antagonist mifepristone to combination therapy gemcitabine-carboplatin significantly reduced tumor burden over the gemcitabine-carboplatin arm alone (Stringer-Reasor et al. 2015).

Taken together, the nonclinical and clinical data indicate that GR antagonism may play a role in enhancing or restoring chemotherapy sensitivity in the treatment of patients with ovarian cancer. The data therefore support the planned evaluation of the combination of CORT125134 and nab-paclitaxel in this indication.

1.4.2 Triple-Negative Breast Cancer

Breast cancer, the most frequent cancer in women, is generally classified into ER-positive and ER-negative subtypes. TNBC lacks expression of the ER, PR, and HER2. TNBC is molecularly complex and increasingly recognized as heterogeneous with several gene expression pattern subtypes or clusters (Shah et al. 2012). TNBC represents 15 to 20% of newly diagnosed breast cancer (Bauer 2007), and is more common in younger, premenopausal, and African American women as well as women with breast cancer 1 (BRCA1) mutations (Morris et al. 2007).

TNBC has high sensitivity to chemotherapy, but there is a higher rate of relapse and worse prognosis compared to other types of breast cancer. In a study of 12,902 women (Lin et al. 2012), there was worse breast-cancer-specific survival (hazard ratio [HR] 2.99, 95% CI 2.59–3.45), worse overall survival (HR 2.72, 95% CI 2.39–3.10), and increased risk of death within 2 years of diagnosis (HR 6.10, 95% CI 4.81–7.74) for TNBC compared with ER- and PR-positive/HER2-negative breast tumors. In the locally advanced/metastatic setting, there are currently no drugs licensed specifically for the treatment of patients with TNBC. The median survival in this patient population is reported as approximately 6 months based on a retrospective review of over 3,700 patients (Kennecke et al. 2010). There is no standard of care, but common treatment practices in metastatic disease include, but are not limited to, a taxane-based regimen or gemcitabine plus platinum (cisplatin or carboplatin) as first-line treatment. The treatment of patients with TNBC represents an unmet medical need largely because of the molecular heterogeneity of the disease.

The following findings have led to the hypothesis that a GR antagonist such as CORT125134 would potentiate the effects of chemotherapy, including paclitaxel, in the treatment of TNBC: (a) high levels of the GR are associated with poor prognosis in ER-negative breast cancer patients; (b) apoptosis is reduced when dexamethasone is added to TNBC cancer cells or xenografts treated with cytotoxic drugs such as paclitaxel; and (c) up-regulation of the GR by dexamethasone in TNBC cell lines induces expression of a number of genes including those involved in anti-apoptosis such as *SGK1* and *MKP1/DUSP1* (Pan et al. 2011). These lines of evidence support the planned evaluation of the combination of CORT125134 and nab-paclitaxel in patients with TNBC.

1.4.3 Pancreatic Cancer

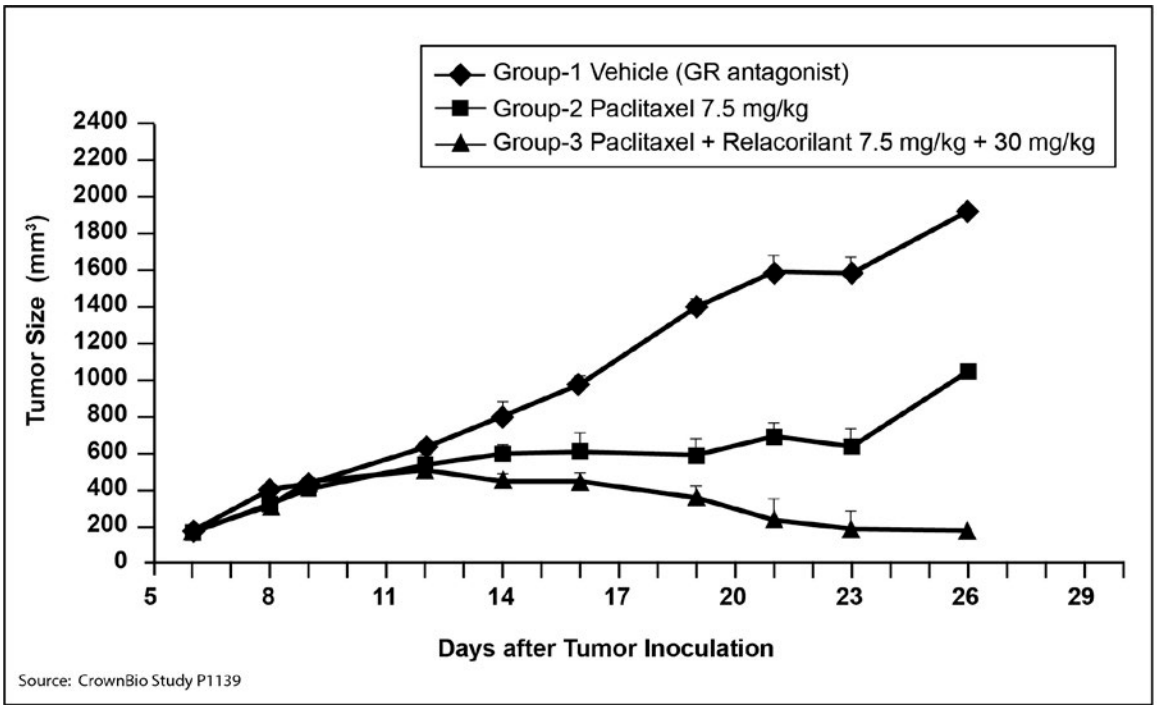
Pancreatic cancer is the third leading cause of cancer-related death in the United States, and is characterized as a highly lethal form of cancer. Typically, patients present with a later stage of cancer when a surgical cure is no longer an option. Five-year survival for node positive disease is 10%, even after surgical resection of disease. Once first and second line treatments are exhausted

for patients with advanced pancreatic cancer, options are limited and patients often move to palliation and pain control.

The role of GR in chemotherapy resistance in pancreatic cancer is of interest. Evaluation and staining for GR in 16 samples of pancreatic cancer from a tumor bank demonstrated a mean H score of 131 with a range of 30–280 using a validated IHC assay for GR (Block et al. 2017), demonstrating a significant GR expression in the tumor samples studied.

A xenograft model in pancreatic cancer with GR + cell line shown below demonstrated that while the model responded to paclitaxel alone, the tumor cells continued to grow despite addition of chemotherapy. The arm with the same dose of paclitaxel plus GR antagonism with CORT125134 showed a reversal of tumor growth and suggests that GR antagonism in this model improved the efficacy of paclitaxel.

Figure 1 Effect of CORT125134 in combination with paclitaxel in a pancreatic cancer xenograft model (MIAPaCa-2 model)



Clinical data from this study (CORT125134-550) in a patient with advanced pancreatic cancer receiving CORT125134 100 mg daily (continuous) and nab-paclitaxel 80 mg/m^2 is promising and merits further exploration. In total, the patient's cancer had progressed on four different prior lines of therapy before entering this study. This includes progression of disease after 4 cycles of nab-paclitaxel/gemcitabine 7 months prior to entry into this study. Since enrollment on the trial, this patient has tolerated treatment well, with a partial response by Cycle 3. The patient continues to do well clinically and is now on cycle 10 of the protocol with a sustained PR. In addition, the patient's tumor tissue was found to stain strongly for GR with the IHC assay for GR.

Based on the combination of preclinical and clinical data in pancreatic cancer to date, the protocol is amended to further explore pancreatic cancer.

1.5 Rationale for the Dosing Regimens

This study will assess the safety and efficacy of two dosing regimens of CORT125134 (continuous dosing in Segment I and intermittent dosing in Segment II) in combination with weekly nab-paclitaxel infusions.

The rationale for assessing two different dosing regimens (continuous and intermittent) is to evaluate and optimize the dose and schedule selection. Continuous dosing confers the potential advantages of (1) allowing continuous coverage of GR chemotherapy resistance pathways and (2) improving immune function through suppression of activity of endogenous glucocorticoids. Intermittent dosing confers the potential advantages of (1) optimizing GR blockade around times of greatest chemotherapy exposure and (2) improving tolerability.

1.6 Rationale for Starting Doses

CORT125134 is a selective GR antagonist, with high affinity for the GR. The compound was studied in a Phase 1, healthy volunteer study (CORT125134-120) evaluating doses ranging from 5 mg to 500 mg in a single-ascending-dose portion of the study, followed by evaluation of 50 mg, 150 mg, and 250 mg for 14 days in a multiple-ascending-dose portion of the study. Additional details of the clinical data summarized below are found in Section 1.1.2 and in the IB. The Phase 1 healthy volunteer data, PK modeling, PD, and assessment for potential of drug-drug interactions support the starting doses of 100 mg CORT125134 for continuous dosing (Segment I) and 200 mg CORT125134 for intermittent dosing (Segment II), with additional rational provided.

In the Phase 1 Study CORT125134-120, single doses of CORT125134 were safe and well tolerated in the dosing range of 5 mg to 500 mg. In the same study, continuous daily dosing with CORT125134 for 14 days was also safe and well tolerated at the doses of 50 mg, 150 mg, and 250 mg. Mild to moderate musculoskeletal adverse events (AEs) were reported with repeat doses up to 250 mg. A transient reduction in platelet count was observed in a non-dose-dependent manner, which resolved at study end. An additional, 500 mg cohort was added by amendment to the protocol and was discontinued early, principally due to musculoskeletal AEs, and a decision by the investigator that this dose level was generally not well tolerated in this group of healthy volunteers. There were no SAEs in this dose group. Doses between 250 mg and 500 mg were not studied. PK analysis in human volunteers supports daily dosing of the compound (see Section 1.1.2.2). Repeat daily dosing resulted in achievement of steady state by Day 7.

PD studies demonstrated that CORT125134, and mifepristone as a positive control, were able to reverse the effect of prednisone on white blood cell (WBC) count, osteocalcin, glucose, and FKBP5, thereby indicating GR blockade. After repeat dosing of CORT125134, Day 13 morning cortisol levels increased in a dose-dependent manner (indicative of GR antagonism), with a numeric but not significant increase over placebo in the 50 mg dose group, and significant increases over placebo in both the 150 mg and 250 mg dose groups (Figure 2).

Taken as a whole, the PD, PK, and safety profile of the Phase 1 formulation of CORT125134 justified a daily dosing range from 50 mg to 250 mg. Based on PK, PD, safety and tolerability data, the DRC in Study CORT125134-550 may recommend doses higher than 250 mg once data are collected through the 250 mg dose groups.

A small Phase 1 study (Study CORT125134-122) was conducted to characterize the current formulation of CORT125134 in healthy volunteers. A single 150-mg oral dose was administered to 8 healthy male subjects. The 150-mg dose of the current formulation of CORT125134 provided lower exposures in Study CORT125134-122 when compared with the 150-mg dose of the earlier, just-in-time formulation used in Study CORT125134-120. At the 150-mg dose level, the mean AUC_{inf} of the current formulation (800 ng•h/mL) is 27.5% of that of the earlier formulation (2912 ng•h/mL) used in Study CORT125134-120.

Based on results from Study CORT125134-120, the clinical PK of CORT125134 are nonlinear, with greater than dose-proportional increases in exposure observed over a dose range of 5 to 150 mg. Over the range of 50 mg to 150 mg of the earlier formulation, a 3-fold increase in dose resulted in a 6.3-fold increase in exposure (AUC_{inf}) to CORT125134 (exposure ratio:dose ratio [ER/DR] ratio = 2.1). The nonlinearity was greater at lower concentrations (namely, a $\geq$ 3.5 ER/DR from 15 mg to 50 mg); thus, lower absorbed doses of the current formulation would result in greater relative differences in exposure at 50 mg compared with 150 mg. The anticipated AUC_{inf} for a 50 mg dose of the current formulation is 92.2 ng•h/mL compared with an AUC_{inf} of 566 ng•h/mL for the 50 mg dose of the earlier formulation.

Starting Dose for Segment I Continuous-Dosing Regimen—This reduction in CORT125134 exposure at the lower dose range of the current formulation is likely to yield BLQ values when tested at 50 mg and is likely to be subtherapeutic. A reasonable correction of the exposure of the current formulation can be achieved with a shift of the starting dose from 50 mg/day to 100 mg/day. The anticipated AUC_{inf} with 100 mg of the current formulation is 645 ng•h/mL. This is comparable to that of 50 mg of the earlier formulation (AUC_{inf} = 566 ng•h/mL) and therefore supports the increase in starting dose from 50 mg/day to 100 mg/day in the Segment I Continuous-Dosing Regimen.

Starting Dose for Segment II Intermittent-Dosing Regimen—The Segment II intermittent-dosing schedule of CORT125134 will provide Day 3 AUC that is 54% of the steady-state exposure expected in the Segment I continuous-dosing cohorts. The anticipated exposures ($AUC_{0–24}$) to CORT125134 at steady-state and exposures ($AUC_{0–24}$) on Day 3 of intermittent daily dosing are presented in Table 1. The calculated mean steady state and Day 3 exposures, even at a dose of 500 mg, all fall below the mean exposure levels (22,390 ng•h/mL) achieved for the 250-mg daily doses of the earlier formulation for 14 days that were well tolerated. A starting dose of 200 mg intermittent dosing yields an anticipated exposure of 2457 ng•h/mL, comparable to the 100 mg continuous-dosing regimen starting dose that yields an exposure of 2000 ng•h/mL.

CORT125134 and Nab-paclitaxel—CORT125134 is an inhibitor of CYP3A4 and CYP2C8, the two CYP isoforms that are involved in the metabolic elimination of nab-paclitaxel (see Section 1.3.2.2). Pharmacokinetic modeling of the possible drug-drug interaction between CORT125134 and nab-paclitaxel suggests that the starting dose level of 100 mg CORT125134 (the current formulation) could cause up to a 1.7-fold increase in systemic exposure to nab-paclitaxel. Therefore, caution will be used in the dose escalation/de-escalation of CORT125134, and patients will be monitored carefully for signs of nab-paclitaxel toxicity. The starting dose of nab-paclitaxel in the Segment I Continuous-Dosing Regimen will be 80 mg/m^2, and the doses of nab-paclitaxel in subsequent cohorts may be increased or decreased based on

safety, PK, and tolerability data. Based on PK and safety data collected during the dose-finding phase of the study and reviewed by the DRC, careful dose escalation/de-escalation of CORT125134 is planned to ensure optimal antagonism of cortisol's activity at the GR (see Section 3.3 for details), as CORT125134 is expected to increase paclitaxel concentration due to its CYP inhibition profile.

2 STUDY OBJECTIVES

These objectives will apply to all regimens evaluated during the study.

Primary Objective

- To determine the MTD and the development regimen of the combination of CORT125134 and nab-paclitaxel in patients with solid tumors.

Secondary Objectives

- To characterize the safety profile of the combination of CORT125134 and nab-paclitaxel.
- To characterize the preliminary anticancer activity (objective response rate [ORR], progression-free survival [PFS], and OS) of the combination of CORT125134 and nab-paclitaxel in patients with solid tumors in a dose-finding phase and in patients with specific tumor types.
- To characterize the preliminary anticancer activity (ORR, PFS, and OS) of the combination of CORT125134 and nab-paclitaxel in patients with GR-positive or GR-negative solid tumors enrolled in any part of the study.
- To characterize the PK and exposure-response of the combination of CORT125134 and nab-paclitaxel in patients with solid tumors in a dose-finding phase and in patients with specific tumor types.
- To characterize the PD of the combination of CORT125134 and nab-paclitaxel indicative of modulation of GR function, including hormonal changes and FKBP5.

Exploratory Objectives

- To evaluate molecular, cellular, and soluble markers in peripheral blood and/or tumor tissue that may be relevant to the mechanism of action of or response/resistance to CORT125134.
- To evaluate pharmacogenomic (PG) markers to assess genetic factors affecting drug metabolism and transporters.

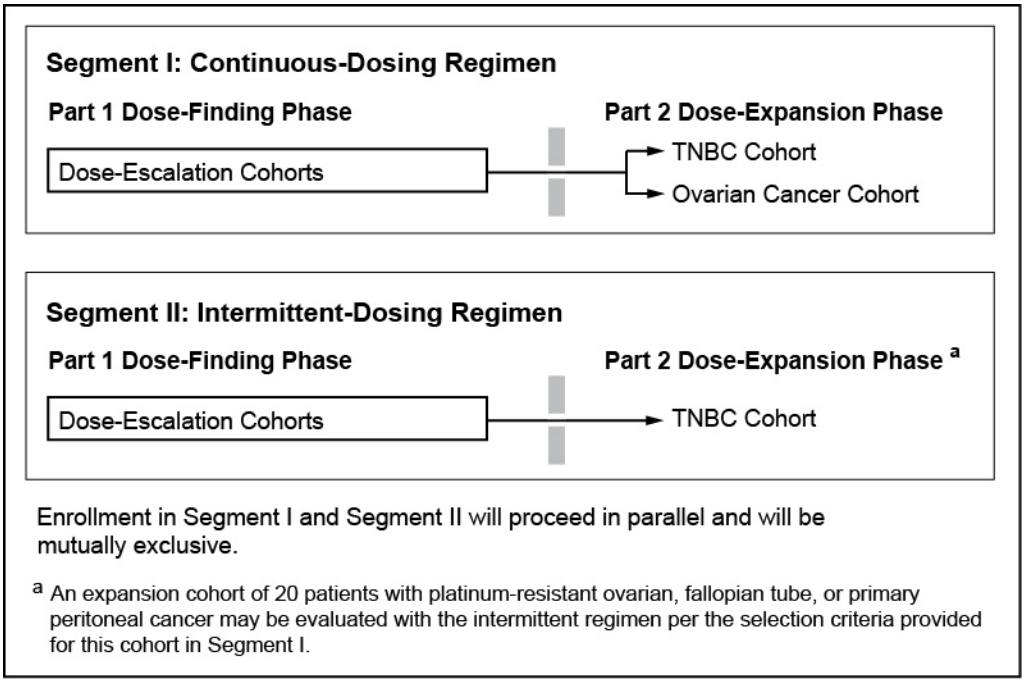
3 STUDY DESIGN

3.1 Overview of Study Design

This is a Phase 1/2 single-arm, open-label, multicenter study to determine the MTD and to assess safety, PK, PD, and preliminary anticancer activity of the combination of CORT125134 and nab-paclitaxel in patients with solid tumors.

The study will consist of two segments to evaluate alternative dosing schedules of CORT125134: Segment I will evaluate a continuous-dosing regimen and Segment II will evaluate an intermittent-dosing regimen (Figure 3). In Segment I, dose-escalation cohorts will be enrolled to determine the maximum tolerated dose (MTD) and the development regimen for the continuous-dosing regimen; thereafter, dose-expansion cohorts will be enrolled and treated with the continuous-dosing development regimen to better characterize the antitumor activity in patients with specific tumor types and to better define the safety profile. In Segment II, dose-escalation cohorts will be enrolled to determine the MTD and the development regimen for the intermittent-dosing regimen; thereafter, dose-expansion cohorts will be enrolled and treated with the intermittent-dosing development regimen to better characterize the antitumor activity of that regimen in patients with specific tumor types and to better define the safety profile for that regimen. Enrollment in Segment I and Segment II will be mutually exclusive, and the two segments will enroll patients concurrently.

Figure 3 Overview of Study Design Showing Segment I and Segment II Regimens



The treatment cycle in each segment will consist of 28 days, and PK, PD, and safety evaluations will be performed throughout along with preliminary evaluations of antitumor activity as shown in the Schedule of Visits and Procedures (Table 9 for Segment I and Table 11 for Segment II). However, the doses and treatment schedules will be different in each segment of the study.

Dose escalation will be guided by safety and PK profiles. Safety will be assessed by review of AEs, including DLTs; clinical laboratory tests, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, physical examinations, and electrocardiograms (ECGs). Anticancer activity will be evaluated using radiographic assessments.

Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 will be used to determine response (Eisenhauer et al. 2009). Objective responses will be confirmed no less than 4 weeks after the criteria for response are first met (if possible, 4–6 weeks). In patients with ovarian, fallopian tube, or primary peritoneal cancer, CA-125 will be assessed at the time of radiologic tumor assessments (baseline and every 6–8 weeks) and response reported per Gynecological Cancer Intergroup (GCIG) criteria (Rustin et al. 2011) in addition to RECIST v1.1. Levels of other tumor markers collected as standard practice (such as cancer antigens 15-3 and 19-9 [CA15-3 and CA19-9], prostate-specific antigen [PSA], and carcinoembryonic antigen [CEA]) will be documented. Patients will be followed for survival for a year after the last dose of study drug is administered in the final patient enrolled.

3.1.1 Overview of Design: Segment I Continuous-Dosing Regimen

- Part 1, Dose-Finding Phase:
  - Patients with any solid tumor for whom nab-paclitaxel is an appropriate therapy in the opinion of the Investigator, will be enrolled according to a standard 3+3 cohort design.
  - The starting dose level will be 100 mg CORT125134, administered once daily (QD), in combination with 80 mg/m^2 nab-paclitaxel administered on Days 1, 8, and 15 of a 28-day cycle.
  - In Part 1 there will be a 1-week nab-paclitaxel lead-in (1 dose of nab-paclitaxel on Day 1) and a 1-week CORT125134 lead-in (CORT125134 daily for 7 days) before the start of Cycle 1, and then 28-day cycles consisting of CORT125134 daily for 28 days plus nab-paclitaxel weekly for 3 weeks.
  - PK will be characterized after dosing with nab-paclitaxel alone, after 7 days of dosing with CORT125134 alone, and after dosing with the combination of nab-paclitaxel and CORT125134, in Cycle 1 only.
  - After a minimum of two dose levels are observed in Part 1, the nab-paclitaxel lead-in may be discontinued per DRC recommendation. If the nab-paclitaxel lead-in is discontinued, the first dose of study drug will be the CORT125134 dose on Day 1 of the CORT125134 lead-in.
  - The DRC will review safety, laboratory, and any available PK data from each cohort before selecting the dose for the next cohort. Dosing will follow the dose-finding Table 2 (see Section 3.3.1.1). DLTs will be identified at each dose level. The MTD and development regimen to be used in Part 2 will be determined.
  - A given dose level may be expanded to further evaluate safety, tolerability, PK, or preliminary efficacy at that dose level or in a more restricted patient population (ie see pancreatic cancer specific cohort).

- Part 2 Dose-Expansion Phase
  - Preliminary anticancer activity will be assessed in patients treated with the development regimen.
  - Patients in Part 2 will have the same dose schedule as patients in Part 1, but without the nab-paclitaxel lead-in.
  - Expansion cohorts will include approximately 20 patients in each, with a plan to evaluate the following tumor types: (1) platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer and (2) triple-negative breast cancer (TNBC). Additional tumor types may be identified by data from Part 1, in which case additional expansion cohorts may be added by amendment.
  - PK will be characterized in Part 2 Cycle 1 only during treatment with combination nab-paclitaxel and CORT125134.

3.1.2 Overview of Design: Segment II Intermittent-Dosing Regimen

- Part 1, Dose-Finding Phase:
  - Patients with any solid tumor, for whom nab-paclitaxel is an appropriate therapy in the opinion of the Investigator, will be enrolled according to a standard 3+3 cohort design.
  - The starting dose level will be 200 mg CORT125134 in combination with 100 mg/m^2 nab-paclitaxel. CORT125134 will be administered once daily on the day before, the day of, and the day after the nab-paclitaxel infusions that will be administered on Days 1, 8, and 15 of the 28-day cycle.
  - PK will be characterized in Cycle 1 only, during treatment with combination nab-paclitaxel and CORT125134.
  - The DRC will review safety, laboratory, and any available PK data from each cohort before selecting the dose for the next cohort. Dosing will follow the dose-finding Table 3 (see Section 3.3.1.2). DLTs will be identified at each dose level. The MTD and development regimen to be used in Part 2 will be determined.

- Part 2, Dose-Expansion Phase:
  - Preliminary anticancer activity will be assessed in patients treated with the development regimen.
  - Patients in Part 2 will have the same dose schedule as patients in Part 1.
  - Expansion cohort(s) will include approximately 20 patients in each, with a plan to evaluate triple negative breast cancer (TNBC). An expansion cohort of 20 patients with platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer may be evaluated with the intermittent regimen, per the same selection criteria as provided for Segment I. Additional tumor types may be identified by data from Part 1, in which case additional expansion cohorts may be added by amendment.
  - PK will be characterized in Cycle 1 only, during treatment with combination nab-paclitaxel and CORT125134.

3.2 Overview of Methodology

3.2.1 Segment I, Continuous-Dosing Regimen

During Segment I, patients will have the following in-clinic visits: Screening; Baseline (if needed, see below); Days 1 and 2 of a 1-week nab-paclitaxel lead-in and Days 1 and 7 of a 1-week CORT125134 lead-in before Cycle 1 (patients in Part 1); Cycle 1 Days 1, 8, and 15 (all patients) and Day 9 (patients in Part 1); Cycle ≥2 Days 1, 8, and 15; and a Posttreatment or Early Termination Visit. Study assessments are summarized below and provided in the Schedule of Visits and Procedures (Table 9).

After signing the Institutional Review Board (IRB)-approved informed consent form (ICF) at a Screening Visit within 28 days before the first dose of study drug, patients will undergo screening procedures including review of inclusion and exclusion criteria, medical/oncologic history, safety assessments (AEs, physical examination, vital signs, ECOG performance status, ECG, and clinical laboratory tests), assessment of levels of PD biomarkers (ie, C-peptide, adrenocorticotropic hormone [ACTH], morning cortisol, and FKBP5), a tumor assessment per Response Evaluation Criteria in Solid Tumors (RECIST), and archival tumor tissue collection or tumor biopsy for determination of GR status. If the Screening Visit is >7 days before the first scheduled dose of study drug, selected screening procedures will be repeated at a Baseline Visit within 7 days before the first dose of study drug. Eligible patients will enroll in the study and will begin dosing with CORT125134 and nab-paclitaxel as described below.

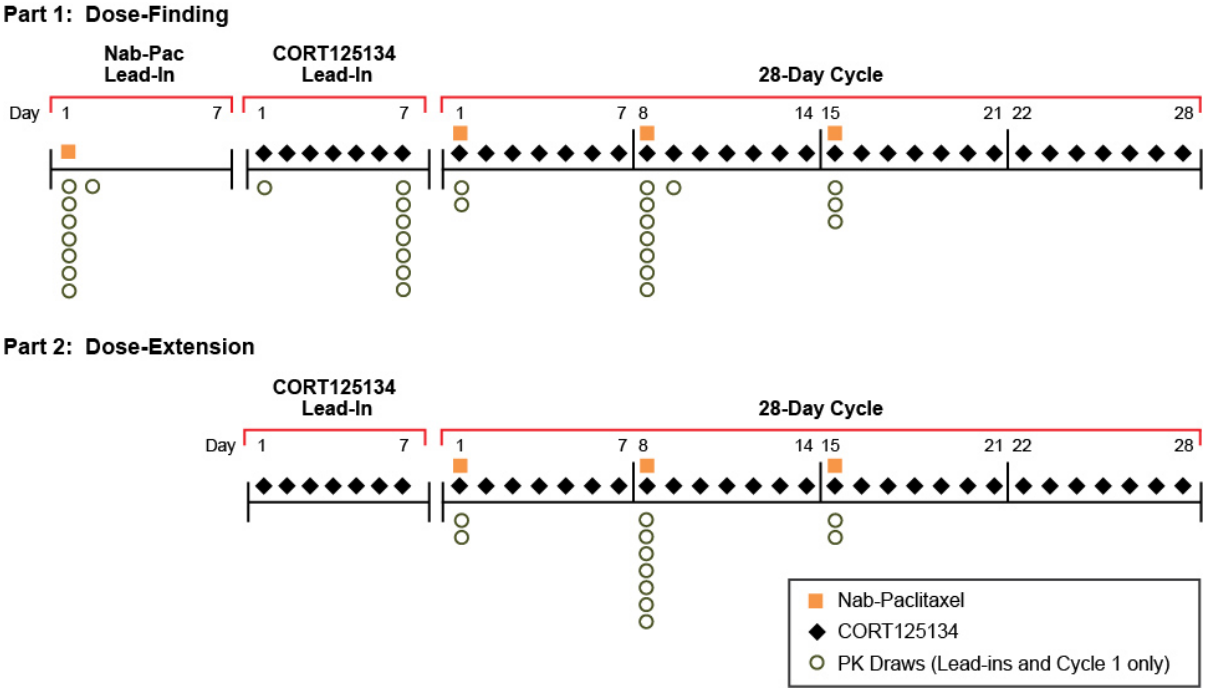
After completing Screening/Baseline assessments, patients in Part 1 of Segment I will return to the clinic to receive nab-paclitaxel as their first dose of study drug on Day 1 of a 1-week nab-paclitaxel lead-in. These patients will not receive study drug for the remainder of the nab-paclitaxel lead-in. On the day after Day 7 of the nab-paclitaxel lead-in, they will receive the first dose of CORT125134 as part of a 1-week CORT125134 lead-in prior to Cycle 1 (CORT125134 daily for 7 days) followed by 28-day cycles of the combination regimen (CORT125134 daily for 28 days plus nab-paclitaxel weekly for 3 weeks). After a minimum of two dose levels are observed, the nab-paclitaxel lead-in may be discontinued per the DRC recommendation.

Patients in Part 2 of Segment I will not have the 1-week nab-paclitaxel lead-in and will receive CORT125134 as their first dose of study drug. After Screening/Baseline, these patients will return to the clinic to receive CORT125134 during a 1-week lead-in prior to Cycle 1 (CORT125134 daily for 7 days) followed by 28-day cycles of the combination regimen (CORT125134 daily for 28 days plus nab-paclitaxel weekly for 3 weeks).

Patients will have safety assessments performed at all scheduled in-clinic visits, PK assessments during the 1-week lead-ins for patients in Part 1 only and during Cycle 1 for all patients, and PD assessments during Cycle 1. Serial PK sampling will be performed for patients in Part 1 and in Part 2.

The study design scheme showing the dose schedule and planned PK sampling for patients in both parts of Segment I is shown in Figure 4.

Figure 4 Segment I Continuous-Dosing Regimen: Schematic of Study Drug Dosing and Pharmacokinetic Sampling Schedule



Abbreviations: Nab-Pac, nab-paclitaxel; PK, pharmacokinetic.

3.2.2 Segment II, Intermittent-Dosing Regimen

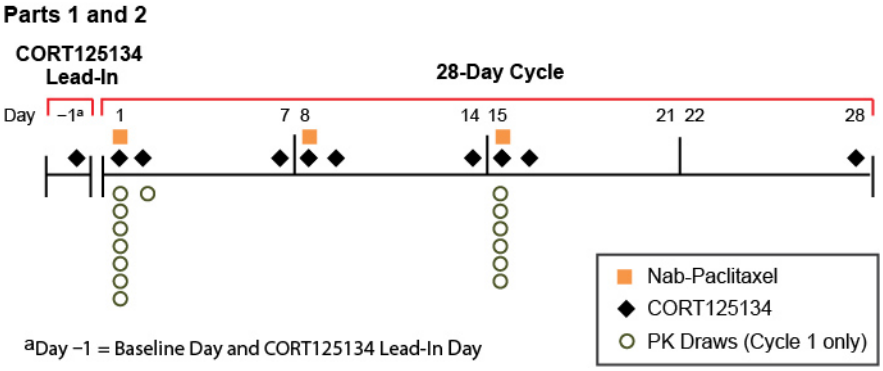
During Segment II, patients will have the following in-clinic visits: Screening; Baseline/ CORT125134 Lead-in (Day −1); Cycle 1 Days 1, 2, 8, and 15 (all patients); Cycle ≥2 Days 1, 8, and 15; and a Posttreatment or Early Termination Visit. Study assessments are summarized below and provided in the Schedule of Visits and Procedures (Table 11).

After signing the IRB-approved ICF at a Screening Visit within 28 days before the first dose of study drug, patients will undergo the same screening procedures as outlined for Segment I. If the Screening Visit is >7 days before the first scheduled dose of study drug, selected screening procedures will be repeated at the Baseline Visit before the first dose of CORT125134. Eligible patients will enroll in the study and will begin dosing with CORT125134 and nab-paclitaxel as described below.

Patients in Parts 1 and 2 of Segment II will follow the same schedule. After completing Screening assessments, patients will visit the clinic on Day −1 to complete their Baseline assessments then take their first dose of CORT125134. They will return to the clinic on Day 1 of Cycle 1 to receive their first infusion of nab-paclitaxel in combination with CORT125134, which is the start of the 28-day regimen of CORT125134 and nab-paclitaxel.

Patients will have safety assessments performed at all scheduled in-clinic visits, and serial PK assessments during the first 24 hours (ie, Day 1 predose through predose on Day 2) and on Day 15 of Cycle 1 only. The study design scheme showing the dose schedule and planned PK sampling for patients in both parts of the Segment II is presented in Figure 5.

Figure 5 Segment II Intermittent-Dosing Regimen: Schematic of Study Drug Dosing and Pharmacokinetic Sampling Schedule



3.2.3 Segments I and II: Assessments

Tumor assessments will occur at Screening (and Baseline if >28 days elapse between Screening and Cycle 1 Day 1), at the end of Cycle 2, and thereafter every 6–8 weeks and at time of suspicion of disease progression. Confirmation of response will be done as needed as per RECIST (see Section 7.2). In patients with ovarian, fallopian tube, or primary peritoneal cancer, CA-125 will be assessed at the time of radiologic tumor assessments (baseline and every 6–8 weeks) and response reported per GCIG criteria (Rustin et al. 2011) in addition to RECIST v1.1.

Patients will continue treatment in 28-day cycles until unacceptable toxicity, disease progression, or another withdrawal criterion is met (see Section 6.7). For patients with ovarian, fallopian tube, or primary peritoneal cancer, PFS will be based on RECIST 1.1 and progression should not be determined early based on increased CA-125 alone.

A Posttreatment Visit for safety will be scheduled within 28 ±7 days after the last dose of study drug. Tumor assessment will be done at this visit if ≥4 weeks have elapsed since the prior tumor assessment and progressive disease has not been documented.

Patients will be contacted by telephone to monitor for survival on a quarterly basis for 1 year after the last dose of study drug (CORT125134 or nab-paclitaxel, whichever is latest) in the last patient on treatment.

3.3 Dose-Finding Phase (Part 1)

Approximately 62 patients with solid tumors for whom nab-paclitaxel is appropriate therapy will be enrolled in Segment I, Part 1 and approximately 24 in Segment II, Part 1. The number of patients will depend on the number of dose levels assessed and the DLTs observed.

3.3.1 Dose Levels

3.3.1.1 Dose Levels in Segment I

In Segment I, the starting dose in Part 1 is 100 mg CORT125134 in combination with 80 mg/m^2 nab-paclitaxel. CORT125134 dose escalation will proceed by a maximum of 50 mg per dose level. Example target dose levels for evaluation in Segment I, Part 1 are shown in Table 2. The

starting dose of 100 mg CORT125134 is at the low end of the anticipated range of doses, yet retains the potential for PD effect. The starting dose of 80 mg/m^2 nab-paclitaxel is at the lower end of the range for a standard dose of nab-paclitaxel. With the starting dose level set in a conservative manner, the plan is to escalate the investigational product, CORT125134, sequentially in 50 mg increments through the dose-finding phase of the study.

Table 2 Segment I Continuous Dosing: Example Dose-Finding Table of CORT125134 / Nab-paclitaxel Dose Levels for Part 1

Dose Level	CORT125134 Dose (mg)	Nab-paclitaxel Dose [a] (mg/m^2)
−1	50	80
1 Starting dose	100	80
2	150	80
3	200	80
4	250 [b]	80

[a] Taking the nab-paclitaxel exposure and safety data into account, the nab-paclitaxel dose may be increased to 100 mg/m^2 or decreased to 60 mg/m^2. Nab-paclitaxel and CORT125134 will not be escalated simultaneously; therefore, an increase in dose for nab-paclitaxel would constitute a separate dose level.
[b] Doses may exceed 250 mg CORT125134 based on safety and PK data and DRC recommendation.

3.3.1.2 Dose Levels in Segment II

In Segment II, the starting dose level in Part 1 is 200 mg CORT125134 in combination with 100 mg/m^2 nab-paclitaxel. CORT125134 dose escalation is expected to proceed by 100 mg per dose level (Table 3). However, CORT125134 doses may be escalated in 50 mg increments if recommended by the DRC. In Segment II, the DRC may recommend modifying the nab-paclitaxel dose to 80 mg/m^2 based on the nab-paclitaxel exposure and safety data. As noted above, enrollment in Segment I and Segment II will be mutually exclusive, and the two segments will enroll patients concurrently.

Table 3 Segment II Intermittent-Dosing Regimen: Example Dose-Finding Table of CORT125134 / Nab-paclitaxel Dose Levels for Part 1

Dose Level	CORT125134 Dose (mg)	Nab-paclitaxel Dose (mg/m^2)
−1	150	100
1 – Starting dose	200	100
2	300	100
3	400 [a]	100

[a] Doses may exceed 400 mg CORT125134 based on DRC recommendation.
Nab-paclitaxel may be dose reduced or dosed increased based on PK and DDI findings.
CORT125134 doses may change in 50, or 100 mg increments based on DRC recommendations.

3.3.2 Dose-Finding Process

Dose-finding decisions including selection of dose levels for cohorts, determination of the MTD and development regimen, and stopping enrollment, as applicable, will be performed by a DRC (Section 3.5). The key principles guiding DRC recommendations for dose levels in dose-finding are to ensure that patients receive nab-paclitaxel at therapeutic exposures and to sequentially increase the dose of CORT125134 as tolerated.

Dose escalation or de-escalation will occur only after review of data from the first cohort by the DRC. If a lower dose level is explored and is well tolerated, the DRC may recommend re-escalating either CORT125134 or nab-paclitaxel.

During the Part 1 Dose-Escalation Phase, on review of safety, laboratory, and available PK data from each cohort, the DRC may recommend proceeding to the next dose level per Table 2 for Segment I and per Table 3 for Segment II. Alternatively, taking PK and safety data into account, the DRC could recommend modifying the nab-paclitaxel dose (eg, with an increase to 100 mg/m^2 or a decrease to 60 mg/m^2 in Segment I) for reasons including:

- Dose finding requires greater resolution to the titration of nab-paclitaxel exposure than may be induced by changes in dose of CORT125134 due to significant metabolic interaction (eg, increasing nab-paclitaxel dose by one step would increase nab-paclitaxel exposure to a lesser degree than increasing CORT125134 dose by one step).
- There is no significant metabolic interaction between CORT125134 and nab-paclitaxel.
- An AE profile is encountered that is not suggestive of a nab-paclitaxel effect and hence may be attributed to CORT125134.

For dose escalation, either CORT125134 or nab-paclitaxel, but not both, will be changed in the next dose level, based on recommendations by the DRC. If a lower dose level is explored and is well tolerated, the DRC may recommend re-escalating either CORT125134 or nab-paclitaxel.

All patients in the Part 1 Dose-Escalation cohorts in Segment I and Segment II will be treated with CORT125134 plus nab-paclitaxel and assessed for 1 cycle. Approximately 5 patients may be initially enrolled in a cohort, and non-DLT evaluable patients may be replaced to allow for a minimum of 3 evaluable patients for each cohort. Depending on the number of patients with DLTs, additional patients will be enrolled in the same cohort or additional cohorts will be enrolled following the criteria described in Table 4.

Table 4 Rules for Dose-Finding to Define Maximum Tolerated Dose in Part 1 of Segments I and II

No. of Evaluable Patients with DLT at a Dose Level (cohort of <6 evaluable patients)	Dose-Escalation Decision Rule in Cycle 1
0	• Enroll cohort at next higher dose level.
1	• Expand current dose level to 6 patients[a] • If 1 of 6 patients (<33%) experiences DLT, enroll cohort at next higher dose level. • If ≥2 of 6 patients (≥33%) experience DLT: – Enroll cohort at next lower dose level, if available. OR – Declare next lower dose level as the MTD.
≥2	• If ≥2 patients experience DLT: – Enroll cohort at next lower dose level, if available. OR – Declare next lower dose level as the MTD.

Abbreviations: DLT, dose-limiting toxicity; MTD, maximum tolerated dose

[a] The DRC may make the recommendation to adjust the size of a cohort to more than 6 patients to further the evaluation of a given dose level, such as further evaluation of PK data or tolerability. If cohorts are >6 patients, the decision rule will be based on the percentage of patients experiencing DLT within that cohort.

The MTD is defined as the highest dose at which <33% (eg, 0 of 3 or 1 of 6 patients, with a minimum of 6 patients if 1 DLT is observed) experiences a DLT during Cycle 1. Alternatively, a different (lower) dose level may be declared the MTD depending on the nature, severity, and frequency of toxicities to date. Safety data that become available for patients remaining on-study after Cycle 1 will be taken into consideration when making decisions about dose escalation.

The dose level selected for the development regimen may be equal to or lower than the MTD and its selection will take into account other issues such as safety data occurring after the first cycle.

A sufficient number of patients will be enrolled in each cohort to ensure that there are DLT-evaluable patients available for determination of the MTD and identification of the development regimen. The number of DLT-evaluable patients may be inclusive of all cohorts at that dose level and schedule (such as advanced solid tumor and pancreatic cancer cohorts in Segment I) for determination of the MTD or dose-finding decisions, per DRC recommendation. If two distinct DLTs, such as events occurring in different MedDRA system organ classes, are observed within a dose level, the DRC may recommend expanding the cohort to >6 patients to further evaluate the tolerability of that dose level.

- DLT-evaluable patients will include those who complete one cycle of treatment or those who withdraw from the study due to toxicity during Cycle 1.
- Non-evaluable patients will include patients who withdraw from the study prior to completion of Cycle 1 for reasons other than toxicity (eg, lost to follow-up, withdrawal of

consent, disease progression, or receipt of ≤80% of CORT125134 dosing due to reasons other than toxicity); these patients may be replaced.

- PK for patients with a history of GI resection or gastric bypass surgery will be considered separately from the remainder of the cohort. The safety data for these patients will be taken into consideration in the assessment of the overall tolerability of a given cohort. A minimum number of patients evaluable for DLT will be enrolled to a cohort to consider the tolerability at this dose level who don't have a history of GI resection/gastric bypass surgery.

Based on safety data from the initial dose-finding cohorts, the DRC may recommend following an alternative dose-finding strategy that evaluates any of the dose levels in the planned Part 1 phases with inclusion of granulocyte colony-stimulating factor (G-CSF).

- A given dose level may be expanded to further evaluate safety, tolerability, PK, or preliminary efficacy at that dose level or in a more restricted patient population.
- A dose of CORT125134 100 mg continuous dosing and nab-paclitaxel 60 mg/m^2 with prophylactic G-CSF support will be explored in patients with pancreatic cancer. Initially, approximately 6–8 patients will be enrolled in this cohort. The DRC will review the safety and tolerability after 6 DLT-evaluable patients complete 1 cycle of therapy. If the dose-limiting toxicity (DLT) rate exceeds 33%, the dose will be declared non-tolerable for this population (tumor type and similar line of therapy) and no additional patients will be enrolled to that cohort. Alternatively, a higher or lower dose level may be evaluated, per the recommendation of the DRC based on safety and PK data. Once the dose level is declared tolerable, the cohort will be expanded to include approximately 12–15 additional patients to further assess the safety and efficacy of this dose level. Safety and efficacy data from all pancreatic cancer patients receiving this dose level will be summarized. The DRC will take into consideration the overall tolerability and toxicities observed in this cohort(s) to inform dose escalation decisions and the recommended Phase 2 dose.

3.3.3 Dose-limiting Toxicity

The DLT evaluation period is from the first dose of CORT125134 through the completion of Cycle 1 during Part 1 of Segment I (Figure 4) and Segment II (Figure 5) of the study. Dose-limiting toxicities are defined below and dose-modification guidelines are provided in Section 5.4.

For non-hematological events, a DLT is defined as *any* TEAE not attributable to disease or disease-related processes that occurs during the observation period (Cycle 1) and that:

- Is Grade 3 or higher according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03, excluding the exceptions listed below. or
- Results in a dose omission or > 1-week delay of nab-paclitaxel.
  Note: if a >1-week delay of nab-paclitaxel occurs for logistical reasons, it will not be considered a DLT.

Exceptions include the following non-hematological AEs that are *not* considered DLTs:

- Grade 3 fatigue lasting <7 days.
- Rigors lasting <24 hours.
- Grade ≥3 nausea or vomiting that has resolved to Grade ≤2 within 48 hours after standard antiemetic therapies.
- Grade 3 diarrhea that has resolved to Grade ≤2 within 48 hours after standard antidiarrheal therapies
  and/or
- Isolated laboratory findings not associated with signs or symptoms including Grade 3/4 ALP, uric acid, amylase, and lipase elevations, and Grade 3 hyponatremia lasting <72 hours.

The following non-hematological AEs *are* considered DLTs:

- Any elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥10 × upper limit of normal (ULN) lasting more than 3 days with discontinuation of therapy.
- Any elevation of AST or ALT >20 × ULN.
- Any elevation of AST and ALT >3 × ULN associated with serum bilirubin >2 × ULN without evidence of another cause for the hyperbilirubinemia is a DLT requiring immediate discontinuation of all study therapy.

For hematologic events, a DLT is defined as follows:

- Grade 4 neutropenia lasting >7 days.
- Grade ≥3 febrile neutropenia (ANC <1000 cells/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour).
- Grade 4 thrombocytopenia or Grade ≥3 thrombocytopenia lasting >7 days or associated with Grade ≥2 bleeding
  and/or
- Dose delay >7 days of scheduled chemotherapy secondary to myelosuppression.

3.4 Dose-Expansion Phase (Part 2)

In both Segment I and Segment II, enrollment in Part 2 (dose-expansion) will occur once the development regimen has been identified in Part 1. Approximately 20 patients will be enrolled in each cohort in Part 2. Expansion cohorts of patients are planned with the following tumor types: (1) platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer or (2) TNBC.

In both Segment I and Segment II, based on data obtained from Part 1, additional expansion cohorts may be enrolled (by amendment), each with approximately 20 patients with specific advanced or metastatic cancer tumor types. In each dose-expansion cohort, patients will be treated with CORT125134 and nab-paclitaxel at the development regimen selected for either continuous or intermittent dosing in repeated 28-day cycles until progression or another withdrawal criterion is met.

3.5 Data Review Committee (DRC)

A DRC consisting of at least one Investigator from each site experienced in evaluating oncology treatments, a clinical pharmacologist, and the Medical Monitor will perform safety monitoring of the study treatment in accordance with procedures detailed in a DRC Charter.

During both Segment I and Segment II, the DRC will convene before each planned dose escalation during the dose-finding phase (Part 1), at least every 6 months during the dose-expansion phase of the study (Part 2), and on an ad hoc basis as necessary throughout study conduct. The DRC will perform the following tasks:

- Evaluate suspected DLTs, using defined criteria (see Section 3.3.3) for adjudication of treatment-related AEs;
- Determine the appropriateness of dose escalation or dose de-escalation and cohort expansion based on all available data leading to a specific recommendation for the next dose to be evaluated during the dose finding phase;
- Make recommendations to hold dosing or enrollment, or to adjust the size of any cohort as needed to further evaluate safety, tolerability, PK, or preliminary efficacy at a given dose level or in a more restricted patient population;
- Make recommendations to adjust the size of any cohort as needed to obtain more PK data (eg, at the development regimen);
- Make recommendations to end dosing or enrollment;
- Make recommendations to enroll specific cohort(s) in dose-finding to investigate the use of G-CSF at a dose level associated with high rates of neutropenia. Once a cohort is defined as a G-CSF cohort, the rules for G-CSF usage may be carried forward to additional cohorts at the recommendation of the DRC.
- Monitor emerging PD, PK, and clinical activity data throughout the dose-finding phase (Part 1) and make recommendations regarding the dose and schedule of CORT125134, the schedule of CORT125134 and nab-paclitaxel (ie, the development regimen) to be evaluated in the dose-expansion phase of the study (Part 2).
- If supported by data, the DRC may recommend changes to schedule of dosing with nab-paclitaxel (ie every other week schedule or two out of three week schedule) in a subsequent cohort.
- The DRC may recommend dose titration of either CORT125134 or nab-paclitaxel to optimize exposure and tolerability. If dose titration is instituted, feasibility of that dose level will be assessed over the number of cycles during which titration occurs.

In the event that a decision is made by the Sponsor to reject a safety recommendation by the DRC, the decision and rationale will be communicated to the FDA and site IRBs before enrolling additional patients.

4 STUDY POPULATION AND ENTRY CRITERIA

4.1 Number of Patients

Approximately 146 patients are planned; estimates are as follows:

- Segment I Continuous-Dosing Regimen—Part 1, approximately 62 patients; In addition to the standard dose finding process, approximately 6–8 patients with pancreatic cancer will be enrolled in Part 1 at a dose level of CORT125134 100 mg continuous dosing and nab-paclitaxel 60 mg/m^2 with prophylactic G-CSF. The DRC will review the safety and tolerability after 6 DLT-evaluable patients complete 1 cycle of therapy. If the dose-limiting toxicity (DLT) rate exceeds 33%, the dose will be declared non-tolerable for this population (tumor type and similar line of therapy) and no additional patients will be enrolled to that cohort. Alternatively, a higher or lower dose level may be evaluated, per the recommendation of the DRC based on safety and PK data. Once the dose level is declared tolerable, the cohort will be expanded to include approximately 12–15 additional patients to further assess the safety and efficacy of this dose level.
  Part 2, approximately 20 patients in each expansion cohort (eg, 20 TNBC patients, 20 patients with platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer)
- Segment II Intermittent-Dosing Regimen—Part 1, approximately 24 patients; Part 2, approximately 20 patients in the expansion cohort (eg, 20 TNBC patients)

The following study entry criteria apply to both Segment I and Segment II.

4.2 Inclusion Criteria

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

For All Patients

1. Signed and dated IRB-approved informed consent form (ICF) prior to study-specific screening procedures. Note: standard-of-care assessments completed before the ICF is signed can be used for eligibility if done within the 28-day screening period.
2. Consent to provide archived tumor tissue (primary or metastatic) or pretreatment tumor biopsy if available for the purpose of staining for GR status. Note: Neither tissue sample nor immunohistochemistry (IHC) results are required prior to starting study treatment due to potential delays in obtaining tumor block or results from GR assay. Tumor biopsy sample proximal to study entry in addition to archived tumor tissue is preferred.
3. Age ≥18 years old.
4. Patients with advanced or metastatic solid tumors who have disease progression after treatment with available therapies that are known to confer clinical benefit, or who are intolerant to treatment and for whom nab-paclitaxel treatment is appropriate.
5. Up to 3 prior cytotoxic chemotherapeutic regimens or myelosuppressive therapies in the advanced setting. (Hormonal or nonmyelosuppressive biologic, targeted, or immune therapies will not be counted toward the maximum lines of prior therapy.)
6. ECOG performance status 0 or 1.
7. Organ and marrow function meeting the following criteria at the Screening Visit:
   – Absolute neutrophil count (ANC) ≥1,500 cells/mm^3

- Platelet count ≥100,000/mm^3
- Hemoglobin ≥9 g/dL
- AST or ALT ≤2.5 × ULN (or ≤5 × ULN in the context of liver metastasis)
- Total bilirubin ≤1.5 × ULN
- Serum creatinine ≤1.5 × ULN
- or
- Creatinine clearance >60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

8. For female patients of childbearing potential, a negative pregnancy test. Female study patients of childbearing potential and male study patients with female partners of childbearing potential must be willing to use two effective methods of contraception (one of which is a barrier method) during the treatment period and for at least 3 months after the last dose of the study drug. Hormonal contraceptives are not permitted (hormonal intrauterine device [IUD] is acceptable).
9. Ability to take oral medications.
10. Albumin ≥3.0 g/dL (≥30 g/L)
11. If patient has undergone gastric bypass surgery and/or surgery of GI or hepatobiliary tract, the patient must demonstrate adequate absorption as evidenced by: albumin ≥3.0 g/dL, controlled pancreatic insufficiency (if present), lack of evidence of malabsorption,

<u>For Patients in Dose-Finding Part 1</u>

12. Measurable or evaluable disease.

<u>For patients enrolled in a specific dose-finding cohort in Part 1 limited to diagnosis of pancreatic cancer.</u>

13. Histologically confirmed diagnosis of pancreatic adenocarcinoma. Patients with pancreatic neuroendocrine tumors, lymphoma of the pancreas, or ampullary cancer are not eligible.
14. CA19-9 (or CEA, CA-125 in non-CA 19-9 elevated tumors) measured within 14 days prior to first dose of study drug
15. Metastatic (non-irradiated) lesion that is measurable by RECIST 1.1

<u>For Patients in Dose-Expansion Part 2</u>

<u>For all patients in Part 2</u>

16. Platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer or TNBC that, in the opinion of the Investigator, is appropriate to treat with nab-paclitaxel.

<u>For patients in Part 2 with ovarian, fallopian tube, or primary peritoneal cancer only</u>

17. Must have a histologic diagnosis of epithelial ovarian, primary peritoneal, or fallopian tube cancer or ovarian carcinosarcoma. Note: mucinous and borderline histologic subtypes are excluded.

18. Treatment-free interval after platinum-based therapy of less than 12 months, or disease progression during platinum-based therapy.
19. Measurable or nonmeasurable disease. Previously irradiated lesions are not allowed as measurable disease, unless there is documented evidence of progression in the lesions. To be eligible with nonmeasurable disease, patients must have evaluable disease with cancer antigen 125 (CA-125) levels of ≥100 U/mL along with radiographically evaluable disease by computed tomography (CT) or magnetic resonance imaging (MRI). A minimum of 10 patients with measurable disease will be enrolled.

For patients in Part 2 with TNBC only

20. Histologically confirmed diagnosis of TNBC: Triple-negative for ER and PR (<1% cells positive for ER/PR) and HER2 per the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) Guidelines (Wolff et al. 2013) (HER2 test results show [a] IHC 1+ negative or IHC 0 negative or [b] in situ hybridization [ISH]-negative using single-probe ISH or dual-probe ISH)
21. Measurable disease as defined by RECIST v1.1 in at least one lesion. Previously irradiated lesions are not allowed as measurable disease, unless there is documented evidence of progression in the lesions.

4.3 Exclusion Criteria

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

1. Clinically relevant toxicity from prior systemic cytotoxic therapies or radiotherapy that in the opinion of the Investigator has not resolved to Grade 1 or less prior to the first dose of study drug (ie, Day 1 of the first scheduled 1-week lead-in).
2. Clinically significant uncontrolled condition(s) or any medical condition which in the opinion of the study investigator places the subject at an unacceptably high risk for toxicities, or puts the patient at high risk for not completing the DLT evaluation period of the study.
3. Any major surgery within 4 weeks prior to the first dose of study drug (ie, Day 1 of the first scheduled 1-week lead-in).
4. Treatment with the following prior to the first dose of study drug (ie, Day 1 of the first scheduled 1-week lead-in):
   - An investigational product within 21 days or 5 half-lives, whichever is longer.
   - Systemic, inhaled, or prescription strength topical corticosteroids for the purposes of treating a chronic non-oncologic indication within 21 days.
   - Systemic cytotoxic agents within 21 days.
   - Monoclonal antibodies (eg, pembrolizumab, nivolumab) or anticancer vaccines within 60 days.
   - Hormonal anticancer therapies within 7 days.
5. Requirement for treatment with chronic or frequently used oral corticosteroids for medical conditions or illnesses (eg, rheumatoid arthritis, immunosuppression after organ transplantation).

6. History of significant cardiac disease defined as New York Heart Association (NYHA) class III or IV, myocardial infarction (MI) within 6 months of first dose of study drug, or unstable angina within 6 months of first dose of study drug.
7. Pregnancy or breast feeding.
8. History of hypersensitivity or severe reaction to either study drug or to similar classes of either study drug.
9. Any intercurrent medical condition that in the opinion of the Investigator would confound study analysis or impair study participation or cooperation.
10. Any patient requiring chronic maintenance of white blood cell counts or granulocyte counts through the use of growth factor support (eg, Neulasta, Neupogen) or transfusion for red blood cell (RBC) or platelet support.

4.4 Concomitant Medications/Treatments

4.4.1 Supportive Care with Granulocyte–Colony-Stimulating Factor

Dosing with filgrastim 5 µg/kg/day (subcutaneous administration) is allowed per protocol after Cycle 1 of both study segments. It may be used to provide G-CSF support for a patient with clinically meaningful neutropenia (ANC <1500 cells/µL) on study. The use of G-CSF during Part 1 Cycle 1 of Segment I or II should be avoided because G-CSF can confound the assessment of DLTs.

Additionally, G-CSF may be used as therapy in a specific G-CSF cohort, but only if the DRC recommends evaluation of a G-CSF cohort based on data from earlier cohorts. In this case, use of G-CSF in cycle 1 does not interfere with a patient's DLT evaluable status.

Filgrastim will be administered, when clinically appropriate, at least 24 hours after completion of dosing with nab-paclitaxel, and greater than or equal to 24 hours prior to the next treatment with nab-paclitaxel. In the case of a G-CSF cohort, the filgrastim would be administered according to above prescribing information within Cycle 1 or administered within a cohort prophylactically.

4.4.2 Permissible Medications/Treatments

Permitted treatments include palliative and supportive care for disease-related symptoms and standard therapies for concurrent medical conditions. Prophylactic anti-emetics may include ondansetron and/or other therapies as appropriate.

The Investigator may prescribe treatment at his/her discretion in the interests of patient safety and acceptable standards of medical care. However, at this stage in the drug development program, available data relating to the possibility of drug-drug interactions are limited (see Section 4.4.4). In prescribing new medication or changing the dose of an existing concomitant medication, the Investigator must consider the general guidance provided herein, specific guidance provided in the IB, and the balance of risk to benefit for the individual patient. If a prohibited medication is required (see Section 4.4.3), the patient should be withdrawn from the study, unless the Investigator, in agreement with the Medical Monitor, considers the benefits of remaining in the study outweigh the risks.

4.4.3 Prohibited and Restricted Medications/Treatments

Prohibited Medications—The following treatments are not allowed:

- Treatment for cancer: any concurrent chemotherapy, radiotherapy, hormonal therapy, immunotherapy, or other systemic therapy other than the study drugs. (Hormonal therapy with GnRH agonists or surgical castration >3 months before study entry is not exclusionary).
- Other investigational products.
- Hormonal contraception (hormonal intrauterine device [IUD] is acceptable).

Restricted Medications—The following treatments are allowed within limits:

- The use of G-CSF during Part 1, Cycle 1, of any segment should be avoided because G-CSF can confound the assessment of DLTs. If G-CSF is used during the DLT evaluation period in absence of a protocol-defined DLT and in the absence of being prespecified as a G-CSF-cohort, the patient will be non-evaluable for the DLT assessment. The patient may continue on the study and will be included in the overall assessment of tolerability and response.
- Transfusional support (packed RBC or platelets) during Part 1, Cycle 1, of any segment should be avoided unless clinically required. If transfusional support is used in absence of a protocol-defined DLT, the patient will be non-evaluable for the DLT assessment.
- Corticosteroids:
  - Systemic corticosteroids. Short courses of prednisone (<100 mg per day for ≤14 days) for rash or non–cancer-related reasons are permitted if clinically required. CORT125134 treatment should be withheld during corticosteroid administration, and the Medical Monitor should be notified.
  - For patients requiring IV corticosteroids for treatment of intractable nausea and vomiting, the Medical Monitor should be contacted to discuss whether the patient should be continued in the study.
  - In addition, potent (Group III) topical corticosteroids should be used with caution due to the potential for systemic absorption, and the Medical Monitor should be contacted to discuss the treatment approach.

4.4.4 Medications Having Potential Drug-Drug Interactions

The following treatments should be used with caution due to potential drug-drug interactions:

- CORT125134 has been shown to inhibit the activity of CYP3A4 and CYP2C8 (see Section 1.3.2.2) and may inhibit CYP3A5, CYP2C9, CYP2C19, and CYP2D6. Drugs metabolized by these isozymes, particularly drugs with a narrow therapeutic ratio, should be used with caution.
- The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. Caution should be exercised when administering nab-paclitaxel concomitantly with medicines/food known to inhibit (eg, ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, nelfinavir, and grapefruit, grapefruit juice, or grapefruit-containing products) or induce (eg, rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A4.

4.4.5 Management of Signs of Excessive GR Antagonism

As noted in Section 1.1.2.3, there is the possibility that patients could experience signs or symptoms related to 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 are present, particularly if co-existent, treatment with CORT125134 should be interrupted and the Medical Monitor should be consulted to assist in evaluating whether treatment should continue. If excessive GR antagonism is suspected, standard supportive care (including fluid resuscitation as indicated) and medical therapy should be administered without delay. Systemic administration of corticosteroids should be considered (eg, dexamethasone 4 mg daily for 3 days and then tapered by 1 mg per day, or as indicated based on clinical response). Full clearance of CORT125134 is expected in 3–5 days (5 half-lives). In the event of significant trauma or surgery through 28 days after the last dose of CORT125134, 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 STUDY DRUG

5.1 Study Drug and Formulations

Study treatments to be used in this study consist of the following:

- Investigational product (CORT125134):
  - CORT125134 is a synthetically prepared small molecule with the following chemical name: (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-1,4,5,6,7,8-hexahydro-4aH-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone.
  - [redacted]
  - CORT125134 50-mg capsules are white, size 2, hard gelatin capsules. The capsules are provided in sealed, foil blister strips.
  - CORT125134 100-mg softgel capsules are yellow, and the 25-mg softgel capsules are brown. The capsules are provided in bottles containing 30 capsules each.
  - At a minimum, the labels on study drug will contain the drug name and number, protocol number, number of capsules, storage conditions, caution statement on investigational use only, and Sponsor details. Labeling will meet country-specific requirements.
  - CORT125134 drug product is to be administered orally once daily in the morning. CORT125134 capsules should be at room temperature when administered, and taken with room temperature liquid.
  - Details are provided in the current IB.
- Nab-paclitaxel (Abraxane) is commercially available (Abraxis Biosciences, LLC, a wholly owned subsidiary of Celgene Corporation) and is supplied in single-use vials.
  - Each single-use 50-mL vial contains 100 mg paclitaxel and approximately 900 mg of human albumin as a stabilizer.
  - Nab-paclitaxel is supplied as a white to off-white sterile lyophilized powder for reconstitution before use, with the reconstituted formulation to be administered as an IV infusion.
  - Details are provided in the Abraxane Prescribing Information (Abraxane 2015).

5.2 Treatment Regimen and Dosing

Study treatments consist of CORT125134 and nab-paclitaxel; study drug (investigational agent) consists of CORT125134.

Dose levels for dose-finding in Part 1 are provided in Section 3.3.1, and the dose-finding process is described in Section 3.3.2. Patients in the dose-expansion phase (Part 2) will be treated with the development regimen identified in Part 1.

5.2.1 Segment I, Continuous-Dosing Regimen

- CORT125134 is administered orally once daily in the morning for 7 days in a 1-week lead-in prior to Cycle 1 and once daily in the morning for 28 days during each 28-day cycle, preferably at the same time each day.
  - On the days nab-paclitaxel is administered, CORT125134 should be taken within 15 minutes before the start of nab-paclitaxel infusion.
  - On in-clinic visit days, CORT125134 should not be taken at home but brought to the clinic and taken after any scheduled predose PK samples are drawn.
- Nab-paclitaxel is administered by IV infusion over 30 minutes (±5 minutes) on Day 1 of a 1-week nab-paclitaxel lead-in *for patients in Part 1* and on Days 1, 8, and 15 of each 28-day cycle *for all patients*. Nab-paclitaxel infusions must be no less than 7 days apart. After a minimum of two dose levels are observed, the nab-paclitaxel lead-in may be discontinued per the DRC recommendation.

5.2.2 Segment II, Intermittent-Dosing Regimen

- CORT125134 is administered orally once daily in the morning the day before, the day of, and the day after nab-paclitaxel infusion.
  - On the days nab-paclitaxel is administered, CORT125134 should be taken within 15 minutes before the start of nab-paclitaxel infusion.
  - On in-clinic visit days, CORT125134 should not be taken at home but brought to the clinic and taken after any scheduled predose PK samples are drawn.
- Nab-paclitaxel is administered by IV infusion over 30 minutes (±5 minutes) on Days 1, 8, and 15 of each 28-day cycle *for all patients*. Nab-paclitaxel infusions must be no less than 7 days apart.

5.3 Duration of Patient Participation

Patients completing Cycle 1 will receive subsequent treatment in repeated 28-day cycles. Patients may remain on treatment until they experience disease progression or unacceptable toxicity, until they meet any of the withdrawal criteria (Section 6.7), or until the study is terminated by the Sponsor.

5.4 Intrapatient Dose Modifications and Delays

The following are guidelines for dose reduction and delay of CORT125134 in combination with nab-paclitaxel.

If in the Investigator's opinion a DLT (see Section 3.3.3) or Grade 3 or 4 toxicity occurs that is not disease-related, the Investigator should interrupt or modify administration of only the drug responsible for the toxicity following the guidelines below. If the toxicity does not resolve to Grade 1 or baseline severity, if Grade 2 toxicity was present at baseline, after interruption of only one study treatment, then both CORT125134 and nab-paclitaxel could be interrupted until the toxicity resolves to Grade 1 or baseline, if Grade 2 toxicity was present at baseline.

5.4.1 Dose Modifications/Dose Delays for Nab-paclitaxel

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

- If delayed by 3 days or less, all subsequent doses for this course will be delayed to keep weekly spacing between doses.

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

Intrapatient nab-paclitaxel dose reductions should be made based on observed toxicities secondary to treatment. Sequential dose reductions may be made at the discretion of the Investigator. A maximum of two dose reductions are allowed.

Neutropenia

Cycle Day 1

- Delay Day 1 for ANC <1500 cells/µL.
- If chemotherapy is delayed for ANC <1000 cells/µL, decrease nab-paclitaxel by 20 mg/m^2 for all subsequent cycles.

Cycle Day 8, 15

- Skip or Delay Day 8 or Day 15 for ANC <1000 cells/µL.
- If chemotherapy is delayed for ANC <1000 cells/µL, decrease nab-paclitaxel by 20 mg/m^2 for all subsequent cycles.
- If chemotherapy is delayed for ANC < 1000 cell/ µL, CBC with differential must be checked on at least a weekly basis until the counts recover to Grade 2 or less

Patients who experience severe neutropenia (neutrophil count less than 500 cells/mm^3 for a week or longer) during nab-paclitaxel therapy should have dosage reduced by 20 mg/m^2 for subsequent courses of nab-paclitaxel. For recurrence of severe neutropenia, additional dose reduction should be made by an additional 20 mg/m^2.

Peripheral Neuropathy

For intolerable Grade 2 peripheral neuropathy, nab-paclitaxel should be dose reduced by 20 mg/m^2 for all subsequent doses.

For Grade 3 peripheral neuropathy that has persisted since the last dose, nab-paclitaxel should be skipped. If peripheral neuropathy improves to less than Grade 2 before the next scheduled cycle, treatment may resume with dose reduction of 20 mg/m^2 for all subsequent doses.

In those patients who experience Grade 4 peripheral neuropathy, nab-paclitaxel should be discontinued.

5.4.2 Dose Modifications/Dose Delays for CORT125134

If the patient misses a daily dose of CORT125134 and it is within 12 hours of the next scheduled dose, the patient should skip that dose and take the next scheduled dose.

For any patient who experiences Grade 3 or 4 toxicity that is attributable to CORT125134 but not nab-paclitaxel or the underlying disease, CORT125134 will be interrupted until the toxicity resolves to Grade ≤1 or to baseline if Grade 2 toxicity was present at study entry. After recovery to Grade ≤1 toxicity, CORT125134 will be resumed at 1 dose level lower than the current level. A maximum of two dose reductions of CORT125134 will be allowed. If a third dose reduction is required, CORT125134 will be discontinued and the patient will continue on nab-paclitaxel alone.

5.4.3 Intra-patient Dose Escalation

In order to maximize the collection of information at relevant doses and to minimize the exposure of individuals to sub-optimal doses, intra-patient dose escalation will be allowed for patients with stable disease or response who may benefit from escalating the dose in the opinion of the investigator. Patients who have not experienced a Grade 3 or greater toxicity or SAE attributed to CORT125134 or nab-paclitaxel may, upon discussion with the Medical Monitor, increase the dose of CORT125134 or nab-paclitaxel to a dose that has been shown to be safe and well-tolerated after studying data from later cohorts.

To be eligible for intra-patient dose escalation, an individual will need to complete at least 2 cycles of therapy without any dose reductions or experiencing any DLT, grade 3 or 4 drug-related toxicities, or SAE attributed to CORT125134 or nab-paclitaxel and have a tumor assessment within the past 4 weeks. The maximum dose level to which a patient may escalate will be to the dose most recently declared safe within the context of a dose escalation decision. CORT125134 and nab-paclitaxel will not be escalated simultaneously. Only one intra-patient dose escalation will be allowed per patient. Patients who receive intra-patient escalated dosing will have a new radiographic baseline established. The most recent tumor assessment (within 4 weeks prior to escalation) will be considered the new baseline.

If a patient meets the above criteria and the investigator recommends dose escalation, a discussion between the site and the Medical Monitor is required prior to escalation the dose. All procedures will be performed according to the schedule of assessments as outlined for the patient's cumulative cycle. In addition, CORT125134 and nab-paclitaxel PK samples will be drawn prior to CORT125134 and nab-paclitaxel dosing and 0.5 hr after nab-paclitaxel infusion on Day 15 following dose escalation.

5.5 Storage of Study Drug

The study drug must be stored in a secure area and administered only to patients entered into the clinical study in accordance with the conditions specified in this protocol.

- The investigational product CORT125134 should be stored at 25°C (77°F); excursions are permitted to 2–30°C (36–86°F). CORT125134 will be dispensed to patients according to their visit schedule. CORT125134 capsules should be at room temperature when administered, and taken with room temperature liquid.

- Un-reconstituted nab-paclitaxel should be stored at 20–25°C (68–77°F) in its carton. Vials should be stored in their original cartons. Reconstituted nab-paclitaxel should be used immediately. If not used immediately, the vial must be placed in its carton and stored at 2–8°C (36–46°F) for a maximum of 8 hours. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel. Partially and completely used vials should be discarded according to the site's guidelines and their disposition should be recorded on the Study Drug Accountability Record Form.

Procedures for inventory, reconciliation, and destruction or return of study drug are provided in Section 10.5.2.

5.6 Treatment Assignment

Enrollment in Segment I and Segment II will be mutually exclusive, and the two segments will enroll patients concurrently. Subjects will be assigned to a dose level in the order of study entry. If escalation in both schedules occurs at the same time, enrollment of the first 3–5 patients to the intermittent schedule will be completed before enrollment in the continuous schedule. If both the continuous-dosing and intermittent-dosing expansion cohorts are open simultaneously, patients will be assigned sequentially (in alternating fashion) to one of the two dosing schedules in the order of study entry. The study site will contact the Sponsor for treatment assignment once a patient is determined to be eligible for enrollment. Patients who meet all eligibility requirements will be assigned to a treatment group as determined by the Sponsor before Screening.

Once assigned, patient numbers for any patients who fail screening, do not receive study treatment, are non-evaluable or who discontinue treatment or withdraw from study will not be reused.

6 STUDY VISIT SCHEDULE AND PROCEDURES

The schedule of visits and timing of procedures for all patients is provided in Table 9 for Segment I and Table 11 for Segment II, and the dosing schedule for Segment II is provided in Table 12. The acceptable visit window is ±3 days for Day 1 of each Cycle after Cycle 1. Nab-paclitaxel infusions must be no less than 7 days apart, and the recommended window for Day 8 and Day 15 is no more than +24 hours. Posttreatment/Early Termination Visit should occur 28 (±7) days after the last dose of study drug. No visit window is allowed due to the planned collection of the 24-hour PK sample for the following visits:

- Segment I, Part 1: Nab-paclitaxel Lead-in Day 2, Cycle 1 Day 1, and Cycle 1 Day 9.
- Segment II, Part 1 and Part 2: Cycle 1 Day 2.

A detailed schedule of PK sampling times is provided in Table 10 for Segment I and in Table 13 for Segment II.

6.1 Patient Entry Procedures for Both Segments

Prospective patients as defined by the criteria in Sections 4.2 and 4.3 (inclusion/exclusion criteria) will be considered for entry into this study. The study will be discussed with the patient, and a patient wishing to participate must give written informed consent prior to any study-related procedures or change in treatment. The patient must also give written authorization regarding privacy requirements prior to any study-related procedures or change in treatment.

Each patient who receives study treatment will be assigned a patient number that will be used on patient documentation throughout the study.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) 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 Table 9, Segment I: Study Visits and Procedures and in Table 11, Segment II: Study Visits and Procedures.

6.2 Segment I: Visits and Associated Procedures

6.2.1 Segment I: Screening Visit (Days −28 to −1)

At the **Screening Visit**, to be done within 28 days before the first scheduled dose of study drug, the following assessments are required:

- Informed consent
- Inclusion/exclusion criteria
- Medical/oncologic history
- Physical examination
- Vital signs (blood pressure, heart rate, respiration rate, temperature)
- Assess for AEs (beginning after signing the ICF)
- Collect prior and concomitant medications
- ECOG performance status
- ECGs (performed in triplicate)

- Local laboratory tests (see Table 5 for details)
  - Serum or urine pregnancy test for female patients of childbearing potential (optionally, can be performed at site or serum test can be performed by central laboratory)
  - Hematology
  - Chemistry
  - Urinalysis
  - Coagulation (international normalized ratio [INR]) for patients taking warfarin
- Tumor assessment:
  - Chest, abdomen and pelvis (CAP) computed tomography (CT) scan with contrast. Tumor assessment documented per RECIST v1.1
  - For patients with ovarian, fallopian tube, or primary peritoneal cancer: serum CA-125
- Consent for archival tumor tissue collection and tumor biopsy if possible for GR-IHC.

6.2.2 Segment I: Baseline Visit, if Needed (Days −7 to −1)

If the Screening Visit was >7 days before the first scheduled dose of study treatment, the following screening assessments must be repeated at a **Baseline Visit** within 7 days before the first scheduled dose of study treatment:

- Inclusion/exclusion criteria
- Physical examination
- Vital signs (blood pressure, heart rate, respiration rate, temperature)
- Assess for AEs
- Review concomitant medications for changes or addition of new medications
- ECOG performance status
- Local laboratory tests (see Table 5 for details)
  - Serum or urine pregnancy test for female patients of childbearing potential (optionally, can be performed at site or serum test can be performed by central laboratory)
  - Hematology
  - Chemistry with fasting glucose and fasting insulin
  - Urinalysis
  - Coagulation (INR) for patients taking warfarin
- Central laboratory tests (samples can be obtained on first day of treatment if obtained predose) (see Table 5 for details)
  - Hormone levels
  - Thyroid function test
  - PD/biomarker tests: C-peptide (obtain at the same time point as fasting glucose and insulin), ACTH, morning cortisol, and FKBP5
  - Optional collection of pharmacogenomic sample

- Tumor assessments (only need to be repeated if done >28 days before the first dose of study drug):
  - CAP CT scan with contrast. Tumor assessment documented per RECIST v1.1.
  - For patients with ovarian, fallopian tube, or primary peritoneal cancer: serum CA-125

6.2.3 Segment I, Part 1 Patients Only: 1-Week Nab-paclitaxel Lead-in (before CORT125134 Lead-in)

Note: After a minimum of two dose levels are observed, the nab-paclitaxel lead-in may be discontinued per the DRC recommendation. If the nab-paclitaxel lead-in is discontinued, the first dose of study drug will be the CORT125134 dose on Day 1 of the CORT125134 Lead-in (see Section 6.2.4 below) and central laboratory samples will be collected at that visit before administration of study drug.

Nab-paclitaxel Lead-in Day 1 (Morning in-clinic infusion visit)

- Patients in Part 1 (see Table 10) will have a morning in-clinic visit for serial PK draws starting within 1 hour before the start of nab-paclitaxel infusion through 6 hours after start of infusion.
- Hematology (obtain predose if drawn >7 days prior)
- Central laboratory tests (obtain predose) (see Table 5 for details)
  - Cytokines and T cells (predose and 4 hours postdose for patients in Part 1)
- Assess for AEs
- Review concomitant medications for changes or addition of new medications
- Vital signs (before nab-paclitaxel infusion and within 5 minutes after stopping nab-paclitaxel infusion)
- Administration of nab-paclitaxel over 30 minutes (±5 minutes) by IV infusion.

Nab-paclitaxel Lead-in Day 2 (Morning in-clinic visit)

- Patients in Part 1 (see Table 10) will have a morning in-clinic visit for a PK draw 24 hours after start of nab-paclitaxel infusion.
- Assess for AEs
- Review concomitant medications for changes or addition of new medications

Note: No study treatment will be administered on Days 2 through 7 of the nab-paclitaxel lead-in; patients in Part 1 will be asked to return to the clinic on the day after nab-paclitaxel lead-in Day 7 to begin the 1-week CORT125134 lead-in.

6.2.4 Segment I: 1-Week CORT125134 Lead-in (before Cycle 1)

All patients in the study will have a 1-week CORT125134 lead-in before Cycle 1. For patients in Part 2, the first dose of study drug will be the CORT125134 dose on Day 1 of the CORT125134 lead-in.

CORT125134 Lead-in Day 1 (Morning in-clinic visit)

- Patients in Part 1 (see Table 10) will have a morning in-clinic visit for a predose (within 1 hour before dose) PK draw.
- Hematology
- Self-administration of oral dose of CORT125134 in the morning
- Assess for AEs
- Review concomitant medications for changes or addition of new medications
- Dispense CORT125134 study drug to patient

CORT125134 Lead-in Days 2 through 6 (at home)

- Self-administration of oral dose of CORT125134 in the morning

CORT125134 Lead-in Day 7 (Morning in-clinic visit)

- Patients in Part 1 (see Table 10) will have a morning in-clinic visit for serial PK draws starting within 1 hour before the CORT125134 dose through 6 hours postdose.
- Assess for AEs
- Review concomitant medications for changes or addition of new medications
- Assess CORT125134 study drug compliance and dispense CORT125134
- ECGs (in duplicate)
  - Pre-CORT125134 dose
  - Postdose (2.5 hours ± 30 minutes)
- Central laboratory tests:
  - Cytokines and T cells (collect predose and at 4 hours postdose only for patients in Part 1)
- Self-administration of oral dose of CORT125134 in the morning

6.2.5 Segment I: Cycle 1

Cycle 1 will begin the day after CORT125134 lead-in Day 7.

Study-related activities to be performed at in-clinic visits and at home during Cycle 1 are listed below.

Cycle 1 Day 1 (Morning in-clinic infusion visit)

- Review of inclusion/exclusion criteria to confirm continued eligibility
- Physical examination (complete exam including weight)
- Vital signs (blood pressure, heart rate, respiration rate, temperature)
- Assess for AEs
- Review concomitant medications for changes or addition of new medications
- Assess CORT125134 study drug compliance and dispense CORT125134
- ECOG performance status

- Local laboratory tests, predose. Samples may be obtained up to 24 hours before dosing (see Table 5 for details)
  - Hematology
  - Chemistry
  - Urinalysis
  - Coagulation (INR) for patients taking warfarin
- Central laboratory tests, before CORT125134 and nab-paclitaxel doses:
  - PK blood sample collection predose (within 1 hour before CORT125134 dose) Note: for patients in Part 1, this is the 24-hour postdose sample for the CORT125134 lead-in Day 7 serial PK; see Table 10.
- Self-administration of oral dose of CORT125134 in the morning
- Vital signs (before nab-paclitaxel infusion and within 5 minutes after stopping nab-paclitaxel infusion)
- Administration of nab-paclitaxel over 30 minutes (±5 minutes) by IV infusion. Start of infusion must be within 15 minutes after CORT125134 dose
- Central laboratory samples (after nab-paclitaxel dose)
  - PK blood sample collection 0.5 hours after start of nab-paclitaxel infusion (see Table 10).

Cycle 1 Days 2 through 7 (at home)

- Self-administration of oral dose of CORT125134 in the morning

Cycle 1 Day 8 (Morning in-clinic infusion visit)

- Physical examination (focused based on patient's clinical presentation; weight)
- Vital signs (blood pressure, heart rate, respiration rate, temperature)
- Assess for AEs
- Review concomitant medications for changes or addition of new medications
- Assess CORT125134 study drug compliance and dispense CORT125134
- ECOG performance status
- Local laboratory tests, predose. Samples may be obtained within 48 hours before dosing (see Table 5 for details)
  - Hematology
  - Chemistry
  - Coagulation (INR) for patients taking warfarin
- Central laboratory sample, predose
  - Patients in Part 1 (see Table 10): PK blood sample collection predose (within 1 hour before CORT125134 dose)
  - Cytokines and T cells (predose and 4 hours postdose)
- Self-administration of oral dose of CORT125134 in the morning
- Vital signs (before nab-paclitaxel infusion and within 5 minutes after stopping nab-paclitaxel infusion)

- Administration of nab-paclitaxel over 30 minutes (±5 minutes) by IV infusion. Start of infusion must be within 15 minutes after CORT125134 dose
- Central laboratory samples postdose (after start of the nab-paclitaxel infusion)
  - PK blood sample collection at time points from 0.5 to 6 hours after start of the nab-paclitaxel infusion (see Table 10)

Cycle 1 Day 9 (Morning in-clinic visit)

- Patients in Part 1 (see Table 10) will have a 24-hour post-nab-paclitaxel infusion, pre-CORT125134 dose PK draw visit.
  - PK blood sample collection predose (24 hours ±30 minutes from start of nab-paclitaxel infusion and within 1 hour before CORT125134 dose)
- Assess for AEs
- Review concomitant medications for changes or addition of new medications
- Self-administration of oral dose of CORT125134 in the morning

Cycle 1 Days 10 through 14 (at home)

- Self-administration of oral dose of CORT125134 in the morning

Cycle 1 Day 15 (Morning in-clinic infusion visit)

- Physical examination (focused based on patient's clinical presentation; weight)
- Vital signs (blood pressure, heart rate, respiration rate, temperature)
- Assess for AEs
- Review concomitant medications for changes or addition of new medications
- Assess CORT125134 study drug compliance and dispense CORT125134
- ECOG performance status
- Local laboratory tests, predose. Samples may be obtained within 48 hours before dosing (see Table 5 for details)
  - Hematology
  - Chemistry with fasting glucose and fasting insulin
  - Coagulation (INR) for patients taking warfarin
- Central laboratory tests, predose (before CORT125134 and nab-paclitaxel doses)
  - PK blood sample collection predose (within 1 hour before CORT125134 dose)
  - PD/biomarker tests: C-peptide (obtain at the same time point as fasting glucose and fasting insulin), ACTH, fasting morning cortisol, and FKBP5
  - Hormone levels (fasting, between 7–9 AM)
- Self-administration of oral dose of CORT125134 in the morning
- Vital signs (before nab-paclitaxel infusion and within 5 minutes after stopping nab-paclitaxel infusion)
- Administration of nab-paclitaxel over 30 minutes (±5 minutes) by IV infusion. Start of infusion must be within 15 minutes after CORT125134 dose

- Central laboratory tests, postdose (after nab-paclitaxel infusion)
  - PK blood sample collection at 30 minutes after start of nab-paclitaxel infusion
  - Patients in Part 1 only (see Table 10): PK blood sample collection at 45 minutes post-start of nab-paclitaxel infusion

Cycle 1 Days 16 through 28 (at home)

- Self-administration of oral dose of CORT125134 in the morning

6.2.6 Segment I: Cycles 2+

Cycle 2 will begin the day after Cycle 1 Day 28, and subsequent 28-day cycles will be done until the patient meets withdrawal or discontinuation criteria (Section 6.8).

Study-related activities to be performed at in-clinic visits and at home during Cycles 2 and greater are listed below.

Day 1, Day 8, and Day 15 (Morning in-clinic visits)

- Physical examination (complete examination at Day 1, focused Days 8 and 15; weight)
- Vital signs (blood pressure, heart rate, respiration rate, temperature)
- Assess for AEs
- Review concomitant medications for changes or addition of new medications
- Assess CORT125134 study drug compliance and dispense CORT125134
- ECOG performance status
- ECG *if clinically indicated*
- Local laboratory tests, predose. Samples may be obtained within 48 hours before dosing (see Table 5 for details)
  - Hematology
  - Chemistry
  - Urinalysis *(only on Cycle 2 Day 1, Cycle 3 Day 1, and then every 12 weeks ±14 days*)
  - Coagulation (INR) for patients taking warfarin
  - Serum or urine pregnancy test for female patients of childbearing potential *every 12 weeks ±7 days*
- Central laboratory tests, before CORT125134 and nab-paclitaxel doses, *every 12 weeks (±14 days) starting from Cycle 1 Day 15*:
  - PD/biomarker tests: ACTH, fasting morning cortisol, FKBP5
  - Thyroid function test (thyroid-stimulating hormone [TSH] with reflex total T3 and free T4 if abnormal TSH values are observed)
- Self-administration of oral dose of CORT125134 in the morning
- Vital signs (before nab-paclitaxel infusion and within 5 minutes after stopping nab-paclitaxel infusion)
- Administration of nab-paclitaxel over 30 minutes (±5 minutes) by IV infusion. Start of infusion must be within 15 minutes after CORT125134 dose

- Tumor assessments: at Cycle 3 Day 1 (±7 days), thereafter every 6 to 8 weeks, and at time of clinical suspicion of disease progression:
  - CAP CT scan with contrast. Tumor assessments will be documented per RECIST v1.1.
  - For patients with ovarian, fallopian tube, or primary peritoneal cancer: serum CA-125.

Days 2 through 7, 9 through 14, and 16 through 28 (at home)

- Self-administration of oral dose of CORT125134 in the morning

6.3 Segment II: Visits and Associated Procedures

In Segment II, patients will take CORT125134 on the day before, the day of, and the day after nab-paclitaxel infusions. For this reason, CORT125134 treatments are on Day −1 (the day before the start of Cycle 1) and Days 1–2, 7–9, 14–16, and 28, and the nab-paclitaxel infusions are on Days 1, 8, and 15 of the 28-day cycles (Figure 5).

6.3.1 Segment II: Screening Visit (Days −28 to −2)

At the Screening Visit, to be done within 28 days before the first scheduled dose of study drug, the following assessments are required:

- Informed consent
- Inclusion/exclusion criteria
- Medical/oncologic history
- Physical examination
- Vital signs (blood pressure, heart rate, respiration rate, temperature)
- Assess for AEs (beginning after signing the ICF)
- Collect prior and concomitant medications
- ECOG performance status
- ECGs (in triplicate)
- Local laboratory tests (see Table 5 for details)
  - Serum or urine pregnancy test for female patients of childbearing potential (optionally, can be performed at site or serum test can be performed by central laboratory)
  - Hematology
  - Chemistry
  - Urinalysis
  - Coagulation (INR) for patients taking warfarin

- Tumor assessments:
  - CAP CT scan with contrast. Tumor assessment documented per RECIST v1.1.
  - For patients with ovarian, fallopian tube, or primary peritoneal cancer: serum CA-125.
- Consent for archival tumor tissue collection and tumor biopsy if possible for GR-IHC.

6.3.2 Segment II: Baseline/CORT125134 Lead-in Visit (Day −1)

If the Screening Visit was >7 days before the first scheduled dose of study treatment, the following screening assessments must be repeated at a **Baseline Visit** within 7 days before the first scheduled dose of study treatment:

- Inclusion/exclusion criteria
- Physical examination
- Vital signs (blood pressure, heart rate, respiration rate, temperature)
- ECOG performance status
- Serum or urine pregnancy test for female patients of childbearing potential (optionally, can be performed at site or serum test can be performed by central laboratory)

The following assessments must be completed at the Baseline/CORT125134 Lead-in Day −1:

- Assess for AEs
- Review concomitant medications for changes or addition of new medications
- Local laboratory testing (see Table 5 for details)
  - Hematology
  - Chemistry with fasting glucose and fasting insulin
  - Urinalysis
  - Coagulation (INR) for patients taking warfarin
- Central laboratory tests, predose samples (see Table 5 for details)
  - Hormone levels
  - Thyroid function test (thyroid-stimulating hormone [TSH] with reflex total T3 and free T4 if abnormal TSH values are observed)
  - PD/biomarker tests: C-peptide, ACTH, fasting morning cortisol, and FKBP5
  - Cytokines and T cells
  - Optional collection of pharmacogenomic sample
- Tumor assessments (only need to be repeated if done >28 days before the first dose of study drug):
  - Tumor assessment RECIST v1.1
  - For patients with ovarian, fallopian tube, or primary peritoneal cancer: serum CA-125
- Provide and observe self-administration of morning oral dose of CORT125134

6.3.3 Segment II: Cycle 1

Study-related activities to be performed at in-clinic visits and at home during Cycle 1 are listed below.

Cycle 1 Day 1 (Morning in-clinic infusion visit)

- Patients in Cycle 1 (see Table 13) will have a morning in-clinic visit for serial PK draws starting within 1 hour before the start of nab-paclitaxel infusion through 6 hours after the start of infusion.
- Vital signs (blood pressure, heart rate, respiration rate, temperature)
- Assess for AEs
- Review concomitant medications for changes or addition of new medications
- Dispense CORT125134
- ECGs (in duplicate)
  - Before CORT125134 dose
  - After start of nab-paclitaxel infusion (2.5 hours ±30 minutes)
- Local laboratory tests, predose - samples may be obtained up to 1 hour before dosing (see Table 5 for details)
  - Hematology
- Central laboratory tests
  - Cytokines and T cells (collected predose and at 4 hours postdose)
- Self-administration of oral dose of CORT125134 in the morning
- Vital signs (before nab-paclitaxel infusion and within 5 minutes after stopping the nab-paclitaxel infusion)
- PK blood sample collection at time points from 0.5 hours to 6 hours after start of nab-paclitaxel infusion (see Table 13)
- Administration of nab-paclitaxel over 30 minutes (±5 minutes) by IV infusion. Start of infusion must be within 15 minutes after CORT125134 dose

Cycle 1 Day 2 (Morning in-clinic visit)

- Patients will have a 24-hour post-nab-paclitaxel infusion, pre-CORT125134 morning dose PK draw visit (see Table 13)
  - PK blood sample collection predose (24 hours ±30 minutes from start of Day 1 nab-paclitaxel infusion and within 1 hour before Day 2 CORT125134 dose)
- Assess for AEs
- Review concomitant medications for changes or addition of new medications
- Self-administration of oral dose of CORT125134 in the morning

Cycle 1 Days 7 and 9, 14 and 16, and 28 (at home)

- Self-administration of oral doses of CORT125134 in the morning

Cycle 1 Day 8 and Day 15 (Morning in-clinic infusion visit)

- Physical examination (focused based on patient's clinical presentation; weight)
- Vital signs (blood pressure, heart rate, respiration rate, temperature)
- Assess for AEs
- Review concomitant medications for changes or addition of new medications
- Assess CORT125134 study drug compliance and dispense CORT125134
- ECOG performance status
- Local laboratory tests, predose – samples may be obtained within 48 hours before dosing (see Table 5 for details)
  - Hematology
  - Chemistry without glucose and insulin on Cycle 1 Day 8
  - Chemistry with fasting glucose and fasting insulin on Cycle 1 Day 15
  - Coagulation (INR) for patients taking warfarin
- Central laboratory tests, predose (before CORT125134 and nab-paclitaxel doses) *Cycle 1 Day 15 only*:
  - Hormone levels (see Table 5 for details)
  - PD/biomarker tests: C-peptide, ACTH, fasting morning cortisol, FKBP5
  - PK blood sample collection at time points from 0.5 to 4 hours after start of nab paclitaxel infusion (see Table 13)
- Self-administration of oral dose of CORT125134 before the nab-paclitaxel infusion
- Vital signs (before nab-paclitaxel infusion and within 5 minutes after stopping nab-paclitaxel infusion)
- Administration of nab-paclitaxel over 30 minutes (±5 minutes) by IV infusion. Start of infusion must be within 15 minutes after morning CORT125134 dose

6.3.4 Cycles 2+

Cycle 2 will begin the day after Cycle 1 Day 28, and subsequent 28-day cycles will be continued until the patient meets withdrawal criteria.

Study-related activities to be performed at in-clinic visits and at home during Cycles 2 and greater are listed below.

Day 1, Day 8, and Day 15 (Morning in-clinic visits)

- Physical examination (complete examination at Day 1, focused Days 8 and 15; weight)
- Vital signs (blood pressure, heart rate, respiration rate, temperature)
- Assess for AEs
- Review concomitant medications for changes or addition of new medications
- Assess CORT125134 study drug compliance and dispense CORT125134
- ECOG performance status
- ECG if clinically indicated

- Local laboratory tests, predose samples may be obtained within 48 hours before dosing (see Table 5 for details)
  - Hematology
  - Chemistry
  - Urinalysis (only *at Cycle 2 Day 1, Cycle 3 Day 1, then every 12 weeks ±14 days thereafter)*
  - Coagulation (INR) for patients taking warfarin
  - Serum or urine pregnancy test for female patients of childbearing potential *every 12 weeks ±7 days*
- Central laboratory tests, before CORT125134 and nab-paclitaxel doses, *starting at Cycle 4 Day 1 and every 12 weeks (±14 days) thereafter:*
  - PD/biomarker tests: ACTH, fasting morning cortisol, FKBP5
  - Thyroid function test (thyroid-stimulating hormone [TSH] with reflex total T3 and free T4 if abnormal TSH values are observed)
- Self-administration of oral dose of CORT125134 before nab-paclitaxel infusion
- Vital signs (before nab-paclitaxel infusion and within 5 minutes after stopping nab-paclitaxel infusion)
- Administration of nab-paclitaxel over 30 minutes (±5 minutes) by IV infusion. Start of infusion must be within 15 minutes after the morning CORT125134 dose
- Tumor assessments at Cycle 3 Day 1 (±7 days), thereafter every 6 to 8 weeks, and at time of clinical suspicion of disease progression:
  - CAP CT scan with contrast. Tumor assessments will be documented per RECIST v1.1
  - For patients with ovarian, fallopian tube, or primary peritoneal cancer: serum CA-125

Days 2, 7 and 9, 14 and 16, and 28 (at home)

- Self-administration of oral doses of CORT125134 in the morning

6.4 Segments I and II: Posttreatment Visit/Early Termination Visit (In-clinic Visit) (28 Days After Last Dose of Study Drug)

For the Posttreatment Visit, the following assessments are required:

- Physical examination (complete examination including weight)
- Vital signs (blood pressure, heart rate, respiration rate, temperature)
- Assess for AEs through 28 days after the last dose of study drug
- Review concomitant medications for changes or addition of new medications
- Assess CORT125134 study drug compliance and collect all unused study drug and remaining empty foil pouches.
- ECOG performance status
- ECG if clinically indicated

- Local laboratory tests (see Table 5 for details)
  - Serum or urine pregnancy test for female patients of childbearing potential (optionally, can be performed at site or serum test can be performed by central laboratory)
  - Hematology
  - Chemistry
  - Urinalysis
  - Coagulation (INR) for patients taking warfarin)
- Central laboratory tests
  - PD/biomarker tests: ACTH, fasting morning cortisol, and FKBP5
- Tumor assessments if ≥4 weeks have elapsed since the prior tumor assessment and progressive disease have not been documented:
  - CAP CT scan with contrast. Tumor assessments will be documented per RECIST v1.1
  - For patients with ovarian, fallopian tube, or primary peritoneal cancer: serum CA-125
- Optional tumor biopsy for patients with disease progression.

6.5 Telephone Follow-up for Survival

Patients will be followed for progression and survival via telephone on a quarterly basis for 1 year after the last dose of study drug (CORT125134 or nab-paclitaxel, whichever is latest) in the last patient on treatment.

6.6 Unscheduled Visits

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

6.7 Study Drug Compliance Procedures

Patients will be instructed to return all used and unused CORT125134 study drug containers at each study visit. Patient compliance with the dosing regimen will be assessed by reconciliation of the used and unused study drug. The quantity dispensed, returned, used, or lost must be recorded. Procedures for return and disposition of study drug by the clinical site are provided in Section 10.5.2.

6.8 Patient Discontinuation and Withdrawal

In this study, "study treatment" refers to study drug (CORT125134) in combination with nab-paclitaxel, "patient discontinuation" refers to discontinuation of study treatment with the possibility of continued assessments, and "patient withdrawal" refers to withdrawal of consent and cessation of assessments.

6.8.1 Discontinuation of Study Treatment

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

- Progressive disease. If the patient is experiencing overall clinical benefit, the Investigator should discuss the situation with the Medical Monitor, and the patient may be allowed to remain on the study, if both the Medical Monitor and the Investigator agree that this is appropriate for the patient.
- Unacceptable toxicity.
- Withdrawal of consent for treatment by patient.
- The Investigator decides it is in the patient's best interest to discontinue treatment and/or participation in the study. Reasons may include the following:
  - The patient requires prohibited medications.
  - The patient is not adherent to the protocol.
- The Sponsor terminates the study.
- Patient is pregnant.

Patients who discontinue study treatment for reasons other than withdrawal of consent (eg, adverse event, Investigator decision) will undergo a Posttreatment/Early Termination Visit and will be followed for progression and survival.

The Investigator should notify the Sponsor within 48 hours if a patient discontinues study treatment.

6.8.2 Withdrawal from Study

Withdrawal from the study (including all follow up assessments) will occur under the following circumstances:

- Withdrawal of consent for follow-up observation by the patient.
- Patient is lost to follow-up.
- Termination by Sponsor
- Death

Patients may withdraw their consent to participate in the study at any time for any reason without prejudice. If a patient withdraws consent, the Investigator should make a reasonable attempt to document the specific reason why consent is withdrawn and it should be documented in the medical record. A patient can discontinue from treatment but still participate in the Posttreatment/End of Treatment Visit and/or Long-term Follow-up (see Section 6.8.1). If a patient withdraws from study, no additional Follow-up will be conducted.

If possible, before the patient withdraws consent or the patient is withdrawn by the Investigator, every effort should be made to complete and report the follow-up assessments listed for the Posttreatment Visit/Early Termination Visit, as thoroughly as possible. The Investigator should notify the Sponsor of the patient's withdrawal within 48 hours.

If a patient is lost to follow-up and cannot be reached by telephone, a certified letter should be sent to the patient (or the patient's legally authorized representative, if appropriate) requesting contact with the Investigator.

6.9 Early Termination of the Study

Corcept reserves the right to terminate the study at any time with appropriate notification. Reasons for terminating the study may include but are not limited to the following:

- Potential health hazard to patients, as indicated by the incidence or severity of AEs in this or other studies.
- Unsatisfactory patient enrollment.
- Inaccurate or incomplete data recording.
- Stopping rules and criteria specific to this protocol.
- Administrative reasons.

In addition, the regulatory agency or the site's IRB has the authority to stop the study.

6.10 Replacement of Patients

Patients withdrawn from Part 1 of Segment I or Segment II for any reasons other than toxicity may be replaced to ensure that a sufficient number of DLT-evaluable patients are enrolled to identify the MTD and development regimen.

6.11 Dose Diary

A dosing diary will be provided and patients will be instructed to return all unused CORT125134 and the dose diary during the patient visits. Patients should complete and entry in the diary for each self-administered dose of CORT125134. Entries will include the number of capsules as well as the date and time of CORT125134 administration. On visit days, CORT125134 should be taken in the clinical during the visit and after initial blood draws. Time and dose administered should be documented in the clinic charts.

7 RESPONSE MEASURES AND SUMMARY OF DATA COLLECTION METHODS

7.1 Safety Measures

Safety will be determined from evaluation of AEs including DLTs, clinical laboratory tests, vital signs, ECOG performance status, physical examinations, and ECGs.

7.1.1 Adverse Events

All AEs will be recorded from the time of signing of the ICF until 28 days after the last dose of study drug. Dose-limiting toxicities as defined in Section 3.3.3 will be assessed throughout the study. Patients should be monitored for AEs consistent with the current IB for CORT125134 and the Prescribing Information for nab-paclitaxel. To help characterize any possible relationships between drug exposure and the clinical event, when an SAE or DLT occurs, ACTH and cortisol should be assessed as close to the time of the event as possible and a PK sample may be drawn at the discretion of the Investigator

Details on definitions and reporting of AEs are provided in Section 9.

7.1.2 Clinical Laboratory Assessments

Clinical laboratory tests for safety and PD are listed in Table 5 and will be performed at the time points shown in Table 9 for Segment I and Table 11 for Segment II. Laboratory draws for PK are described in Section 7.3.

Samples will be processed at local and central laboratories as follows:

- Local laboratory: hematology, chemistry, insulin, coagulation (INR) for patients taking warfarin, urinalysis, and serum or urine pregnancy test (optionally, serum pregnancy can be performed by central laboratory at Screening, Baseline, and Posttreatment/Early Termination Visits) and tumor markers (eg, CA-125 for patients with ovarian, fallopian tube, or primary peritoneal cancer).
  Note: hematology, serum chemistry, and coagulation (INR) assessments may be performed at a local laboratory outside of the investigative site laboratory as long as laboratory reports are provided to the Investigator within 48 hours of sample draw.
- Central laboratory: hormone levels (estradiol, testosterone, FSH, LH and DHEA-S), thyroid function tests (TSH with reflex total T3 and free T4 if abnormal TSH values are observed), C-peptide, morning cortisol, ACTH, and tumor characterization and mRNA expression tests, including FKBP5 and glucocorticoid-induced genes or biomarkers of GR activity, PG, and PK (PK details in Section 7.3).

Table 5 Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis (dipstick)
Red blood cell (RBC) count	Sodium	Bacteria
Hemoglobin	Potassium	Blood
Hematocrit	Calcium	Urobilinogen
Mean corpuscular volume (MCV)	Chloride	Nitrites
Platelet count	Phosphorus	Color
White blood cell (WBC) count	Magnesium	Clarity
WBC with 5-part differential:	Serum Creatinine	pH
Neutrophils	Total bilirubin	Specific gravity
Lymphocytes	Albumin	Ketones
Monocytes	Alkaline phosphatase (ALP)	Protein
Eosinophils	Lactate dehydrogenase (LDH)	Glucose
Basophils	Aspartate aminotransferase (AST)	Bilirubin
Coagulation	Alanine aminotransferase (ALT)	Leukocyte esterase
International normalized ratio (INR) (only for patients taking warfarin)	Glucose, fasting	**Other [a]**
	Blood urea nitrogen (BUN)	Serum or urine pregnancy test, if applicable
Pharmacodynamic [a]	Uric acid	Thyroid-stimulating hormone (TSH)
C-peptide	Bicarbonate	Total T3 [b]
ACTH	Total protein	Free T4 [b]
Fasting morning cortisol [c]		Estradiol
FKBP5 [c]		Testosterone, total, free, and percent free
Insulin, fasting		Follicle-stimulating hormone (FSH)
Cytokine and T cell profiles		Luteinizing hormone (LH)
		Dehydroepiandrosterone-sulfate (DHEA-S)
		Optional pharmacogenomic sample

Note: Laboratory draws for PK are described in Section 7.3.
[a] Pharmacodynamic and other laboratory test samples are to be drawn predose.
[b] Reflex testing only with abnormal TSH values.
[c] May represent a panel of mRNA expression/glucocorticoid-modulated pathways.

Pregnancy tests will be done only for female patients of childbearing potential. A female is considered to be of childbearing potential unless she is postmenopausal and without menses for 12 months or without a uterus and/or both ovaries. If treatment with CORT125134 is stopped for 7 days or more, a patient should have a negative pregnancy test before restarting drug.

Any abnormal test results determined to be clinically significant by the Investigator should be repeated (at the Investigator's discretion) until the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or the Investigator determines that the abnormal value is no longer clinically significant. All abnormal clinical laboratory result pages should be initialed and dated by an Investigator, along with a comment regarding whether or not the result is clinically significant. Guidance on recording abnormal laboratory findings as AEs is provided in Section 9.5.

7.1.3 Vital Signs

Vital signs (heart rate, systolic and diastolic blood pressure, temperature, and respiration rate) will be assessed at the time points shown in Table 9 and Table 11. On days of nab-paclitaxel IV administration, vital signs should be collected predose and within 5 minutes after stopping the nab-paclitaxel infusion.

Systolic and diastolic blood pressure will be measured after patients have been at rest (seated) for at least 3 minutes. Blood pressure will be recorded in mmHg. Heart rate will be measured in beats per minutes after the patient has been in a resting state (seated) for at least 3 minutes.

7.1.4 ECOG Performance Status

The ECOG scales and criteria (Table 6) are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis (Oken et al. 1982). ECOG performance status will be assessed at the time points shown in Table 9 and Table 11.

If a patient's ECOG performance status declines to ≥2 between Screening/Baseline and Day 1, the patient will no longer be eligible and will be withdrawn from the study.

Table 6 ECOG Performance Status

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, eg, light housework or 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.
5	Dead

Abbreviation: ECOG, Eastern Cooperative Oncology Group

7.1.5 Physical Examinations

Complete physical examinations are to be performed at Screening/Baseline; at Day 1 of each cycle (except in Segment II, Cycle 1 Day 1 when it is performed on Day −1); and at the Posttreatment/Early Termination Visit. Other scheduled physical examinations shown in Table 9 and Table 11 may be focused, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms.

Weight will be reported at each visit and height will be recorded at Screening only. Height (without shoes) will be measured in centimeters (cm) using an appropriate measuring device. Weight (without shoes) will be measured in kilograms (kg) using a scale. Historical patient information and/or patient reports should not be used for either measurement.

7.1.6 Electrocardiogram

An ECG will be obtained at the time points shown in Table 9 and Table 11. ECGs will be performed and read per ECG vendor specifications. The Investigator may do additional ECG measurements on a "for cause" basis as determined by clinical judgment. The Investigator or Subinvestigator (physician) will be responsible for review and interpretation of the safety ECG results on site and determining whether the ECG is normal, abnormal clinically insignificant, or abnormal clinically significant. The ECG report result should be initialed and dated.

7.2 Measures of Anticancer Activity

While this study does not have a formal primary efficacy objective, secondary objectives of this study are to make a preliminary assessment of the anticancer activity of the combination of CORT125134 and nab-paclitaxel in patients with solid tumors in the dose-finding phase, and in patients in the dose-expansion phase. Tumors will be assessed radiologically and response to treatment will be determined by using RECIST (v1.1) (Eisenhauer et al. 2009; http://www.eortc.be/recist/). Documented tumor measurements are required using computed tomography (CT) scans, or magnetic resonance imaging (MRI), as appropriate. In patients with ovarian, fallopian tube, or primary peritoneal cancer, CA-125 will be assessed at the time of radiologic tumor assessments (baseline and every 6–8 weeks) and response reported per GCIG criteria (Rustin et al. 2011) in addition to RECIST v1.1. Other tumor markers collected as standard practice (such as cancer antigens 15-3 and 19-9 [CA15-3 and CA19-9], prostate-specific antigen [PSA], and carcinoembryonic antigen [CEA]) will be documented in the case report form.

At Screening, CAP CT scans that were done with contrast as standard of care within ≤30 days of Screening may be used if they meet study quality criteria. If CAP CT scans with contrast were done ≤28 days before the first dose of study drug, they do not need to be repeated for the baseline measurement.

Subsequent tumor assessments will be performed at Cycle 3 Day 1 (±7 days) and thereafter every 6–8 weeks (no more than 8 weeks between scans) and at time of clinical suspicion of disease progression. To ensure comparability, the baseline radiographs/scan, and subsequent radiographs/scans to assess response, should be performed using consistent methods and identical techniques. The same method (radiological or physical) should be employed and assessed by the same individual on each occasion, if possible. RECIST v1.1 will be used to determine response (Eisenhauer et al. 2009).

Confirmation of objective responses is defined as responses that persist on repeat imaging for two assessments with a time period of at least 4 weeks between two assessments (4- to 6-week window). In the event of a confirmed response, the timing of subsequent tumor assessment will be reset at the 6–8 week interval from confirmatory scan. At the Posttreatment/Early Termination Visit, tumor assessment will be done if ≥4 weeks have elapsed since the last tumor assessment, unless there is documented progressive disease. If progressive disease is documented, an additional tumor assessment is not required as part of the final visit.

Patients will be followed (contacted by telephone) to monitor for survival quarterly for 1 year following the last dose of study drug (CORT125134 or nab-paclitaxel, whichever is latest) in the last patient on treatment.

7.3 Pharmacokinetic Measures

Segment I—Blood samples (2-mL sample for analysis of single analyte or 3-mL sample for analysis of both analytes) will be collected for determination of the plasma concentrations of CORT125134 and its metabolites and nab-paclitaxel at the time points shown in Table 10. In the event of an SAE or DLT, a PK sample may be drawn at the discretion of the investigator.

Serial PK data (approximately 29 samples during the study) will be obtained from all patients in Part 1 and approximately 11 samples will be obtained from all patients in Part 2 as shown in Figure 4 and Table 10.

Segment II—Serial PK data (approximately14 samples) will be obtained from all patients in Part 1 and Part 2 as shown in Figure 5 and Table 13.

Should a patient require a dose reduction on study, a PK profile at the new dose level may be obtained with patient consent.

PK Analyses (Both Segments)—Plasma samples will be assayed for CORT125134 and its metabolites using liquid chromatography-tandem mass spectrometry method (LC/MS/MS). Instructions for collection, sample handling, and shipment are provided in the laboratory manual. Instructions for the collection, sample handling, and shipment of plasma samples for analysis of nab-paclitaxel levels are provided in the laboratory manual.

Standard PK parameters will be included in the PK characterization and evaluation of the dose-exposure relationship and related analyses. An assessment of the correlation between AEs and anticancer activity parameters with plasma concentrations will be undertaken.

An optional PG sample will be collected to assess genetic factors affecting drug metabolism, transporters and other PK parameters.

7.4 Pharmacodynamic and Biomarker Measures

Collection of blood samples for determination of PD biomarkers is described in Section 7.1.2.

The development and improvement of cancer therapies increasingly depends on insights gained from analysis of biomolecules. During this study and with the consent of patients (see Section 10.1.1), biological samples (eg, blood, plasma, serum, or 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 CORT125134 and which do not.

Candidate biomarkers that will be investigated during the study include the PD biomarkers noted in Section 7.1.2 (insulin, C-peptide, ACTH, morning cortisol, and FKBP5). An optional baseline sample will be obtained for pharmacogenomic assessments that will enhance our understanding of drug metabolism. Glucocorticoids have immunosuppressive properties, and many of these are effects known to enable cancer cells to evade immune detection and promote tumorigenesis (Olnes et al. 2016, Xing et al. 2015). The immunological profile (cytokines and T cell profiling) will be assessed to determine the impact of GR antagonism as relevant to enhancing antitumor immunity with potential consideration for future combinations with immunotherapies. The T-cell profiles may include interferon-gamma; prostaglandin E2; tumor necrosis factor-alpha;

transforming growth factor-beta; interleukins (IL-) 2, 4, 10, 12, and 13; T-cell profiling by flow cytometry of type 1, 2, and 17 T helper cells (Th1, Th2, Th17 cells), and regulatory T cells (Treg cells). Other explorations may include, but are not limited to, potential biomarkers related to the following:

- Disease response
- GR activation/inhibition
- GR expression
- mRNA molecular profiling and assessment of glucocorticoid-regulated pathway and panel of GR housekeeping genes
- Tumor characteristics
- Cell-free DNA
- Mechanisms of treatment resistance

The tests will be conducted a central laboratory using a variety of techniques (eg, IHC, DNA/RNA analysis). Pharmacodynamic assays may be performed to correlate results of biomarker assessments to the physiological effects of CORT125134. Refer to the schedules of assessments in Section 12.1 for Segment I and Section 12.2 for Segment II for the timing and frequency of all sample collections. Instructions for the collection, handling, and shipment of samples are found in the laboratory manual provided for sample collection and handling (see Section 10.7).

7.5 Pharmacogenomic Testing

An optional blood sample will be collected at baseline from patients who consent to collection for PG analysis to assess genetic factors affecting drug metabolism, transporters and other PK parameters.

7.6 Tumor Tissue Collection

For patients enrolling in the study, consent and availability to archived tissue biopsy are required for eligibility. If archived tissue is not available, a fresh tumor biopsy can be obtained. Specimens obtained closest to the time of study enrollment are preferred, but not required. In addition, optional biopsies may be obtained if collected during standard-of-care procedures during the study or at the time of disease progression and with consent of the patient. Approximately 15 FFPE slides, slices, or curls will be required for each tumor tissue collection (tissue block preferred). Refer to the study laboratory manual for complete instructions.

7.7 Summary of Methods of Data Collection

Sponsor personnel or designees will visit the study site before initiation of the study to review with the site personnel information about the study drugs, protocol and other regulatory document requirements, source document requirements, electronic case report forms (eCRFs), monitoring requirements, and procedures for reporting AEs, including SAEs.

At visits during and after the study, a clinical research associate (CRA) will monitor the site for compliance with regulatory documentation, with a focus on accurate and complete recording of

data on eCRFs from source documents, adherence to protocol, SAE reporting, and drug accountability records.

Data quality control and analysis will be performed by the Sponsor or a designee, based on a predefined analysis

8 STATISTICAL PROCEDURES

Detailed procedures for statistical analyses to be performed for this study will be provided in a separate Statistical Analysis Plan that will be finalized before database lock.

8.1 Analysis Populations

The following populations will be defined for this study:

- The Safety population will include all patients who received at least one dose of study drug.
- Modified Intent-to-Treat (mITT) population will include all patients who received at least one dose of CORT125134.
- The DLT-evaluable population will include all patients in Part 1 (dose-finding phase) who complete 1 cycle of treatment and assessment or who receive at least one dose of CORT125134 and discontinue before completing the first cycle because of toxicity.
- The Response-evaluable population will be the subset of the Safety population with at least one post-baseline tumor assessment.
- The PK-evaluable population will be the subset of the Safety population with adequate PK data.

8.2 General Statistical Considerations

All analyses of safety and anticancer activity for this open-label Phase 1/2 study will be descriptive in nature and presented by dose group, tumor type, GR status, and overall, as appropriate. Descriptive statistics (eg, number of observations, means, standard deviations, medians, maximum and minimum values) will be used to summarize continuous variables. Frequencies and proportions will be used to summarize categorical variables. Patient listings will be provided as appropriate.

8.2.1 Summary of Demographics and Study Conduct

Demographic variables such as age, sex, race/ethnicity, and baseline characteristics will be summarized for all patient populations.

Enrollment, major protocol violations and discontinuations from the study will be summarized. The reasons for discontinuation will be tabulated.

8.2.2 Safety Analyses

Safety Analyses will be conducted on all patients in the Safety population.

The study primary objective of determining MTD/development regiment will be achieved through evaluation of the incidence, nature, duration, and severity of toxicities according to the NCI-CTCAE, version 4.03.

Safety will be assessed based on the evaluation of TEAEs including DLTs, clinical laboratory tests, vital signs, ECOG performance status, physical examinations, and ECGs.

All DLTs, and their severity according to the NCI-CTCAE, version 4.03 will be listed by study drug dosing regimen. Study drug exposure to both CORT125134 or nab-paclitaxel for each of

the DLTs will be listed. Relevant laboratory values will be summarized where appropriate to aid in the determination of the MTD. Changes in NCI CTCAE grade will be tabulated.

The incidence and duration of TEAEs, defined as AEs occurring after the first dose of study drug through 28 days after the last dose of either study drug, will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study drug. All laboratory results and vital sign measurements will be summarized using appropriate descriptive statistics.

The following adverse events will be summarized separately: adverse events leading to withdrawal of study drug, adverse events leading to dose reduction or interruption, Grade >=3 adverse events, Grade 5 adverse events, serious adverse events, and adverse events of special interest.

All TEAEs will be listed.

All AEs recorded from the time of signing of the ICF until the first dose of study drug will be listed separately.

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

8.2.3 Analyses of Anticancer Activity

A secondary objective of this study is to make a preliminary assessment of the anticancer activity as assessed by the investigator of CORT125134 in combination with nab-paclitaxel in patients with the selected tumor types.

All efficacy analyses will be performed on the mITT population (primary analysis population), unless otherwise specified. Selected analyses will be performed on the Response-Evaluable Population subset. Further details will be specified in the Statistical Analysis Plan (SAP).

Secondary analyses will characterize anticancer activity for the following endpoints:

- ORR consisting of the percent of patients with an objective tumor response: measurable disease with partial response (PR) or complete response (CR) as defined by RECIST v1.1 and confirmed on a second, consecutive scan obtained no less than 4 weeks after the criteria for response are first met in cohorts of patients treated with the development regimen.
- Best response defined as the best response recorded from the date of the first dose of CORT125134 or nab-paclitaxel, whichever is earliest, across all time points during study observation period (including both confirmed and unconfirmed responses).
- Clinical benefit rate (CBR) defined as the percentage of patients who have achieved CR or PR, or SD for 6 months or greater.
- Progression-free survival will be defined as the time from the date the patient receives the first dose of CORT125134 or nab-paclitaxel, whichever is earliest, to the date the patient experiences unequivocal disease progression per RECIST v1.1 or death (all causes of mortality).
- Duration of response as measured from the date that the criteria are met for complete response (CR) or partial response (PR) until the first date that progressive disease is objectively documented.

- Overall survival defined as the time from date of the first dose of CORT125134 or nab-paclitaxel, whichever is earliest, until the date of death from any cause.

Number and percent of patients achieving each category of response as defined by RECIST 1.1 will be summarized. Visual displays that incorporate timing and magnitude of response (eg, swimmer plots, waterfall plots) will be created.

PFS and OS will be analyzed using the Kaplan-Meyer method. The Brookmeyer-Crowley method will be used to construct 95% percent confidence interval for the median PFS and OS. For PFS, patients without a data of disease progression will be analyzed as censored observations on the date of last tumor measurement. For OS, patients who are not reported as having died will be analyzed as censored observations on the date they were last known to be alive.

Duration of response, best response and ORR will be assessed only in patients with at least one measurable lesion at baseline. Best response with percentage change from baseline will be shown in a waterfall plot. An estimate of ORR and 95% confidence interval will be calculated using Clopper-Pearson method. Analysis of ORR may include patients who were treated with the development regimen in Part 1 and have the tumor type selected for evaluation in the dose-expansion phase (Part 2). For patients with ovarian, fallopian tube, or primary peritoneal cancer, CA-125 response per (GCIG) criteria (Rustin et al. 2011) will also be recorded. Summaries of efficacy outcomes by GR status will include patients with evaluable tissue enrolled in any part of the study.

Duration of Response (DOR): Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. Kaplan-Meier methodology will be used to estimate median DOR.

Further details of analyses, including analyses of Clinical Benefit Rate, Best Response Rate and details of censoring will be specified in the Statistical Analysis Plan.

8.2.4 Pharmacokinetic Analyses

Blood samples for serial PK analyses will be collected from all patients in Part 1 (see Section 7.3). For patients undergoing serial PK sampling, PK parameters of nab-paclitaxel and CORT125134 (and any relevant metabolites) will be calculated and the analyte concentration versus time plots will be provided. The following parameters will be included in the PK characterization and evaluation of the dose-exposure relationship and related analyses:

- C_{max}, the maximum plasma concentration
- AUC_{last}, the area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration
- AUC_{inf}, area under the plasma concentration-time curve from time 0 to infinity, calculated as AUC_{last} + Clast/λz
- CL, the systemic plasma clearance
- Vss, volume of distribution at steady state
- $T_{1/2}$, the terminal elimination half-life
- T_{max}, time at which the observed maximum is seen
- C_{min}, predose plasma concentration

- Partial AUCs

8.2.5 Pharmacodynamic Analyses

Pharmacodynamics will be assessed by measuring blood levels of insulin, C-peptide, adrenocorticotropic hormone (ACTH), morning cortisol, tumor characterization, and mRNA expression tests, including FKBP5 and glucocorticoid-induced genes or biomarkers of GR activity. Cytokines and T-cell profiles will be assessed to explore the effect of CORT125134 when given alone and in combination with nab-paclitaxel.

8.3 Sample Size Calculation

An adequate number of DLT-evaluable patients will be enrolled to determine the MTD and development regimen in Segment I, Part 1 (approximately 62 patients) and Segment II, Part 1 (approximately 24 patients). Approximately 20 patients will be enrolled in each expansion cohort in Part 2 of the study.

9 SAFETY EVENT DOCUMENTATION AND REPORTING

9.1 Investigator's Responsibilities

Investigators are responsible for monitoring the safety of patients who have entered this study and for providing appropriate medical care. Investigators are required to report promptly to Corcept or its designee any AE that may reasonably be regarded as caused by, or probably caused by, the study drug. If the adverse effect is alarming, the Investigator should report the adverse effect immediately. In addition, the Investigators are responsible for alerting Corcept or its designee to any event that seems unusual, even if the event may be considered an unanticipated benefit to the patient, and for reporting the event on the appropriate eCRF or safety report form.

By exercising appropriate health-care options, the Investigator remains responsible for managing AEs that are serious or that cause a patient to withdraw before completing the study. Frequency of follow-up of any particular AE is left to the discretion of the Investigator. Duration of follow-up and requirements for immediate SAE reporting (within 24 hours of the event) are described below.

9.2 Monitoring Safety Data during Study

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

9.3 Definition of an Adverse Event

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

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

9.4 Definition of a Serious Adverse Event

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

- Results in death (ie, the AE caused or led to the fatality)
- Is life-threatening (ie, the AE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires hospitalization or prolongation of existing hospitalization (ie, hospitalizations for scheduled treatments and elective medical/surgical procedures are not SAEs by this criterion)
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial reduction of the patient's ability to perform activities of daily living)

- Results in a congenital anomaly or birth defect (ie, an adverse finding in a child or fetus of a patient exposed to the study medication before conception or during pregnancy)
- Involves other medically important conditions (ie, the AE does not meet any of the above serious criteria but based on appropriate medical judgment, may jeopardize the patient or require medical or surgical intervention to prevent one of the serious outcomes listed in these criteria)

9.5 Clinical Laboratory Adverse Events

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

9.6 Documentation of Adverse Events

Patients will be evaluated and questioned to identify AEs during the study.

Collection of AEs will start immediately following signing of the ICF and will continue until 28 days after the last dose of CORT125134 or nab-paclitaxel. Illnesses present before the patient signs the ICF are considered pre-existing conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF. Adverse events that occur from the first dose of CORT125134 through 28 days after administration of the last dose of study drug will be considered treatment-emergent AEs and will be recorded on the AE eCRF. Any AEs reported more than 28 days after the last dose of study drug will be considered posttreatment AEs.

All AEs will be documented on the AE pages of the eCRF and in the patient's medical record. The following attributes must be assigned: (1) description, (2) dates of onset and resolution, (3) intensity (see Section 9.7.1), (4) relationship to the study drug (see Section 9.7.2), (5) "serious" criteria if applicable (see Section 9.4), and (6) action taken. The Investigator will actively solicit this information and assess the AEs from the patient in terms of severity and relationship to study drug. 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).

In the event that 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 considered to be related (see Section 9.7.2) to study drug and all SAEs will be followed until resolved or until a stable status has been achieved.

9.7 Adverse Event Classification

9.7.1 Severity (Intensity) Grades of Adverse Events

The seriousness of an AE should not be confused with its intensity. To describe the maximum intensity of the AE on the AE eCRF, the Investigator will use the NCI-CTCAE, version 4.03 (CTCAE 2010). The NCI-CTCAE version 4.03 is the common standard of AE grading within

oncology centers. For events not listed in the CTCAE, the definitions from the CTCAE provided in Table 7 should be used to evaluate the grade of severity for the AE.

Table 7 Adverse Event Grades 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 adverse event

Source: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 (CTCAE 2010).

9.7.2 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 8. The Investigator's assessment of causality must be provided for all AEs (serious and nonserious). For each TEAE, causality will be attributed to each study drug (CORT125134 and nab-paclitaxel). Regardless of the causality assessment for individual AE/SAE reports, Corcept 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.

Table 8 Causal Attribution Guidance for Adverse Events

Not related to study drug	An AE that is judged to be clearly due only to extraneous causes such as diseases, environment, and the like. 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, eg, 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, eg, concomitant drug(s) or concurrent disease(s).

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

9.8 Procedures for Reporting Adverse Events

Patients will be evaluated and questioned generally to identify AEs during the study. Please refer to Section 9.6 for documentation detail.

All AEs that are drug-related and unexpected (not listed as treatment-related in the current IB or approved Prescribing Information) must be reported to the governing IRB) as required by the IRB, local regulations, and the governing health authorities. Any AE that is marked "ongoing" at the exit visit must be followed-up until resolved or stable.

9.9 Procedures for Reporting a Serious Adverse Event

Any SAE occurring during the study period (beginning with informed consent) and for at least 28 days after the last dose of study drug must be immediately reported to the designated safety contact and recorded on the SAE Form. All patients with an SAE must be followed and the outcomes reported. The Investigator must supply the Sponsor and the IRB with any additional requested information (eg, autopsy reports and terminal medical reports).

In the event of an SAE, the Investigator must:

1. Notify the Sponsor or designee by telephone and in writing within 24 hours of discovery as described in the study manual. The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax or email to the Sponsor.
2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.
3. Provide the Sponsor or designee complete documentation regarding the event, including a statement as to whether the event was or was not related to the use of the investigational drug.
4. Promptly inform the governing IRB of all serious, unexpected, drug-related events that occur at his or her site. It is the responsibility of each site to submit Investigational New Drug Application Safety Reports provided to them by the Sponsor to their IRB as required by the IRB, local regulations, and the governing health authorities.
5. Email/fax additional follow-up information, if required or available, to the Sponsor or designee within 24 hours of receipt and include the information on a follow-up SAE form and place with the original SAE information and keep with the appropriate section of the eCRF and/or study file

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

9.10 Adverse Event Follow-up

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

9.11 Pregnancy

Pregnancy is not considered an AE, although a patient will be withdrawn from the study if a pregnancy occurs and the Early Termination Visit will be completed. The pregnancy must be immediately reported to the Sponsor or designee. Additional follow-up may be required.

9.12 Emergency Sponsor Contact

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

[redacted]
Corcept Therapeutics
149 Commonwealth Drive
Menlo Park, CA 94025
[redacted]

10 ADMINISTRATIVE ITEMS

10.1 Protection of Human Patients

10.1.1 Compliance with Informed Consent Regulations (21 CFR Part 50) and Relevant Country Regulations

Written informed consent is to be obtained from each patient before enrollment into the study, and/or from the patient's legally authorized representative. The signed ICF(s) will be retained with the study center's records. Each patient will also be given a copy of his or her signed ICF(s).

The ICF must include information about the possible retention of biological samples at the conclusion of this study; with the patient's permission, blood, plasma, serum and tumor tissue samples may be obtained for future analysis to help identify biomarkers of disease or CORT125134 treatment. In addition, samples may be retained for future determination of drug metabolism and pharmacogenomic characteristics that may impact course of disease and/or drug response. The purpose of assessing possible biomarkers in this study is to understand their potential role in the pathogenesis of cancer and in clinical outcomes. It is understood that some countries, municipalities, institutions, or local IRBs do not allow the study of genetic polymorphisms. Therefore, the biomarker assessments will only be conducted only at institutions in which such research is in accordance with country and local law and institutional regulations. Patient participation for such assessments is voluntary and declining participation will in no way influence eligibility for this study. Patients agreeing to participate will sign a separate informed consent form.

10.1.2 Compliance with IRB Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable local regulations. The Investigator must obtain approval from a properly constituted IRB before initiating the study and re-approval or review at least annually. Corcept is to be notified immediately if the responsible IRB has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB correspondence with the Investigator should be provided to Corcept.

10.2 Patient Confidentiality

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. The Investigator must ensure that any subject data or records that are transmitted are de-identified. Patients should be identified only by their initials and/or patient ID number on the eCRFs or other transmitted study related documents.

Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the regulatory authority, national and local health authorities, Corcept or its designee, and the investigative site's IRB.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but patient identifying information will not be disclosed in these documents.

10.2.1 Patient Privacy

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

Written authorization is to be obtained from each patient before enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (ie, the HIPAA Standards for Privacy of Individually Identifiable Health Information).

In accordance with HIPAA requirements, additional purposes of this study include the following:

- To publish anonymous patient data from the study; and
- To create and maintain a data repository.

10.3 Changes to the Protocol

The Investigator must not implement any deviation from or changes to the protocol without approval by Corcept and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.4 Documentation

10.4.1 Source Documents

Source documents may include a patient's medical records, hospital charts, clinic charts, the Investigator's patient study files, as well as the results of diagnostic tests such as x-rays, laboratory tests, and ECGs. All data entered into the eCRF must be substantiated by a source document.

10.4.2 Case Report Form Completion

The Investigator is responsible for ensuring that data are properly recorded on each patient's eCRFs and related documents in a timely manner.

Corcept or designee will review all completed eCRFs for completeness.

10.4.3 Retention of Documentation

All study-related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and eCRF data should be maintained on file.

For countries (including the United States) falling within the scope of the International Conference on Harmonisation (ICH) guidelines, the Sponsor-specific essential documents should be retained until at least 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 at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

Corcept requires that it be notified in writing if the Investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

10.5 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 and study procedures. Storage of study drug is described in Section 5.6.

10.5.1 Clinical Supply Inventory

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

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

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of study drug(s) received, patients to whom study drug is dispensed (patient-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 CRA) has confirmed the accountability data and Sponsor has approved return or destruction.

10.5.2 Return or Disposal of Study Drug and/or Supplies

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

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

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

10.6 Monitoring, Audit, and Inspection

A representative of the Sponsor will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Monitoring will be conducted according to Good Clinical Practice (GCP) and standard operating procedures for compliance with applicable government regulations. The Investigators must agree to allow the monitor access to the clinical supplies, dispensing, and storage areas and to the clinical files of the study patients, and, if requested, agrees to assist the monitors.

The investigators/institutions will permit study-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents.

Representatives of FDA or other regulatory and health authorities may also conduct an inspection of the study. If informed of such an inspection, the Investigator should notify the Sponsor *immediately*.

10.7 Handling of Biological Specimens

Samples of blood and urine for evaluation of hematology, chemistry, and urinalysis will be analyzed locally at Clinical Laboratory Improvement Amendments (CLIA) certified local laboratories.

Blood samples for determination of the plasma concentrations of CORT125134 and its metabolites and nab-paclitaxel will be analyzed at central laboratories designated by Corcept.

Blood samples to evaluate the PD of CORT125134 will be analyzed at central laboratories designated by Corcept.

Tumor tissue samples will be analyzed for GR expression at a laboratory designated by Corcept.

10.8 Publications

Corcept as the Sponsor, has a proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple Investigators and sites and Corcept personnel. Authorship will be established before the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed before completion of the final report of the multicenter study except as agreed with Corcept.

11 REFERENCES

Abraxane® (nab-paclitaxel) Full Prescribing Information, July 2015.

Amsterdam A, Sasson R. The anti-inflammatory action of glucocorticoids is mediated by cell type specific regulation of apoptosis. *Mol Cell Endocrinol*. 2002;189:1-9.

Balbas MD, Evans MJ, Hosfield DJ, et al. Overcoming mutation-based resistance to antiandrogens with rational drug design. *Elife*. 2013;2:e00499

Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2011:29.

Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: A population-based study from the California Cancer Registry. *Cancer*. 2007;109:1721-1728.

Block TS, Murphy TI, Munster, PNM, et al. Glucocorticoid receptor expression in 20 solid tumor types using immunohistochemistry assay. Cancer Management and Research 2017:9 65–72

Conzen SD. Nuclear receptors and breast cancer. Mol Endocrinol. 2008;22(10):2215-2228.

CTCAE. 2010. Common Terminology Criteria for Adverse Events, version 4.03, dated 14 June 2010. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Accessed at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_ 4.03_2010-06-14_QuickReference_8.5x11.pdf

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;54:228-247.

Engelbrecht Y, de Wet H, Horsch K, Langeveldt CR, Hough FS, Hulley PA. Glucocorticoids induce rapid upregulation of mitogen-activated protein kinase phosphatase-1 and dephosphorylation of extracellular signal-regulated kinase and impair proliferation in human and mouse osteoblast cell lines. Endocrinology. 2003; 144:412-22.

Gradishar WJ, Krasnojon D, Cheporov S, et al. Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. 2009;22(1):3611-3619.

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

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

Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. *J Clin Oncol*. 2010;28:3271-3277.

Lin NU, Vanderplas A, Hughes ME, et al. Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network. *Cancer*. 2012;118:5463-5472.

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

Mikosz CA, Brickley DR, Sharkey MS, Moran TW, Conzen MS. Glucocorticoid receptor-mediated protection from apoptosis is associated with induction of the serine/threonine survival kinase gene, *sgk-1*. *J Biol Chem*. 2001;276:16649-16654.

Moran TJ, Gray S, Mikosz CA, Cozen SD. The glucocorticoid receptor mediates a survival signal in human mammary epithelial cells. *Cancer Research*. 2000;60:867-872

Morris GJ, Naidu S, Topham AK, et al. Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients: single-institution compilation compared with the NCI SEER database. *Cancer*. 2007;110:876-884.

Nanda R, Stringer-Reasor EM, Saha P, Kocherginsky M, Gibson J, Libao B, et al. A randomized phase I trial of nanoparticle albumin-bound paclitaxel with or without mifepristone for advanced breast cancer. SpringerPlus. 2016;5:947. DOI 10.1186/s40064-016-2457-1

Olnes MJ, Kotliarov Y, Biancotto A, Cheung F, Chen J, Shi R, et al. Effects of systemically administered hydrocortisone on the human immunome. Scientific Reports Published online: 14 March 2016: 6:23002 DOI: 10.1038/srep23002. Available at http://www.nature.com/articles/srep23002 . Accessed January 2017.

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

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

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

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

Shah SP, Roth A, Goya R, et al. The clonal and mutational evolution spectrum of primary triple-negative breast cancers. *Nature*. 2012;486:395-399.

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

Stringer EM, Skor MN, Fleming GF, Conzen SD. The role of the glucocorticoid receptor (GR) in inhibiting chemotherapy-induced apoptosis in high-grade serous ovarian carcinoma (HGS-OvCa). *J Clin Oncol.* 2013;31 Suppl:Abstr 11101.

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

Szmulewitz RZ, Chung E, Al-Ahmadie H. Serum/glucocorticoid-regulated kinase1 expression in primary human prostate cancers. *The Prostate*. 2012;72:157-164.

Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. 2013. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update**.** J Clin Oncol. 31(31):3997–4013.

Wu W, Chaudhuri S, Brickley DR, Pang D, Karrison T, Conzen SD. Microarray analysis reveals glucocorticoid-regulated survival genes that are associated with inhibition of apoptosis in breast epithelial cells. *Cancer Res*. 2004;64:1757-1764.

Wu W, Pew T, Zou M, Pang D, Conzen SD. Glucocorticoid receptor-induced MAPK phosphatase-1 (MPK-1) expression inhibits paclitaxel-associated MAPK activation and contributes to breast cancer cell survival. *J Biol Chem*. 2005;280:4117-4124.

Xing K, Gu B, Zhang P, Wu X. Dexamethasone enhances programmed cell death 1 (PD-1) expression during T cell activation: an insight into the optimum application of glucocorticoids in anti-cancer therapy. BMC Immunology 2015; 16:39. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4480888/pdf /12865_2015_Article_103.pdf. Accessed January 2017.

Zhang C, Beckermann B, Kallifatiditis G, et al. Corticosteroids induce chemotherapy resistance in the majority of tumour cells from bone, brain, breast, cervix, melanoma and neuroblastoma. *Int J Oncol*. 2006;29:1295-1301.

12 ATTACHMENTS

12.1 Segment I: Schedules of Visits and Procedures

Table 9 Segment I: Study Visits and Procedures

Procedures/ Examinations [a]	Screening	Baseline [b]	1-wk Nab-paclitaxel Lead-in [c]		1-wk CORT125134 Lead-in		Cycle 1 (28-day cycle)				Cycle 2+ (28-day cycles)			Post -Tx / ET
	Day -28 to -1	Day -7 to -1	Day 1	Day 2	Day 1	Day 7	Day 1	Day 8	Day 9	Day 15	Day 1	Day 8	Day 15	
Informed consent [d]	X													
Inclusion/exclusion criteria [b]	X	X					X							
Medical/oncologic history [e]	X													
Physical examination (PE) [b,f]	X	X					X	X		X	X	X	X	X
Vital signs [b,g]	X	X	X				X	X		X	X	X	X	X
ECOG performance status [b]	X	X					X	X		X	X	X	X	X
ECG	X					X[h]					If clinically indicated			
Pregnancy test [i]	X	X					Every 12 wk (±7 d)							X
Hematology [b,j]	X	X	X		X		X	X		X	X	X	X	X
Chemistry and INR [b,k]	X	X					X	X		X	X	X	X	X
Fasting insulin		X								X[k]				
Thyroid function test [l]		X[l]					Every 12 weeks (±14 d)							
Hormone levels [m]		X[m]								X				
Urinalysis (dipstick) [b,n]	X	X					X				X[n]			X
Tumor assessment (RECIST v1.1) [o]	X	X									C3 D1 (±7 d) then every 6–8 wk			X[o]
PD/biomarker blood sample [p]		X[p]								X	Every 12 wk (±14 d)			X
Cytokine and T cell sample [q]			X			X		X						
Optional PG sample		X												
Tumor tissue for GR IHC: [r] archival or biopsy [s]	X													
Follow-up for survival [t]														X[t]
Adverse events [u]	X	←	—	—	—	—	—	—	—	—	—	—	→	X
Concomitant medications [v]	X	←	—	—	—	—	—	—	—	—	—	—	→	X
PK/metabolites sample collection [w]			X	X	X	X	X	X	X	X				
Study treatment administration														
CORT125134 – oral [x,y]					←	—	—	—	—	—	—	—	→	
Nab-paclitaxel – IV [x,y]			X				X	X		X	X	X	X	

Note: The acceptable visit window is ± 3 days for Day 1 of each Cycle after Cycle 1. Nab-paclitaxel infusions must be no less than 7 days apart, and the recommended window for Day 8 and 15 is no more than +24 hours. No visit window is allowed for Nab-paclitaxel Lead-in Day 2, Cycle 1 Day 1, and Cycle 1 Day 9 due to the planned collection of the 24-hour PK samples. Posttreatment/Early Termination Visit to occur 28 (±7) days after the last dose of study drug.

a. All procedures and examinations should be performed before the administration of study treatment(s), unless specifically stated otherwise.
b. Inclusion/exclusion criteria and selected safety assessments (vital signs, ECOG, PE, and laboratory tests) are required to be repeated only for patients for whom screening assessments were performed >7 days before Day 1 of the 1-week lead-in (first dose of study treatment).
c. Patients in Part 1 will have a 1-week Nab-paclitaxel Lead-in before the 1-week CORT125134 Lead-in. After a minimum of two dose levels are observed, the nab-paclitaxel lead-in may be discontinued per the DRC recommendation.
d. The IRB-approved ICF must be signed before any study-specific procedures or examinations are performed.
e. Including prior cancer treatments. Any new or clinically significant changes in the patient's medical or oncologic history between signing of the IRB-approved ICF and the first dose of study treatment will be recorded on the AE CRF page.
f. Physical examinations at Screening/Baseline, at Day 1 of each cycle, and at the Posttreatment/Early Termination Visit should be complete assessments. Other weekly examinations may be focused, to identify changes from Screening/Baseline or evaluate changes based on the patient's clinical symptoms. Weight to be reported at each visit, height at Screening/Baseline Visit only.
g. On days of nab-paclitaxel IV administration, vital signs (heart rate, systolic and diastolic blood pressure, temperature, and respiration rate) should be collected pre-infusion and within 5 minutes after stopping the nab-paclitaxel infusion.
h. ECGs to be done at Screening (in triplicate) and at CORT125134 Lead-in Day 7 predose and 2.5 hours ±30 minutes postdose (in duplicate).
i. For women of childbearing potential, serum or urine pregnancy test is required at Screening/Baseline and at Posttreatment/Early Termination Visits. Serum or urine pregnancy test to be performed every 3 cycles (approximately every 12 weeks ±1 week). If treatment with CORT125134 is stopped for ≥7 days, patient should have a negative pregnancy test before restarting drug.
j. Hematology: see list in Table 5. Nab-paclitaxel Lead-in Day 1 hematology to be obtained if previous hematology done >7 days prior. If weekly hematology tests demonstrate CTCAE Grade 3/4 cytopenias, increase frequency as clinically appropriate. Hematology assessments scheduled for the day of study drug dosing must be available and assessed for toxicity before dosing. The sampling for hematology assessment may be drawn within 48 hours before dosing.
k. Chemistry: see list in Table 5. Baseline (Nab-paclitaxel Lead-in Day 1) and Cycle 1 Day 15 laboratory samples should be obtained in a fasting state to collect the fasting glucose and fasting insulin samples. Coagulation (INR) performed weekly for patients on warfarin. Samples for these assessments can be drawn within 48 hours before dosing.
l. TSH is to be measured at Baseline (Nab-paclitaxel Lead-in Day 1 [predose]) and every 12 weeks (±14 days) for the first year and then every 6 months thereafter. Post-Screening, testing can be on the same schedule as pregnancy testing. Free T4 and total T3 will be measured if TSH values are abnormal.
m. Estradiol, testosterone, FSH, LH, and DHEA-S. Draw predose at Baseline (Nab-paclitaxel Lead-in Day 1) and Cycle 1 Day 15. A fasting, early morning specimen (7–9 AM) is preferred.
n. Urinalysis at Screening, Baseline, Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, then every 12 weeks (±14 days) thereafter and at the Posttreatment Visit. Microscopy is required only to follow-up clinically significant urine dipstick findings (see list in Table 5).
o. Tumor assessments (TAs): Screening—CAP CT scans done with contrast as standard of care ≤30 days of Screening may be used if they meet study quality criteria. Baseline—CAP CT scans with contrast done ≤28 days before the first dose of study drug will not need to be repeated for this time point. Subsequent TAs occur at Cycle 3 Day 1 (±7 days) and thereafter every 6–8 weeks (no more than 8 weeks between scans) and at time of clinical suspicion of disease progression. In patients with ovarian, fallopian tube, or primary peritoneal cancer, CA-125 levels will be assessed at the time of radiologic tumor assessments; levels of other biomarker collected as standard practice (such as CA15-3 and CA19-9, PSA, and CEA) will be documented in the case report

form. At the Posttreatment/Early Termination Visit, TA will be done if ≥4 weeks have elapsed since the prior TA and progressive disease as not been documented.

p. Draw fasting, morning (7–9 AM) C-peptide, ACTH, morning cortisol, and FKBP5 at Baseline (Day 1 of Nab-paclitaxel Lead-in) and at Cycle 1 Day 15 before administration of any study treatment. FKBP5, morning cortisol, and ACTH will be repeated every 12 weeks (±14 days) for the first year and then approximately every 6 months thereafter and at the Posttreatment/End of Treatment Visit.
q. Cytokines and T cell samples for patients in Part 1 are drawn predose and at 4 hours (±30 minutes) postdose to coincide with the PK time points in Table 10 on Nab-paclitaxel Lead-in Day 1, on CORT125134 Lead-in Day 7, and Cycle 1 Day 8. For patients in Part 2, samples are drawn at Cycle 1 Day 8 before and at 4 hours (±30 minutes) after nab-paclitaxel infusion. Samples at all time points can be drawn with PK sample collections.
r. Tumor tissue for GR IHC (archival or biopsy) is mandatory for patients in the study. Optional tumor tissue biopsy at the time of disease progression.
s. Archival tumor tissue may consist of tumor block or 15 unstained formalin-fixed, paraffin-embedded slides (tissue block preferred). Tumor biopsy for screening GR IHC analysis is to be performed if archival tumor tissue is not available.
t. Patients will be followed for progression and survival via telephone on a quarterly basis for 1 year after the last dose of study drug in the last patient on treatment.
u. All AEs, including SAEs, will be recorded from the time of signing of the IRB-approved ICF until 28 days after the last dose of study treatment. An SAE related to study procedures or study conduct must be reported to the Sponsor if it occurs before first dose of study drugs. SAEs must be reported as described in Section 9.9 of the protocol. Treatment-related AEs ongoing at the Posttreatment Visit should be followed to resolution or until the Investigator considers them “chronic” or “stable”. At the occurrence of a SAE or DLT, an additional ACTH, and cortisol blood sample and a PK sample will be drawn at the discretion of the Investigator, as close to the event as possible to help characterize any possible relationships between drug exposure and the clinical event.
v. All concomitant medications (including over-the-counter and herbal treatments) should be recorded from 28 days before the first dose until 28 (±7 days) after the last dose of study drug.
w. See Table 10 for PK sampling times.
x. CORT25134 will be dispensed to patients as blister packs of capsules to be self-administered orally once daily in the morning, starting with CORT125134-550 Lead-In Day 1. Patients should return all unused CORT125134 capsules and the dose diary during the patient visits, and patient adherence to treatment should be assessed. On visit days, CORT125134 should be taken in the clinical during the visit and after initial blood draws with time and dose administration documented in the clinic charts. On days when CORT125134 and nab-paclitaxel are administered in combination, CORT125134 is to be administered within 15 minutes before the start of nab-paclitaxel infusion.
y. All clinical laboratory results must be available and reviewed by the Investigator or Subinvestigator before each IV infusion of nab-paclitaxel and start of subsequent treatment cycles of CORT125134/nab-paclitaxel.

Table 10 Segment I: Study Pharmacokinetic Sampling Times

Cycle	Day (Scheduled dosing)	Sample	Planned Time	Nab-paclitaxel Sample	CORT125134 Sample	Note
Serial PK Sampling Schedule – All Patients in Part 1						
Nab-paclitaxel Lead-in (beforeCORT125134 Lead-in)	Day 1 (nab-paclitaxel infusion)	1	Predose	X		<1 h before start of nab-paclitaxel infusion
		2	0.5 h	X		From start of nab-paclitaxel infusion ±10 min
		3	0.75	X		From start of nab-paclitaxel infusion ±10 min
		4	1 h	X		From start of nab-paclitaxel infusion ±10 min
		5	2 h	X		From start of nab-paclitaxel infusion ±10 min
		6	4 h	X		From start of nab-paclitaxel infusion ±30 min
		7	6 h	X		From start of nab-paclitaxel infusion ±30 min
	Day 2 (no study drug)	8	24 h	X		From start of nab-paclitaxel infusion ±30 min
CORT12534 Lead-in (before Cycle 1)	Day 1 (CORT125134 oral dose)	9	Predose		X	<1 h before CORT125134
	Day 7 (CORT125134 oral dose)	10	Predose		X	<1 h before CORT125134
		11	0.5 h		X	±10 min
		12	0.75		X	±10 min
		13	1 h		X	±10 min
		14	2 h		X	±10 min
		15	4 h		X	±30 min
		16	6 h		X	±30 min
Cycle 1	Day 1 (CORT125134 oral dose + nab-paclitaxel infusion)	17	Predose	X	X[a]	<1 h before CORT125134[b]
		18	0.5 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
	Day 8 (CORT125134 oral dose + nab-paclitaxel infusion)	19	Predose	X	X[a]	<1 h before CORT125134
		20	0.5 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		21	0.75 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		22	1 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		23	2 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		24	4 h	X	X[a]	From start of nab-paclitaxel infusion ±30 min
		25	6 h	X	X[a]	From start of nab-paclitaxel infusion ±30 min
	Day 9 (CORT125134 oral dose)	26	24 h	X	X[a]	From start of nab-paclitaxel infusion ±30 min and <1 h before CORT125134
Cycle 1	Day 15 (CORT125134 oral dose + nab-paclitaxel infusion)	27	Predose	X	X[a]	<1 h before CORT125134
		28	0.5 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		29	0.75 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min

Continued on next page

Cycle	Day (Scheduled dosing)	Sample	Planned Time	Nab-paclitaxel Sample	CORT125134 Sample	Note
Sampling Schedule – All Patients in Part 2						
Cycle 1	Day 1 (CORT125134 oral dose + nab-paclitaxel infusion)	1	Predose	X	X[a]	<1 h before CORT125134
		2	0.5 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
	Day 8 (CORT125134 oral dose + nab-paclitaxel infusion)	3	Predose	X	X[a]	<1 h before CORT125134
		4	0.5 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		5	0.75 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		6	1 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		7	2 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		8	4 h	X	X[a]	From start of nab-paclitaxel infusion ±30 min
		9	6 h	X	X[a]	From start of nab-paclitaxel infusion ±30 min
	Day 15 (CORT125134 oral dose + nab-paclitaxel infusion)	10	Predose	X	X[a]	<1 h before CORT125134
		11	0.5 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min

Abbreviation: PK = pharmacokinetic

Notes: Samples for PK analysis should be drawn on a line separate from that used for nab-paclitaxel infusion. At time points when samples for analysis of a single analyte (either nab-paclitaxel or CORT125134) are drawn, the sample volume will be 2 mL.

After a minimum of two dose levels in Part 1 are observed, the nab-paclitaxel lead-in may be discontinued per the DRC recommendation.

[a] A 3-mL sample for analysis of both CORT125134 and nab-paclitaxel sample will be collected.

12.2 Segment II: Schedules of Visits and Procedures

Table 11 Segment II: Study Visits and Procedures

Procedures/ Examinations[a]	Screening	Baseline/CORT125134 Lead-in [b]	Cycle 1 (28-day cycle)			Cycle 2+ (28-day cycles)		Post-Tx / ET
	Day −28 to −2	Day −1	Day 1	Day 2	Day 8, 15	Day 1	Day 8, 15	
Informed consent [c]	X							
Inclusion/exclusion criteria [b]	X	X						
Medical/oncologic history [d]	X							
Physical examination (PE) [b,e]	X	X			X	X	X	X
Vital signs [b,f]	X	X	X		X	X	X	X
ECOG performance status [b]	X	X			X	X	X	X
ECG [g]	X		X[g]			If clinically indicated		
Pregnancy test [h]	X	X	Every 12 weeks (±7 days)					X
Hematology [b,i]	X	X	X		X	X	X	X
Chemistry and INR [b,j]	X	X			X	X	X	X
Fasting insulin		X			X[i]			
Thyroid function test [k]		X	Every 12 wk (±14 days)					
Hormone levels [l]		X			X[l]			
Urinalysis (dipstick) [b,m]	X	X				X		X
Cytokine and T cell sample [n]		X	X					
Optional PG sample		X						
Tumor assessment (RECIST v1.1) [o]	X	X				Cycle 3 Day 1 (±7 days) then every 6–8 wk		X[o]
PD/biomarker blood sample collection [p]		X[p]			X	Every 12 wk (±14 d)		X
Tumor tissue for GR IHC:[q] archival or biopsy [r]	X							
Follow-up for survival [s]								X[s]
Adverse events [t]	X ←	—	—	—	—	—	—	→ X
Concomitant medications [u]	X ←	—	—	—	—	—	—	→ X
PK/metabolites sample collection [v]			X[v]	X[v]	X[v]			
Study treatment administration (see Table 12) [w,x]								

Note: The acceptable visit window is ±3 days for Day 1 of each Cycle after Cycle 1. Nab-paclitaxel infusions must be no less than 7 days apart, and the recommended visit window for Day 8 and Day 15 is no more than +24 hours. On Cycle 1 Day 2 no visit window is allowed due to the planned collection of the 24-hour PK samples. Posttreatment/Early Termination Visit to occur 28 (±7) days after the last dose of study drug.

a. All procedures and examinations should be performed before the administration of study treatment(s), unless specifically stated otherwise.
b. Inclusion/exclusion criteria and selected safety assessments (vital signs, ECOG, PE, and laboratory tests) are required to be repeated only for patients for whom screening assessments were performed >7 days before Day −1 (first dose of CORT125134).
c. The IRB-approved ICF must be signed before any study-specific procedures or examinations are performed.
d. Including prior cancer treatments. Any new or clinically significant changes in the patient's medical or oncologic history between signing of the IRB-approved informed consent form and the first dose of study treatments will be recorded on the AE CRF page.
e. Physical examinations at Screening, at Day 1 of each cycle except Cycle 1 Day 1 when it is performed on Baseline/Day −1, and at the Posttreatment/Early Termination Visit should be complete assessments. Other weekly examinations may be focused, to identify changes from Screening/baseline or evaluate changes based on the patient's clinical symptoms. Weight to be reported at each visit, height at Screening/Baseline visit only.
f. On days of nab-paclitaxel IV administration, vital signs (heart rate, systolic and diastolic blood pressure, temperature, and respiration rate) should be collected pre-infusion and within 5 minutes after stopping the nab-paclitaxel infusion.
g. ECGs to be done at Screening (in triplicate) and at Cycle 1 Day 1 pre-CORT125134 dose and 2.5 hours ±30 minutes after start of nab-paclitaxel infusion (in duplicate).
h. For women of childbearing potential, serum or urine pregnancy test is required at Screening/Baseline and at Posttreatment/Early Termination Visits. Serum or urine pregnancy test to be performed every 3 cycles (approximately every 12 weeks ±1 week). If treatment with CORT125134 is stopped for ≥7 days, patient should have a negative pregnancy test prior to restarting drug.
i. Hematology: see list in Table 5. If weekly hematology tests demonstrate CTCAE Grade 3/4 cytopenias, increase frequency as clinically appropriate. Hematology assessments scheduled for the day of study drug dosing must be available and assessed for toxicity before dosing. The sampling for hematology assessment may be drawn within 48 hours prior to dosing.
j. Chemistry: see list in Table 5. Baseline/Day –1 and Cycle 1 Day 15 laboratory samples should be obtained in a fasting state to collect the fasting glucose and fasting insulin samples. Coagulation (INR) performed weekly for patients on warfarin. Samples for these assessments can be drawn within 48 hours before dosing.
k. TSH is to be measured at Baseline/Day–1 and every 12 weeks (±14 days) for the first year and then every 6 months thereafter. After Screening, testing can be on the same schedule as pregnancy testing. Free T4 and total T3 will be measured if TSH values are abnormal.
l. Estradiol, testosterone, FSH, LH, and DHEA-S. Draw predose at Baseline/Day −1 and Cycle 1 Day 15. A fasting, early morning specimen (7–9 AM) is preferred.
m. Urinalysis at Screening, Baseline/Day–1, Cycle 2 Day 1, Cycle 3 Day 1, then every 12 weeks (±14 days) thereafter and at the Posttreatment Visit. Microscopy is required only to follow-up clinically significant urine dipstick findings (see list in Table 5).
n. Cytokine and T cell samples are drawn at Baseline/Day -1 predose, and Cycle 1 Day 1 predose and at 4 hours (±30 minutes) after nab-paclitaxel infusion. All samples can be drawn with PK sample collections.
o. Tumor assessments (TAs): Screening—CAP CT scans done with contrast as standard of care ≤30 days of Screening may be used if they meet study quality criteria. Baseline—CAP CT scans with contrast done ≤28 days before the first dose of study drug will not need to be repeated for this time point. Subsequent TAs occur at Cycle 3 Day 1 (±7 days) and thereafter every 6–8 weeks (no more than 8 weeks between scans) and at time of clinical suspicion of disease progression. In patients with ovarian, fallopian tube, or primary peritoneal cancer, CA-125 levels will be assessed at the time of radiologic tumor assessments; levels of other biomarker collected as standard practice (such as CA15-3 and CA19-9, PSA, and CEA) will be documented in the case report

form. At the Posttreatment/Early Termination Visit, TA will be done if ≥4 weeks have elapsed since the prior TA and progressive disease as not been documented.

p. Draw fasting, morning (7–9 AM) C-peptide, ACTH, cortisol, and FKBP5 at Baseline/Day −1 before administration of any study treatment and at Cycle 1 Day 15. FKBP5, morning cortisol, and ACTH will be repeated every 12 weeks (±14 days) for the first year and then approximately every 6 months thereafter and at the Posttreatment/End of Treatment assessment
q. Tumor tissue for GR IHC (archival or biopsy) is mandatory for patients in the study. Optional tumor tissue biopsy at the time of disease progression.
r. Archival tumor tissue may consist of tumor block or 15 unstained, formalin-fixed, paraffin-embedded slides(tissue block preferred). For patients enrolled in the study, tumor biopsy for screening GR IHC analysis is to be performed if archival tumor tissue is not available.
s. Patients will be followed for survival via telephone on a quarterly basis for 1 year after the last dose of study drug in the last patient on treatment.
t. All AEs, including SAEs, will be recorded from the time of signing of the IRB-approved ICF until 28 days after the last dose of study drug. An SAE related to study procedures or study conduct must be reported to Sponsor if it occurs prior to first dose of study drugs. SAEs must be reported as described in Section 9.9 of the protocol. Treatment-related AEs ongoing at the Posttreatment Visit should be followed to resolution or until the Investigator considers them “chronic” or “stable”. At the occurrence of a SAE or DLT, an additional cortisol and ACTH sample and a PK sample will be drawn, at the discretion of the Investigator, as close to the event as possible to help characterize any possible relationships between drug exposure and the clinical event.
u. All concomitant medications (including over-the-counter and herbal treatments) should be recorded from 28 days before the first dose until 28 (±7 days) after the last dose of study drug.
v. See Table 13 for PK sampling times.
w. CORT25134 will be dispensed to patients as blister packs of capsules to be self-administered orally once daily in the morning, starting with CORT125134-550 Lead-In Day 1. Patients should return all unused CORT125134 capsules and the dose diary during the patient visits, and patient adherence to treatment should be assessed. On visit days, CORT125134 should be taken in the clinical during the visit and after initial blood draws with time and dose administration documented in the clinic charts. On days when CORT125134 and nab-paclitaxel are administered in combination, CORT125134 is to be administered within 15 minutes before the start of nab-paclitaxel infusion.
x. All clinical laboratory results must be available and reviewed by the Investigator or Subinvestigator before each IV infusion of nab-paclitaxel and start of subsequent treatment cycles of CORT125134/nab-paclitaxel.

Table 12 Segment II: Study Dosing Schedule

	Study Days																		
	Baseline/CORT125134 Lead-in	Cycle 1 (28-day cycle)									Cycles 2+ (28-day cycles)								
Study Treatment	**−1**	**1**	**2**	**7**	**8**	**9**	**14**	**15**	**16**	**28**	**1**	**2**	**7**	**8**	**9**	**14**	**15**	**16**	**28**
CORT125134 morning dose [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nab-paclitaxel infusion [b]		X			X			X			X			X			X		

[a] CORT25134 will be dispensed to patients as blister packs of capsules to be self-administered orally once daily in the morning, starting with Baseline/ Day −1. Patients should return all unused CORT125134 capsules and the dose diary during the patient visits. On visit days, CORT125134 should be taken in the clinical during the visit and after initial blood draws with time and dose administration documented in the clinic charts. On days when CORT125134 and nab-paclitaxel are administered in combination, CORT125134 is to be administered within 15 minutes before the start of nab-paclitaxel infusion.

[b] All clinical laboratory results must be available and reviewed by the Investigator or Subinvestigator before each IV infusion of nab-paclitaxel and start of subsequent treatment cycles of CORT125134/nab-paclitaxel.

Table 13 Segment II: Study Pharmacokinetic Sampling Times

Cycle	Day (Scheduled Dosing)	Sample	Planned Time	Nab-paclitaxel Sample	CORT125134 Sample	Note
Serial PK Sampling Schedule – All patients in Parts 1 and 2, Cycle 1						
Day −1: Patient self-administers morning CORT125134 doses						
Cycle 1	Day 1 (CORT125134 morning oral dose + nab-paclitaxel infusion)	1	Predose	X	X[a]	<1 h before CORT125134
		2	0.5 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		3	0.75 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		4	1 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		5	2 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		6	4 h	X	X[a]	From start of nab-paclitaxel infusion ±30 min
		7	6 h	X	X[a]	From start of nab-paclitaxel infusion ±30 min
	Day 2 (CORT125134 morning oral dose)	8	24 h	X	X[a]	From start of nab-paclitaxel infusion ±30 min and <1 h before CORT125134[b]
	Day 15 (CORT125134 morning oral dose + nab-paclitaxel infusion)	9	Predose	X	X[a]	<1 h before CORT125134
		10	0.5 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		11	0.75 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		12	1 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		13	2 h	X	X[a]	From start of nab-paclitaxel infusion ±10 min
		14	4 h	X	X[a]	From start of nab-paclitaxel infusion ±30 min

Abbreviation: PK = pharmacokinetic
Note: *Only patients in Cycle 1* will have serial PK sampling on Day 1 (1 h predose to 6 h postdose) and Day 2 predose and on Day 15 (1 h predose to 4 h postdose).
Samples for PK analysis should be drawn on a line separate from that used for nab-paclitaxel infusion.
[a] A 3-mL sample for analysis of both CORT125134 and nab-paclitaxel sample will be collected.
[b] Note: this is the 24-h time point for the Day 1 serial PK.

12.3 Investigator's Brochure and Package Insert

The current IB for CORT125134 and package insert for nab-paclitaxel will be supplied to Investigators in the study materials.

12.4 Summary of Changes in Protocol CORT125134-550 Amendment 6

Significant changes in Amendment 6 of the protocol (dated 13 January 2020) compared with the Amendment 5 (dated 29 May 2018) are summarized below with additional details in Table 14. Deleted text is shown as a strikethrough and new text is shown in bold font. Tables of Contents, lists of tables or figures, in-text cross-references updated without redline.

Significant changes in Amendment 6:

- Addition of relacorilant softgel capsules, 25 mg and 100 mg

Table 14 Summary of Changes in Protocol CORT125134-550 Amendment 6

Section	Revision
Global administrative or editorial changes	Changed Amendment 5 to Amendment 6 and changed the date from 29 May 2018 to 13 January 2020
Sponsor Signature Page	Updated signatory for the Sponsor to reflect organizational staffing changes [redacted]
Investigator Signature Page	Update ICH information …ICH document "~~Guideline for Good Clinical Practice, E6 (R1)~~**E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1),**" dated ~~10 June 1996~~**9 Nov 2016**.
Synopsis	Add relacorilant 25-mg and 100-mg softgel capsules Investigational product (CORT125134): Drug product contains CORT12534 drug substance, a synthetically prepared small molecule, [redacted] CORT125134 50-mg capsules are white, size 2, hard gelatin capsules. **The hard gelatin capsules are provided in sealed, foil blister strips. CORT125134 100-mg softgel capsules are yellow, and the 25-mg softgel capsules are brown. The softgel capsules are provided in bottles containing 30 capsules each.**
5.1 Study Drug and Formulations	Changes to Investigational product (CORT125134) *3rd subbullet separated into two separate bullets because the label requirements are applicable to both hard gelatin and softgel capsules, modified later half for clarity.* - CORT125134 50-mg capsules are white, size 2, hard gelatin capsules. The capsules are provided in sealed, foil blister strips. Added - **CORT125134 100-mg softgel capsules are yellow, and the 25-mg softgel capsules are brown. The capsules are provided in bottles containing 30 capsules each.** - At a minimum, the labels on ~~each package of~~ study drug **will** contain~~s~~ the drug name and number, protocol number, number of capsules, storage conditions, caution statement on investigational use only, and Sponsor details. Labeling will meet country-specific requirements.